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ORIGINAL PAPER

Cost-of-illness analysis and regression modeling in cystic fibrosis: a retrospective prevalence-based study

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Abstract

Background Economic data pertaining to cystic fibrosis (CF), is limited in Europe generally, and completely lacking in Central and Eastern Europe. We performed an analysis of all direct costs associated with CF relative to key disease features and laboratory examinations.

Methods A retrospective prevalence-based cost-of-illness (COI) study was performed in a representative cohort of 242 CF patients in the Czech Republic, which represents about 65 % of all Czech CF patients. Medical records and invoices to health insurance companies for reference year 2010 were analyzed.

Results The mean total health care costs were €14,486 per patient, with the majority of the costs going towards medicinal products and devices (€10,321). Medical procedures (€2676) and inpatient care (€1829) represented a much smaller percentage of costs. A generalized linear model showed that the strongest cost drivers, for all cost categories, were associated with patient age and lung disease severity (assessed using the FEV1 spirometric parameter), when compounded by chronic *Pseudomonas aeruginosa* airway infections. Specifically, maximum total costs are around the age 16 years; a FEV1 increase of 1 % point represented a cost decrease of: 0.9 % (medicinal products), 1.7 % (total costs), 2.8 % (procedures) and 7.0 % (inpatient care).

Conclusions COI analysis and regression modeling using the most recent data available can provide a better understanding of the overall economic CF burden. A comparison of our results with other methodologically similar studies demonstrates that although overall costs may differ, FEV1 can nonetheless be utilized as a generally transferrable indicator of the relative economic impact of CF.

Keywords Cystic fibrosis · Cost-of-illness · Disease severity · Health care costs · FEV1 · Generalized linear model

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Introduction

Cystic fibrosis (CF) is a chronic progressive monogenic disorder requiring lifelong medical care that becomes increasingly costly and complex with age. CF-causing mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene (www.cftr2.org) determine the overall disease severity and its progression by altering the function of the CFTR protein [1]. CF is a multisystem disease associated with chronic pulmonary, liver and pancreatic dysfunctions that are responsible for the majority of CF morbidity and mortality in a decreasing order, respectively. CF symptoms vary between CF patients and may also reflect patient adherence to therapy [2].

Several cost-of-illness (COI) studies have assessed the mean annual health care costs of CF in various European countries, Australia, and the USA. After conversion to euros (€; 2013), annual totals ranged between €6000 and €38,000 per patient [3, 4]. The main costs associated with standardized CF treatment have been shown to be antibiotics, mucolytics, and inpatient/hospital care. Moreover, CF is associated with substantial indirect and lost-productivity costs in affected families. Recent estimates derived from the European Cystic Fibrosis Registry (https://www.ecfs.eu/projects/ecfs-patient-registry/intro), together with previous EuroCareCF.eu European Union project demographic surveys, indicate that there are over 29,000 CF patients in Europe alone. Some patients still remain undiagnosed, mainly in Eastern European countries [5–7]. Overall, CF represents a major medical and socio-economic issue for all health care systems [3, 8].

Substantiation of costs related to CF care, and in particular with regards to the age of patients and disease severity, has become increasingly important due to budgetary constraints and austerity measures in recent years. In particular, health care payers often require establishment of costs of CF care prior to the introduction of CFTR-modulating therapies (CFTR-MT) that utilize (ultra-) orphan medicinal products (OMP), which markedly increase per patient expenditures [3].

The aim of our study was to retrospectively assess CF health care costs within a representative cohort of Czech patients drawn from the Prague CF Center, which is the national tertiary center in the Czech Republic (CZ). Besides stratification of costs, according to e.g., patient age and disease severity, we also explored the main cost predictors. Data from this study could also be used as future inputs into cost-effectiveness analyses that will evaluate the real value (ratio of costs and effectiveness) of newly introduced CF interventions.

Methods

A retrospective prevalence-based [9] COI study focused on health care costs related to age, gender, BMI z-score in children and BMI in adults (reflective of their general nutritional status), severity of CF lung disease (using spirometric parameter, FEV1), and whether or not it was compounded by chronic *Pseudomonas aeruginosa* (*P. aeruginosa*) and/or *Burkholderia cepacia* complex (*BC*C) airway infections was carried out. In addition, the potential impact of *CFTR* mutation classes was assessed [5]. Our COI study focused on clinical and health economic data from 2010 in order to produce a "baseline" of costs prior to the introduction of CFTR-MT, the reimbursement of which will likely be based on "center-care contracts" between Czech CF centers and major health insurance payers.

