Survival Estimates in European Cystic Fibrosis Patients and the Impact of Socioeconomic Factors: A Retrospective Registry Cohort Study

Edward F. McKone[1], Cono Ariti[2], Abaigeal Jackson[3], Anna Zolin[4], Siobhán B. Carr[5], Annalisa Orenti[4], Jacqui van Rens[6], Lydia Lemonnier[7], Milan Macek Jr[8], Ruth H. Keogh[2], Lutz Naehrlich[9] on behalf of the European Cystic Fibrosis Society Patient Registry*.

Institute(s): [1]St. Vincent's University Hospital & University College Dublin School of Medicine, Dublin, Ireland, [2]London School of Hygiene & Tropical Medicine, London, United Kingdom, [3]Cystic Fibrosis Registry of Ireland, Dublin, Ireland, [4]Department of Clinical Sciences and Community Health, Laboratory of Medical Statistics, Epidemiology and Biometry G. A. Maccacaro, University of Milan, Milan, Italy. [5]Royal Brompton Hospital and NHLI, Imperial College, London, United Kingdom, [6]University Hospital Leuven, Leuven, Belgium, [7]Vaincre La Mucoviscidose, Paris, France, [8]Department of Biology and Medical Genetics, Charles University, Prague, Czech Republic, [9] Department of Pediatrics, Justus-Liebig-University Giessen, Giessen, Germany.

*List of collaborating authors in Appendix 1:

Corresponding Author: Prof. Edward F. McKone MD, FRCPI

National Referral Centre for Adult Cystic Fibrosis,

St. Vincent's University Hospital & University College Dublin,

Elm Park, Dublin, Ireland.

Word Count: 2793 words

Conflict of Interest: The authors have no conflicts of interest.

ABSTRACT

Background: Median survival for cystic fibrosis (CF) patients in Europe is unknown and is likely to be influenced by socioeconomic factors. Using the European Cystic Fibrosis Society Patient Registry (ECFSPR), median survival estimates were obtained for CF patients across Europe and the impact of socioeconomic status on survival was examined.

Methods. CF subjects known to be alive and in the ECFSPR between 2010 and 2014 were included. Survival curves were estimated using the Kaplan-Meier (KM) method. Differences in the survival curves were assessed using the log rank test. Cox regression was used to estimate the association between socioeconomic factors and the age-specific hazard of death, with adjustment for sex, age at diagnosis, *CFTR* genotype and transplant status.

Findings: The final analysis included 13 countries with 31,987 subjects (135,833 person years of follow-up) and 1,435 deaths. Median survival age for these patients in the ECFSPR was 51.7yrs (95% C.I. 50.0-53.4). After adjusting for potential confounders age at diagnosis, sex, *CFTR* genotype and transplant status, there remained strong evidence of an association between socioeconomic factors and mortality ($p<0.001$). Countries with higher health care spending had a 46% lower hazard of mortality (HR: 0.54, 95% CI: 0.45-0.64) than countries with lowest health care spending.

Interpretation: Median survival for patients with CF in Europe is comparable to that reported in other jurisdictions and differs by socioeconomic factors.

Funding: No external funding. Statistical analysis was funded through a grant from the ECFSPR to London School of Hygiene & Tropical Medicine. (239 words)

KEY WORDS

Survival, Epidemiology, Socioeconomic factors, F508del homozygotes, Cystic fibrosis.

ABBREVIATIONS

CF = Cystic Fibrosis

CFTR = Cystic fibrosis Transmembrane Conductance Regulator

FEV_1 = Forced expiratory volume in one second

FVC = Forced Vital Capacity

ECFSPR = European Cystic Fibrosis Society Patient Registry

ECFS = European Cystic Fibrosis Society

EU = European Union

HR = Hazard ratio

GNI = Gross National Income

GDP = Gross Domestic Product

SD = Standard deviation of the mean

SES = Socioeconomic Status

INTRODUCTION: Cystic fibrosis (CF) is one of the most common autosomal recessive genetic conditions in Europe that causes progressive lung disease and premature death. Median survival age for patients with CF is estimated to be in the mid-40s although estimates can vary across countries[1]. Reasons for this variation in survival outcomes include genetic and environmental factors[2]. A recent comparison of CF survival between United States and Canadian CF registries[3] identified differences in median survival that were attributed in part to differences in nutrition, access to lung transplantation and socioeconomic factors[4]. To date, median survival estimates for European CF patients as a whole are not known although disparities in outcomes across Europe have been identified[5,6].

