ORIGINAL ARTICLE

UDC: 1616.24
https://doi.org/10.2298/VSP171114005G

Pulmonary exacerbations as a risk factor for lung function decline – experiences of the National Cystic Fibrosis Center

Egzacerbacije plućne bolesti kao faktor rizika od sniženja funkcije pluća – iskustva Nacionalnog centra za cističnu fibrozu

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Abstract

Background/Aim. Pulmonary exacerbations have negative impact on clinical course of cystic fibrosis (CF) lung disease being associated with a steeper decline in the lung function, unfavorable prognosis and impaired quality of life. The aim of this study was to determine whether an increased number of exacerbations had influence on the lung function in the patients with CF, as well as to estimate the nutritional status, gender, presence of comorbid conditions and bacterial colonization of airways as predictive factors for pulmonary exacerbations. **Methods.** This retrospective cohort study included 83 pediatric and adult patients, treated from 2011–2015 in the Mother and Child Health Institute of Serbia „Dr Vukan Čupić". The best result of forced expiratory volume in the first second (FEV1) and forced vital capacity (FVC) in each year of follow-up was taken into account to calculate the five-year trend values of these indicators. The number of exacerbations per year of follow-up and its impact on the FEV1 decline was evaluated. **Results.** Mean annual decline of FEV_1 and FVC were 2.4% and 1.7% respectively. The malnourished patients had the lower initial values of FEV_1 and FVC, and more frequent exacerbations in comparison with the normal weight and overweight patients. The frequency of exacerbations was significantly higher in the patients chronically colonized with *Burkholderia cepacia* ($p = 0.023$). The increased number of exacerbation was proved to be the most important factor in a prediction of FEV_1 decline over time ($p = 0.013$). **Conclusion.** Pulmonary exacerbations lead to the more progressive lung function decline in the patients with CF. Malnourishment and chronic airway colonization with *Burkholderia cepacia* result in more frequent pulmonary exacerbations.

Key words:
burkholderia cepacia; cystic fibrosis; forced expiratory volume; lung diseases; recurrence; respiratory function tests.

Apstrakt

Uvod/Cilj. Egzacerbacije plućne bolesti imaju negativan uticaj na klinički tok cistične fibroze (CF), a njihova veća učestalost povezuje se sa izraženijim sniženjem vrednosti funkcije pluća i lošijim kvalitetom života. Cilj ovog istraživanja bio je da se utvrdi uticaj broja egzacerbacija na trend funkcije pluća kod obolelih od CF, kao i značaj stanja uhranjenosti i pola ispitanika, komorbidnih stanja i kolonizacije disajnih puteva patogenim bakterijama na trend funkcije pluća i učestalost egzacerbacija plućne bolesti. **Metode.** Istraživanjem su obuhvaćena 83 ispitanika, deca i odrasle osobe, obolela od CF, lečena u periodu od 2011. do 2015. godine u Institutu za zdravstvenu zaštitu majke i deteta Srbije „Dr Vukan Čupić". Najbolji rezultat forsiranog ekspirijumskog volumena u prvoj sekundi (FEV_1) i forsiranog vitalnog kapaciteta (FVC) svake godine praćenja uziman je u obzir pri računanju petogodišnjeg trenda vrednosti ovih pokazatelja. Procenjivan je broj egzacerbacija po godini praćenja i ukupan broj na kraju perioda praćenja. **Rezultati.** Prosečno smanjenje vrednosti FEV_1 bilo je 2,4%, a FVC 1,7% godišnje. Neuhranjeni ispitanici su imali niže vrednosti FEV_1 i FVC i veći broj egzacerbacija u odnosu na normalno i prekomerno uhranjene ($p = 0,001$). Učestalost egzacerbacija je bila statistički značajno viša kod ispitanika hronično kolonizovanih bakterijom *Burkholderia cepacia* ($p = 0,023$). Povećanje broja egzacerbacija bilo je statistički najznačajniji prediktivni činilac pogoršanja FEV_1 u posmatranom periodu ($p = 0,013$). **Zaključak.** Veća učestalost egzacerbacija plućne bolesti kod obolelih od CF dovodi do izraženijeg

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smanjenja vrednosti parametara funkcije pluća. Niže vrednosti funkcije pluća imaju neuhranjeni bolesnici i bolesnici kolonizovani bakterijom *Burkholderia cepacia* čije prisustvo dovodi do češćih egzacerbacija plućne bolesti.