Patients and health care costs

Altogether, 330 CF patients from the Prague CF Center, which manages approximately 65 % of the known Czech CF patients, were initially included in the study. Since patient identities were automatically assigned a unique identification number that assures full anonymity, specific informed consent was not required and thus not solicited.

Clinical and laboratory data were drawn from the national CF registry (www.cfregistr.cz) and/or individual patient electronic or archived medical records, in cases where the data registry was incomplete. Health care costs and data about health care utilization were drawn from the University Hospital Motol registry of invoices to major national health insurance companies (www.vzp.cz; www.szpcr.cz).

Young patients ($n = 62$) for whom spirometric parameters were not reliable, i.e., all patients less than 4 years, or non-cooperative children under 6 years of age, or those patients who passed away ($n = 5$) within the data collection period, were excluded. Patients who underwent lung transplantation ($n = 11$) were also omitted due to biased FEV1 values and since costs associated with this intervention are specific [10]. Only ten eligible cases had incomplete health insurance or medical records (see case selection flowchart in the Appendix).

Following the aforementioned selection process, a total of 242 eligible CF cases, with the classic form of the disease, underwent clinical and health economic analyses. These patients were clinically diagnosed using consensus diagnostic criteria [11], and included several patients from a pilot neonatal screening project (CF NBS) [12] and/or the subsequent nationwide CF NBS scheme, which has been in operation since October 2009 (data not shown).

These patients were stratified according to their age (4–6, 7–12, 13–18, 19–24 and older than 24 years), gender,

BMI *z*-score/BMI, chronic airway infection with *P. aeruginosa*, *BC*C, and *CFTR* mutation classes (I–V). The severity of their lung disease was categorized according to FEV1 values ("mild" $\geq$70 %; "moderate" 40 $\geq$ to $<$ 70 % and "severe" $<$40 % of predicted FEV1, respectively). The maximum value of FEV1 in a given year was utilized and referenced as the "percentage predicted" in the healthy Czech children reference population [13] and in CF adults relative to European Respiratory Society standards [14].

Presence of bacterial lung infections was based on regular (every 3 months) microbiological cultures and/or molecular microbiological examinations (with at least four microbiologic examinations per year in all cases) that were categorized as: (1) negative, (2) sporadically positive (single positive test in a given year), (3) intermittent infection (two positive samples in a given year), (4) chronic airway infection (more than two positive samples in a given year), and (5) sporadically positive in the past (single positive test historically, i.e., detected more than 1 year prior), (6) anamnestic infection (intermittent or chronic airway infection historically, i.e., detected more than 1 year prior), with the two latter categories being similar to the commonly applied "*P. aeruginosa/BC*C free" terminology.

In order to minimize selection bias, health care costs reflected a 3-year data collection period (i.e., from January 1, 2009 to December 31, 2011). Furthermore, to achieve the maximum aggregate dataset and to account for missing individual variables from the studied period (e.g., mainly missing health insurance records), we only analyzed the "total dataset," which was referenced towards year 2010 ($n = 233$), complemented with data from 2009 ($n = 6$) and 2011 ($n = 3$). Annual health care costs and clinical data for each patient, in a given year, were analyzed.

Health care costs were considered (i.e., were "clustered") within categories representing: (a) Inpatient Care (IC, reflecting mainly hospitalization costs), (b) Medicinal Products and Devices (MPD; mainly accounting for drug costs), and (c) Procedures (i.e., laboratory examinations, diagnostics, and outpatient care). All costs were in 2010 prices [15] and converted to euros (€) using an average yearly exchange rate for 2010 [16].

Statistical analysis

Means, medians, IQR (interquartile range), standard deviation (SD), and proportion of patients within given categories were calculated. Since the data were not normally distributed, the Kruskal–Wallis test and the Mann–Whitney test (two-tailed) were used to assess statistical significance. Multivariate regression analysis (generalized linear model; GLM) identified the main cost drivers of total costs as well as their subgroups (STATA 13.1 software; StataCorp LP, USA). We chose gamma regression, with a log-link function, because the costs exhibited a gamma distribution and this type of regression analysis is more appropriate for this type of data. Results were considered statistically significant if the p values were less than 0.05.

