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Journal of Cystic Fibrosis xx (2017) xxx – xxx
Journal of Cystic Fibrosis
www.elsevier.com/locate/jcf

Original Article

Up-to-date and projected estimates of survival for people with cystic fibrosis using baseline characteristics: A longitudinal study using UK patient registry data☆

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Received 26 September 2017; revised 20 November 2017; accepted 29 November 2017
Available online xxxx

Abstract

Background: Cystic fibrosis (CF) is the most common inherited disease in Caucasians, affecting around 10,000 individuals in the UK today. Prognosis has improved considerably over recent decades with ongoing improvements in treatment and care. Providing up-to-date survival predictions is important for patients, clinicians and health services planning.
Methods: Flexible parametric survival modelling of UK CF Registry data from 2011 to 2015, capturing 602 deaths in 10,428 individuals. Survival curves were estimated from birth; conditional on reaching older ages; and projected under different assumptions concerning future mortality trends, using baseline characteristics of sex, CFTR genotype (zero, one, two copies of F508del) and age at diagnosis.
Findings: Male sex was associated with better survival, as was older age at diagnosis, but only in F508del non-homozygotes. Survival did not differ by genotype among individuals diagnosed at birth. Median survival ages at birth in F508del homozygotes were 46 years (males) and 41 years (females), and similar in non-homozygotes diagnosed at birth. F508del heterozygotes diagnosed aged 5 had median survival ages of 57 (males) and 51 (females). Conditional on survival to 30, median survival age rises to 52 (males) and 49 (females) in homozygotes. Mortality rates decreased annually by 2% during 2006–2015. Future improvements at this rate suggest median survival ages for F508del homozygous babies of 65 (males) and 56 (females).
Interpretation: Over half of babies born today, and of individuals aged 30 and above today, can expect to survive into at least their fifth decade.

Research in context

Evidence before this study

We searched PubMed with terms "(cystic fibrosis survival) and (projection OR model OR registry OR United Kingdom OR UK)" to identify relevant studies on survival estimates for individuals with cystic fibrosis (CF). We also considered the most recent annual report from the UK Cystic Fibrosis Registry (Cystic Fibrosis Trust, 2016), a review by Buzzetti and colleagues (2009), the chapter on Epidemiology of Cystic Fibrosis by MacNeill (2016), the study of MacKenzie and colleagues (2014), and references therein. There have been many studies of factors associated with survival in CF; most have focused on identifying risk factors, and only a few have presented estimated survival curves, which are the focus of this work. The most recent study of survival in the UK is by Dodge and colleagues (2007), who used data obtained from CF clinics and the national death register, and gave an estimate of survival for babies born in 2003. We found no previous studies that have obtained detailed information on survival using UK Cystic Fibrosis Registry data. Jackson and colleagues obtained survival estimates for the US and Ireland using registry data (Jackson et al., 2011). MacKenzie and colleagues used US Cystic Fibrosis Foundation Patient Registry data from 2000 to 2010 to project survival for children born and diagnosed with CF in 2010, accounting for sex, genotype and age at diagnosis (MacKenzie et al., 2014). Previous studies on estimated survival in CF

☆ Funding: MRC Fellowships MR/M014827/1 (RHK), MR/P008577/1 (DTR); US NIH Grant K25 HL125954 (RS).
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https://doi.org/10.1016/j.jcf.2017.11.019
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Please cite this article as: Keogh RH, et al, Up-to-date and projected estimates of survival for people with cystic fibrosis using baseline characteristics: A longitudinal stud..., J Cyst Fibros (2017), https://doi.org/10.1016/j.jcf.2017.11.019

have become out of date or have not accounted for the full range of patient characteristics available at birth. Few have presented conditional survival estimates (Dodge et al., 2007).