In 2003, the European Cystic Fibrosis Society (ECFS) developed a patient registry to collect clinical and demographic data on CF patients attending specialised CF centres throughout Europe[7,8]. The European CF Society Patient Registry (ECFSPR) now contains longitudinal data on more than 50,000 CF patients attending CF centres in 38 European countries[9]. The goal of this study was to estimate median survival for European CF patients and determine the association between country-level socioeconomic factors and CF survival across European countries.

METHODS: The study design is a retrospective cohort study using the ECFSPR during the observation period from 2010 to 2014. The primary aim of the study was to estimate median survival for CF patients throughout Europe and the secondary

aim was to examine the association between country-level socioeconomic factors and survival. All procedures were approved by the St. Vincent's University Hospital Research and Ethics Committee and by the ECFSPR Steering Committee.

Patient Population. Once a year, annual summary data for each CF patient enrolled in the ECFSPR is uploaded to the registry[9]. Demographic and clinical characteristics of the patient population were extracted from the ECFSPR for all patients in the registry between 2010 and 2014. These characteristics were: sex, age, vital status during year (alive/dead), transplant status, age at diagnosis, *CFTR* genotype, highest annual forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), height and weight.

Due to concerns relating to incomplete data, only countries with national registries and high enrolment (>80 of estimated percent of CF patient population enrolled) with annual data for the 5-year period from 2010-2014 were included. Belgium, a national registry with high enrolment, only had annual data from 2010-2013 and was also included. The survival outcome of interest was all-cause mortality including deaths post-transplant.

Socioeconomic Factors. Three validated metrics of country-level socioeconomic status (SES) were used[10]. Two were measures of country healthcare spending and one was a measure of country wealth. These were i) Proportion of Gross Domestic Product (GDP) spent on Healthcare and ii) Average numbers of

physicians per 1,000 people and iii) Gross National Income (GNI) as estimated by World Bank.[11] For the analysis, GDP spent on health care and average number of physicians per 1,000 people were divided into thirds using terciles as the cut-off points. GNI was also initially analysed in thirds using terciles as the cut-off points, but as the highest and middle-income thirds were similar, this was dichotomised into highest/middle versus lowest income.

Statistical Analysis. Descriptive statistics were used to present the demographics and clinical data of the CF cohort. Definitions of clinical variables are as determined by the ECFSPR[12]. Overall survival curves were estimated using the Kaplan Meier method and Cox proportional hazards modelling was used to estimate hazard ratios in the cohort. The time scale was age. Patients were considered to be at risk from age of entry into the cohort until the earliest of: age of exit, death or end of follow-up period on 31st December 2014. Death was defined as all-cause mortality either before or after transplant. Loss to follow-up was defined as present if two or more years of observation were missing before the end-date for the cohort (31st December 2014 for all countries except Belgium, whose end-date was 31st December 2013)[3]. Due to incomplete follow-up of CF patients post-transplant in many countries, analysis was repeated using the composite outcome of death or transplant as well as censoring at time of transplant.

Univariable Cox regression analysis was carried out examining the association between age at diagnosis, sex, cystic fibrosis transmembrane conductance

regulator (CFTR) genotype as well as transplant status and survival. *CFTR* genotype was characterised by the presence or absence of *F508del* mutations and by the presence of compound heterozygosity for two *CFTR* Class I-III mutations using the classification system proposed by Welsh and Tsui[13,14]. Transplant status was defined as a transplant of any type (primarily lung and/or liver) and was used as a time-dependent variable. Measures associated with survival in univariable analysis were included in a multivariable model for the adjusted association between SES and survival. Due to the difference in *CFTR* genotype across Europe and the known association of *CFTR* genotypes with survival, sensitivity analyses were also carried out limiting the population to CF patients homozygous for F508del and to CF patients compound heterozygous for two *CFTR* Class I-III mutations. Proportional hazards assumption was assessed using graphical methods (log-log plot of survival) and methods based on Schoenfeld residuals with no significant deviations found. All statistical analysis was carried out using Stata (14.0) software (San Antonio, Texas).

Role of the funding source. There was no external funding to ECFSPR for this study. Statistical analysis was supported through a grant from ECFSPR to the London School of Hygiene & Tropical Medicine. The corresponding author had full access to all the data and the final responsibility for the decision to publish. All authors were involved in data collection or the study design as well as manuscript preparation and review.