Results

Patient characteristics and health care costs

CF patient demographics, clinical data, and microbiology status of the analyzed cohort are outlined in Table 1. The average (median) patient age was 16.5 (15.0) years. The average (median) FEV1 was 86.9 % (94.0 %): 76.8 % patients had "mild," 13.6 % "moderate," and 9.5 % "severe" CF lung disease, which was used as a "proxy" for overall CF disease severity. A statistical correlation between patient age and decline of FEV1, using Spearman's rho -0.47 ($p < 0.0001$), was observed. Figure 1 demonstrates that the severity of overall lung disease positively correlates with patient age (in both genders) and that deterioration in overall CF disease status generally accelerates from approximately 18 years onward.

Overall, 17.7 % of patients were underweight, i.e., had BMI z-score less than -1.04 (equaling "bottom 15 %" in children) or BMI less than 18.5 (in adults) [17–19]. A total of 23.6 % of cases had chronic *P. aeruginosa* airway infection (see point 4 in the paragraph regarding infection types in the "Methods" section), while 17.4 % of all patients had *BC*C airway infection (Table 1). CF-related diabetes (CFRD) was present in 17.7 %, and 84.3 % of all cases had pancreatic insufficiency. Two "severe" *CFTR* mutations (classes I–III) were observed in 84.7 %, and 15.3 % of patients had at least one class I–III allele, while the "milder" class IV–V mutations [3] influence the overall disease severity (data available upon request and see Ref. [20]).

Table 2 depicts a detailed costs analysis: the annual total mean (median) costs per patient were €14,486 (€10,934) based on the 2010 euro rate. Mean (median) annual costs in given subgroups for MPD were €10,341 (€9053) (approximately 20 % consist of medical devices), Procedures: €2676 (€960), and IC: €1829 (€0). Interestingly, 80 % (mean €8331) of MPD costs were spent on several relatively costly medicinal products (comprising e.g., antibiotics—*tobramycin, meropenem, piperacillin/tazobactam, linezolid*; antifungal agents—*vorikonazole, caspofungin* and mucolytics—*dornase alfa*; all under their generic names). While most patients had their CF treatment-related costs around the lower monetary values, there were younger outliers whose costs vastly exceeded those of other

Table 1 General description of the study cohort

Variable	Value
Mean age years (median; IQR)	16.51 (15;10–21)
Mean FEV1 (median; IQR)	86.9 (94.0;72.6–106.2)
Age groups	
Age 4–6, *n* (%)	24 (9.9 %)
Age 7–12, *n* (%)	70 (28.9 %)
Age 13–18, *n* (%)	63 (26.0 %)
Age 19–24, *n* (%)	38 (15.7 %)
Age >24, *n* (%)	47 (19.4 %)
CF lung disease severity	
Mild CF (FEV1 ≥70 %), *n* (%)	186 (76.8 %)
Moderate CF (FEV1 ≥40 to <70 %), *n* (%)	33 (13.6 %)
Severe CF (FEV1 <40 %), *n* (%)	23 (9.5 %)
Female, *n* (%)	125 (51.6 %)
CF related diabetes mellitus, *n* (%)	43 (17.7 %)
Pancreatic insufficiency, *n* (%)	204 (84.3 %)
Underweight (children and adults), *n* (%)	43 (17.7 %)
One severe *CFTR* mutation, *n* (%)	37 (15.3 %)
Two severe *CFTR* mutations, *n* (%)	205 (84.7 %)
P. aeruginosa, n (%)	
Negativity	36 (14.8 %)
Sporadic positivity	15 (6.2 %)
Intermittent infection	45 (18.6 %)
Chronic infection	57 (23.6 %)
Sporadic positivity past	56 (23.1 %)
Anamnestic infection	33 (13.6 %)
BCC, *n* (%)	
Negativity	182 (75.2 %)
Sporadic positivity	0 (0 %)
Intermittent infection	3 (1.24 %)
Chronic infection	42 (17.4 %)
Sporadic positivity past	1 (0.41 %)
Anamnestic infection	14 (5.8 %)

n = number of cases (total = 242 patients); FEV1 values = % predicted; IQR, interquartile range (the range between the 25th and 75th percentile) was used to complement median/standard deviation due to the overall skewing of data; underweight = BMI *z*-score <1.04 in children and BMI < 18.5 in adults and *CFTR* mutation severity reflected respective mutation classes (i.e., I–III denoted as "severe"; IV–V denoted as "mild")

