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The influence of pulmonary rehabilitation on the exacerbations of chronic obstructive pulmonary disease in Serbia

Утицај респираторне рехабилитације на појаву егзацербација хроничне опструктивне болести плућа у Србији

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SUMMARY

Introduction/Objective The chronic obstructive pulmonary disease (COPD) exacerbations have a major impact on outcomes of COPD patients. Pulmonary rehabilitation (PR) interrupts the vicious circle caused by exacerbations. It has not yet been widely implemented as standard of COPD treatment. The aim of study was to examine the effectiveness of PR in prevention of exacerbations.

Method The prospective observation study included stable COPD patients between Jan. 2015–Dec 2018. The effects of PR on exacerbation rates were evaluated using univariate and multivariate logistic regression analysis, taking into account age, comorbidity, vaccination status (against seasonal flu), body mass index (BMI).

Results Study included 1,674 patients (956 males, age 65.93 ± 8.45, current or ex-smokers 94.9 %; 21≥BMI 1406 patients, 84 %, Fev1<80% 1448 patients, 86.5%). The PR rate was 48.1%. There was significant difference in PR status with respect to age (p=0.020), comorbidities (p = 0.015), FEV_1 (p<0.001), respiratory symptoms using CAT score (p<0.001), vaccination against seasonal flu (p < 0.001). Exacerbations occurred more frequently in non-PR patients (415 (51.6%) *vs*. 641 (73.7%), p < 0.001). In multivariate analysis, pulmonary rehabilitation (RR 0.421; 95% CI (0.307–0.577); p < 0.001) and BMI ≥ 21kg/m2 (RR 0.605; 95% CI (0.380–0.965); p = 0.035) were independent protective factors and CAT score > 10 (RR 2.375; 95% CI (1.720–3.280); p < 0.001) and FEV1< 80% (RR 2.021; 95% CI (1.303–3.134); p = 0.002) were independent risk factors from exacerbations.

Conclusion Patients who successfully completed PR treatment had significantly less frequent exacerbations compared to patients that not pass through PR program.

Keywords: AECOPD; COPD; CAT score; pulmonary rehabilitation

САЖЕТАК

Увод/циљ Егзацербације хроничне опструктивне болести плућа (ХОБП) имају велики утицај на ток болести. Плућна рехабилитација (ПР) прекида зачарани круг услед понављаних егзацербација. Међутим, ПР још увек није широко заживела као стандардни део терапије. Циљ рада је био да се утврди ефективност ПР у превенцији егзацербација.

Метод Проспективна опсервациона студија је укључила стабилне ХОБП пацијенте (јануар 2015 – децембар 2018) у Поликлиничкој служби Института за плућне болести Војводине, Сремска Каменица. Повезаност ПР и ХОБП егзацербација, као и старости, индекс телесне масе (БМИ), коморбидитета, вакцинације против сезонског грипа, испитивана је у униваријантној и мултиваријантној логистичкој регресионој анализи.

Резултати Студија је обухватила 1.674 пацијената (956 мушкараца, старости 65,93 ± 8,45, пушачи и бивши пушачи 94,9 %; 21 ≥ БМИ 1.406 пацијената, 84%; *Fev1* < 80% 1.448 пацијента, 86,5%).Утврђена је значајна разлика у ПР статусу у односу на старост (p = 0,020), коморбидитете (p = 0,015), FEV_1 (p < 0.001), респираторне симптоме – *CAT* упитник (p < 0,001), вакцинацију (p < 0,001). Егзацербације су се чешће јављале код пацијената који нису били на ПР (415 (51,6%) *vs*. 641 (73,7%), p < 0,001). У мултиваријантној анализи, независни протективни предиктори појаве егзацербације били су плућна рехабилитација (*RR* 0,421; 95% *CI* (0,307–0,577); p < 0,001) і БМИ ≥ 21kg/m^2(*RR* 0,605; 95% *CI* (0,380–0,965); p = 0,035). Независни фактори ризика за појаву егзацербација су били *CAT* > 10 (*RR* 2,375; 95% *CI* (1,720–3,280); p < 0,001) і *FEV1*< 80% (*RR* 2,021; 95% *CI* (1,303–3,134); p = 0,002).

Закључак Пацијенти који су успешно завршили ПР имали су значајно мање егзацербација у поређењу са пацијентима који нису били на ПР.

Кључне речи: *AECOPD*, *COPD*, *CAT* скор, плућна рехабилитација

INTRODUCTION

The acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are a challenge for all physicians. After exacerbation, patient is at increased risk of re-exacerbation and hospitalization [1, 2]. Since

there is no solid evidence that any intervention decreases COPD mortality, treatment of COPD has two goals. First is the control of symptoms, second is reduction and prevention of COPD exacerbations [3].