RESULTS

There were 31,987 CF patients in the ECFSPR between 2010 and 2014 from 13 countries that met all of the inclusion criteria. The ECFSPR patient population included in the study is outlined in Table 1. There were 1,435 deaths with an average patient follow-up of 4.2 years and 135,833 person-years at risk. There were 983 (3.0%) lost to follow-up. Demographics of ECFSPR countries excluded from the study are shown in Supplemental Table 1. Demographics and clinical characteristics for patients during their first year of entry into the cohort are summarised in Table 2. Standardised all-population survival rates for each county and country classification of SES measures are shown in Table 3. As would be expected, there was variation seen across European countries for the different measures of SES.

Survival Analysis: Median age of survival for all European patients included in the study was 51.7 years (95% C.I. 50.0-53.4, $p<0.001$). The Kaplan Meier curve for the study cohort all-cause mortality is shown in Figure 1. Results including median survival for CF genetic subgroups and when transplant is considered as a death are shown in Table 4. Median survival with the composite outcome of death or transplant was 38.5 years (95% C.I. 37.5-39.4, $p<0.001$). The Kaplan Meier curve for the study cohort with the composite outcome of death or transplant is shown in Figure 2. Median survival censoring at transplant was 56.8 years (95% C.I. 54.0-60.2, $p<0.001$). The Kaplan Meier curve for the study cohort censored at transplant is shown in Figure 3.

In univariable analyses, age at diagnosis, gender, *CFTR* genotype and transplant status were all strongly associated with differences in survival (Table 5). Female gender was associated with a 28% increased hazard of death compared to males.

Socioeconomic factors and survival. All measures of country-level SES were associated with increased hazard for death in univariable analyses. After adjusting for age at diagnosis, sex, *CFTR* genotype and transplant status, the proportion of GDP spent on healthcare and number of physicians per capita were each independently associated with survival. Countries in the highest third of GDP spend on healthcare had a 45% lower hazard than those in the lowest third (HR 0.544, 95% CI (0.448,0.641)). Similarly, countries in the highest third of physicians per capita had a 47% lower hazard than those with the lowest third of physician per capita ratio (HR 0.523, 95% CI (0.385, 0.661)). These results are shown in Table 6. The Kaplan Meier curve for GDP spend on healthcare and physicians per capita is shown in Figure 3. After multivariable adjustment high GNI was associated with a lower hazard, however this finding was not statistically significant (HR for high versus low GNI 0.859, 95% CI (0.667, 1.051)).

DISCUSSION.

We have shown that median survival in patients with cystic fibrosis across Europe is comparable to that of Canada and the United States and that there is variation across Europe that is associated with socioeconomic factors.

Survival for patients with CF is variable and is influenced by factors including background *CFTR* genetics and environmental exposures[2]. *CFTR* genotypes with at least one Class IV-V *CFTR* mutation have a milder phenotype and better survival[15,16]. Likewise, environmental factors such as acquisition of *Pseudomonas aeruginosa*[17], *Staph aureus* and *Burkholderia cepacia complex*[18] also influence mortality. In the United States, there is a clear association between SES and CF outcomes with absence of private medical insurance and lower median income independently associated with higher mortlality[19,20]. This relationship between SES and survival in CF is multi-factorial with access to healthcare, education, adherence and expectations all contributing to differences in outcomes[21]. In Europe, McCormick at al, using the European CF Demographics Registry dataset (a precursor of ECFSPR), demonstrated differences in demographics across Europe with a median patient age of 17.0 years in the European Union (EU) countries compared to a median patient age of 12.1 years in non-European Union countries[6]. The proportion of patients aged older than 40 years of age was twice as high in EU countries than non-EU countries raising concerns about under-diagnosis of CF and increased childhood mortality as a result of unequal access to specialist CF care and CF medicines. This was consistent with the earlier work of Fogarty et al who also found differences in median age of death for CF patients across countries which they attributed to possible underdiagnosis and diagnostic misclassification of CF as well as socioeconomic factors[5].