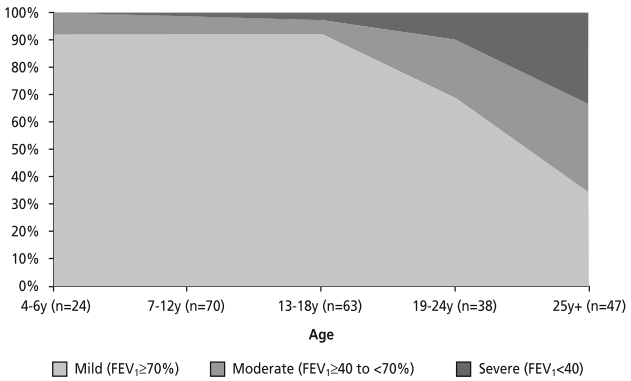

Fig. 1 Distribution of CF lung disease severity with patient age. Lung disease severity was assessed using FEV1 spirometric values (% predicted in children and adults [13, 14]); *y*, years of age; *n*, number of patients in each age category

Table 2 Cost analysis based on standardized COI variables

Variable	Mean	Median	IQR	SD
MPD	10,341	9053	1242–14,932	9561
Procedures	2676	960	637–1524	6378
IC	1829	0	0–221	6264
Total costs	14,846	10,934	2169–18,209	18,439
	Mild CF	Moderate CF	Severe CF	*p*
MPD	10,301 (8458)	9350 (8785)	12,091 (11,807)	0.3857
Procedures	2065 (952)	2684 (863)	7599 (3131)	0.0404
IC	1234 (0)	1875 (0)	6576 (2115)	0.0001
Total	13,601 (9936)	13,910 (10,814)	26,265 (15,015)	0.0693

Mean (median) costs; *SD* standard deviation, *MPD* medicinal products and devices, *IC* inpatient care; general categories Mild CF, Moderate CF, Severe CF refer to the severity of CF lung disease expressed using FEV1 values (% predicted in children and adults [12, 13]); costs are expressed in 2010 euros; statistical differences among the three disease categories were assessed using the Kruskal–Wallis test; IQR, interquartile range (the range between the 25th and 75th percentile) was used to complement median/standard deviation due to the overall skewing of data; and $p = p$ value of statistical significance. We observed strong positive skewing towards zero in all cost groups

patients (ref. Figure A.2 in the Appendix). This table also shows stratified total costs in relation to the overall severity of CF lung disease, based on FEV1 values. As expected, we observed a trend towards increased costs in the more severe cases (see Table 2). The total mean (median) costs of mild, moderate, and severe categories were €13,601 (€9936), €13,910 (€10,814), and €26,265 (€16,015), respectively. However, such an increase of costs was of borderline statistical significance relative to the total costs ($p = 0.0693$). In the case of Procedures, IC respective costs significantly differed among the three disease categories ($p = 0.0404/p < 0.0001$; respectively). In this regard, the higher costs in more severe cases were particularly pronounced for IC. MPD costs were generally comparable among these groups ($p = 0.3857$).

Patients with chronic *P. aeruginosa* airway infection had substantially higher costs than those without *P. aeruginosa* infections, with the average (median) costs being €27,455

Table 3 Regression analyses based on the generalized linear model

Variable	Dependent variable			
	Total costs Reg. 1	IC Reg. 2	Procedures Reg. 3	MPD Reg. 4
FEV1 (%)	−0.017	−0.068	−0.028	−0.009
	(0.003)***	(0.012)***	(0.005)***	(0.003)**
P. aeruginosa	0.830	0.895	0.387	0.864
	(0.165)***	(0.522)	(0.240)	(0.149)***
*BC*C chronic	−0.216	−1.584	−0.546	−0.009
	(0.230)	(0.858)	(0.332)	(0.206)
2 "severe" *CFTR* mutations	0.019	1.128	0.043	−0.020
	(0.191)	(0.658)	(0.280)	(0.169)
Gender (male)	−0.114	−0.004	−0.232	−0.064
	(0.134)	(0.437)	(0.198)	(0.121)
Underweight	−0.019	0.070	0.132	−0.064
	(0.182)	(0.559)	(0.265)	(0.164)
Age	0.074	0.066	0.043	0.075
	(0.031)**	(0.109)	(0.045)	(0.028)**
Age^2	−0.002	−0.003	−0.002	−0.002
	(0.001)***	(0.002)	(0.001)	(0.001)***
Constant	10.369	11.454	9.962	9.328
	(0.427)***	(1.590)***	(0.618)***	(0.395)***
n	242	242	242	242

n = number of cases (total = 242 patients) for all cost categories; IC = inpatient costs; MPD = medicinal products and devices; % = % predicted FEV1 values; *P. aeruginosa*/*BC*C = chronic airway infection caused by these bacterial strains; 2 "severe" mutations = presence of two class I–III *CFTR* mutations in *trans*; underweight = BMI *z*-score <1.04 in children and BMI < 18.5 in adults; Age^2 = age square value; constant = a point where the regression curve begins; ** $p < 0.01$ and *** $p < 0.001$. Results were estimated using the generalized linear model with gamma regression and log-link function; standard errors are indicated in parentheses