Ključne reči:
burkholderia cepacia; cistična fibroza; ekspiratorni volumen, forsirani; pluća, bolesti; recidiv; respiratorna funkcija, testovi.

Introduction

Cystic fibrosis (CF) is the most frequent autosomal recessive disease in the Caucasians. In its typical form, CF is manifested by failure to thrive, repeated lung infections and impaired mucus clearance which leads to suppurative lung disease, characterized by a decline in the lung function during a lifetime, which gradually progresses to respiratory insufficiency [1]. Recent data show that the mean life expectancy in the USA is 40 years and in Serbia is around 30 years [2]. Many factors contributed to a significant life prolongation and improvements of quality of life. Among these factors, the major influence have an early diagnosis, especially by introduction of neonatal screening programmes, hypercaloric diet and efficient treatment of pulmonary exacerbations (PE) [3].

A clinical stage of the disease can be expressed by several indicators (biomarkers) whose standardization enables an objective assessment of a patient's condition and final outcome. The most commonly used biomarker is the value of the forced expiratory volume in the first second (FEV_1), which is influenced by the frequency and course of PE [4]. Although there is no widely used standardized definition of PE, the ideal definition should cover the objective clinical, biochemical and physiological factors. In clinical research settings, the hospitalization and intravenous use of antibiotics are listed as the undeniable indicators [5]. PE is characterized by the increased cough and sputum production, haemoptysis, fever, loss of appetite and weight loss, dyspnea, tachypnea, exercise intolerance and sinus discharge [6]. It was shown that more frequent exacerbations led to a steeper lung function decline, poorer quality of life and earlier fatal outcome [4, 7].

In the patients with CF, in an ideal clinical course, the annual decrease of FEV_1 is about 2% [8]. In a majority of patients, PE is associated with a significant reduction in lung function, with gradual, but often not complete recovery thereafter. In 25% of cases, the lung function decline persists, despite the aggressive systemic antimicrobial therapy [7].

A favorable clinical response to the treatment is FEV_1 recovery to ≥ 90% of the baseline value [9]. Certain risk factors can contribute to an unfavorable outcome and partial recovery besides initially lower lung function. These risk factors are: female gender, impaired glucose tolerance, chronic colonization of respiratory tract with specific bacterial pathogens [e.g. *Pseudomonas aeruginosa* (*P. aeruginosa*) or *Burkholderia cepacea* (*B. cepacia*) and initially lower FEV_1 values [9]. Despite the novel treatment modalities, the incidence of PE did not significantly decreased in the last two decades [8].

The aim of the study was to determine if an increased number of exacerbations during the five-years period had influence on the lung function in our cohort of patients with CF. Additionally, we evaluated if the nutritional status, presence of comorbid conditions and bacterial colonization of airways affect the lung function decline and if they can be used as the predictive factors for PE.

Methods

This retrospective cohort study included 110 pediatric and adult patients. All patients were treated at the national CF center – Mother and Child Health Institute of Serbia "Dr Vukan Čupić". The demographic data, current therapy, bacterial colonization of lower airways and lung function results were obtained from the European CF registry and patient's medical history files. The patients performed the regular physical therapy on daily basis during the study. The best annual values of FEV_1 and forced vital capacity (FVC) were taken into account in calculating the five-year trend value of these indicators. The number of exacerbations per year and the total number at the end of the monitoring period were evaluated for each patient. Nutritional status was estimated according to the Z score of body mass index (BMI). The patients were stratified into three groups: (underweight – BMI < 18.5 [or ≤ 1 standard deviation (SD)] kg/m^2 normal weight – BMI 18.5-24.9 (-1–+1 SD) and overweight – BMI > 24.9 (or ≥ 1 SD) kg/m^2.

