CHANGES IN FEV1 PERCENT OF PREDICTED OF PEOPLE WITH CYSTIC FIBROSIS IN THE LAST DECADE: USE OF DIFFERENT STATISTICAL METHODS

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Introduction

Cystic fibrosis (CF) is the most common severe autosomal recessive disease in Europe, but despite remarkable improvements in health outcomes, it remains a life-shortening condition with pulmonary insufficiency as the main cause of death. Forced Expiratory Volume in 1 second compared to the predicted in a reference population (FEV1pp) is regarded as the best measure for assessing CF lung disease [1]. FEV1pp is an influential driver for defining illness stage and decisions on treatment [2] with a primary outcome measure for clinical studies and for regulatory approval of CF respiratory therapies.

Aims

The goal of the present work was to provide an epidemiological evaluation of changes in lung function over the last decade, which typically decreases over time, and it is linked to severity disease. To evaluate the lung function, longitudinal data of FEV1pp were used.

Methods

The European Cystic Fibrosis Society Patient Registry (ECFSPR) collects demographic and longitudinal clinical data of people with Cystic Fibrosis (pwCF) from 40 countries from Europe and neighbouring countries for a period spanning from 2008 to 2021 [3,4]. To have a more stable cohort we concentrate on the last decade: 2011-2021 and we excluded from the analysis: children younger than 6 years, adults older than 60 years, pwCF who had lung transplantation and pwCF from countries with less than 10 years of follow up in ECFSPR. We further selected pwCF homozygote for F508del mutation, the most frequent one in pwCF. The final study population included 18749 pwCF.

We tested if changes of FEV1pp over age, included using cubic spline with 5 degrees chosen by AIC, were different according to a set of variables: chronic Pseudomonas Aeruginosa (PsA), Underweight status, Cystic Fibrosis Related Diabetes (CFRD), genotype and country group. To consider economical differences, 27 countries were classified in three groups, lower, middle, and higher income according to Gross National Income.

Two regression models, including a random effect for patients and with FEV1pp as response variable, were fitted using R software: a linear mixed model (LMM) implemented with *lmer* function from "lme4" package and, since FEV1pp has an asymmetric distribution and it is often summarized using median and quartiles, a linear quantile mixed model (LQMM) [6] implemented with the *lqmm* function from "lqmm" package. Two different scenarios were explored: in the first one the year of follow-up is included as a continuous variable, in the second one it is included using dummy variables.

Results

The multiple regression analysis using dummy variable (Table 1) show that there was a gradual and consistent increase during the 10-year study period for FEV1pp in all age groups, but a larger increase in FEV1pp was observed in 2021 for pwCF carrying the F508del mutation when modulators, a class of drugs that act by improving production, intracellular processing, and function of the defective CFTR protein, became available for pwCF carrying this mutation.

The results of the different models are comparable in terms of coefficient estimates. LMM provides a narrower confidence interval than LQMM when year is included as a continuous variable, and the linear mixed model gives a narrower Confidence Intervals when year is included as dummy variables too. The main problem in fitting models in R software on our big dataset, is the long computational time for the LQMM: the model runs for 3 minutes to obtain only coefficient estimates and approximately 5 hours to obtain a complete summary, with year included as continuous, and 1 minute for coefficient estimates only and 3 hours for a complete summary when year is insert as a dummy. The summary of this model is very demanding in terms of computational time, on the contrary, the LMM runs for only a few seconds for the coefficient estimates and for the summary.

Conclusions

This pan-European analysis of the ECFSPR annual data, demonstrates a consistent improvement in pulmonary function over the last decade which started even before the highly effective CFTR modulators were available. A remarkable increase in FEV1pp was observed in 2021 in pwCF who carry the F508del mutation when Elexacaftor/Tezacaftor/Ivacaftor (ETI), newest CFTR modulator drug, became available. While the findings of this study are encouraging, there are still a significant number of pwCF who cannot benefit from ETI and alternative therapeutic interventions for this group are needed. A less optimistic picture was observed in fact in low-income countries: despite the availability of the guidelines recommending standard treatments, improvement in disease outcomes was only minimal [7,8].

This registry-based study has its limitations, such as the problems with adherence to the definitions, data quality process, missing data, and data entry errors. On the other hand, over the last years, the ECFSPR introduced a data quality control project to check and reduce these limitations. Moreover, the European Medicines Agency (EMA) qualified the ECFSPR as a resource for collecting CF-specific data for Pharmacoepidemiology Studies.

