Clinical Characteristics and Predictors of Reduced Survival for Adult-Diagnosed Cystic Fibrosis Patients – A population based study

by

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Abstract

Background: Approximately 5-10% of cystic fibrosis (CF) diagnoses are made during adulthood. These patients are a minority, and there is a paucity of literature describing their characteristics and prognosis. The objectives of this study are to describe the clinical characteristics, estimate survival, and identify clinical predictors of reduced survival at the time of diagnosis in adult-diagnosed CF patients.

Methods: There were 362 newly diagnosed adult CF (≥18 years) patients from 1990 to 2014 in the Canadian CF Patient Registry. Clinical characteristics were described, the Kaplan-Meier method was employed for 10- and 15-year lung transplant-free survival estimates and multivariable Cox regression analysis was conducted to identify significant predictors of reduced survival at baseline. Adjusted survival curves were used to illustrate the impact of the significant predictors on lung transplant-free survival.

Results: The median follow-up time observed was 7.7 years (range: 0.0-23.6) and included 33 deaths and 15 transplants for a total of 48 events in 3,106 patient years (15.5 events per 1,000 PYs). The median age at diagnosis was 34.3 years (range: 18.0-73.8), with the majority presenting with pulmonary and/or gastrointestinal symptoms (70%) and a nearly equal distribution of males and females. During the study period, 15% were diagnosed with CF-related diabetes (CFRD), 35% with pancreatic insufficiency and 50% were culture positive for *P. aeruginosa*. The most common genotype identified was ΔF508 heterozygous (38%). Lung transplant-free survival was 88% at 10 years and 86% by 15 years. Age at diagnosis (HR: 1.32 per 5-year increase, 95% CI: 1.13-1.54), CFRD (HR: 7.86, 95% CI: 2.09-29.55) and lower lung function (HR: 0.76 per 5% increase, 95% CI: 0.69-0.83) at baseline were significant predictors of reduced survival. In terms of clinical utility, low lung function (FEV_1 % predicted < 60%) and CFRD were predictors that impacted lung transplant-free survival substantially.

Conclusions: Adult-diagnosed CF patients have a milder phenotype of disease and a better prognosis than previously reported. Older age at diagnosis, lower lung function, and CFRD were important predictors of reduced survival. Adult CF clinicians and other CF caregivers can use this information to educate patients about their prognosis and to guide treatment.

Lay Abstract

Cystic fibrosis (CF) is the most common genetic disease affecting children and young adults. More adults are being diagnosed with CF due to increased awareness among doctors and more sensitive diagnostic methods. Being diagnosed with CF as an adult is very rare; currently, they represent only 5-10% of all CF patients in Canada. These patients face unique challenges, issues, and needs compared to other CF patients diagnosed at younger ages. Information about life expectancy and prognosis is important, particularly for mature, older diagnosed patients. However, due to the rarity of this disease, doctors have little information to inform them. The main purpose of this study was to evaluate disease prognosis in this group of CF patients and we found that these patients have higher survival rates than previously reported. Also, being older at diagnosis and having low lung function at the time of diagnosis are important factors for poor survival. Having CF-related diabetes is also another potentially important factor. Doctors can now use this information to educate patients and guide treatment.

Preface

I was responsible for reviewing the literature, protocol development, ethics registration, statistical data analysis, interpretation of the analysis, and drafting of the manuscript (thesis).

Dr. Joel Singer was involved with the concept and design of the project, statistical advice and interpretation of the analysis. Dr. Bradley Quon was involved with the concept and design of the project, acquisition of data, interpretation of analysis, and overall project coordination. Dr. Hubert Wong was involved with providing statistical advice and interpretation of the analysis.

This project, titled "Clinical Characteristics and Predictors of Reduced Survival for Adult-Diagnosed Cystic Fibrosis Patients" was approved by the Research Ethics Board at St Paul's Hospital, Vancouver, Canada (REB # H15-01439).

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List of Abbreviations and Acronyms

Abbreviation	Meaning
BMI	Body mass index
CCFR	Canadian Cystic fibrosis registry
CF	Cystic fibrosis
CFFPR	Cystic fibrosis foundation patient registry
CFRD	Cystic fibrosis related diabetes
CFTR	Cystic fibrosis transmembrane conductance regulator
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
FEV_1	Forced expiratory volume in one second
GI	Gastrointestinal
GLI	Global lung initiative
HR	Hazard ratio
LTFU	Lost to follow-up
MRSA	Methicillin-resistant staphylococcus aureus
NTM	Non-tuberculosis mycobacteria
PH	Proportional hazards
PY	Patient years
US	United States

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1 Introduction

Cystic fibrosis (CF) is the most common, fatal genetic disease affecting Canadian children and young adults. Approximately 4,100 Canadians are currently living with CF and it has an annual incidence of 1 in 3600 live births (1). CF is caused by a defective protein called the CF transmembrane conductance regulator (CFTR), responsible for secretion of chloride in the epithelial cells of our bodies. Defective chloride secretion leads to the development of thick mucus in the airways which results in chronic pulmonary infections. Other common clinical manifestations include difficulty digesting fats and proteins, CF-related diabetes (CFRD) and sinus infections. Ultimately, recurrent pulmonary infections cause permanent lung destruction and continual loss of lung function over time, resulting in the need for a lung transplant or premature death in the majority of CF patients.

The current diagnostic criteria for CF includes identification of at least one clinical feature of CF (e.g. family history, bronchiectasis, hemoptysis, etc.) and evidence of CFTR dysfunction by a biochemical marker (i.e. elevated sweat chloride) or confirmation of CF-causing mutations on both alleles (2). Approximately 60% of CF cases are diagnosed within the first year of life and about 90% are diagnosed by eighteen years of age (1,3,4) (Figure 1). The remaining 5-10% represent a very rare sub-population of CF cases that are diagnosed in adulthood and will be the focus of the current study. Although historically rare, recently researchers have noted a rise in adult-diagnosed cases, possibly attributed to increased awareness of disease heterogeneity among physicians, more wide-spread genotyping availability, and more streamlined diagnostic criteria (5,6). Though, it is likely that implementation of routine newborn and prenatal screening programs will reduce the incidence of adult-diagnosed CF in the future, thus limiting the ability to discriminate this rare sub-population from the overall CF population (7).

Despite being in the minority, adult-diagnosed patients face unique challenges, issues, and needs compared to childhood-diagnosed patients. For instance, they are more likely to be married, attending educational institutions, working full-time and raising a family at the time of diagnosis (8). For most adult-diagnosed patients, the diagnosis of CF is accompanied by shock, fear, and depression. For others, the diagnosis could be an explanation for symptoms they had experienced for a long time and bring a sense of relief (9). Regardless, they are concerned about the prognostic implications of the disease and it is not surprising that the most common question at the time of diagnosis is about life expectancy (9). However, due to the relative rarity of adult-diagnosed CF cases and the paucity of available prognostic

literature for this population, this question remains difficult to answer by most physicians leaving the patient confused and frustrated (9,10). Some patients resort to online resources and material which focuses on childhood-diagnosed CF and cites life spans that are relatively short and sometimes briefer than the patients' ages, adding to their perplexity. Others are unwilling to attend CF care centers and adhere to rigorous CF treatment modalities (many of which are nebulized and thus time-consuming) due to limited data on expected disease progression. As a result, clinicians often also find it challenging to educate these patients on the need for treatments (5).

1.1 Review of the literature

Clinical Characteristics

The first published report of an adult-diagnosed CF patient occurred in 1946 (11). Since then, there have been numerous case studies describing these patients in further detail (12–15). Most of these studies conclude that adult-diagnosed patients are atypical with a milder form of the disease than what is typically observed in childhood-diagnosed CF. Case studies are an important first step in research. However, they lack the ability to generalize the findings due to small sample sizes, thus preventing researchers from making meaningful inferences regarding the population of interest.

The first population-based study on this population was conducted by Widerman et al. in 2000 (8). They sought to describe clinical characteristics and socio-demographic differences between adults diagnosed in childhood (<18 years) and adulthood (>18 years) using the United States (US) Cystic Fibrosis Foundation Patient Registry (CFFPR) for the year of 1996. There were 786 adult-diagnosed patients included, representing approximately 10.9% of all CF patients for that year. In terms of social factors, they found that they were more likely to be college graduates, employed full-time, and married, as expected. They also experienced fewer complications, cultured less severe bacterial organisms, had a lower prevalence of common mutations, fewer hospitalizations, less oxygen use, less enzyme use, and lived longer than childhood-diagnosed patients. Based on these findings, Widerman et al. concluded that adult-diagnosed patients are a unique subgroup of adults with CF. Although this study offered great insight into the characterization of adult-diagnosed CF patients using a large sample size, there were several limitations. Firstly, they queried the CFFPR registry which does not adequately cover all CF patients, particularly those diagnosed in adulthood (5). Secondly, Widerman et al. did not employ multivariable modeling to account for confounders when comparing childhood-diagnosed to adult-

diagnosed CF patients, which could affect their conclusions regarding some statistically significant bivariable associations. Lastly, many comparisons were examined in which an excess of 10% of missing data for at least one of the variables was noted, possibly biasing the results.

Gilljam et al. (6) conducted the first Canadian study examining adult-diagnosed CF patients using a retrospective comparative cohort study design from 1960 to 2001, with an emphasis on the period from 1990 to 2001. They observed an exponential increase in adult diagnoses from 1960 to 2001, possibly due to increased physician and patient awareness. They further confirmed Widerman et al.'s findings that adult-diagnosed CF patients exhibited a milder form of the disease compared to the childhood-diagnosed patients based on clinical characteristics. Moreover, Gilljam et al. (6) emphasized that these patients are a unique subset of the overall CF population with a wider heterogeneity of disease. Notably, one-third of the patients did not have a conclusive sweat test and needed additional diagnostic testing to confirm their diagnosis. However, this study only examined patients from two clinics in Toronto, Canada and thoroughly investigated just 46 adult-diagnosed patients from 1990 and onwards due to incomplete data for patients diagnosed prior to that year – thus limiting the generalizability of the results.