The descriptive statistics, including mean and standard deviation of numerical variables, and frequencies and percentages of categorical variables were used to characterize the study sample. Differences between groups regarding the numerical variables were analyzed by use of the Kruskal-Wallis test, while the Fisher exact test or the Pearson's χ^2 test were used for the categorical variables. The linear regression models were used to assess relationship between the number of exacerbations, or changes of FEV1, as the dependent variables and the independent variables. The R environment for statistical computing (R Core Team, 2016) was used to conduct the statistical analyses. A significance level (alpha level) was set at 0.05.

Results

Data of 83 patients out of the 110 screened ones were included in the analysis. Others (27 patients) were excluded from the analysis due to the incomplete medical records. The average age of patients at the beginning of the follow-up period was 17.1 ± 7.1 years, and the average age at the time of diagnosis was 3.7 ± 4.3 years, with similar sex distribution. A majority of study participants had normal weight, with the average Z score of BMI of -0.97 ± 1.4 SD.

During the five year of follow-up, the subjects had an average of 0.6 exacerbations annually. Other demographic data are shown in Table 1.

Table 1
Demographic data of patients with cystic fibrosis

Variable	Value
Gender, n (%)	
male	42 (51)
female	41 (49)
Age (years), mean ± SD	17.1 ± 7.1
Age at diagnosis (years), mean ± SD	3.7 ± 4.3
BMI (kg/m^2), mean ± SD	18.1 ± 3.5
Z score BMI, mean ± SD	-0.97 ± 1.4
Colonization with *Pseudomonas aeruginosa*, n (%)	53 (62)
Colonization with *Burkholderia cepacia*, n (%)	10 (12)
Diabetes, n (%)	12 (14)
Asthma, n (%)	23 (27)
Liver disease, n (%)	17 (20)

n – number of patients; BMI – body mass index; SD – standard deviation.

The average decrease of FEV_1 in the five-year period was 11.9% ± 14.5%, and annual decrease was 2.4% ± 2.9%. The average decrease of FVC was 8.6% ± 1.8%, and 1.7% ± 3.6% respectively. The annual decrease of FEV_1 and FVC was not different in regard to the patient's sex ($p = 0.2$ and $p = 0.7$, respectively).

The underweight patients had the significantly lower values of FEV_1 in comparison with the normal and overweight patients ($p = 0.001$). Similar difference was shown between the groups according to the FVC values ($p < 0.001$).

Furthermore, in the underweight subjects, exacerbations were more frequent over five years of follow-up compared to other two groups ($p = 0.02$) (Table 2).

It was shown that exacerbations were more frequent in the patients chronically colonized with *B. cepacia* (0.8 average annual exacerbations) than in those colonized with *P. aeruginosa*, or other pathogens ($p = 0.023$).

The presence of diabetes mellitus ($p = 0.796$) and regular use of recombinant DNase ($p = 0.282$) and hypertonic saline ($p = 0.791$), were not proven to be the risk factors for PE.

The univariant analysis with the number of exacerbations as the dependent variable showed that the presence of *B. cepacia* in the underweight patients significantly increased the number of exacerbations ($p = 0.018$) (Table 3).

Table 3
Regression models for the underweight patients with the number of exacerbations as a dependent variable

Variable	B	*p*
Burkholderia cepacia	0.90	0.018*
Pseudomonas aeruginosa	0.33	0.20
Diabetes mellitus	0.11	0.33
Hepatic cirrluosis	0.01	0.96

*** – statistically significant.**

The univariate linear regression had shown that the number of exacerbations ($p = 0.002$) and the BMI Z-score ($p = 0.028$) were the statistically significant predictors for FEV_1 decline in five years of follow-up ($dFEV_1$). Both variables were entered into the multiple regression model with $dFEV_1$ as the dependent variable. This analysis showed that there was a statistically significant association between the number of exacerbations and $dFEV_1$. With an increase in the number of exacerbations, there was a tendency for greater deterioration of FEV_1 in the observed period ($p = 0.013$) (Table 4).