The applied regression analysis approach is for a hypothetical 15-year-old female CF patient with FEV_1 = 80 % predicted, without chronic *P. aeruginosa* and/or *BC*C airway infection, who is not underweight and bears 2 severe class I-III *CFTR* mutations in *trans*. The total costs predicted by our regression analysis model were calculated as follows: exp(10.369 + 80*(−0.017) + 15*0.074 + (15^2)*(−0.002)) , which is equal to €15,820; while MPD costs were calculated: exp(9.328 + 80*(−0.009) + 15*0.075 + (15^2)*(−0.002)), which is equal to €10,754

(€21,232) versus €10,962 (€8940) (Mann–Whitney test, $p < 0.0001$). Overall, costs were mostly clustered around the lower monetary values, but increased markedly with decreasing FEV1 (see Figure A.2 in the Appendix with linear association between FEV1 and total costs) [21].

Regression analysis

Table 3 presents the results of four statistical regression models. Since the coefficients are on the log-scale, it is necessary to exponentiate them in order to assure proper study results and interpretation (see Table 3 legend with an example of calculations). Based on previously published approaches [21, 24], our regression analysis utilized only variables that were related to direct costs of CF care and predicted overall patient survival, i.e., variables that determined the overall mortality. In this regard, FEV1 was used as a continuous variable and thus we did not test disease severity using the three aforementioned subgroups.

In terms of total costs of care, overall disease severity, assessed using a "FEV1 continuum," had the most significant impact. For instance, a 10 percentage point (pp) decrease reflected a relative increase (further only an "increase") in costs by approximately 17 %. Chronic *P. aeruginosa* airway infections increased costs by 129 % (i.e. 2.29 times). Correlation of costs with age and age squared (age^2) were also statistically significant. Although negative values of age^2 indicate that the total costs increased with age, the increase leveled off in adulthood and eventually total costs of care started to decline. In other words, the maximum total costs occur at about age 16 years and from then on the overall costs start to drop. Other studied variables (gender, nutritional status, chronic *BC*C airway infections, and severity of *CFTR* mutations) did not significantly influence total costs.

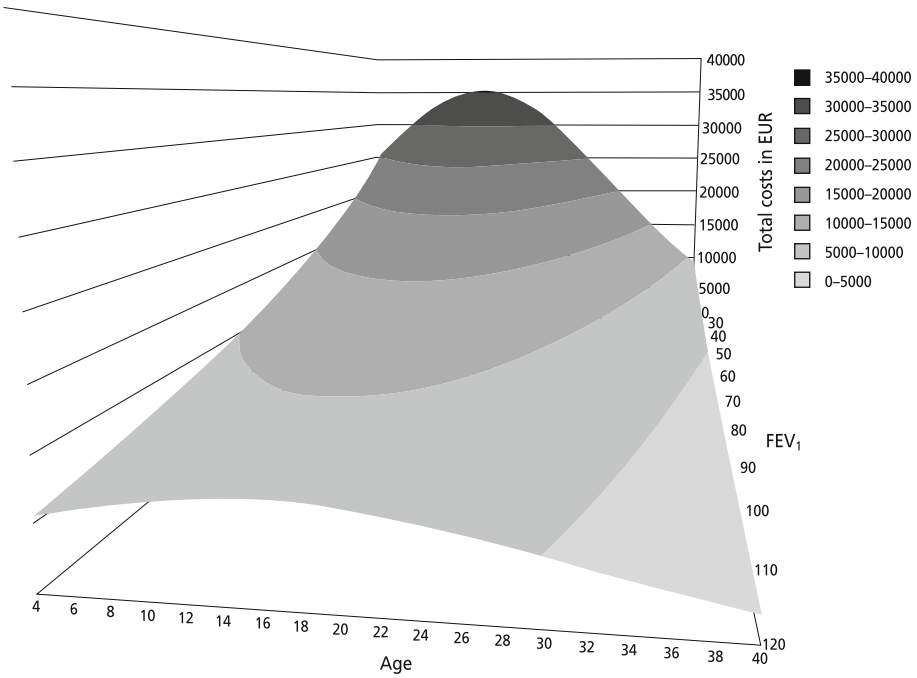

Fig. 2 3D plot of fitted values of total costs with regards to patient age and FEV1 values. *3D plot*, 3-dimensional plot; *total costs* are in euros (2010); FEV1 = % predicted values; *age* is in years