The main non-pharmacologic COPD therapy is the pulmonary rehabilitation (PR). PR reduces dyspnea and fatigue and improves psychological status of patients. It is evidence-based program that helps improve the well-being of patients. There are many national to worldwide guidelines (Global Initiative for Chronic Obstructive Lung Disease, GOLD; American Thoracic society, ATS; European respiratory society, ERS) which recommend PR for COPD (Evidence Level A) [4, 5, 6].

The PR is one of the most cost-effective therapies for COPD. Despite this fact and the recommendations of the international and national guidelines, PR has not yet become well-recognized standard of care of COPD and also because a lack of medical staff specifically qualified in PR (physiotherapist, pulmonologist) in Europe [7, 8]. In addition, many of the patients had denied to take the PR programs.

The PR effects among COPD patients have been demonstrated in most of the studies coming from highly-developed countries as opposed to low- or middle-income countries where there has not been much research regarding this issue. Among these countries is Serbia, where there has been no research on the effects of PR on COPD exacerbations, since 2007 [9]. This problem continues to be a great burden because of great health budget outlays from society as well as the patients themselves. This study has arisen from the need for continued education in COPD patients and the medical community regarding PR.

The aim of this study was to examine the frequency and effectiveness of the pulmonary rehabilitation among COPD patients in Serbia. Also, we examined the influence of patient related factors and PR on reducing COPD exacerbations.

METHODS

Prospective cohort study was conducted over four years and it included consecutive ambulatory patients with COPD (January 2015 – December 2018), at the Polyclinic department of the Institute for Pulmonary Diseases of Vojvodina (IPDV) in Sremska Kamenica, Serbia. We collected basic demographics data and medical histories of the patients with an established COPD diagnosis. The criteria for being included in the study were: patient age over 40, COPD diagnosis (based on a post-bronchodilator FEV1/FVC ratio of < 0.70) (3) of at least one year.

The patients were divided into two groups according to pulmonary rehabilitation status and followed for one-year study period. The demographic data included sex, age, smoking habits (packs per year), and body

mass index (BMI). Pulmonary rehabilitation (PR) was conducted at Polyclinic department at IPDV. Status of PR, COPD assessment test (CAT), spirometry test (forced expiratory volume in first second, FEV1), 6-minute walking distance (6MWD), comorbidity and vaccination against seasonal flu were obtained from the patient files and medical history at IPDV, but also as given by the patient. Exclusion criteria were active tuberculosis, cancer, unstable cardiovascular diseases, neuro disorder, musculoskeletal disorder, who passed away or didn't finish the PR course.

Every outpatient had the PR course according to the ATS-ERS statement and recommendations [5]. The course was 3-week from one to three times per year. The 60 min exercise session was conducted every day, consisted of aerobic and muscle strength training for upper and lower extremities [10]. The patients were also advised to exercise at least twice a week on their own rather finishing PR program. Physiotherapists were previously instructed to homogenize the type and duration of all activities.

The study encompassed a once-per-year monitoring of each patient. The major outcomes were moderate and/or severe exacerbations during the one year follow up. Moderate exacerbation requires treatment with systemic corticosteroids or antibiotics; severe requires hospitalization or evaluation in the emergency department [11].

All research procedures and patients were in accordance with the ethics standards of the institute where the research took place and in accordance with good clinical practices and declarations of the Helsinki committee and its later amendments or comparable ethical standards. The research was approved by the IPDV Ethics committee.

Descriptive statistics were generated for all study variables, including mean and standard deviation (SD) for continuous variables and relative frequencies for categorical variables. The chi-squared test was used to determine whether there is a significant difference between the expected frequencies and the observed frequencies in one or more categories. The predictive values of evaluated variables for COPD exacerbations were evaluated with univariate and multivariate logistic regression analysis. All univariate statistically significant predictors were included in multivariate logistic regression analysis. All probability values were calculated by assuming a 2-tailed α value of 0.05 with confidence intervals at the 95% level. All statistical analyses were performed with SPSS for Windows version 17 (SPSS Inc., Chicago, IL, USA).

RESULTS

The study included 1,674 patients (956 males, aged 65.93 ± 8.45, current or ex-smokers 94.9 %, packs-years 44.31 ± 25.09). The average duration of COPD was 7.54 ± 5.32 years (range 1–38 years). The average BMI was 27.24 ±4.89 (range 16.8–41.3), 268 patients had BMI below 21 (16%). Most of the patients, according to Fev1, were in stages from 2–4 (1448, 86.5%), every second was stage 2, every third in stage 3 (Table 1).