Nick et al. investigated long-term survivors of CF (>40 years of age) and compared those diagnosed in childhood to those diagnosed in adulthood. This study was single center and identified 55 patients between 1992 and 2004 who were 40 years and older, and of those 27, were diagnosed as adults. The findings supported the conclusions of previous reports. Namely, adult-diagnosed CF patients have less severe lung disease, were more likely to have pancreatic sufficiency, lower prevalence of *P. aeruginosa,* and lower prevalence of severe mutations (16). Interestingly, the authors also noted an unusually high prevalence of non-tuberculous mycobacteria (NTM) in the adult-diagnosed group relative to the childhood-diagnosed group; a novel finding for this cohort but potentially biased as the National Jewish Hospital is a regional referral center for difficult to treat cases of NTM. The greatest strength of this study was comparing a homogenous group of age-matched childhood-diagnosed CF patients to adult-diagnosed CF patients to account for possible age-associated effects. Adult-diagnosed patients are not diagnosed until adulthood, whereas childhood-diagnosed patients are diagnosed in early childhood leading to differential follow-up characteristics and the heightened potential for biased conclusions if age is not taken into account. Though, the authors acknowledged that the included patients consist of many out-of-state referrals for specialized assessment at their institution, therefore the

generalizability of the results are greatly affected since it most likely does not represent the general adult-diagnosed CF population.

Prognosis

Nick et al. conducted another study, focusing again on long-term survivors, aged 40 years and older from nearly the same period (1992 to 2008) but now the goal was to evaluate disease progression in this population using the CFFPR (17). It was found that adult-diagnosed patients exhibited similar age-related lung function decline and frequency of death from respiratory failure from age 40 and onwards compared to childhood-diagnosed CF patients (17). This result was unexpected because previous literature established adult-diagnosed patients to have a milder form of CF. However, this was the first prognostic study in this population at that time, and it appeared that the pulmonary manifestations at the time of diagnosis are not mild but delayed and represent an equally serious form of CF compared to age-matched childhood-diagnosed CF patients. Since this study specifically selected CF patients who lived until the age of 40, the results from this cohort would be subject to survivor bias. In other words, the results would only apply to those patients who live until 40 years of age, with no information regarding those who were diagnosed as adults but died before the age of 40.

The most recent prognostic study by Keating et al. (18) used the CFFPR to study lung function decline and survival in different age groups, including adult-diagnosed CF patients from 1993 to 2003 and followed up until 2010. They found the rate of lung function decline in adult-diagnosed patients to be -1.13% per year, almost double the rate found in Nick et al.'s study (17). Unadjusted 10 and 15-year survival was 76% and 65%, respectively, with *P. aeruginosa* and *Burkholderia* complex infections as the only significant factors associated with survival. Additional regression models with lung function decline as the outcome also found that baseline lung function, body mass index (BMI), the presence of a ΔF508 mutation and *P. aeruginosa* were associated with faster rates of decline. This study, however, had many drawbacks that may affect the conclusions. Firstly, they only included patients with complete follow-up, which resulted in approximately 35% of the original sample to be excluded from the final analysis. Generally, patients with complete follow-up are systematically different than those loss to follow-up. Also, Nick et al cross-referenced adult-diagnosed patients in their institutional database to the CFFPR and found missing deaths in up to 50% of patients beyond the age of 45 years and concluded that long-term survivors of CF, with majority being adult-diagnosed patients, are not frequently seen at CF centers and many die without being accounted for in the CFFPR. The large number of patients lost to

follow-up, together with the potential of missing deaths may be biasing the results from Keating et al.'s study. In fact, Sykes et al empirically assessed the impact of missing deaths and loss to follow-up in prognostic studies in CF and determined by simulations that missing just 15% of deaths can result in overestimation of survival by 3.5 years and having 25% of patients loss to follow-up can underestimate survival by 3.3 years (19).

Overall, the current body of evidence supports adult-diagnosed CF patients to be a unique subset of the overall CF population that exhibit a milder form of disease in comparison to childhood-diagnosed patients, while recognizing the wide disease heterogeneity among adult-diagnosed patients. However, current evidence concerning life expectancy and prognosis is limited and remains poorly characterized.

1.2 Rationale and objectives of the study

The lack of high-quality evidence specifically about the prognosis of adult-diagnosed CF patients in the current literature and the recent increase in the frequency of this diagnosis provides the rationale for this study. The objectives of this population-based study are to describe the clinical characteristics, estimate lung transplant-free survival, and identify significant clinical predictors of reduced survival at the time of diagnosis in adult-diagnosed CF patients. The findings from this study will help CF clinicians educate these patients on the need for treatments, expected disease course, and life expectancy.

2 Methods

2.1 Data source

The Canadian Cystic Fibrosis Registry (CCFR) was created in the 1970s with the goal of monitoring important clinical trends in the Canadian CF population. The CCFR captures individuals with a confirmed diagnosis of CF based on current diagnostic guidelines (20). It contains detailed demographic and clinical information on CF patients receiving care in 42 accredited CF centers across Canada (1). These data undergo routine validation checks and discrepancies are resolved by contacting the reporting CF Center to cross-reference with original data. Additionally, CF Canada provides funding to centers dependent on data submission to the registry and CF patients must attend CF centers as many expensive medications are covered by provincial drug plans if prescribed by a CF physician. For these reasons, the CCFR is recognized for its completeness, accuracy and comprehensive coverage of CF patients across Canada (21).

2.2 Study design and sample

Population-based cohort study using the CCFR of newly diagnosed adult CF patients ≥ 18 years of age between the years 1990 and 2014 (Figure 2). The year 1990 was chosen as the study start date because it was after the discovery of the CF gene in 1989 (22) which allows for consistent diagnostic pathways during the study period. Additionally, prior to 1990 the CCFR had very limited clinical data which made it more appropriate to start from 1990 given the objectives of the present study.

2.3 Study variables

Demographic variables of age at diagnosis, sex (male or female) and race (caucasian, black, asian, south asian, other or unknown) were included in the descriptive analysis. Other clinical variables such as symptoms at diagnosis (asymptomatic, gastrointestinal, minor manifestations, pulmonary, pulmonary and GI, other or unknown), genotype (ΔF508 heterozygous, ΔF508 homozygous, one mutation only, two non-ΔF508 or unknown), CFRD (yes or no) which was defined as hyperglycemia based on oral glucose tolerance test results or random blood sugar measurements requiring insulin therapy (23), pancreatic insufficiency (yes or no) based on enzyme usage, *P. aeruginosa* culture positive (yes or no), and cause of death (pulmonary, cardiovascular, gastrointestinal, transplant-related, infection/sepsis or other) were also described. For the characterization of the disease, CFRD, pancreatic insufficiency, and *P.*

aeruginosa culture positive were considered ever variables, which means that if an individual was assigned positive status (yes), for these variables at any time point during the study period, they remained that status for the entire study period. The reason for this distinction was due to limitations in the CCFR database, in which the start/end date was not included for patients diagnosed with CFRD or administered enzymes (pancreatic insufficiency) and therefore it can be considered the approximate life-time prevalence of these characteristics.

Baseline variables available at the time of diagnosis (defined as ≤ two years from diagnosis date) were also evaluated. These variables included the demographic factors, symptoms at diagnosis, genotype, CFRD, BMI, stable lung function measurements, and *P. aeruginosa* culture. Lung function was measured by forced expiratory volume in one second (FEV_1) and expressed as a percentage of predicted based on the GLI equation (24,25). For variables which had multiple measurements within the baseline period, the one closest to the diagnosis date was selected. Additionally, it was assumed that any patient with no cultures tested was negative for *P. aeruginosa* culture. The study variables of race, symptoms at diagnosis, and genotype were collapsed into broader categories during modelling because many of their categories contained small cell numbers affecting the convergence of the regression models.

The outcome variable was death or transplant (i.e. lung transplant-free survival), whichever occurred first. The selection of transplant recipients is based on the recommendations by the Pulmonary Council of the International Society for Heart and Lung Transplantation (ISHLT) and shown in Table 1 (26). Generally, patients are considered for transplantation when their condition is worsening and have a 2-year predicted survival of <50%. The survival time was calculated from the diagnosis date to the outcome date and since the objective of the analysis was to identify variables predictive of lung transplant-free survival only, time since diagnosis was the time scale selected (27). If the outcome did not occur or the patient was loss to follow-up (defined as those patients alive with their last verified contact occurring more than two years before the study end date), the patient was censored at their last reported visit.

2.4 Statistical analysis

All analyses were conducted using R statistical programming (28). Patient demographics and clinical characteristics were described using simple descriptive statistics (medians, means and proportions). A Kaplan-Meier Curve was computed to estimate the overall 10 and 15-year lung transplant-free survival probability of the entire cohort. Cox proportional hazards (PH) models were used to determine the

predictive utility of clinical factors after accounting for the other model variables. The PH assumption was tested for each variable (and was found to be violated for the age at diagnosis variable) with a plan to split the follow-up period at a time point where the assumption appeared to begin to fail and a time interaction term was included to assess the change in hazard ratio. Moreover, the functional form of the continuous covariates was also checked by examining the martingale residuals and adding a quadratic term. Based on the final model, adjusted survival curves were then generated using the corrected group prognosis method (29). Briefly, this method calculates survival curves for each patient in the study assuming each patient was exposed for a given variable; then the predictions are averaged. The same predictions are obtained and averaged assuming each patient is now non-exposed for that same given variable. This method allows for an adjusted assessment of the potential absolute impact of a given predictor by considering differences in the survival curves arising from varying the values of each predictor. The associated 95% CIs for the predicted survival probabilities were calculated by non-parametric bootstrapping with 1000 replications using the percentile interval method.