When respective subgroups of health care costs (i.e., IC, MPD and Procedures) were taken into account, the spirometric parameter FEV1 and chronic *P. aeruginosa* airway infection were found to be the main "drivers" of total costs. This observation substantiates the defining role of CF lung disease in this regard. For example, a decrease in FEV1 by 1 pp is equal to an inpatient costs increase of 7.0 %. Therefore, IC (reflecting the rate of patient hospitalizations) was the most "sensitive" of all studied COI categories in terms of their correlation with FEV1 values. Moreover, in patients with chronic *P. aeruginosa* airway infections, IC-related costs increased by 144 % ($p = 0.065$). IC costs also increase with age, but at a proportionally decreasing rate, whilst their maximum peaked at the age of 12 years.

Similarly, costs of MPD were inversely correlated with decreasing FEV1 values. Thus, a 1 pp decrease in FEV1 resulted in a 0.9 % increase in MPD costs. The "strongest" driver of MPD costs was associated with chronic *P. aeruginosa* airway infections, as reflected by a substantial increase in MPD costs, of up to 137 %. MPD costs also correlated significantly with increasing age, with their maximum being at the age of 17 years, followed by their gradual decline throughout adulthood.

Procedures were also positively and statistically significantly correlated to the severity of CF lung disease. For example, a decrease in FEV1 by 1 pp resulted in an increase in costs of 2.8 %. In this regard, it is important to stress that costs of Procedures are not dependent on patient age, since e.g., routine diagnostics in CF are performed in a standardized manner, i.e., according to the ECFS/ERS "standards of care," and thus are standardised and unrelated to patient age [22, 23].

Figure 2 presents fitted values of total costs (based on our regression analyses) in relation to patient age and FEV1 values. In this regard, we fixed other parameter values from the regression results at their median values, i.e., a hypothetical "median patient" had two severe *CFTR* mutations in *trans*, was a female, had normal nutritional status (i.e., was not underweight), and did not have chronic *P. aeruginosa* and/or *BCC* airway infections. Notably, results of regression analyses are based on an extrapolated "median patient" (see Table 1) and do not take into account extreme values in outliers, which may occur in clinical practice (see Figure A.2 in the Appendix). In summary, regression analysis outcomes indicate that not only FEV1 values, but also increasing age (with the maximum "peak" around 16 years of age), represent significant predictors of the total costs of CF care.

Discussion

This is the first CF COI study conducted in the CZ, where the general level of care is comparable to that in other Western European countries [6]. Moreover, this is also the first European CF COI that was conducted outside of Germany or France. The overall number of analyzed CF patients was similar to, or even relatively larger than, previously published COI studies [24, 25]. In comparison to other cost studies in CF, our dataset has the most recent data available [4]. Other studies that utilized regression

modeling are from the years 2004 [24] and 2005 [4]. Obviously, health care patterns have changed substantially since then. Finally, this study utilized datasets from 2010 that reflect the status of care prior to the introduction of CFTR-MT in the CZ.

The Prague CF Center is internationally recognized, since, following external peer review of its diagnostic and clinical standards, it became a partner of the European Cystic Fibrosis Society "Clinical Trials Network" (www.ecfs.eu/ctn). This center has a tertiary status and thus monitors care of patients residing in other parts of the country, all of which substantiates the representativeness of the studied patient cohort and minimizes potential ascertainment/selection bias. Furthermore, the Prague CF Center coordinates care rendered by the consortium of collaborating regional CF centers located in Brno, Hradec Králové, Olomouc, and Pilsen, which are evenly distributed throughout main population centers of the country. This nationwide association of centers was officially established based on the Ministry of Health Bulletin (4/2012), and thus guarantees standardization and harmonization of CF care throughout the country in accordance with the most recent "standards of care" [22].

