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

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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 been widely implemented as standard of COPD treatment yet. 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 January 2015 and December 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 1,406 patients, 84%, FEV 1 < 80% 1,448 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 COPD assessment test (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, PR (RR 0.421; 95% CI (0.307–0.577); p < 0.001) and BMI ≥ 21kg/m 2 (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

INTRODUCTION
The acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are challenging 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 chronic obstructive pulmonary disease (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, American Thoracic society (ATS), and 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 patients had denied taking the PR programs.

The PR effects among COPD patients have been demonstrated in most of the studies coming from developed countries as opposed to developing or undeveloped countries where there has not been much research regarding this issue. Serbia is among these countries, 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 on the health care system budget because of other outlays. This study has risen 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 PR among COPD patients in Serbia. In addition, 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 aged over 40, COPD diagnosis (based on a post-bronchodilator FEV1/FVC ratio of < 0.70) at least once a year.

The patients were divided into two groups according to PR status and followed during a one-year study. The demographic data included sex, age, smoking habits (packs per year), and body mass index (BMI). PR was conducted at the Polyclinic department of IPDV. Status of PR, COPD assessment test (CAT), spirometry test (forced expiratory volume in first second, FEV1), six-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, neurological and musculoskeletal disorders, patients who passed away or did not finish the PR course.

Every outpatient had the PR course according to the ATS-ERS statement and recommendations [5]. The course lasted three weeks, one to three times per year. The 60-minute 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 after 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 standards of the Committee on ethics as well as 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 for continuous variables and relative frequencies for categorical variables. The χ² test was used to determine whether there was 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 two-tailed a 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, age 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 2–4 (1,448; 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 once per year (Table 2). Exactly 33 (4.1%) patients dropped out the PR due to comorbidities (heart failure, locomotor disability). Unfortunately, 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 = 1,241; 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%) patients 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 350 m on 6MWD [210 (66.2%) vs. 108 (33.8%); p = 0.035] were more often treated with PR (Table 2). There was no statistically significant difference in the frequency of PR implementation according to the sex, smoking status, BMI categories, number of previous exacerbation, and number of comorbidities.

During the previous year (prior to entering the study), 1,402 patients (83.7%) had COPD exacerbations. After 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 had undergone PR [641 (73.7%) vs. 415 (51.6%), p < 0.001]. Patients who passed 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 a univariate analysis, significant protective factors against exacerbations were PR, BMI ≥ 21 kg/m², and vaccination, while significant risk factors were smoking, number of previous exacerbations > 2, CAT score > 10, and FEV1 < 80%. In multivariate analysis, PR and BMI ≥ 21 kg/m² were independent protective factors and CAT score > 10, FEV1 < 80%, and number of previous exacerbations > 2
Table 1. Patient characteristics, pulmonary rehabilitation, and acute exacerbation of chronic obstructive pulmonary disease

| Characteristic                  | 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           | 1590 (94.9)    | 766 (48.2)               | 824 (51.8) |      |
| BMI* ≥ 21                      | 1406 (84)      | 685 (48.7)               | 721 (51.3) | 0.363 |
| BMI < 21                       | 268 (16)       | 119 (44.4)               | 149 (55.6) |      |
| Comorbidities                  | 1436 (85.7)    | 721 (50.2)               | 715 (49.8) | 0.015 |
| Without comorbidity            | 238 (14.3)     | 83 (34.9)                | 155 (65.1) |      |
| CMBD – one                     | 596 (35.6)     | 285 (47.9)               | 311 (52.1) | 0.612 |
| CMBD – two                     | 474 (28.3)     | 233 (49.3)               | 241 (50.7) |      |
| CMBD ≥ three                   | 366 (21.8)     | 193 (52.3)               | 173 (47.7) |      |

Table 2. Frequency of chronic obstructive pulmonary disease* exacerbations in several patient groups according to pulmonary rehabilitation* 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 (69.5) | < 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 (26.7) | 0.332 |
| Source 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 (60.6) | < 0.001 |
| Comorbidity                    | 942 (89.2)     | 394 (55.8)               | 548 (75.2) | < 0.001 |
| Comorbidity no                 | 114 (10.8)     | 21 (24.1)                | 93 (75.9) | < 0.001 |
| FEV1* ≥ 80%                    | 139 (13.2)     | 60 (41.6)                | 79 (58.4) | < 0.001 |
| FEV1* < 80%                    | 917 (86.8)     | 355 (35.7)               | 602 (64.3) | < 0.001 |
| CAT ≥ 10                       | 595 (56.4)     | 199 (43.3)               | 396 (56.7) | < 0.001 |
| CAT < 10                       | 461 (43.6)     | 216 (62.8)               | 245 (37.2) | 0.018 |
| 6MWD* ≥ 350 m                  | 855 (80.9)     | 302 (42.5)               | 553 (57.5) | < 0.001 |
| 6MWD < 350 m                   | 201 (18.1)     | 113 (53.8)               | 88 (46.2) | < 0.001 |
| Vaccination yes                | 300 (28.4)     | 157 (52.3)               | 143 (47.7) | 0.008 |
| Vaccination no                 | 756 (71.6)     | 258 (52.6)               | 498 (71.5) | < 0.001 |