Multiple imputation using the fully conditional specification algorithm was employed to account for missing data, under the assumption that missing data was missing at random. Eleven imputed datasets were created and then pooled using Rubin's rules (30) for Cox regression analysis. Eleven imputed datasets were preferred based on White and Bodner's recommendation of using the same number of imputations as to the percentage of incomplete cases missing in the dataset (31,32). Satisfactory convergence with no definitive trends was reached for the incomplete variables during imputation.

All variables that were found to have p-values below the *a priori* defined cut-off ($p<0.25$) in univariable testing or those with strong *a priori* hypotheses were added to the final multivariable model. BMI is a surrogate for the nutritional status of a patient and it is well-established in the overall CF population that increased BMI and nutritional status leads to better clinical outcomes, including survival (33–35). Thus, it is considered a pivotal metric of health among patients with CF and included in the final multivariable model. Moreover, numerous studies postulate a significant "gender gap" in CF where females have been found to have worse survival for a variety of reasons, some of which include genetic modifications, socioenvironmental factors as well as psychosocial factors (36,37). Therefore, sex was also added to the final multivariable model. Finally, the present study spanned a long time-period, thus diagnosis year was added into the final model to mitigate any cohort effects.

The level of significance was $p < 0.05$ for all statistical analyses, and all reported p-values reflect

two-tailed tests. All patients within the registry provided informed consent to have their data collected and be used for research purposes. The study was approved by the Research Ethics Board at St Paul's Hospital, Vancouver, Canada (PHC-REB# H15-01439).

3 Results

3.1 Study sample characteristics

In total, 362 patients were diagnosed with CF as adults between 1990 and 2014. The median follow-up time observed was 7.7 years (range: 0.0-23.6) and included 33 deaths and 15 transplants for a total of 48 events in 3,106 patient years (15.5 events per 1000 PYs). Forty-eight patients (13.3%) were lost to follow-up (defined as those patients not seen for at least 2 years before study end date) over the study period. Table 1 describes the clinical characteristics of the overall sample during the study period. The study sample was nearly equally distributed among males and females with a median age at diagnosis of 34.3 (range: 18.0-73.8). The majority of the sample was caucasian (90.3%) and patients primarily presented with pulmonary and/or gastrointestinal (GI) symptoms (70.5%). Sixty-two patients (17.4%) also presented with no symptoms or minor manifestations (e.g. clubbing on its own, hyponatremia, nasal polyps, etc.) and the remaining proportion (12.0%) either had other symptoms that could not be categorized or it was not clear or known what the presenting symptoms were. The most common genotype was ΔF508 heterozygous (38.1%), followed closely by one mutation only (31.2%). Only seventeen patients (4.7%) were ΔF508 homozygous. During the study period, the prevalence of CFRD (ever) was 15%, 35% of the sample was pancreatic insufficient (ever), and 50% were culture positive for *P. aeruginosa*. At baseline, the mean BMI was 23.6 ± 4.3 kg/m^2, the mean FEV_1 % predicted was 77.6 ± 23.7%, 3.0% presented with CFRD and 30.4% were culture positive for *P. aeruginosa.*

3.2 Descriptive statistics by event status

Table 2 also presents patient demographics and clinical characteristics by event status at the end of the follow-up period. The most common cause of death was due to pulmonary issues (54.5%). Patients who died or transplanted were more likely to be older at diagnosis, have pulmonary/GI symptoms, CFRD, and culture positive for *P. aeruginosa* at baseline. Additionally, lung function at baseline was substantially lower and the prevalence of CFRD (ever) and pancreatic insufficiency (ever) was also higher in these patients. Overall, patients who died or transplanted during the study period demonstrated a more severe manifestation of CF at baseline.

3.3 Survival analysis

Figure 3 displays the Kaplan-Meier survival curve for all patients in the study. The 10-year and 15-year lung transplant-free survival probability was 87.7% (95% CI: 82.9%, 91.3%) and 86.1% (95% CI: 80.7%, 90.1%).

Table 3 presents the univariable and the final model Cox regression hazard ratios (HRs) for all variables available at baseline. During univariable testing, age at diagnosis, *P. aeruginosa* culture positive, CFRD and FEV_1 % predicted all reached statistical significance ($p<0.05$) and were included in the final model. Additionally, symptoms at diagnosis was below the *a priori* defined p-value cut-off ($p<0.25$) and added to the final model, whereas sex and BMI were considered strong *a priori* hypothesized variables and also added to the final model. The PH assumption was tested for each variable and found to be unsatisfied for the age at diagnosis variable and therefore, the follow-up period was split at the 10-year time point (Figure 4), with a time interaction included in the final model to satisfy assumptions. In the final multivariable model, adult-diagnosed patients were more likely to die or be transplanted in the first 10 years following diagnosis if they were older at diagnosis (HR: 1.32 per 5 years, 95% CI: 1.13, 1.55). However, the effect of age at diagnosis was not sustained after the 10-year period (HR: 0.98, 95% CI: 0.75, 1.29). In addition, those with lower lung function (HR: 0.76 per 5% increase, 95% CI: 0.69, 0.83) at baseline were also more likely to die or be transplanted during the study period. CFRD was also identified as a significant predictor of reduced survival (HR: 7.86, 95% CI: 2.09, 29.55), however, the confidence interval indicates imprecision with a very wide width.

The influence of the significant predictors on reduced survival identified in the final multivariable model were illustrated by considering differences in adjusted survival curves and 15-year lung-transplant free survival probabilities using the corrected group prognosis method.

Scenario 1: Age at diagnosis was increased by 10 year increments (30 vs 40 vs 50 vs 60)

Scenario 2: Baseline FEV_1 % predicted was increased by 10% (40% vs 50% vs 60% vs 70% vs 80%)

Scenario 3: CFRD positive patients compared with CFRD negative patients

Scenario 4-5: The values of the first and third quartiles for age at diagnosis (27.1 years and 44.1 years) and baseline FEV_1 % predicted (62.4% and 94.3%)

Table 4 presents the predicted survival probabilities for each scenario from above. The adjusted survival curves for scenario 1 demonstrated that increasing age at diagnosis by 10 years reduced survival (Figure

5), although the survival difference between each 10-year increment appears to be minimal for the first 10 years post-diagnosis while becoming more pronounced over time. The predicted 15-year lung transplant-free survival probabilities for age at diagnosis were high for the younger ages at diagnosis (30 and 40) but reached below 60% for a diagnosis made in the oldest age at diagnosis (60 years). For scenario 2, the adjusted survival curves for each 10% increase in baseline FEV_1 % predicted were distinctive immediately from diagnosis, with the survival difference becoming even larger as the baseline FEV_1 % predicted decreased further. The predicted 15-year lung transplant-free survival probabilities for FEV_1 % predicted decreased from 84.0% (95% CI: 43.2%, 96.5%) for having 80% FEV_1 % predicted (high lung function) to 43% (95% CI: 22.2%, 75.3%) survival for having 40% FEV_1 % predicted (low lung function) equating to a 41% difference in survival. Patients with CFRD also experienced a marked decrease in lung transplant-free survival, with the adjusted difference being 33% at 15-years post-diagnosis (Figure 7). Standardized comparisons for age at diagnosis and FEV_1 % predicted showed that the difference in adjusted curves were larger for FEV_1 % predicted compared to age at diagnosis (Figure 8). Additionally, the predicted 15-year lung transplant-free survival probability difference for FEV_1 % predicted was 23.1% (from 91.9% to 68.8%) compared to 11.2% (from 83.9% to 73.7%) for age at diagnosis.

3.4 Sensitivity analyses

Since the present study assumed patients who had no cultures examined for *P. aeruginosa* were negative at baseline, a sensitivity analysis was conducted for possible misclassification. *P. aeruginosa* culture status was extended to five years after diagnosis and included in the final model as a substitute for the original *P. aeruginosa* at baseline variable. It resulted in no changes in the overall conclusions of the model (Table 5). Additionally, CFRD status at baseline was identified as a significant predictor in the present study; however, the number of patients with CFRD was small (n=10, 3%) which resulted in wide confidence intervals and a large standard error (Table 3). Therefore, an investigation of the final model (data not shown) which substituted CFRD at baseline with the CFRD ever variable was conducted to see if this association persisted. The HR for the CFRD ever variable was attenuated and variable (HR: 1.51, 95% CI: 0.81, 2.81) compared with CFRD at baseline (HR: 7.86, 95% CI: 2.09, 29.55), but was still demonstrating harmful effects. This finding corroborates the conclusions of CFRD status at baseline being a significant predictor of reduced survival in the adult-diagnosed population, but it likely is less pronounced than what the multivariable model indicates. Lastly, the patients lost to

follow-up (LTFU) had significantly less pulmonary/GI symptoms, less prevalence of *P. aeruginosa* positivity, one mutation only, higher baseline lung function and more likely to be male. These findings suggest that the LTFU patients appear to be healthier than those not lost to follow-up and most likely not attending their visits because they are feeling well. However, these patients will have little to no impact on the current study results as studies show LTFU rates of 10% or lower do not change results (19). At most, the HRs in the present study may be slightly over-estimated for some predictors as the LTFU patients are healthier but not enough to change the overall conclusions of the model.

4 Discussion

4.1 Summary of findings

The current study used a comprehensive, national population-based CF patient registry known for its completeness and accuracy to describe the characteristics of adult-diagnosed CF patients, estimate their 10 and 15-year lung transplant-free survival, and identify significant predictors of reduced survival. The clinical characteristics of this population were generally consistent with the literature, however they had less severe disease based on lower rates of pancreatic insufficiency, CFRD, *P. aeruginosa* culture positive and a reduced prevalence of severe mutations compared to previous studies examining adult-diagnosed CF patients (6,8,16,18). They also had 10-and 15-year transplant-free survival of 88% and 86%, respectively. The study also identified older age at diagnosis, lower lung function, and CFRD to be significant predictors of reduced survival in this population. However, adjusted survival curves demonstrated lung function and CFRD to have the most clinical utility for prognosis.