One of the challenges of comparing differences in survival across countries has been differences in statistical methodology in single country registry annual

reports.[22,23] In a recent study looking at survival in the US and Canadian CF patient registries, using the same methodology for survival analysis[24], there was an almost 10 year difference in median survival that has been increasing since 2005[3]. Socioeconomic factors, nutrition and access to lung transplantation were all considered to influence this difference in survival[4]. Median survival in CF patients in the US was 40.6 years compared to 50.9 years in Canada. The median survival estimated in our ECFSPR study, using a similar statistical methodology, was 51.7 years. However, a limitation of our study is that many European patients in the ECFSPR have limited data after lung transplant as many transplant centres are not enrolled in the ECFSPR. This results in individuals tending to be lost to follow-up at the time of transplant, which is likely to induce some bias in the survival estimates. In the US-Canada study, censoring at time of transplant resulted in increased median survival in the US to 44.0 years and to 57.1 years in Canada[3]. Our median survival censoring at transplant of 56.8 years lies between these estimates for the United States and Canada which is likely to be a more accurate comparison.

The difference between median survival including post-transplantation follow-up (51.7 years) and using the composite outcome of death or transplant (38.5 years) highlight the impact of transplantation and the improved survival after transplantation[25]. This difference may be due to uncounted deaths in patients lost to follow-up post-transplant, as well as differences in access to transplantation in some countries reflected by a highly different percentage of transplanted patients among those seen in the year, which varied between 10% in France and 0% in

some Eastern European countries[9]. There were also differences in median survival when we limited the cohort to those homozygous for F508del which is similar to other reports[15]. The distribution of F508del differs across European countries[9] and because of this, the influence of SES on survival was adjusted for *CFTR* genotype to account for differences in genotype frequencies in countries with lower measures of SES.

Our study also demonstrates that survival outcomes vary depending on different socioeconomic factors. Studies of SES and CF outcomes in the United States have shown that medical insurance status[20] and median house household income[19] are both independently associated with difference in CF survival outcomes, even within a country with a high GNI. In the UK, a validated deprivation score was associated with poorer outcomes including increased infection with *Pseudomonas aeruginosa* and decreased access to and use of CF medications, all of which are associated with reduced CF survival[26]. This is the first study in Europe to quantify the association between national measures of SES and survival and shows that countries with the lowest measures of health-care spending have hazard rates for death that are almost twice that of countries with higher measures of health-care spending. This increase in hazard with lower SES was consistent across three separate measures of SES. Despite common European Standards of Care for CF and a national health insurance systems in almost all European countries, access to care and medication varies widely across Europe, especially in Eastern Europe[27]. The association between SES and CF survival is not unexpected as standardised mortality from all causes differs across Europe (as shown in Table

3), although the magnitude of effect in CF is greater than that seen for the general population and demonstrates the need for further research in this area within Europe.

There are a number of limitations to our study. Missing data and data quality are always challenging in studies using registry data. The analysis was limited to countries with a national registry and coverage of >80% of their CF population. It was assumed that missing data on covariates within countries were missing completely at random. By restricting to countries with a national registry, we assumed that the combined population is representative of that in Europe as a whole. The overall median survival age could be subject to bias if this is not the case. However, the findings about association between SES and survival would only be biased if the association between SES and survival differed in countries that were not a part of this study. All of the included national registries have rigorous approaches to data quality. This, in addition to the data quality requirements of the ECFSPR[28], increase the likelihood that the results are reliable. At the time of the study completion, data from two large European countries (Germany and Spain) were not available and it is possible that the survival estimates may change with the inclusion of these large countries. This will require a further follow-up study. Likewise, it is important that these survival estimates for Europe cannot be extrapolated to an individual patient with CF or to all European countries as the median estimates are influenced by the survivorship in the larger European countries. The three largest countries (UK, France and Italy) contribute 23,849 patients (75%) and 1,093 deaths (76%) indicating that the median survival

largely reflects the median survival of these three countries. We chose not to weight the survival estimates by country population as we were studying regional differences and used a similar methodology to that of Canada and the United States. Also, to ensure as accurate a survival estimate as possible, we restricted the cohort to include countries with the highest coverage and the most complete data. Future analysis including more countries, especially Eastern European countries, will be planned once the ECFSPR has sufficient data to do so. It is also worth noting that these estimates reflect a cohort of CF patients followed before the widespread availability of CFTR modulator therapy, and future survival estimates may change as these highly-effective novel CF therapies become more widely used across Europe.