Our country has uniform health insurance coverage and a social system with marginal regional differences in terms of access to or provision of medical/social care (Institute of Health Information and Statistics; www.uzis.cz). In addition, the incidence of the disease is well established and there are no regional differences [12]. The absolute majority of cases from our study were clinically diagnosed [12], mostly within their first 6 months of life, i.e., prior to the introduction of the nationwide CF NBS scheme [12]. The applied study design further limits potential bias and ensures standardization of the underlying data sets to be analyzed based on the "common denominator" of the clinical diagnosis of CF.

A subsequent confirmatory analysis provided evidence that there are no significant differences for the key cost drivers identified between the Prague CF Centre (covering, in terms of patient referral, mainly western districts of the country) and the Brno CF Centre that predominantly includes its eastern districts, and represents approximately an additional 15 % of all known CF patients in the country (data available upon request). Therefore, health economic findings obtained from this study are representative for the entire CF population of the CZ with approximately 10.5 million inhabitants (2010; www.czso.cz).

Total health care costs as well as costs for each of the standard COI variables (i.e., IC, MPD and Procedures) were mainly influenced by patient age and overall disease severity, generally reflecting the severity of CF lung disease (assessed using FEV1 values) and presence of the chronic *P. aeruginosa* airway infection. Identification of the dominant cost drivers was in accordance with previous CF COI studies [21, 24, 25]. A recently published French COI study [30] also documented similar effects in terms of increasing total costs of care with age (or, as reported by the authors, with "disease duration"). However, costs started to decrease only in those French CF patients in whom "disease duration" exceeded 30 years. However, we would like to note that the study did not provide a regression analysis, which accounts for the effect of age on total costs separately from other influences, and thus the study is not comparable from a methodological point of view. Nonetheless, our adult CF patients could have benefited from improved care during their early childhood [26]; however, this was true only from the early 1990s when state-of-the-art CF treatment started to gradually become available in the CZ. Such "therapeutic deficiency" in early childhood likely had a negative influence on the overall course of CF in these patients [27].

Results of our regression modeling show fairly similar outcomes to the recently published Australian COI study [4]. The authors utilized a comparable, although, not exactly the same approach (i.e., regression modeling with logarithmic transformation). Thus, if we compare a decrease in total costs due to improved FEV1 by 1 pp (our approach) and by 1 % (their approach, since they worked with percentages rather than percentage points of FEV1) our results show a 1.7 % decrease, while their results demonstrated a 1.4 % decrease in associated costs. However, if we take into account the mean FEV1 in our patients (86.9 %), then a 1 % increase in this spirometric parameter (i.e., an 0.869 increase in absolute terms) resulted in a decrease in total costs by approximately 1.5 % (i.e., 0.869×1.7) which is in line with previously published results [4]. Likewise, the increase in total costs due to chronic *P. aeruginosa* infections was 129 % in our study, and 163 % in the aforementioned study [4]. Their results regarding the impact of age on the total costs seem to also exhibit an inverted U-shaped curve, although in their instance the impact of age squared (age^2) was not statistically significant [4]. Such comparisons prove the validity of our methodological approach and the comparable quality of underlying Czech data.

Furthermore, our study also provided evidence that although the absolute magnitude of the costs is inherently different among countries (or rather health care systems), relative changes indicated by respective FEV1 values are analogous. Thus, this observation suggests that relative differences in direct costs of care assessed by using this spirometric parameter are internationally transferable.

More severe CF lung impairment (reflected by lower FEV1 values) and chronic *P. aeruginosa* airway infections not only increased costs, but also negatively influenced the overall quality of life (QoL) and life-expectancy of CF

patients. These features are currently assessed using the European Union Burquol-RD project-developed methodology [21, 23, 24, 30]. The absence of QoL data and inclusion of other costs/losses (i.e., productivity, and informal and formal care, etc.) represent a limitation of our study, and are inherently due to its retrospective design. Inclusion of indirect costs and patient-reported outcomes would have improved our understanding of the overall societal costs and disease burden, including direct assessment of country-specific patient and caregiver perspectives.

The relatively lower overall prevalence of chronic *P. aeruginosa* airway infection at the Prague CF center compared to e.g., UK standards [28, 29] may be due to (a) earlier commencement of antibiotic treatment [18], (b) systematic CF patient separation procedures and/or (c) a generally younger age distribution of Czech patients compared to other COI studies carried out in Germany, Italy and the USA [19, 24, 25]. In accordance with the aforementioned argument regarding the lack of modern therapy prior to 1990, our cohort could be skewed by the absence of older CF patients due to their premature mortality compared to their Western European "peers." Such differences in early CF mortality are currently being observed in other economically less favored, e.g., Eastern European and non-European, patient populations [7]. Nevertheless, the mean (median) age of 16.5 (15) years was similar to that found in studies recently performed in Australia and France [21, 30].