4.2 Key findings in the context of existing literature

Although, the clinical characteristics of the study sample were generally consistent with prior studies in the literature, adult-diagnosed CF patients followed in the CCFR have a milder disease at the time of diagnosis (6,38). Particularly, rates of pancreatic insufficiency, CFRD, severe mutations and *P. aeruginosa* culture positive were markedly lower in the present study in comparison to previous evidence for this population. This might be explained by most studies using the CFFPR from the US as their data source which has been reported to underrepresent adult-diagnosed patients (17) and potentially biasing the clinical characteristics toward more severe adult-diagnosed patients who are more likely to be followed due to more active disease. The present study utilized a registry known for comprehensive coverage of CF patients in Canada, and the current results may indicate that the CCFR follows patients with a wider spectrum of the disease compared to the CFFPR that tends to capture the severest.

Life expectancy is a major concern for adult-diagnosed patients at the time of diagnosis (9) but there are limited studies investigating this. Recently, Keating et al reported that 10- and 15-year survival rates using the CFFPR were estimated at 76% and 65%, respectively, compared to the present study which estimated the 10- and 15-year survival rates to be much higher at 87.7% (95% CI: 82.9%, 91.3%) and 86.1% (95% CI: 80.7%, 90.1%). Even the lower bound of the CIs for the present study's survival

rates exceed Keating study's findings. The higher survival rate in the present study further supports the above hypothesis that CCFR follows a more diverse spectrum of adult-diagnosed CF patients who have a milder phenotype compared to the CFFPR which includes more severe adult-diagnosed patients. Nick et al also investigated survival in this population and concluded that the median survival in their adult-diagnosed cohort was 76.9 years, higher than childhood manifested patients (17). However, Nick et al only studied long-term survivors of CF who survived up to 40 years of age, resulting in biased estimates and therefore, their findings are not comparable to Keating et al (18) and the present study. Nonetheless, it should be reassuring for newly diagnosed adult CF patients that their survival is lengthier than previously reported in the literature.

Increased survival in this population could be attributable to an attenuated disease course because of less CFTR dysfunction compared to the more classic childhood-diagnosed CF patients. Typically, severe mutations in the CFTR protein disrupt either its quantity or function leading to minimal CFTR activity, however, milder mutations often result in residual CFTR function and milder phenotype including preserved pancreatic function (39). In the present study, 84.2% of the patients had genotypes with at least one non-ΔF508 mutation and another 11% had unknown mutations, whereas only 5% were homozygous for the ΔF508 mutation, a severe genotype. Homozygous ΔF508 prevalence in the present study was less than what is reported in the literature for the adult-diagnosed population (8,17) and substantially less than the overall CF population which is primarily made up of patients diagnosed in childhood. For instance, the CFFPR reports 50.6% of their overall CF population that are ΔF508 homozygote and the CCFR also reports 48.1% of their patients that are ΔF508 homozygote (3,21); a stark increase relative to the adult-diagnosed patients in the present study.

Many of the factors associated with survival in adult-diagnosed CF population are derived from childhood-diagnosed CF studies and since adult-diagnosed patients are less severe, these previous studies may not be relevant. Only one study to date has analyzed predictors of survival in this specific adult-diagnosed population and identified *P. aeruginosa* positive, *Burkholderia* complex positive and Methicillin-resistant *staphylococcus aureus* (*MRSA*) positive as the only significant predictors of reduced survival (18). The present study identified FEV_1 % predicted, CFRD and age at diagnosis to also be significant predictors of reduced survival. While this study evaluated *P. aeruginosa* as a potential prognostic factor, it did not find sufficient evidence to conclude that an association exists between *P. aeruginosa* and survival (HR: 0.74, 95% CI: 0.39, 1.42). The reason for the conflicting results may be related to the selection of variables in the Cox regression model. Keating et al's study

which identified *P. aeruginosa* as an important prognostic factor, did not include age at diagnosis and lung function as covariates in their model. Although the present study showed a strong association between *P. aeruginosa* and survival during univariable testing (Table 2), this effect was no longer present after including age at diagnosis and lung function in the multivariable model. It appears that *P. aeruginosa* at baseline in this population may be redundant once extent of lung function impairment and age at diagnosis have been accounted for. Furthermore, a post-hoc analysis in the present study (Table 6) confirmed that patients with *P. aeruginosa* culture positive were older and had lower lung function, suggesting overlap in the predictive utility of these two variables. It is also plausible that milder adult-diagnosed patients may be less affected by the infection, particularly if it is a less virulent, non-mucoid strain potentially resulting in less pathogenic consequences or easier eradication than what is observed in the general CF population. However, the severity of infection could not be evaluated in the current study because *P. aeruginosa* was considered a binary variable and perhaps not sufficient to capture an association.

The present study identified older age at diagnosis during the first 10 years as a significant predictor of reduced survival in this population, but this effect subsides after 10 years. This finding means that older aged patients are at the highest risk of dying or being transplanted during the first 10 years post-diagnosis. After 10 years, many of the older patients will have died or transplanted, while the remaining patients will have been diagnosed in early adulthood and within this group of younger patients, the effect of age at diagnosis is not as strong. The comparison of characteristics by event status in Table 1 supports this explanation. Patients who died or transplanted were diagnosed approximately 8 years later with a substantially lower lung function at baseline and more severe symptoms. Furthermore, the median age at death or transplant in this cohort was 54.8 years; a relatively old age. These findings could mean that a combination of natural age and CF-related lung function decline may be a possible reason older aged adult-diagnosed patients are more likely to die or be transplanted.

CFRD at baseline was also another significant predictor of reduced survival, but the HR and confidence intervals suggest a great deal of uncertainty for this finding. The large HR and wide confidence intervals might be due the small number of patients with CFRD at baseline (n=10) and shortened follow-up compared to patients without CFRD as well as collinearity with other variables in the model. The results from the present study need to be replicated in future studies with larger sample sizes. However, the present study conducted a sensitivity analysis by substituting the CFRD at baseline variable with the CFRD ever variable in the final model increasing the number of patients with CFRD

and there was a trend towards significance in the relationship. Nonetheless, the current results warrant physicians to be cognizant of adult-diagnosed patients presenting with CFRD at baseline and its probable harmful effects on survival. Many previous studies have associated CFRD with increased mortality (40), however, there are no studies to date that have studied CFRD in the adult-diagnosed population. The mechanism by which developing CFRD impacts survival is unclear but it is hypothesized that CFRD adds an additional inflammatory burden that together with CF-related pulmonary inflammation creates a greater risk of death (40).

Lung function is considered one of the most important measures of disease severity, as well as progression, and therapeutic efficacy in the CF population (41). The present study is consistent with the existing evidence and supports the importance of lung function, as measured by FEV_1% predicted to be a prominent prognostic factor in the adult-diagnosed CF population (17,18). To put this into perspective, the mean baseline lung function in the present study of adult-diagnosed CF patients was 77.6 ± 23.7 % predicted whereas the mean lung function from two population-based studies of healthy, non-smoking caucasian adult subjects in Canada was 98.7 ± 13.9 % predicted for women and 99.4 ± 13.0 % predicted for men (42). Furthermore, the lung function in the present study was also much worse than subjects suffering from another respiratory disease, chronic obstructive pulmonary disease (COPD) from the Canadian Obstructive Lung Disease study, in which approximately 6% of never smoking and 15% of ever smoking COPD subjects had FEV_1 % predicted below 80%, compared to 47.9% (data not shown) in the current study (43). Thus, adult-diagnosed CF patients may be considered milder and less severe compared with the overall CF population but their lung function is much worse compared to the general population and other diseased populations.

Based on the comparisons of adjusted survival curves and predicted 15-year lung transplant-free survival probabilities, FEV_1 % predicted and CFRD were strong predictors of reduced survival and may have clinical utility and importance (Table 4). CFRD positive patients exhibited a 33% decrease in predicted 15-year lung transplant-free survival compared with CFRD negative patients, whereas patients with low lung function (40% predicted) had a 23.3% and 41% decrease in 15-year predicted lung transplant-free survival probability compared with moderate lung function (60%) and high lung function at baseline (80%), respectively. On the contrary, it appears that age at diagnosis adds only moderate value to the final multivariable model, particularly for younger ages at diagnosis for which lung transplant-free survival was high. The adjusted curves and predicted survival probabilities only showed modest decreases in survival as the age at diagnosis increased but the survival differences become more

noticeable at the older ages (age at diagnosis > 50 years). This is not surprising as older aged individuals would have a high baseline risk because of their age and are more likely to die regardless. It is important to note that the survival probabilities are derived from a model that does not include potentially important predictors (e.g. treatment) and may change substantially if that information were considered. The uncertainty of the survival probabilities is also reflected by the wide confidence intervals and therefore, the results from these models are best interpreted as a rough guide on the potential usefulness of each predictor in the model.

4.3 Weaknesses of study

There were some limitations to the present study. Firstly, since data was extracted from a registry, there were variables unavailable or only recently began to be captured in the CCFR, such as frequency of hospitalizations, sweat chlorides, and detailed specific microbiology (*MRSA*, *S. maltophilia*). Therefore, not all potential predictors were assessed in the present study and future studies should incorporate these variables in their analysis. Additionally, CCFR only recently began to capture treatment data and as a result, they were also not included in the model. Therefore, it is difficult to know if the survival analysis reflects the natural history of the disease or is confounded by the effects of treatment. Secondly, since our patient population only includes Canadian adult-diagnosed CF patients, the generalizability of the present study is limited to Canada. There may be differences in outcome due to healthcare delivery and policy differences for care of CF patients between countries (44). Thirdly, adult-diagnosed CF patients are rare, and therefore the present study was restricted to a relatively small sample size and number of events. Ultimately, this affects the power of the final multivariable model and careful attention must be given to the bounds of the confidence intervals for non-significant predictors; in some cases, the present study was unable to rule out important effects. Likewise, one must be cautious in extrapolating these results to individual patients because the current multivariable model was not validated in a training dataset or an independent cohort. Additionally, the results of the current study span a 24-year period starting from 1990, raising the possibility of cohort effects, but the present study did include diagnosis year in the final multivariable model in an attempt to adjust for these effects. Despite this, the relationships identified in the present study could have evolved and may not be entirely reflective of recently adult-diagnosed CF patients. Lastly, baseline measurement was accepted to occur within two years of diagnosis, allowing the use of data from as many patients as possible. Many adult-diagnosed patients, particularly the milder and asymptomatic, may not undergo routine clinical care during their

first visit to a CF clinician. As such, it does not truly reflect the raw baseline values, although it is unlikely that these measures would have changed drastically within the designated period. Nonetheless, epidemiological studies provide tremendous insight into understanding the natural history of a disease and more precisely, to identify risk-factors for outcomes at the population level.