Finally, a number of deaths may have been missing. It is anticipated that this number is low as most CF patients were attending CF centres who would generally know each patient's vital status, although we acknowledge that outcomes post-transplant may be incomplete. The absence of follow-up post-transplant in some countries limits the interpretation of the overall survival estimates. The median survival estimate may be biased due to the exclusion of post-transplant deaths. As seen in Table 1, the proportion of deaths when censored at transplant compared to total deaths is highly variable across European countries. This is likely to be due to differences in European countries' access to transplant, post-transplant loss to follow-up in the registry and transplant centre survival rates. As all of these factors may all influence the median survival estimate, attempts are underway to audit data quality and number of deaths as well as include post-transplant centre data

in the ECFSPR. We also included transplant status as a time-dependent covariate in multivariable Cox regression analyses. However, this may be a mediator of the association between SES and mortality, for example if access to transplant is affected by SES. We also did not allow the hazard ratio for transplant to depend on time-since-transplant. Another potential source of bias is non-informative censoring. All survival models assume censoring (due to loss to follow-up) is uninformative for the event of interest. Loss to follow-up rates were generally low but it is possible that co-variates not included in our model may have influenced differences in each countries loss to follow-up. Unfortunately, there is no way to formally test this. This does not apply in the analysis in which we censor patients at transplant, when the focus is on cause-specific hazards for pre-transplant mortality.

In conclusion, this study demonstrates that median survival for patients with CF in Europe is comparable to that reported in the US and Canada and that survival across Europe is highly influenced by SES. A more detailed understanding of how these differences in SES lead to poorer survival is critical to improving outcomes for CF patients from European countries with lower health care spending.

Acknowledgement: We thank the people with CF, and their families, for consenting to their data being included in the ECFSPR. We thank the centres and individual country representatives for allowing the use of the data, and the ECFSPR for providing access to pseudonymised patient data.

REFERENCES:

1. Elborn JS. Cystic fibrosis. *Lancet* 2016; **388**(10059): 2519-31.
2. Cutting GR. Modifier genes in Mendelian disorders: the example of cystic fibrosis. *Ann N Y Acad Sci* 2010; **1214**: 57-69.
3. Stephenson AL, Sykes J, Stanojevic S, et al. Survival Comparison of Patients With Cystic Fibrosis in Canada and the United States: A Population-Based Cohort Study. *Ann Intern Med* 2017; **166**(8): 537-46.
4. Flume PA, VanDevanter DR. The Cystic Fibrosis Survival Gap: Why Do Canadians Fare Better Than Americans? *Ann Intern Med* 2017; **166**(8): 599-600.
5. Fogarty A, Hubbard R, Britton J. International comparison of median age at death from cystic fibrosis. *Chest* 2000; **117**(6): 1656-60.
6. McCormick J, Mehta G, Olesen HV, et al. Comparative demographics of the European cystic fibrosis population: a cross-sectional database analysis. *Lancet* 2010; **375**(9719): 1007-13.
7. Mehta G, Macek M, Jr., Mehta A. Cystic fibrosis across Europe: EuroCareCF analysis of demographic data from 35 countries. *J Cyst Fibros* 2010; **9 Suppl 2**: S5-S21.
8. Viviani L, Zolin A, Mehta A, Olesen HV. The European Cystic Fibrosis Society Patient Registry: valuable lessons learned on how to sustain a disease registry. *Orphanet J Rare Dis* 2014; **9**: 81.
9. Zolin A, Orenti A, Naehrlich L, Jung A, van Rens J et al, ECFS Patient Registry Annual Data Report 2018, 2020.
10. de Cos PH, Moral-Benito E. Determinants of health-system efficiency: evidence from OECD countries. *Int J Health Care Finance Econ* 2014; **14**(1): 69-93.
11. World Bank: World Development Indicators. 2019. https://datacatalog.worldbank.org/dataset/world-development-indicators.
12. ECFSPR Registry Variables and Definitions. https://www.ecfs.eu/projects/ecfs-patient-registry/variables-definitions (accessed 4/2/20.
13. Welsh MJ, Smith AE. Molecular mechanisms of CFTR chloride channel dysfunction in cystic fibrosis. *Cell* 1993; **73**(7): 1251-4.
14. Tsui LC. The spectrum of cystic fibrosis mutations. *Trends Genet* 1992; **8**(11): 392-8.
15. McKone EF, Emerson SS, Edwards KL, Aitken ML. Effect of genotype on phenotype and mortality in cystic fibrosis: a retrospective cohort study. *Lancet* 2003; **361**(9370): 1671-6.
16. McKone EF, Goss CH, Aitken ML. CFTR genotype as a predictor of prognosis in cystic fibrosis. *Chest* 2006; **130**(5): 1441-7.
17. Nixon GM, Armstrong DS, Carzino R, et al. Clinical outcome after early Pseudomonas aeruginosa infection in cystic fibrosis. *J Pediatr* 2001; **138**(5): 699-704.
18. Liou TG, Adler FR, Fitzsimmons SC, Cahill BC, Hibbs JR, Marshall BC. Predictive 5-year survivorship model of cystic fibrosis. *Am J Epidemiol* 2001; **153**(4): 345-52.