A total of 804 patients (48.1%) completed PR course, minimum one per year (Table 2). Thirty-three (4.1%) patients dropped out the PR due to comorbidities (heart failure, locomotor disability); 14 patients passed away in both group (seven in both groups, PR and non-PR); five due to severe exacerbation with respiratory failure, one due to pneumonia, four due to heart failure, five at home.

There were 1,473 patients with comorbidities; the most frequent were arterial hypertension (n = 1241; 74.1%), ischemic heart disease (n = 432, 25.8%), diabetes mellitus (n=357; 21.3%) and arrhythmia (n=363, 19.2 %). One comorbidity was present in 596 patients (35.6%), two in 474 (28.3%) and three or more in 366 (21.8%). There were 238 (14.3%) were without comorbidities (Table 2).

Patients aged under 65 years (420 (52.2%) *vs*. 384 (47.8 %); p = 0.020), those with comorbidities (721 (50.2%) *vs*. 715 (49.8 %); p = 0.015), patients with FEV1 > 80% (144 (63.7%) *vs*. 82 (36.3 %); p < 0.001), patients with CAT < 10 (344 (51.3 *vs*. 332 (48.7%); p<0.001), those vaccinated against seasonal flu (301 (57.6%) vs. 222 (42.4%); p<0.001) and those walked less than 350m on 6MWD (210 (66.2%) vs. 108 (33.8%); p=0.035) were more often treated with pulmonary rehabilitation (Table 2). There was no statistically significant difference in the frequency of PR implementation according to sex, smoking status, BMI categories, number of previous exacerbation sand number of comorbidities.

1,402 patients (83.7%) had COPD exacerbations during the previous year (prior to entering the study). During one year of monitoring, 1,056 patients (63,08%) had exacerbations. Exacerbations more frequently occurred in patients who were not treated with PR compared to those who undergone PR (641 (73.7%) *vs*. 415 (51.6%), p < 0.001). Patients who pass the PR program had less frequent COPD exacerbations among all analyzed categories of age, presence of comorbidities, categories of BMI, immunization against seasonal flu, and results of 6MWD test (p < 0.01) (Table 2).

In univariate analysis, significant protective factors against exacerbations were pulmonary rehabilitation, BMI ≥ 21kg/m2 and vaccination, while significant risk factors were smoking, number of previous exacerbations > 2, CAT score > 10 and FEV1< 80%. In multivariate analysis, pulmonary rehabilitation and BMI ≥21kg/m2 were independent

protective factors and CAT score > 10, FEV1< 80% and number of previous exacerbations > 2 were independent risk factors from exacerbations, while vaccination (p = 0.086) were not (Table 3).

DISCUSSION

The results of this study demonstrated that COPD patients receiving PR experienced significant reduction in COPD exacerbations compared to non-PR patients during one year follow up. The observed effects were more pronounced in patients with comorbidities, low BMI, CAT ≥ 10 and vaccination against seasonal flu.

A Cochrane meta-analysis by Puhan [12] has shown the results of 20 studies regarding the efficacy of the pulmonary rehabilitation in reducing the acute exacerbation of chronic obstructive pulmonary disease (AECOPD). In our study, the effects on AECOPD were comparable to other studies. Schuler et al. [13] noted on 383 COPD patients decreased number of exacerbations (moderate and severe) one year after PR. Katajisto et al. [14] showed the decreasing of hospitalization due to exacerbation after PR, but the study was limited by small number of patients. Seymour et al. [15] analyzed 60 patients, the proportion of patients that experienced an exacerbation in previous period resulting in an unplanned hospital attendance was 57% in the non-PR group and 27% in those receiving PR. Meta-analysis from Moore [16] showed that results from randomized controlled trials (RCT) suggest PR reduces AECOPD rehospitalization but results from the cohort studies did not. This was probably caused by varying standard of PR programs and the heterogeneous groups of COPD patients.

Compared to our study, Hassan et al. [17] demonstrated similar results in number of comorbidities (85 %). Crisafulli et al. [18] showed that every second patient, from 2962 patients, had at least one comorbidity, in our study, it was 35.6%. Two years later, 2010, he demonstrated reducing AECOPD among moderate and severe COPD patients with comorbidities (316 patients) after completed outpatient exercise training program, which we confirmed [19]. Franssen and Rochester had similar results in 2014 [20]. Carreiro et al. [21] showed there is no association between the number of comorbidities and PR outcomes, a finding that we also observed.

