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

3

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7

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30

31 **ABSTRACT**

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

37 **Methods.** CF subjects known to be alive and in the ECFSPR between 2010 and  
38 2014 were included. Survival curves were estimated using the Kaplan-Meier (KM)  
39 method. Differences in the survival curves were assessed using the log rank test.  
40 Cox regression was used to estimate the association between socioeconomic  
41 factors and the age-specific hazard of death, with adjustment for sex, age at  
42 diagnosis, *CFTR* genotype and transplant status.

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

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

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

55 **KEY WORDS**

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

58

59 **ABBREVIATIONS**

60 CF = Cystic Fibrosis

61 CFTR = Cystic fibrosis Transmembrane Conductance Regulator

62 FEV<sub>1</sub> = Forced expiratory volume in one second

63 FVC = Forced Vital Capacity

64 ECFSR = European Cystic Fibrosis Society Patient Registry

65 ECFS = European Cystic Fibrosis Society

66 EU = European Union

67 HR = Hazard ratio

68 GNI = Gross National Income

69 GDP = Gross Domestic Product

70 SD = Standard deviation of the mean

71 SES = Socioeconomic Status

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

82

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

91

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

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

98

99 *Patient Population.* Once a year, annual summary data for each CF patient  
100 enrolled in the ECFSPR is uploaded to the registry<sup>9</sup>. Demographic and clinical  
101 characteristics of the patient population were extracted from the ECFSPR for all  
102 patients in the registry between 2010 and 2014. These characteristics were: sex,  
103 age, vital status during year (alive/dead), transplant status, age at diagnosis, *CFTR*  
104 genotype, highest annual forced expiratory volume in one second (FEV<sub>1</sub>), forced  
105 vital capacity (FVC), height and weight.

106

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

113

114 *Socioeconomic Factors.* Three validated metrics of country-level socioeconomic  
115 status (SES) were used<sup>10</sup>. Two were measures of country healthcare spending  
116 and one was a measure of country wealth. These were i) Proportion of Gross  
117 Domestic Product (GDP) spent on Healthcare and ii) Average numbers of



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

124

125 *Statistical Analysis.* Descriptive statistics were used to present the demographics  
126 and clinical data of the CF cohort. Definitions of clinical variables are as determined  
127 by the ECFSPR<sup>12</sup>. Overall survival curves were estimated using the Kaplan Meier  
128 method and Cox proportional hazards modelling was used to estimate hazard  
129 ratios in the cohort. The time scale was age. Patients were considered to be at  
130 risk from age of entry into the cohort until the earliest of: age of exit, death or end  
131 of follow-up period on 31st December 2014. Death was defined as all-cause  
132 mortality either before or after transplant. Loss to follow-up was defined as present  
133 if two or more years of observation were missing before the end-date for the cohort  
134 (31st December 2014 for all countries except Belgium, whose end-date was 31st  
135 December 2013)<sup>3</sup>. Due to incomplete follow-up of CF patients post-transplant in  
136 many countries, analysis was repeated using the composite outcome of death or  
137 transplant as well as censoring at time of transplant.

138

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

141 regulator (CFTR) genotype as well as transplant status and survival. *CFTR*  
142 genotype was characterised by the presence or absence of *F508del* mutations and  
143 by the presence of compound heterozygosity for two *CFTR* Class I-III mutations  
144 using the classification system proposed by Welsh and Tsui<sup>13,14</sup>. Transplant status  
145 was defined as a transplant of any type (primarily lung and/or liver) and was used  
146 as a time-dependent variable. Measures associated with survival in univariable  
147 analysis were included in a multivariable model for the adjusted association  
148 between SES and survival. Due to the difference in *CFTR* genotype across Europe  
149 and the known association of *CFTR* genotypes with survival, sensitivity analyses  
150 were also carried out limiting the population to CF patients homozygous for  
151 *F508del* and to CF patients compound heterozygous for two *CFTR* Class I-III  
152 mutations. Proportional hazards assumption was assessed using graphical  
153 methods (log-log plot of survival) and methods based on Schoenfeld residuals with  
154 no significant deviations found. All statistical analysis was carried out using Stata  
155 (14.0) software (San Antonio, Texas).