19. O'Connor GT, Quinton HB, Kneeland T, et al. Median household income and mortality rate in cystic fibrosis. *Pediatrics* 2003; **111**(4 Pt 1): e333-9.
20. Schechter MS, Shelton BJ, Margolis PA, Fitzsimmons SC. The association of socioeconomic status with outcomes in cystic fibrosis patients in the United States. *American journal of respiratory and critical care medicine* 2001; **163**(6): 1331-7.
21. Buu MC, Milla CE. Tear Down This Wall: Diversity and Disparities in Cystic Fibrosis. *American journal of respiratory and critical care medicine* 2018; **198**(8): 983-4.
22. Jackson AD, Daly L, Jackson AL, et al. Validation and use of a parametric model for projecting cystic fibrosis survivorship beyond observed data: a birth cohort analysis. *Thorax* 2011; **66**(8): 674-9.
23. Stephenson AL, Tom M, Berthiaume Y, et al. A contemporary survival analysis of individuals with cystic fibrosis: a cohort study. *Eur Respir J* 2015; **45**(3): 670-9.
24. Sykes J, Stanojevic S, Goss CH, et al. A standardized approach to estimating survival statistics for population-based cystic fibrosis registry cohorts. *J Clin Epidemiol* 2016; **70**: 206-13.
25. Chambers DC, Cherikh WS, Goldfarb SB, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-fifth adult lung and heart-lung transplant report-2018; Focus theme: Multiorgan Transplantation. *J Heart Lung Transplant* 2018; **37**(10): 1169-83.
26. Taylor-Robinson DC, Smyth RL, Diggle PJ, Whitehead M. The effect of social deprivation on clinical outcomes and the use of treatments in the UK cystic fibrosis population: a longitudinal study. *Lancet Respir Med* 2013; **1**(2): 121-8.
27. Walicka-Serzysko K, Peckova M, Noordhoek JJ, Sands D, Drevinek P. Insights into the cystic fibrosis care in Eastern Europe: Results of survey. *J Cyst Fibros* 2018; **17**(4): 475-7.
28. Naehrlich L FA, Krasnyk M, Orenti A, Zolin A, Van Rens J, on behalf of the ECFSPR. The European Cystic Fibrosis Society Patient Registry (ECFSPR) data validation programme: accuracy and consistency of data. *J Cyst Fibros* 2019; **18**.

Table 1: Study Population in Cohort from 2010 to 2014*

Country	Patients	Person Years	Lost to Follow-up**	Total Deaths	Deaths (censoring at transplant)
All countries	31987	135833.3	983	1435	1086
Patient Country					
Belgium*	1276	4570.5	34	29	15
Czech Republic	643	2788.4	2	52	50
Denmark	514	2278.2	8	22	7
France	7133	30864.5	153	299	142
Hungary	691	2780.1	54	15	12
Ireland	1247	5141.4	25	88	77
Israel	755	2746.2	124	24	17
Italy	5627	23312.3	300	192	147
Netherlands	1618	6708.5	122	73	62
Portugal	321	1007.7	22	7	7
Slovak Republic	393	1282.3	117	9	8
Sweden	680	3055.4	8	23	9
United Kingdom	11089	49297.8	14	602	533

*Belgium - data was only present from 2010-2013
**Loss to follow up definition: patients who are alive but whose last year of data was >2 years before the cohort end year.

Table 2: Baseline Demographics and Clinical Data at time of entry into ECFSPR

Subject number (n)	31987
Age (yrs)	16.6 ± 13.8
Age at diagnosis (yrs)	4.6 ± 10.2
Male Sex (%)	53%
F508del homozygous (%)	40%
FEV_1 (% predicted)	79 ± 25
FVC (% predicted)	86 ± 21
Height (cm)	145 ± 34
Weight (kg)	44.5 ± 22.7
BMI (kg/m^2) for Adults≥18 yrs	21.8 (3.6)
BMI (%tile) for Children <18 yrs	-0.2 (1.1)
Pseudomonas aeruginosa	25%
CF Liver Disease	10%
CF Related Diabetes Mellitus	12%
Lung transplantation (%)	4.5%