5 Conclusion

The present study took advantage of a reliable and comprehensive data source to describe the clinical characteristics and evaluate the prognosis of adult-diagnosed CF patients. It found that these patients have a milder phenotype of the disease and better prognosis than previously reported. Additionally, older age at diagnosis, lower lung function at baseline, and CFRD were identified as significant predictors of reduced survival in this population. In terms of clinical utility, older age at diagnosis (> 50 years), baseline lung function (FEV_1 % predicted < 60%), and CFRD were the important predictors of lung transplant-free survival. Adult CF clinicians and other CF caregivers can use this information to educate their patients about their prognosis and to guide treatment, specifically for those patients at high-risk for a worse prognosis in this population.

6 Future Directions

Future studies in this population should closely examine longitudinal lung function decline, an important predictor in the present study, using more sophisticated techniques such as mixed modelling approaches that enable estimation of population average rates of decline as well as individual patient variation. A longitudinal analysis of lung function may provide further insight into the prognosis of adult-diagnosed CF patients. Additionally, studies should incorporate more potentially important predictors of survival with larger sample sizes that will yield more accurate and reliable predictions of survival probabilities, possibly providing greater clinical utility than the present study. Lastly, studies should begin to explore the eligibility and efficacy of promising new therapies such as CFTR modulators to determine if this population may stand to benefit, particularly due to the advent of newborn screening in many countries that will enable early identification of CF disease in patients with milder genotypes and likely asymptomatic. Initiating therapies early or later in this population will be an important clinical question for future studies.

7 Figures

Figure 1. Distribution of CF patients by age at diagnosis (from CF Canada Registry Annual Report, 2015)