There is a great variety of duration PR programs worldwide, from 3–9 weeks [4, 5, 22], Crisafulli et al. [19] used a 3-week PR duration per course just like our study. Houchen-Wolloff et al. [23] had the similar number of patients (823, 54.3 %) who completed PR from 1515. In many highly developed countries (UK, Canada, Sweden) only 0.4–1.2% of all COPD patients have access to PR. [24, 25, 26] But also, many of the patients denied to take the PR programs. IPDV started with outpatient PR courses in 2014. Our study showed that younger patients (< 65), patients without respiratory symptoms and better FEV1 above 80 % are active and

are more likely to accept PR programs in order to improve their health status and avoid the sick leave. Similarly, patients with comorbidities and vaccinated against seasonal flu are more familiar with the problems that carry exacerbations and are more likely to accept interventions that reduce the risk, as Ilic showed [27]. Mihaltan et al. [28] recently showed that physical activity levels were low in his study with 2,190 patients (multinational COPD cohort, in which was Serbia). Our patients, who are less mobile (under 350 m of 6MWD), probably wanted to improve their strength and daily activities with PR as in Garrod study [29]. After PR program, there were a significant improvement in reduction of AECOPD among both younger and older, BMI < 21 and ≥ 21, CAT < 10 and ≥ 10, patient who had < 350 m and ≥ 350 m of 6MWD.

This study has some limitations. First not all COPD patients were referred for PR but unfortunately some specialist did not explain the true value of pulmonary rehabilitation or did not say anything to their patients. In addition, many physicians, on the primary health level, did not know about PR program for COPD. Second limitation is related to observational study design. As this was not a randomized controlled trial the baseline group were unbalanced. Nevertheless the PR turned to be significant negative predictor of exacerbations when adjusted for confounding factors. Third, there were probably varying criteria for hospitalization or observation in emergency room at health institutions. Despite these limitations, to our knowledge, this is a first longitudinal study investigating PR effects in exacerbations of COPD in this region (southeast Europe – west Balkans). We believe our study is important as it underlines that in resource-limited settings there is a great area for improvement in COPD care using low cost interventions such as pulmonary rehabilitation.

CONCLUSION

Patients who successfully completed the PR treatment had significantly less frequent COPD exacerbations compared to patients that not pass through PR program. Multivariable analyses confirmed that CAT score > 10, FEV1< 80% and number of previous exacerbations > 2 were independent risk factors, while pulmonary rehabilitation program and BMI ≥ 21 were independent protective factors from COPD exacerbations. From the aforementioned, the study demonstrates that there is a great need for consistent information and education of all COPD patients and physicians with emphasis on prevention of exacerbation and progression of disease.

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Table 1. Patient characteristics, pulmonary rehabilitation, and AECOPD

Characteristics	N (%)	Pulmonary rehabilitation		p
		Yes (804)	No (870)	
Male	956 (57.1)	443 (46.6)	513 (53.4)	0.268
Female	718 (42.9)	360 (50.2)	358 (49.8)	
Age < 65	804 (48.1)	420 (52.2)	384 (47.8)	0.020
Age ≥ 65	870 (51.9)	384 (44.1)	486 (55.9)	
Non-smoker	84 (5.1)	38 (45.2)	46 (54.8)	0.740
Smoker and ex-smoker	1,590 (94.9)	766 (48.2)	824 (51.8)	
BMI ≥ 21	1,406 (84)	685 (48.7)	721 (51.3)	0.363
BMI < 21	268 (16)	119 (44.4)	149 (55.6)	
Comorbidities	1,436 (85.7)	721 (50.2)	715 (49.8)	0.015
Without comorbidity	238 (14.3)	83 (34.9)	155 (65.1)	
Comorbidity – one	596 (35.6)	285 (47.9)	311 (52.1)	0.612
Comorbidity – two	474 (28.3)	233 (49.3)	241 (50.7)	
Comorbidity ≥ three	366 (21.8)	193 (52.3)	173 (47.7)	
FEV1*≥ 80%	226 (13.5)	144 (63.7)	82 (36.3)	< 0.001
FEV1 < 80%	1,448 (86.5)	660 (45.6)	788 (54.4)	
CAT*≥ 10	998 (59.6)	460 (46.1)	538 (53.9)	< 0.001
CAT < 10	676 (40.4)	344 (51.3)	332 (48.7)	
Number of patients with previous exacerbations >2 (N=1402)	298 (17.8)	137 (45.9)	161 (54.1)	0.615
Number of patients with previous exacerbations ≤ 2	1,104 (65.9)	520 (47.1)	584 (52.9)	
6MWD ≥ 350 m	1,356 (81.9)	594 (43.8)	762 (56.2)	0.035
6MWD < 350 m	318 (18.1)	210 (66.2)	108 (33.8)	
Vaccination	523 (31.2)	301 (57.6)	222 (42.4)	< 0.001
Vaccination – no	1,151 (68.8)	493 (42.8)	658 (57.2)	