Data are Mean ± SD unless otherwise stated

Table 3: Standardised Death Rates and Socioeconomic Measures by Country

Country	Standardised Death Rates/100,000*	GNI per capita (US$000) 2015	Healthcare spend (% GDP) 2014	Physicians per 1,000 (2008-2014)
Belgium	1,036	44.3	10.6	4.9
Czech Republic	1,321	18.1	7.4	3.6
Denmark	1,091	58.5	10.8	3.5
France	874	40.5	11.5	3.2
Hungary	1,518	13.0	7.4	3.1
Ireland	1,035	52.6	7.8	2.7
Israel	N/A	35.8	7.8	3.3
Italy	906	32.8	9.2	3.8
Netherlands	1,008	48.9	10.9	2.9
Portugal	1,034	20.5	9.5	4.1
Slovak Republic	1,450	17.6	8.1	3.3
Sweden	964	57.9	11.9	3.9
United Kingdom	996	43.4	9.1	2.8

*data for 2013, accessed Oct 2020 from https://ec.europa.eu/eurostat

Table 4: Summary of time-to-event data and median survival estimate for 2010-2014 cohort

	Patients	Person Years	Deaths	Median survival age (years)	95% CI
All patients	31987	135833	1435	51.7	(50.0, 53.4)
F508del Homozygotes	12918	57023	698	45.5	(43.1, 47.6)
Two Class I-III Mutation	18267	80529	947	47.0	(44.8, 47.9)
Composite (Death/Transplant)	30885	129034	2177	38.5	(37.5, 39.5)
Censoring at Transplant	30885	129044	1086	56.8	(54.0. 60.2)

Table 5: Univariable Predictors of Survival

Variable	Patients	Person Years	Deaths	Hazard ratio	95% CI	p-value
Sex						
Male	16840	74106	687	1.000	-	<0.001
Female	15145	66535	748	1.281	(1.148, 1.414)	
Age category at diagnosis						
0-6 months	17292	76510	703	1.000	-	<0.001
6 - 12 months	2426	11148	142	0.952	(0.779, 1.125)	
1 - 6 years	6764	30004	343	0.810	(0.704, 0.917)	
6 - 18 years	2953	12771	129	0.554	(0.449, 0.660)	
18+ years	2552	10210	118	0.269	(0.204, 0.334)	
Transplant (any type)						
No	30877	131166	1086	1.000	-	<0.001
Yes	1110	9476	349	3.591	(3.137, 4.045)	
Presence of F508del mutation						
F508del - homozygotes	12918	59645	698	1.000	-	<0.001
F508del - heterozygotes	11227	49491	379	0.594	(0.519, 0.669)	
F508del/Unknown	1175	4861	102	1.289	(1.016, 1.562)	
Not F508del	4352	18333	132	0.558	(0.453, 0.664)	
Not F508del/Unknown	567	2211	22	0.624	(0.358, 0.891)	
Unknown	1748	6102	102	0.910	(0.718, 1.101)	

Notes: Hazard ratios, confidence intervals and p-values estimated from Cox regression models

Table 6: Socioeconomic Predictors of Survival: Results from multivariable Cox models*. The SES variables did not appear together in the same model.

Variable	Patients	Person Years	Deaths	Crude Hazard Ratio	95% CI	Adjusted* Hazard ratio	95% CI
Country level SES variables							
Healthcare Expenditure (% of GDP)							
Tercile 1: 7.4 – 7.8	3336	13919	179	1.000	-	1.000	-
Tercile 2: 8.1 – 9.5	17430	76440	810	0.695	(0.582, 0.809)	0.733	(0.613, 0.853)
Tercile 3 : 10.6 – 11.9	11221	50283	446	0.618	(0.510, 0.725)	0.544	(0.448, 0.641)
GNI per Capita ($ per 1000 people)							
Lower: <32.8	2048	8101	83	1.000	-	1.000	-
Higher: ≥32.8	29939	132541	1352	0.811	(0.645, 1.013)	0.859	(0.667, 1.051)
Physicians (per 1000 people)							
Tercile 1: 2.7 – 3.2	21778	98465	1077	1.000	-	1.000	-
Tercile 2: 3.3 – 3.8	7932	33174	299	0.804	(0.700, 0.907)	0.983	(0.852, 1.113)
Tercile 3: 3.9 – 4.9	2277	9004	59	0.568	(0.419, 0.717)	0.523	(0.385, 0.661)

*adjusted for age at diagnosis, sex, *CFTR* genotype and transplant status.