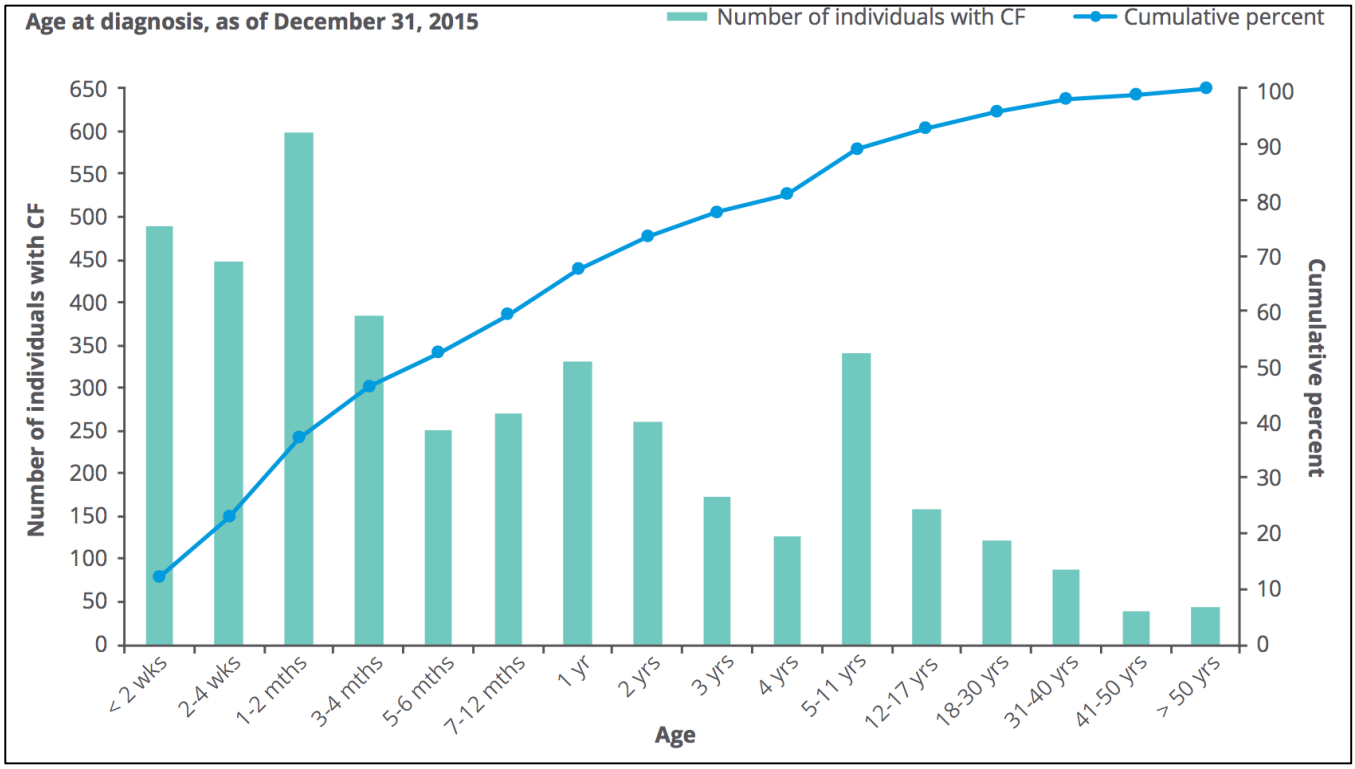


Figure 2. Study Flow Chart

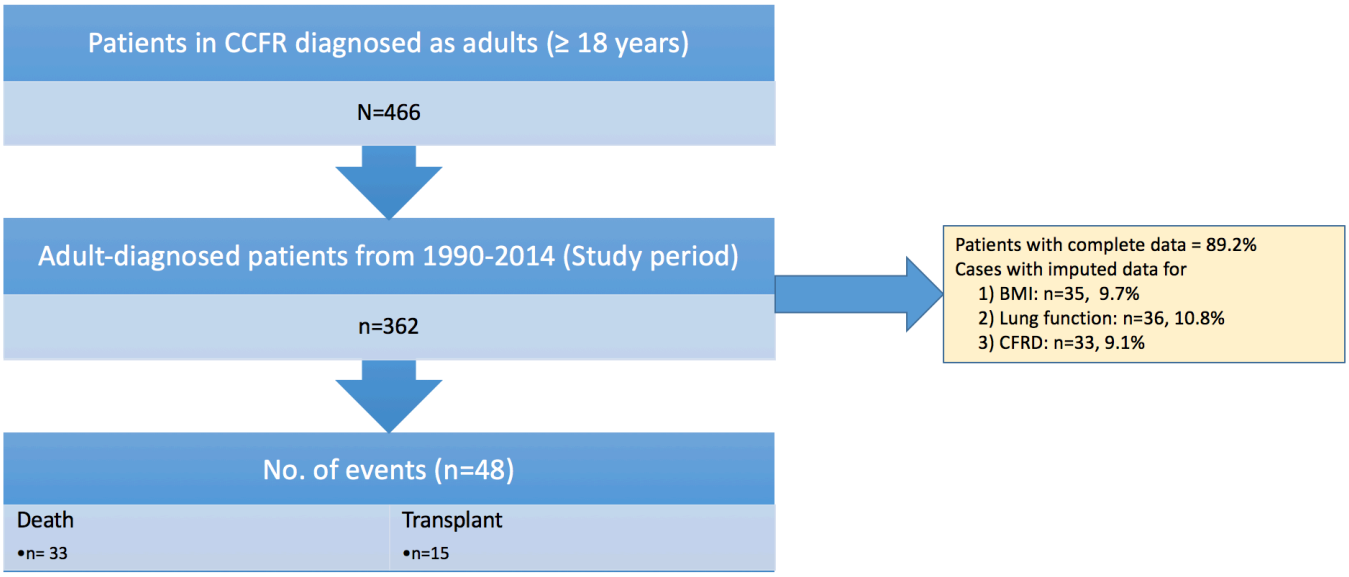


Figure 3. Lung transplant-free survival curve of entire cohort, 1990-2014

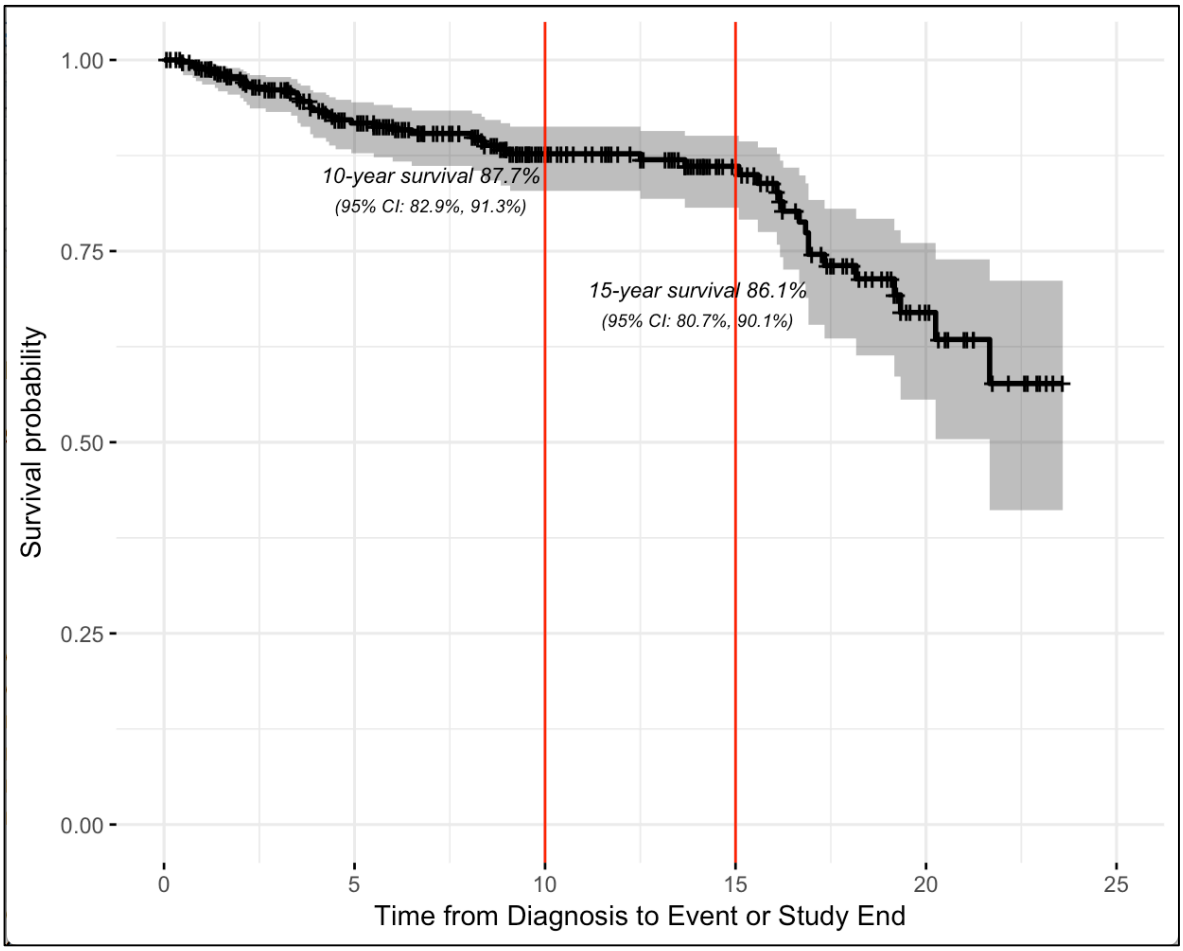


Figure 4. Plot of schoenfeld residuals for age at diagnosis variable (p<0.05)

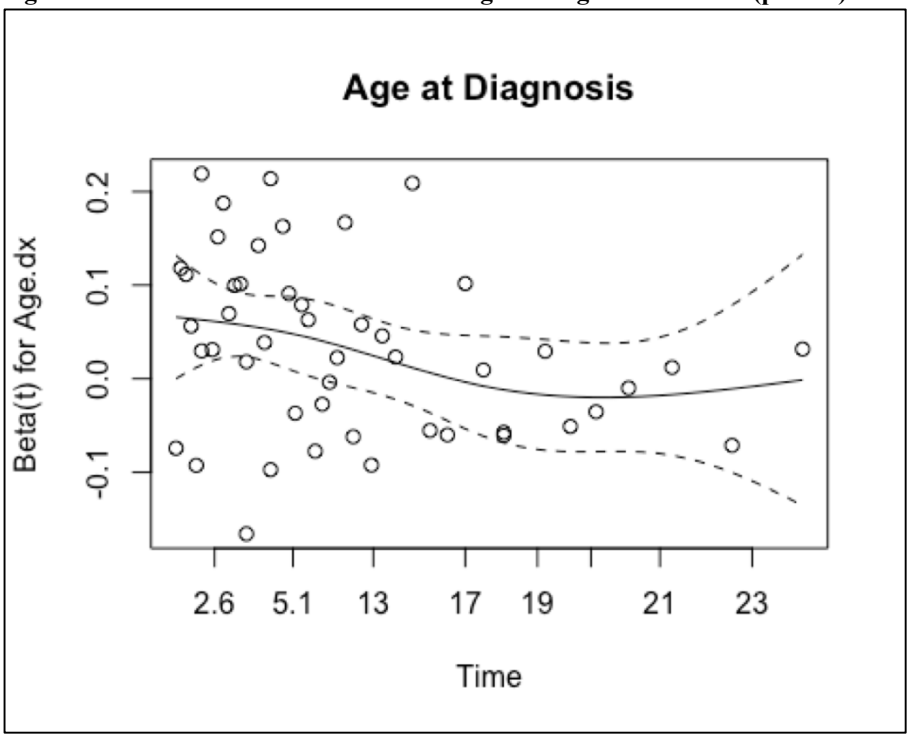


Figure 5. Adjusted survival curves from final multivariable model:
Age at diagnosis varied by 10 years from age 30 to 60

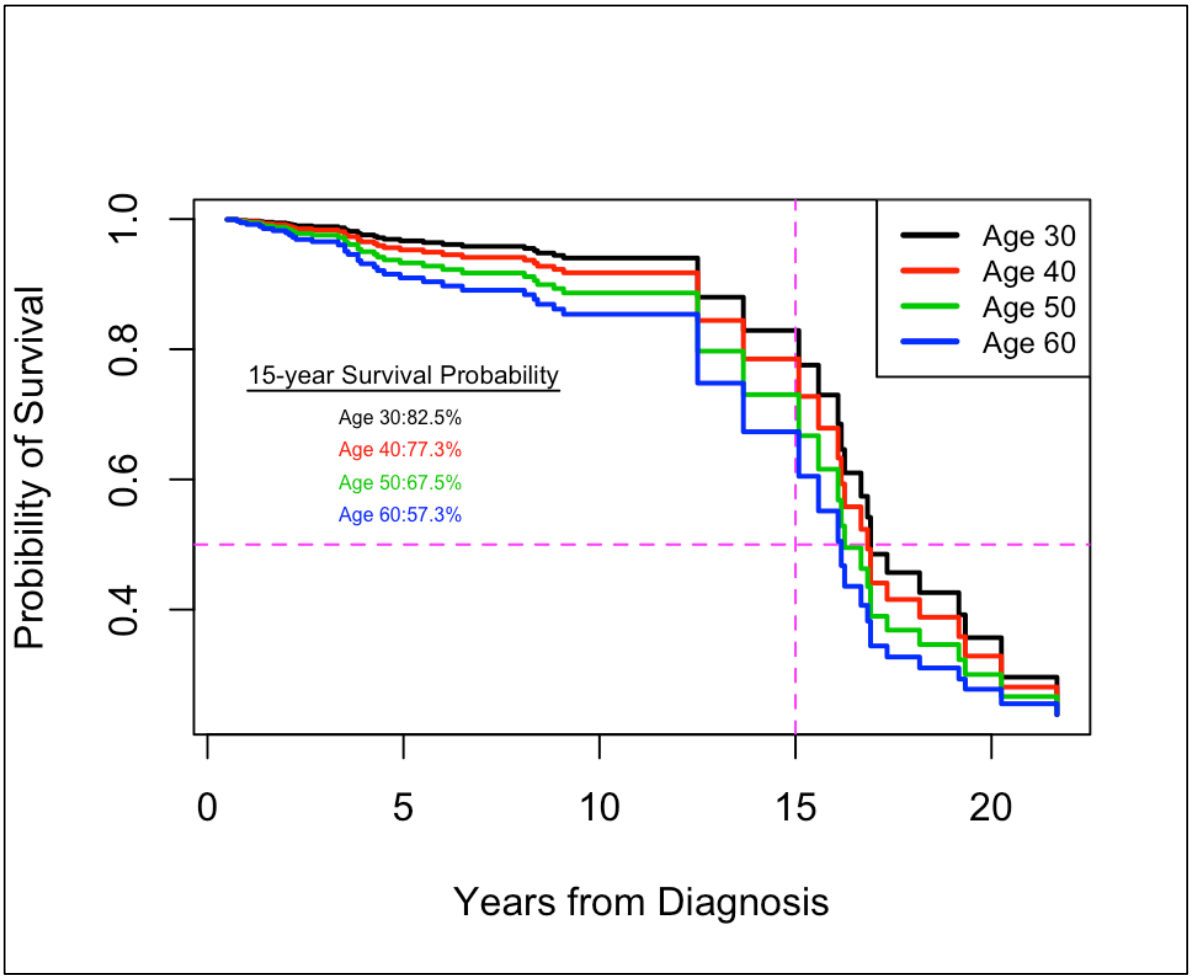


Figure 6. Adjusted survival curves from final multivariable model: FEV_1 % predicted at baseline varied by 10%, starting from 40%