In conclusion, the models presented in the present study need to be additionally compared in detail for diagnostic measures, further research is needed to fulfill the unmet need of providing robust regression coefficient estimates on mixed effects models on big datasets, and simulation studies mimic real world practice are necessary.

	LMM			LQMM		
Scenario 1	**Estimate**	**SE**	**CI**	**Estimate**	**SE**	**CI**
Intercept	-795.944	18.699	(-832.59; -759.3)	-1335.900	30.008	(-1394.74; -1277.11)
year	0.439	0.009	(0.42; 0.46)	0.711	0.015	(0.68; 0.74)
Age FEV1, spline1	-9.944	0.464	(-10.85; -9.04)	-9.787	1.054	(-11.85; -7.72)
Age FEV1, spline2	-33.737	0.854	(-35.41; -32.06)	-33.752	1.992	(-37.66; -29.85)
Age FEV1, spline3	-33.568	1.231	(-35.98; -31.16)	-27.583	2.960	(-33.38; -21.78)
Age FEV1, spline4	-36.030	0.959	(-37.91; -34.15)	-26.606	2.329	(-31.17; -22.04)
Age FEV1, spline5	-42.098	0.607	(-43.29; -40.91)	-30.050	1.176	(-32.36; -27.75)
PsA	-2.195	0.063	(-2.32; -2.07)	-11.256	0.173	(-11.59; -10.92)
CFRD	-2.701	0.086	(-2.87; -2.53)	-8.258	0.199	(-8.65; -7.87)
Underweight	-7.309	0.102	(-7.51; -7.11)	-20.286	0.264	(-20.80; -19.77)
Country group middle vs low	6.169	0.328	(5.53; 6.81)	2.789	0.277	(2.25; 3.33)
Country group high vs low	7.244	0.349	(6.56; 7.93)	4.679	0.269	(4.15; 5.21)
Scenario 2	**Estimate**	**SE**	**CI**	**Estimate**	**SE**	**CI**
Intercept	88.818	0.323	(88.19; 89.45)	89.159	0.755	(87.68; 90.64)
2012 vs 2011	-0.358	0.089	(-0.53; -0.18)	-0.184	0.110	(-0.4; 0.03)
2013 vs 2012	0.026	0.087	(-0.15; 0.2)	0.135	0.109	(-0.08; 0.35)
2014 vs 2013	1.224	0.086	(1.06; 1.39)	1.269	0.094	(1.08; 1.45)
2015 vs 2014	-0.206	0.084	(-0.37; -0.04)	-0.102	0.103	(-0.3; 0.1)
2016 vs 2015	-0.024	0.078	(-0.18; 0.13)	0.162	0.084	(-0.002; 0.33)
2017 vs 2016	0.254	0.072	(0.11; 0.4)	0.265	0.063	(0.14; 0.39)
2018 vs 2017	0.139	0.071	(0; 0.28)	0.217	0.069	(0.08; 0.35)
2019 vs 2018	0.124	0.070	(-0.01; 0.26)	0.263	0.053	(0.16; 0.37)
2020 vs 2019	0.906	0.070	(0.77; 1.04)	0.778	0.079	(0.62; 0.93)
2021 vs 2020	3.849	0.071	(3.71; 3.99)	3.575	0.087	(3.41; 3.75)
Age FEV1, spline1	0.460	272198.01	(-12.21; -10.41)	-10.481	1.079	(-12.6; -8.37)
Age FEV1, spline2	0.847	278423.38	(-33.86; -30.54)	-35.535	2.555	(-40.54; -30.53)
Age FEV1, spline3	1.220	280644.93	(-37.59; -32.81)	-33.473	3.284	(-39.91; -27.04)
Age FEV1, spline4	0.952	290400.70	(-37.51; -33.78)	-33.999	2.353	(-38.61; -29.39)
Age FEV1, spline5	0.605	161779.37	(-44.16; -41.79)	-38.696	1.683	(-42; -35.4)
PsA	-1.940	0.063	(-2.06; -1.82)	-3.365	0.222	(-3.8; -2.93)
CFRD	-2.673	0.085	(-2.84; -2.51)	-3.853	0.305	(-4.45; -3.26)
Underweight	-7.086	0.101	(-7.28; -6.89)	-8.498	0.296	(-9.08; -7.92)
Country group middle vs low	6.169	0.329	(5.52; 6.81)	7.959	1.023	(5.96; 9.96)
Country group high vs low	7.297	0.350	(6.61; 7.98)	8.096	1.251	(5.65; 10.55)

Table 1. Results of the different models fitted: LMM and LQMM on scenario 1 and 2

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