Added value of this study

This is the first study to yield detailed survival statistics using the UK Cystic Fibrosis Registry, which is one of the largest national CF registries outside of the US and has almost complete coverage of the UK CF population. The primary goal was to leverage the long-term follow-up of the nearly complete UK CF population available in the Registry for the purposes of producing accurate, precise predictions in the modern era of CF care. Estimates are presented from birth and conditional on survival to older ages. These are the first conditional estimates in CF to also account for genotype, sex and age at diagnosis, which were each included in the modelling using a flexible approach. Projections are also provided under different scenarios based on downward trends in mortality rates. Our use of flexible parametric survival models is novel in this field, and our approach could be used to provide modern survival statistics for other chronic diseases and disorders.

Implications of all the available evidence

Our estimates of future survival in CF under a range of different scenarios are based on data on nearly all individuals living with the disease in the UK in recent times, reflective of a modern era of care, and are most appropriate for the families of babies being born in the present day with CF. Conditional estimates inform patients who have already reached an older age, and their clinicians. Over half of babies born today, and of individuals aged 30 years and above alive today, can expect to survive into their fifth decade. Insights based on our survival projections can be used to inform future needs in CF health care provision.

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Keywords: CFTR genotype; Cystic fibrosis; Flexible parametric survival model; Longitudinal study; Patient registry; Survival

1. Introduction

Cystic fibrosis (CF) is the most common inherited disease in Caucasian populations, affecting around 10,000 individuals in the UK today [1]. Most patients with CF die prematurely from respiratory failure and require support from healthcare services from diagnosis onwards [2]. Survival of people with CF has improved considerably over recent decades due to improvements in treatment and care and the estimated median survival age is one of the headline results reported in national registry reports. Information on predicted survival based on up-to-date data is important for people with CF, their families and the health professionals who care for them [3–5].

Survival estimates for people with CF are typically limited to median survival age at birth, stratified by sex, for instance, 48 years for males and 43 years for females in the UK [1]. However, these estimates are of limited use to patients who have already survived to a given age, and they do not take into account the full range of patient characteristics available at birth. Furthermore, current survival estimates in CF do not account for ongoing improvements in treatment and care. Mortality rates continue to decrease over time and this is anticipated to continue in the future, not least due to new targeted therapies [6,7].

We therefore use novel survival analysis approaches to make projections of survival for babies born with CF in the present day, and for people who have survived to particular ages. We do this while taking into account baseline patient characteristics, and decreasing mortality trends over time, making use of the long term follow-up in the UK Cystic Fibrosis Registry, which is one of the largest national CF registries outside of the US and has almost complete coverage of the UK CF population [8]. Our aim is to provide more individually relevant information on survival for people with CF in the UK and projections that are relevant for planning future health care resource needs. Summary survival statistics are accompanied by clear interpretations and estimates of their uncertainty.

2. Methods

2.1. Study design and data source

This cohort study used longitudinal data from the UK CF Registry collected between 2006 and 2015. The UK CF Registry is a secure centralised database, sponsored and managed by the Cystic Fibrosis Trust, which records data on the demographics, health and treatment of almost all people with CF in the UK [8]. The analysis progressed in two parts. For the main analysis we used data on all individuals followed in the UK CF Registry during the 5-year period from 1st January 2011 to 31st December 2015 to estimate survival based on the latest age-specific mortality rates. Covariates in this analysis were sex, CFTR genotype (coded as the number of F508del alleles: two (homozygous), one (heterozygous), zero copies), and age at diagnosis. For our second analysis, in order take into account secular trends in survival, we used 10 years of longitudinal follow-up data, from 1st January 2006 to 31st December 2015, in order to obtain a more precise estimate of changes in hazards with calendar time.

Individuals who did not die during the analysis period were right-censored as follows. For those observed in the registry in 2015, we used their age at 31st December 2015 as the age of censoring; for those who were lost to follow-up, we used their age at the 31st December on their last year of providing data to the Registry plus two years. Individuals who were not seen for a period in the middle of the study period and then reappeared were considered to be observed for the full intervening time in the analysis. Ages were left-truncated at the later of: age at 1st January 2011 (main analysis) or age at 1st January 2006 (second analysis), age of diagnosis, or age at first joining the Registry.

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