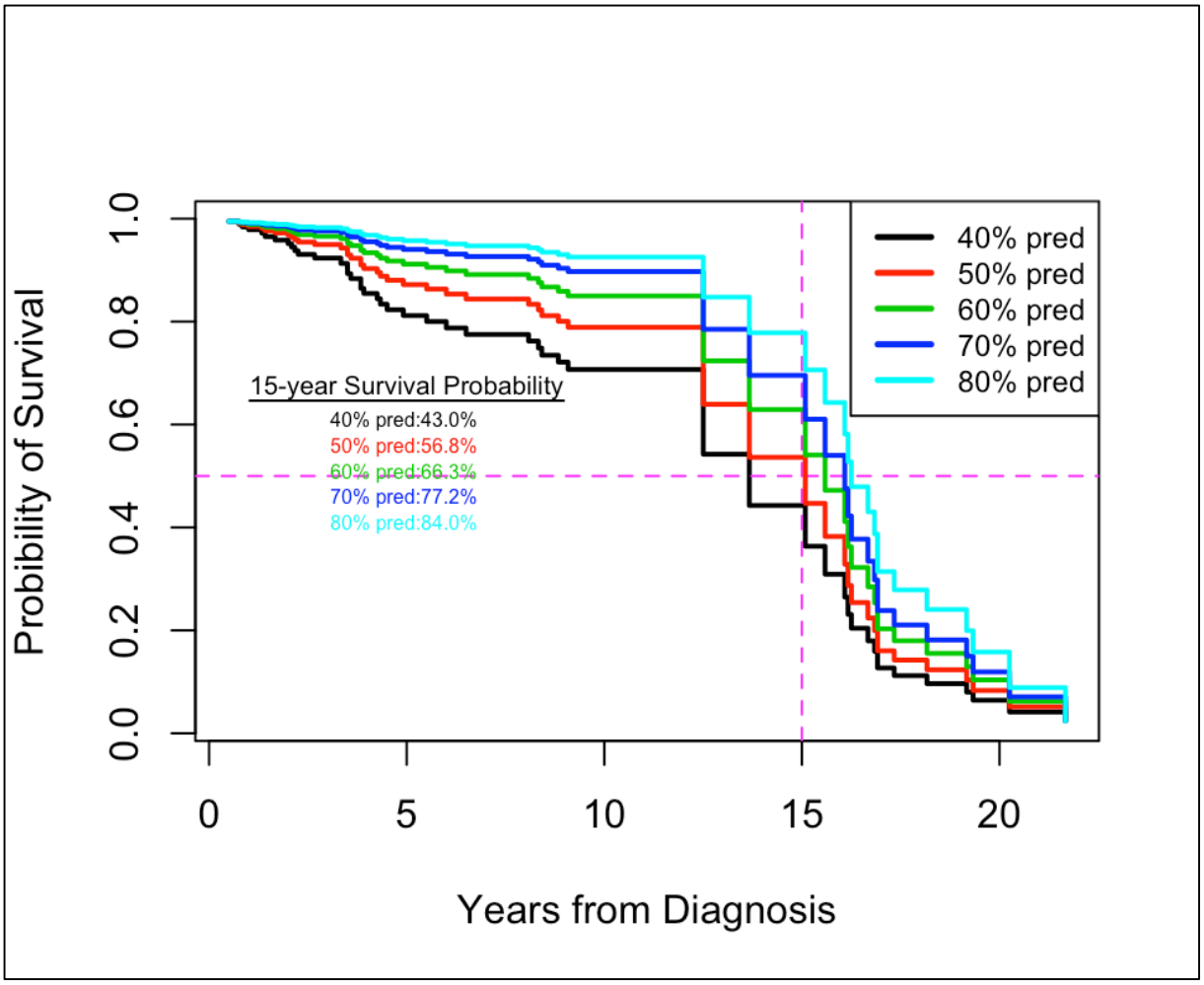


Figure 7. Adjusted survival curves from final multivariable model: CFRD positive versus CFRD negative at baseline

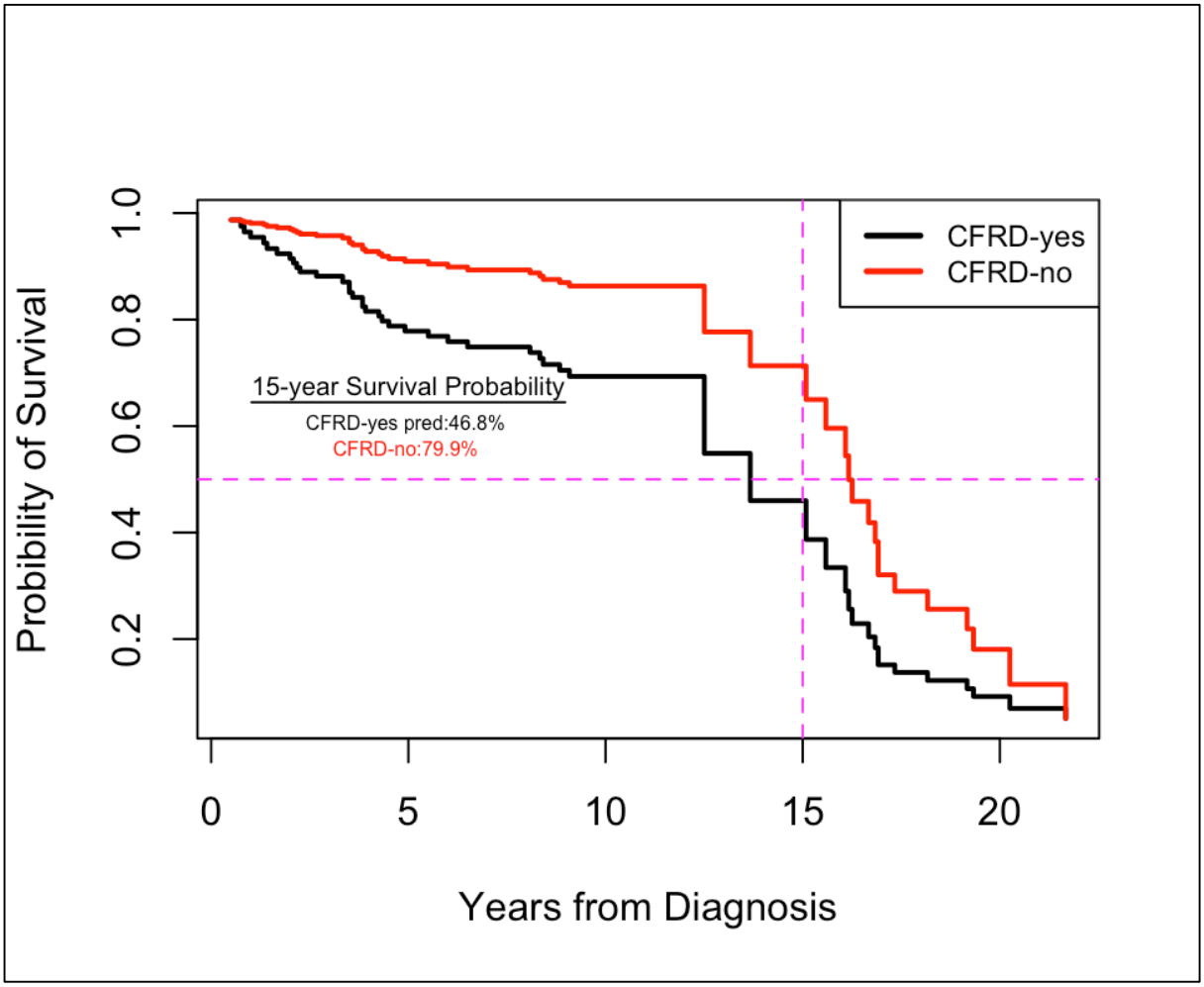
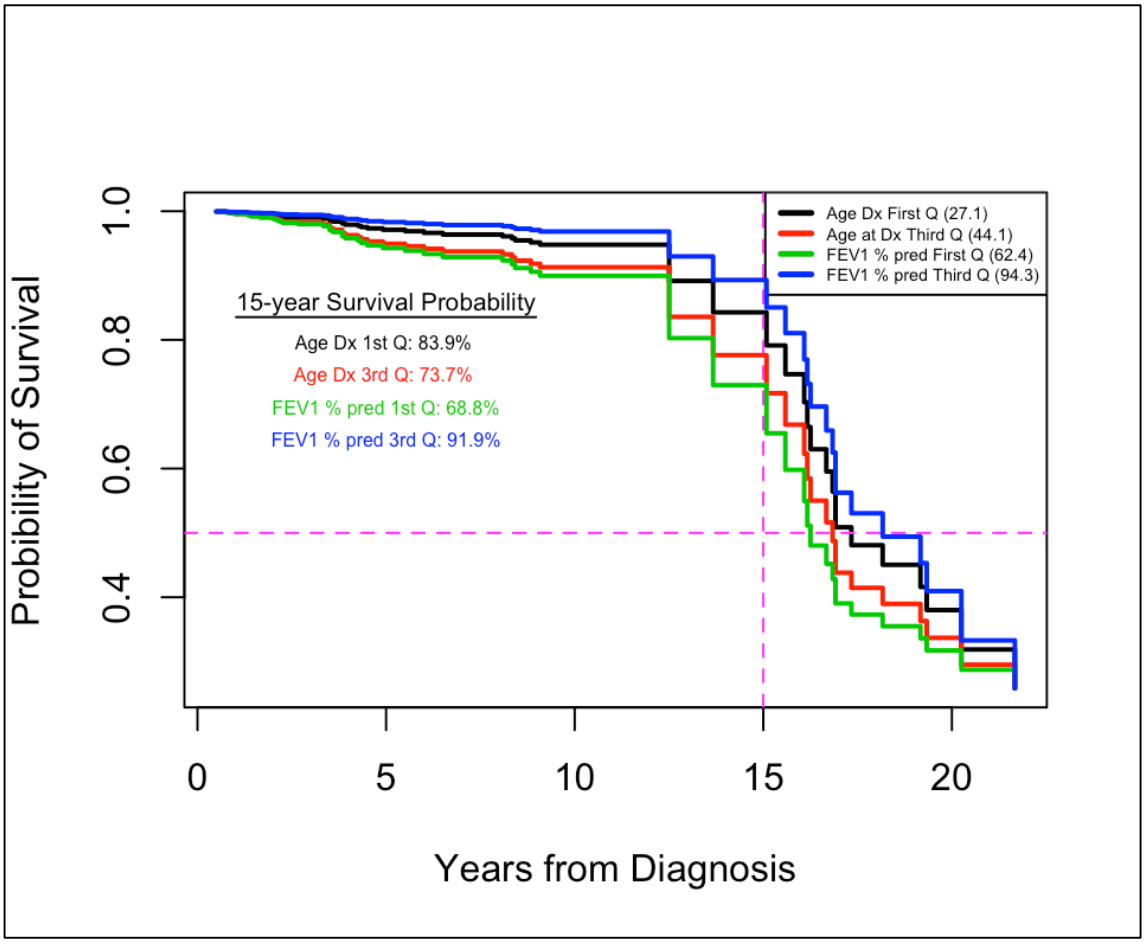