Table 2
The lung function and frequency of exacerbations in the patients with cystic fibrosis according to the nutritional status

Parameter	Underweight (n = 40)	Normal weight (n = 38)	Overweight (n = 4)	*p*
FEV_1 (%), mean ± SD	64.0 ± 24.4	83.7 ± 24.4	91.5 ± 17.2	0.001
FVC (%), mean ± SD	71.2 ± 20	90.3 ± 19	98.3 ± 12.5	< 0.001
Average annual number of exacerbations during the study	0.8	0.5	0.0	0.02

FEV_1 – forced expiratory volume in the first second; FVC – forced vital capacity; SD – standard deviation; *p* – value for statistical significance defined as $p < 0.05$.

Table 4
Regression models with dFEV1 as a dependent variable

Variable	Univariate regression models		Multiple regression models	
	B	*p*	B	*p*
Age at diagnosis	-0.21	0.587		
Initial FEV_1% value	0.02	0.796		
Number of exacerbations	-7.22	0.002*	-6.10	0.013*
Z score BMI	2.75	0.028*	1.77	0.158
Asthma	5.26	0.145		

FEV_1 – forced expiratory volume in the first second; $dFEV_1$–FEV_1 – decline in the five-years follow-up; BMI – body mass index.
*** – statistically significant.**

Discussion

Exacerbations of lung disease are significant factor of morbidity that affects decline in the lung function in the patients with CF. We showed that the most significant risk factor for the exacerbation occurrence in our cohort of patients was chronic airway colonization with *B. cepacia*.

The natural course of CF lung disease is characterized by a gradual deterioration with the intermittent episodes of acute endobronchial infection [10]. The lung function mostly has steeper decline in the female patients from adolescence, which was not the case in our study. Exacerbations of pulmonary disease present a major burden for the patients and their families with a negative affection on quality of life. Due to inexistence of dedicated home care providers, all patients in Serbia are hospitalized for the intravenous antibiotic therapy and intensive physical rehabilitation. The burden is even more significant for the health system, as antimicrobial therapy in hospital significantly increases medical expenses [8]. In a large observational study, which involved more than 11,000 patients, 42% of patients had exacerbation during a six-months follow-up [11]. In the etiology of exacerbation, the respiratory viruses play an important role by reactivation of chronic bacterial infection in the lower respiratory tract with common CF pathogens such as *P. aeruginosa* or *Staphylococcus aureus*, which lead to prolongation of hospital stay [6, 12].

Despite the high prevalence of chronic *Pseudomonas* colonization in our cohort (62%), it was not shown to be a significant predictor of appearance of PE. The patients with the higher exacerbation score and shorter interval between it, had a greater overall FEV_1 decline [4]. Our research in the relatively heterogeneous CF population confirmed that the increased number of exacerbations correlated with a more significant loss of lung function. The annual FEV_1 decline in our cohort was 2.4%, which was significantly higher compared to the results of other studies (1.8%–2%) [8, 11]. Although the treatment of patients with CF in our country is mostly performed without delay in a specialized center according to the international guidelines, there are several reasons which may explain this negative trend.

The most likely reasonses are malnutrition and a high prevalence of chronic *Burkholderia* colonization, which is in accordance with previous studies [13, 14]. Colonization with *B. cepacia* is associated with higher mortality and morbidity, including more frequent exacerbations, weight loss and rapid lung function decline [15, 16]. The patients colonized with *B. cepacia* in our cohort had the higher exacerbation score. Association of chronic *B. cepacia* colonization with malnutrition, leads to even more frequent exacerbations compared to the patients with normal weight.

The results of large cohort study showed that the nutritional status and pulmonary function are the dependent variables in CF, which is in concordance with our results [17]. More frequent PE and steeper decline in the lung function in the malnourished patients is directly related to the poorer prognosis and unfavorable outcome.

Conclusion

Pulmonary exacerbations lead to a progressive lung function decline in the patients with CF over time. Malnourishment and chronic airway colonization with *B. cepacia* result in more frequent PE.

The objective assessment of the symptoms and signs of PE allows vigorous antimicrobial therapy. This usually leads to a favorable clinical course with preservation of the lung function, which is an important indicator of respiratory health in the patients with CF.

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Received on October 14, 2017.
Accepted on January 15, 2018.
Online First January, 2018.