Figure Legend.

Figure 1: Estimated Survival (all-cause mortality) and 95% confidence intervals for European CF Patients

Figure 2: Estimated Survival (composite outcome of all-cause mortality or transplant) and 95% confidence interval for European CF Patients.

Figure 3: Estimated Survival (censoring at transplant) and 95% confidence interval for European CF Patients.

Figure 4: Estimated Survival by SES and 95% confidence interval for European CF Patients.

Appendix 1: List of Collaborating Authors:

The ECFSPR contributors list consists of the representatives of the countries whose data is used in this manuscript, and the members Committee who reviewed the initial data-application and the final manuscript.

Bardin E	Cystic Fibrosis Europe, Brussels, Belgium	emmanuelle.bardin@cf-europe.eu
Burgel PR	Respiratory Medicine and National Cystic Fibrosis Reference Centre, Hôpital Cochin, AP-HP and Paris Descartes University, Paris, France	pierre-regis.burgel@cch.aphp.fr
Cosgriff R	Cystic Fibrosis Trust, London, United Kingdom	Rebecca.Cosgriff@cysticfibrosis.org.uk
Daneau G	Sciensano, Health Services Research, Epidemiology and Public Health, Brussels, Belgium	Geraldine.Daneau@sciensano.be
de Monestrol I	Stockholm CF centre, Karolinska University Hospital, Stockholm, Sweden	Isabelle.demonestrol@ki.se
Drevinek P	Department of Medical Microbiology, Second Faculty of Medicine, Charles University and Motol University Hospital, Prague, Czech Republic	pavel.drevinek@Lfmotol.cuni.cz
Farge A	Vaincre la Mucoviscidose, Medical Department, Paris, France	llemonnier@vaincrelamuco.org
Fletcher G	The Cystic Fibrosis Registry of Ireland, Dublin, Ireland	gfletcher@cfri.ie
Gulmans V	Dutch Cystic Fibrosis Foundation (NCFS), Baarn, The Netherlands	V.Gulmans@ncfs.nl
Kayserova H	Cystic Fibrosis Centre, University Hospital of Bratislava, Bratislava, Slovakia	kayserov.hana@gmail.com
Lindblad A	CF Centre, Queen Silvia Children's Hospital, The Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden	anders.lindblad@vgregion.se
Mei-Zahev M	Pulmonary Institute, Schneider Children's Medical Centre of Israel, Petah Tikva, Israel; Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel	mmeizahav@gmail.com
Olesen HV	Department of Pediatrics and Adolescent Medicine, Cystic Fibrosis Centre, Aarhus University Hospital, Aarhus, Denmark	hannoles@rm.dk
Padoan R	Cystic Fibrosis Support Centre, Department of Paediatrics, Children's Hospital, ASST Spedali Civili, Brescia, Italy	Ritaf54@gmail.com
Párniczky A	Heim Pál National Pediatric Institute,, Budapest, Hungary	andrea.parniczky@gmail.com
Pereira L	Centre for Cystic Fibrosis, Hospital de Santa Maria, Lisbon, Portugal	mluisafpereira@gmail.com

Supplemental Table 1: Demographics and Socioeconomic Measures of ECFSPR Countries Excluded from the Analysis.

ECFSPR Data (2008-2014)				Country characteristics			
Country	Patients	Person Years	Deaths	Population (millions) 2015	GNI per capita (US$000) 2015	Healthcare spend (% GDP) 2014	Doctors per 1,000 popn (2008-2014)
Austria	750	3622	15	9	47.4	11.2	4.8
Germany	6284	15643	100	81	45.9	11.3	3.9
Greece	537	1103	15	11	20.3	8.1	6.2
Latvia	43	222	3	2	15.0	5.9	3.6
Republic of Moldova	83	307	8	4	2.2	10.3	3.0
Serbia	196	941	15	7	5.5	10.4	2.1
Slovenia	108	513	1	2	22.2	9.2	2.5
Spain	1825	7781	61	46	28.5	9.0	4.9
Switzerland	856	3455	12	8	84.6	11.7	4.0
Russian Federation	2321	6596	114	144	11.5	7.1	4.3
Romania	44	143	1	20	9.5	5.6	2.4
Lithuania	14	48	2	3	14.9	6.6	4.1
Ukraine	146	420	7	45	2.6	7.1	3.5
Republic of Macedonia	108	380	0	2	5.1	9.7	3.5