As previously reported by other COI studies, the overall costs of CF care are considerable [21]. The direct costs detected in our study are comparable to those reported in other European CF cohorts [19, 21, 24, 25, 30]. When the different price levels, assessed by the purchasing power parity €/CZK exchange rate (€PPP) [31], are taken into account, the average total costs after PPP adjustment were €PPP 20,518 (vs €14,846) in 2010. The mean costs of given subgroups in PPP euros are equal to €PPP 14,291 (MPD), €PPP 3698 (Procedures) and €PPP 2527 (IC). In addition, the proportion of the cost subgroups were similar for MPD (70 %) in Germany (76 %) [24] or Italy (70 %) [25]. Interestingly, the percentage of particular health care expenses was different in Australia and France where MPD accounts only for approximately 30 and 45 %, respectively [21, 30]. This dissimilarity could be due to different cost ratios, whereby hospitalizations (i.e. IC) and outpatient consultations may be relatively more expensive than pharmacological treatment (i.e. MPD), where usually there are similar pricing policies by respective transnational pharmaceutical companies across different health care markets.

The observed inverted U-shape pattern of costs (Fig. 2) is similar to that presented in Australian studies [4, 21] and could likely be due to a combination of multiple factors. First, the costs are skewed due to a relatively small number of very expensive young CF patients, aged 10–16 years. Thus, the ten most expensive patients had an average cost of €82,378 (Figure A.2 in the Appendix). These outliers had been repeatedly hospitalized for long periods of time and had multiple complications. If data from these cases were disregarded, age still would have remained as a statistically significant predictor for MPD-, but not for IC- and Procedure-related costs, including total costs (data available upon request). Second, pediatric CF care more often utilizes intravenous antibiotic therapy in patients with chronic *P. aeruginosa* airway infections, in addition to inhaled antibiotics. Moreover, *tobramycin* is used more often than *colistin* in children, and some procedures such as high resolution computed tomography chest scans are also more often performed in pediatric than in adult CF care (data not shown). Third, patients may be less compliant during adolescence and thus may have a higher risk of chronic airway infections, including lung disease exacerbations, which are both rather costly. Lastly, there are generally slightly higher health insurance reimbursement rates for hospitalization of minors (i.e., including CF) in CZ, hence proportionally higher IC costs compared to adult care.

With the introduction of CFTR-MT, MPD costs would likely become more pronounced [3]. On the other hand, utilization of OMP will be consequently accompanied by generally higher QoL and longer life-expectancies [3]. Usually, the higher costs of such "stratified" care are generally compensated by lower IC and "standard therapy-related" MPD costs due to e.g., less frequent lung disease exacerbations [32]. Increased costs in terms of MPD in OMP could be offset by lower social service expenditures [3]. Moreover, given the effectiveness of some OMP in CF there are improved prospects of adults in terms of their active participation within the job market. Thus, there is reasonable expectation in terms of their positive financial contribution to the mandatory health insurance coverage in CZ.

Conclusions

Our results, which are in accordance with the outcomes of other previously published COI CF studies, indicate that CF is a relatively costly disease: one in which treatment-related costs generally increase with age. These results have application not only for the Czech Health Care System but also for socio-economically similar Central and Eastern European countries with comparable health care systems (e.g., Croatia, Hungary, Slovakia, Slovenia, etc.).

Our results also provide valuable information on the overall level of economic burden associated with CF. We

observed that the major cost drivers in terms of total health care costs and also for each of the COI variables (IC, MPD, and Procedures) were positively associated with patient age and overall disease severity, which was generally reflected by the severity of CF lung disease (substantiated by FEV1 values) and potentially compounded by chronic *P. aeruginosa* airway infections. The majority of MPD costs were associated with antibiotics, antifungal agents, and mucolytics. Due to the retrospective nature of our study, indirect costs, QoL parameters, and patient reported outcomes could not be assessed. COI analyses and regression modeling are crucial for the better understanding of the overall burden of CF. Consequently, they facilitate the assessments of new health technologies and interventions, such as CFTR-MT.

Although comparisons of our results with other analogous studies showed that overall costs may differ among different health care systems, the values of FEV1 could be generally transferable. Therefore, this spirometric parameter may serve as an "indicator" of the relative economic impact of the quality of medical care in CF.

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