Figure 8. Adjusted survival curves from final multivariable model: Standardized to values of first and third quartile



8 Tables

Table 1: Indications for transplantation in CF patients (from ISHLT Consensus Document, 2015)

Timing of Referral	Timing of Listing
FEV1 that has fallen to 30% or a patient with advanced disease with a rapidly falling FEV1 despite optimal therapy (particularly in a female patient), infected with non-tuberculous mycobacterial (NTM) disease or B cepacia complex (see previous comment on B cenocepacia and subsequently) and/or with diabetes.	Chronic respiratory failure. ▪ With hypoxia alone (partial pressure of oxygen [PaO2] o8 kPa or o60 mm Hg). ▪ With hypercapnia (partial pressure of carbon dioxide [PaCO2] 46.6 kPa or 450 mm Hg).
A 6-minute walk distance <400 m	Long-term non-invasive ventilation therapy
Development of pulmonary hypertension in the absence of a hypoxic exacerbation (as defined by a systolic pulmonary arterial pressure (PAP) 435 mm Hg on echocardiography or mean PAP 425 mm Hg measured by right heart catheterization)	Pulmonary hypertension
Clinical decline characterized by increasing frequency of exacerbations associated with any of the following: ▪ An episode of acute respiratory failure requiring non- invasive ventilation. ▪ Increasing antibiotic resistance and poor clinical recovery from exacerbations. ▪ Worsening nutritional status despite supplementation. ▪ Pneumothorax. ▪ Life-threatening hemoptysis despite bronchial embolization.	Frequent hospitalization
	Rapid lung function decline
	World Health Organization Functional Class IV

Table 2: Clinical characteristics for adult-diagnosed CF patients* in the CF Canada Registry from 1990 – 2014

Variable	Total Sample (n=362)	Event (n= 48)	Censored (n= 314)
Median Age at Diagnosis (years)	34.3 (18.0-73.8)	43.8 (18-73.8)	33.9 (18-71.7)
Sex			
Male	189 (47.8)	24 (50.0)	165 (47.5)
Female	173 (52.2)	24 (50.0)	149 (52.6)
Race			
Caucasian	327 (90.3)	45 (93.8)	282 (89.8)
Non-Caucasian	11 (3.0)	2 (0.04)	9 (2.9)
Unknown	24 (6.7)	1 (0.02)	23 (7.3)
Symptoms at Diagnosis			
Asymptomatic	37 (10.2)	0 (0.0)	37 (12.3)
Gastrointestinal	21 (5.8)	0 (0.0)	21 (7.0)
Pulmonary	166 (45.9)	28 (63.6)	138 (46.0)
Pulmonary and GI	68 (18.8)	13 (29.6)	55 (18.3)
Minor Manifestations	26 (7.2)	0 (0.0)	26 (8.7)
Other	18 (5.0)	1 (2.3)	17 (5.7)
Unknown	26 (7.2)	2 (4.6)	6 (2.0)
Mutation			
Homo ΔF508	17 (4.7)	1 (2.1)	16 (5.1)
Hetero ΔF508	138 (38.1)	17 (35.4)	121 (38.5)
One mutation only	113 (31.2)	15 (31.3)	98 (31.2)
Two Non-ΔF508	54 (14.9)	10 (20.8)	44 (14.0)
Unknown	40 (11.1)	5 (10.4)	35 (11.2)
CFRD (ever)			
Yes	56 (15.5)	18 (37.5)	38 (12.1)
No	306 (84.5)	30 (62.5)	276 (87.9)
Pancreatic Insufficiency (ever)			
Yes	127 (35.1)	22 (45.8)	105 (33.4)
No	235 (64.9)	26 (54.2)	209 (66.6)
***P. aeruginosa* Positive**			
Yes	181 (50.0)	36 (75.0)	145 (46.2)
No	181 (50.0)	12 (25.0)	169 (53.8)
Cause of Death			
Pulmonary		18 (54.5)	
Cardiovascular		3 (9.0)	
Gastrointestinal		1 (3.0)	
Infection/Sepsis		1 (3.0)	
Other		7 (21.6)	
Unknown		3 (9.0)	
Median Age at Death or Transplant (years)		52.9 (26.8-78.8)	
Median Follow-up time (years)	7.7 [0.0-23.6]	5.8 [0.4-21.7]	7.9 [0.0-23.6]
Lost to follow-up[a]	48 (13.3)		
Baseline variables[b]			

Mean BMI (kg/m^2)	23.6 ± 4.3	22.4 ± 4.6	23.8 ± 4.3
Mean FEV_1 (% Predicted)	77.6 ± 23.7	50.1 ± 18.1	81.7 ± 21.6
CFRD			
Yes	10 (3.0)	4 (9.3)	6 (2.1)
No	319 (97.0)	39 (90.6)	280 (97.9)
***P. aeruginosa* Positive**			
Yes	110 (30.4)	24 (50.0)	86 (27.3)
No	252 (69.6)	24 (50.0)	228 (72.7)

*** Numeric summaries are median (range) or mean ± SD and categorical summaries are n (%)**

^ Denominator for Cause of Death is No. of deaths in study (n=33)

[a]Lost to follow-up defined as those patients alive with their last verified year of contact occurring more than 2 years before the end of the study period (Dec 31, 2014)

[b]Baseline variables are summarised from those patients with available baseline data, defined as within 2 years of CF diagnosis

Table 3: Univariable and Final model Cox PH Regression results (Hazard Ratios) for event using baseline[#] characteristics of adult diagnosed CF Patients (n=362 patients and n=48 events in the final model)

	Univariable HRs (95% CIs)	Final Model HRs (95% CIs)
Age at Dx (per 5 years)	1.39 (1.24, 1.56)*	
Time 0 to 10		1.32 (1.13, 1.55)**
Time 10 to 24		0.98 (0.75, 1.29)
Symptoms		
Non-Pulmonary/GI	Reference	Reference
Pulmonary/GI	1.69 (0.71, 3.55)*	0.94 (0.38, 2.30)
Sex		
Female	Reference	Reference
Male	0.93 (0.53,1.63)	0.84 (0.45, 1.57)
Race		
Non-Caucasian	Reference	
Caucasian	0.91 (0.28, 2.96)	
Mutation Type		
ΔF508 Absent	Reference	
ΔF508 Present	0.94 (0.48, 1.84)	
Unknown	1.90 (0.67, 5.45)	
BMI	0.95 (0.87, 1.02)	0.97 (0.89, 1.06)
P. aeruginosa		
No	Reference	Reference
Yes	2.01 (1.14, 3.54)*	0.74 (0.39, 1.42)
CFRD		
No	Reference	Reference
Yes	5.14 (1.79, 14.74)*	7.86 (2.09, 29.55)**
FEV_1 % Pred (per 5%)	0.75 (0.69, 0.80)*	0.76 (0.69, 0.83)**
Diagnosis Year		1.07 (1.00, 1.16)

[#] All variables were available at baseline, defined as any data within 2 years of diagnosis for CF
*** Statistically significant at alpha level = 0.25 for univariable testing**
**** Statistically significant at alpha level = 0.05 for multivariable testing**

Table 4: Predicted survival probabilities for various scenarios using the corrected prognosis method for covariate adjustment

	15-year Survival Probability (%)	95% CI
Age at Diagnosis		
Age 30	82.5	58.1, 98.3
Age 40	77.3	37.2, 98.3
Age 50	67.5	14.5, 98.4
Age 60	57.3	3.2, 98.8
1st quartile value (27.1)	83.9	63.0, 98.3
3rd quartile value (44.1)	73.7	27.6, 98.2
Lung Function		
40% predicted	43.0	22.2, 75.3
50% predicted	56.8	26.4, 82.9
60% predicted	66.3	30.8, 89.3
70% predicted	77.2	36.1, 93.7
80% predicted	84.0	43.2, 96.5
1st quartile value (62.4)	68.8	32.1, 90.6
3rd quartile value (94.3)	91.9	53.4, 98.7
CFRD		
Yes	46.8	17.7, 86.8
No	79.9	46.4, 92.3

Table 5: Sensitivity Analysis substituting *P. aeruginosa* at baseline to up to 5 years post-diagnosis

	Final Model HRs (95% CIs)	Sensitivity Analysis Model‡ (95% CIs)
Age at Dx (5 years)		
Time 0 to 10	1.32 (1.13, 1.55)**	1.30 (1.11, 1.51)**
Time 10 to 24	0.98 (0.75, 1.29)	0.98 (0.75, 1.28)
Symptoms		
Non-Pulmonary/GI	Reference	Reference
Pulmonary/GI	0.94 (0.38, 2.30)	0.71 (0.30, 1.69)
Sex		
Female	Reference	Reference
Male	0.84 (0.45, 1.57)	1.15 (0.62, 2.13)
BMI	0.97 (0.89, 1.06)	0.99 (0.91, 1.08)
P. aeruginosa		
No	Reference	Reference
Yes	0.74 (0.39, 1.42)	0.58 (0.30, 1.12)
CFRD		
No	Reference	Reference
Yes	7.86 (2.09, 29.55)**	8.67 (2.68, 28.12)**
FEV_1 % Predicted (5 %)	0.76 (0.69, 0.83)**	0.73 (0.67, 0.80)**
Diagnosis Year	1.07 (1.00, 1.16)	1.06 (0.99, 1.14)

‡**Sensitivity analysis conducted on one imputed dataset (not pooled)**

** **Statistically significant at alpha level = 0.05**

Table 6: Mean age at diagnosis and FEV_1 % Predicted for individuals with and without *P. aeruginosa* at baseline

	***P. aeruginosa* – Yes (n=110)**	***P. aeruginosa* – No (n=252)**
Mean Age at Diagnosis (years)	38.7 ± 15.5	35.6 ± 11.6
Mean FEV_1 % Predicted	64.1 ± 22.0	84.5 ± 21.4

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