156

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

163

164 **RESULTS**

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

176

177 *Survival Analysis:* Median age of survival for all European patients included in the  
178 study was 51.7 years (95% C.I. 50.0-53.4,  $p < 0.001$ ). The Kaplan Meier curve for  
179 the study cohort all-cause mortality is shown in Figure 1. Results including median  
180 survival for CF genetic subgroups and when transplant is considered as a death  
181 are shown in Table 4. Median survival with the composite outcome of death or  
182 transplant was 38.5 years (95% C.I. 37.5-39.4,  $p < 0.001$ ). The Kaplan Meier curve  
183 for the study cohort with the composite outcome of death or transplant is shown in  
184 Figure 2. Median survival censoring at transplant was 56.8 years (95% C.I. 54.0-  
185 60.2,  $p < 0.001$ ). The Kaplan Meier curve for the study cohort censored at transplant  
186 is shown in Figure 3.

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

190

191 *Socioeconomic factors and survival.* All measures of country-level SES were  
192 associated with increased hazard for death in univariable analyses. After adjusting  
193 for age at diagnosis, sex, *CFTR* genotype and transplant status, the proportion of  
194 GDP spent on healthcare and number of physicians per capita were each  
195 independently associated with survival. Countries in the highest third of GDP  
196 spend on healthcare had a 45% lower hazard than those in the lowest third (HR  
197 0.544, 95% CI (0.448,0.641)). Similarly, countries in the highest third of physicians  
198 per capita had a 47% lower hazard than those with the lowest third of physician  
199 per capita ratio (HR 0.523, 95% CI (0.385, 0.661)). These results are shown in  
200 Table 6. The Kaplan Meier curve for GDP spend on healthcare and physicians per  
201 capita is shown in Figure 3. After multivariable adjustment high GNI was  
202 associated with a lower hazard, however this finding was not statistically significant  
203 (HR for high versus low GNI 0.859, 95% CI (0.667, 1.051)).

204

## 205 **DISCUSSION.**

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

209

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

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

233 reports.<sup>22,23</sup> In a recent study looking at survival in the US and Canadian CF patient  
234 registries, using the same methodology for survival analysis<sup>24</sup>, there was an almost  
235 10 year difference in median survival that has been increasing since 2005<sup>3</sup>.  
236 Socioeconomic factors, nutrition and access to lung transplantation were all  
237 considered to influence this difference in survival<sup>4</sup>. Median survival in CF patients  
238 in the US was 40.6 years compared to 50.9 years in Canada. The median survival  
239 estimated in our ECFSPR study, using a similar statistical methodology, was 51.7  
240 years. However, a limitation of our study is that many European patients in the  
241 ECFSPR have limited data after lung transplant as many transplant centres are  
242 not enrolled in the ECFSPR. This results in individuals tending to be lost to follow-  
243 up at the time of transplant, which is likely to induce some bias in the survival  
244 estimates. In the US-Canada study, censoring at time of transplant resulted in  
245 increased median survival in the US to 44.0 years and to 57.1 years in Canada<sup>3</sup>.  
246 Our median survival censoring at transplant of 56.8 years lies between these  
247 estimates for the United States and Canada which is likely to be a more accurate  
248 comparison.

249 The difference between median survival including post-transplantation follow-up  
250 (51.7 years) and using the composite outcome of death or transplant (38.5 years)  
251 highlight the impact of transplantation and the improved survival after  
252 transplantation<sup>25</sup>. This difference may be due to uncounted deaths in patients lost  
253 to follow-up post-transplant, as well as differences in access to transplantation in  
254 some countries reflected by a highly different percentage of transplanted patients  
255 among those seen in the year, which varied between 10% in France and 0% in

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

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

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

282 There are a number of limitations to our study. Missing data and data quality are  
283 always challenging in studies using registry data. The analysis was limited to  
284 countries with a national registry and coverage of >80% of their CF population. It  
285 was assumed that missing data on covariates within countries were missing  
286 completely at random. By restricting to countries with a national registry, we  
287 assumed that the combined population is representative of that in Europe as a  
288 whole. The overall median survival age could be subject to bias if this is not the  
289 case. However, the findings about association between SES and survival would  
290 only be biased if the association between SES and survival differed in countries  
291 that were not a part of this study. All of the included national registries have  
292 rigorous approaches to data quality. This, in addition to the data quality  
293 requirements of the ECFSPR<sup>28</sup>, increase the likelihood that the results are reliable.  
294 At the time of the study completion, data from two large European countries  
295 (Germany and Spain) were not available and it is possible that the survival  
296 estimates may change with the inclusion of these large countries. This will require  
297 a further follow-up study. Likewise, it is important that these survival estimates for  
298 Europe cannot be extrapolated to an individual patient with CF or to all European  
299 countries as the median estimates are influenced by the survivorship in the larger  
300 European countries. The three largest countries (UK, France and Italy) contribute  
301 23,849 patients (75%) and 1,093 deaths (76%) indicating that the median survival