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

| Characteristic                  | RR  | 95% CI      | p    |
|--------------------------------|-----|-------------|------|
| Pulmonary rehabilitation       | 0.409 | 0.305–0.547 | < 0.001 |
| Age ≥ 65                       | 0.880 | 0.662–1.170 | 0.279 |
| Smoking (previous and actual)  | 2.204 | 1.182–4.111 | 0.013 |
| BMI* ≥ 21 kg/m²                | 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 | 3.166 | 2.379–7.514 | < 0.001 |

BMI – body mass index; CMBD – comorbidity; FEV1 – forced expiratory volume in the first second; CAT – chronic obstructive pulmonary disease assessment test; 6MWD – six-minute walking distance

AECOPD – acute exacerbation of chronic obstructive pulmonary disease; BMI – body mass index; FEV1 – forced expiratory volume in the first second; CAT – chronic obstructive pulmonary disease assessment test; 6MWD – six-minute walking distance
were independent risk factors from exacerbations, while vaccination (p = 0.086) was 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 et al. [12] has shown the results of 20 studies regarding the efficacy of the PR in reducing the AECOPD. In our study, the effects on AECOPD were comparable to other studies. Schuler et al. [13] on 383 COPD patients noted a decreased number of exacerbations (moderate and severe) one year after PR. Katajisto and Laitinen [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 et al. [16] showed that results from randomized controlled trials 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 2,962 patients, had at least one comorbidity, while in our study, it was 35.6%. Two years later, 2010, Crisafulli et al. [19] demonstrated reducing AECOPD among moderate and severe COPD patients with comorbidities (316 patients) after having completed the outpatient exercise-training program, which we confirmed. Franssen and Rochester [20] had similar results in 2014. 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 in PR programs worldwide, 3–9 weeks [4, 5, 22], Crisafulli et al. [19] used three-week PR duration per course, just like we did in our study. Houchen-Wolloff et al. [23] had the similar number of patients (823; 54.3% out of 1,515) who had completed PR. In many developed countries (United Kingdom, Canada, Sweden) only 0.4–1.2% of all COPD patients have access to PR [24, 25, 26]. But also, many of the patients refuse 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%, who are active, are more likely to accept PR programs in order to improve their health status and avoid sick leave. Similarly, patients with comorbidities and those 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 et al. [27] showed. Mihaltan et al. [28] recently showed that physical activity levels were low in his study that comprised 2,190 patients (multinational COPD cohort, which also included Serbia). Our patients, who are less mobile (under 350 m of 6MWD), probably wanted to improve their strength and daily activities with PR that Garrod et al. [29] proved in their study. After PR program, there were significant improvements in reduction of AECOPD among patients both younger and older, BMI < 21 and ≥ 21, CAT < 10 and ≥ 10, patients who could walk < 350 m and ≥ 350 m of 6MWD.

This study has some limitations. First not all COPD patients were given the option of PR, as, unfortunately, some specialist did not explain the true value of PR or did not say anything to their patients. Also, many physicians, on the primary health care 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 the 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 (SouthEastern Europe – Western 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 PR.

CONCLUSION

Patients who successfully completed the PR treatment had significantly less frequent COPD exacerbations compared to patients that do not pass through PR program. Multi-variable analyses confirmed that CAT score > 10, FEV1 < 80% and number of previous exacerbations > 2 were independent risk factors, while PR 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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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 спречавању егзацербација.

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

Резултати
Студија је обухватила 1674 болесника (956 мушкараца, старости 65,93 ± 8,45, 94,9% пушача и бивших пушача; 21 ≥ BMI 1406 болесника, 84%; FEV1/FEV1, < 80% 1448 болесника, 86,5%). Утврђена је значајна разлика у ПР статусу у односу на старост (p = 0,020), коморбидитете (p = 0,015), FEV1 (p < 0,001), респираторне симптоме коришћењем упитника ХОБП (CAT) (p < 0,001), вакцинацију (p < 0,001). Егзацербације су се чешће јављале код болесника 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 \( RR = 0,421; 95\% CI (0,307–0,577); p < 0,001 \) и \( BMI \geq 21 \text{ kg/m}^2 (RR = 0,605; 95\% CI (0,380–0,965); p = 0,035) \). Независни фактори ризика за појаву егзацербација су били \( CAT > 10 (RR = 2,375; 95\% CI (1,720–3,280); p < 0,001) \) и \( FEV1 < 80\% (RR = 2,021; 95\% CI (1,303–3,134); p = 0,002) \).

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

Кључне речи: AECOPD; COPD; CAT скор; плућна рехабилитација

Заклопач: Болесници који су успешно завршили ПР имали су значајно мање егзацербација у поређењу са болесницима који нису били на ПР.