AECOPD – acute exacerbation of the chronic obstructive pulmonary disease; BMI – body mass index; FEV1 – Forced expiratory volume in first second; CAT – chronic obstructive pulmonary disease assessment test; 6MWD – 6 minute walking distance.

Table 2. Frequency of the chronic obstructive pulmonary disease exacerbations in several patient groups according to PR status

Characteristic	N (%)	Pulmonary rehabilitation		p
		Yes (804)	No (870)	
AECOPD	1056	415 (51.6)	641 (73.7)	< 0.001
Moderate	758 (71.8)	334 (44.8)	424 (55.2)	
Severe	51 (4.8)	28 (55.6)	23 (44.4)	
Both severe and moderate	247 (23.4)	53 (22.6)	194 (77.8)	
None	618 (100)	389 (48.4)	229 (26.3)	< 0.001
Age < 65	528 (50)	228 (54.5)	300 (77.7)	< 0.001
Age ≥ 65	528 (50)	187 (48.8)	341 (70)	< 0.001
Non-smoker	63 (5.9)	29 (73.3)	34 (73.9)	0.332
Smoker and ex-smoker	993 (94.1)	386 (50.4)	607 (73.6)	< 0.001
BMI ≥ 21	868 (82.2)	362 (52.8)	506 (70.2)	< 0.001
BMI< 21	188 (17.8)	53 (44.5)	135 (90.6)	< 0.001
Comorbidity	942 (89.2)	394 (55.8)	548 (75.2)	< 0.001
Comorbidity no	114 (10.8)	21 (24.1)	93 (61.2)	< 0.001
FEV1 ≥ 80%	139 (13.2)	60 (41.6)	79 (96.3)	< 0.001
FEV1 < 80%	917 (86.8)	355 (53.7)	602 (76.4)	< 0.001
CAT ≥ 10	595 (56.4)	199 (43.3)	396 (73.6)	< 0.001
CAT < 10	461 (43.6)	216 (62.8)	245 (73.8)	0.018
6MWD ≥ 350 m	855 (80.9)	302 (42.5)	553 (85.6)	< 0.001
6MWD < 350 m	201 (18.1)	113 (53.8)	88 (81.5)	< 0.001
Vaccination yes	300 (28.4)	157 (52.3)	143 (64.7)	0.008
Vaccination no	756 (71.6)	258 (52.6)	498 (75.1)	< 0.001

PR – pulmonary rehabilitation; AECOPD – acute exacerbation of chronic obstructive pulmonary disease; BMI – body mass index; FEV1 – Forced expiratory volume in first second; CAT – chronic obstructive pulmonary disease assessment test; 6MWD – 6-minute walking distance.

Table 3. Predictors of chronic obstructive pulmonary disease exacerbations according to logistic regression analysis

Univariate analysis	RR	95% CI	p
Pulmonary rehabilitation	0.409	0.305–0.547	< 0.001
Age ≥ 65	0.880	0.662–1.170	0.379
Smoking (previous and actual)	2.204	1.182–4.111	0.013
BMI ≥ 21 kg/m^2	0.513	0.334–0.788	0.002
Comorbidities	1.340	0.872–2.058	0.182
FEV1< 80%	3.101	2.071–4.645	< 0.001
CAT score ≥ 10	3.380	2.512–4.549	< 0.001
Number of previous exacerbations > 2	5.928	3.404–10.324	< 0.001
6MWD	1.169	0.768–1.574	0.294
Vaccination	0.737	0.550–0.987	0.040
Multivariate analysis			
Pulmonary rehabilitation	0.421	0.307–0.577	< 0.001
BMI ≥ 21 kg/m^2	0.605	0.380–0.965	0.035
FEV1 < 80%	2.021	1.303–3.134	0.002
CAT score ≥ 10	2.375	1.720–3.280	< 0.001
Number of previous exacerbations > 2	4.222	2.372–7.514	< 0.001

FEV1 – Forced expiratory volume in first second; CAT – chronic obstructive pulmonary disease assessment test; BMI – body mass index; 6MWD – 6-minute walk distance.