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

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

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

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

342

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344 consenting to their data being included in the ECFSPR. We thank the centres and  
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**Table 1: Study Population in Cohort from 2010 to 2014\***

| <b>Country</b>         | <b>Patients</b> | <b>Person Years</b> | <b>Lost to Follow-up**</b> | <b>Total Deaths</b> | <b>Deaths (censoring at transplant)</b> |
|------------------------|-----------------|---------------------|----------------------------|---------------------|---|
| <b>All countries</b>   | 31987           | 135833.3            | 983                        | 1435                | 1086                                    |
| <b>Patient Country</b> |                 |                     |                            |                     |   |
| 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**

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|   |             |
|---|-------------|
| 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 <sub>1</sub> (% predicted)              | 79 ± 25     |
| FVC (% predicted)                           | 86 ± 21     |
| Height (cm)                                 | 145 ± 34    |
| Weight (kg)                                 | 44.5 ± 22.7 |
| BMI (kg/m <sup>2</sup> ) 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%        |

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Data are Mean ± SD unless otherwise stated

**Table 3: Standardised Death Rates and Socioeconomic Measures by Country**

| <b>Country</b>  | <b>Standardised Death Rates/100,000*</b> | <b>GNI per capita (US\$000) 2015</b> | <b>Healthcare spend (% GDP) 2014</b> | <b>Physicians per 1,000 (2008-2014)</b> |
|-----------------|--|--------------------------------------|--------------------------------------|---|
| 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**

|                                     | <b>Patients</b> | <b>Person<br/>Years</b> | <b>Deaths</b> | <b>Median<br/>survival age<br/>(years)</b> | <b>95% CI</b> |
|-------------------------------------|-----------------|-------------------------|---------------|--|---------------|
| <b>All patients</b>                 | 31987           | 135833                  | 1435          | 51.7                                       | (50.0, 53.4)  |
| <b>F508del Homozygotes</b>          | 12918           | 57023                   | 698           | 45.5                                       | (43.1, 47.6)  |
| <b>Two Class I-III Mutation</b>     | 18267           | 80529                   | 947           | 47.0                                       | (44.8, 47.9)  |
| <b>Composite (Death/Transplant)</b> | 30885           | 129034                  | 2177          | 38.5                                       | (37.5, 39.5)  |
| <b>Censoring at Transplant</b>      | 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 |
|-------------------------------------|----------|--------------|--------|--------------|----------------|---------|
| <b>Sex</b>                          |          |              |        |              |                |         |
| Male                                | 16840    | 74106        | 687    | 1.000        | -              | <0.001  |
| Female                              | 15145    | 66535        | 748    | 1.281        | (1.148, 1.414) |         |
| <b>Age category at diagnosis</b>    |          |              |        |              |                |         |
| 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) |         |
| <b>Transplant (any type)</b>        |          |              |        |              |                |         |
| No                                  | 30877    | 131166       | 1086   | 1.000        | -              | <0.001  |
| Yes                                 | 1110     | 9476         | 349    | 3.591        | (3.137, 4.045) |         |
| <b>Presence of F508del mutation</b> |          |              |        |              |                |         |
| 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         |
|--|----------|--------------|--------|--------------------|----------------|------------------------|----------------|
| <b>Country level SES variables</b>         |          |              |        |                    |                |                        |                |
| <b>Healthcare Expenditure (% of GDP)</b>   |          |              |        |                    |                |                        |                |
| 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) |
| <b>GNI per Capita (\$ per 1000 people)</b> |          |              |        |                    |                |                        |                |
| 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) |
| <b>Physicians (per 1000 people)</b>        |          |              |        |                    |                |                        |                |
| 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, *CFTF* 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.

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**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                                |