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Risk factors as outcome predictors of pulmonary rehabilitation in patients with chronic obstructive pulmonary disease

Фактори ризика као предиктори исхода респираторне рехабилитације код болесника са хроничном опструктивном болести плућа

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SUMMARY

Introduction/Objective Chronic obstructive pulmonary disease (COPD) is a primary lung disease. Today, pulmonary rehabilitation (PR) is the basis of non-pharmacological treatment of these patients, with numerous confirmed effects on the most significant symptoms of the disease and quality of life (QoL). The aim of this study was to determine the relationship between certain risk factors and the outcome of PR, as well as to determine the percentage of respondents who had a positive outcome of PR.

Methods The study included 500 patients with COPD, determined according to the guidelines of the GOLD, all stages I–IV, in the stable phase of the disease, who completed the outpatient PR program. Disease stage, comorbidities, forced expiratory volume in the first second, 6-minute walk test (6MWT), COPD Assessment Test (CAT) and Medical Research Council dyspnea scale, BODE index, were measured before and after the program. The last four parameters have been observed as risk factors that affect the outcome of PR, but also as parameters by which we monitor the outcome of PR.

Results A successful outcome of PR was achieved by as many as 452 (90.4%) patients. As independent predictors of a positive outcome of PR were determined: lower number of comorbidities, absence of heart failure, higher BMI and CAT ≥ 10.

Conclusions PR in our group of patients leads to statistically significant improvements in most of the examined subjective and objective parameters, in patients at all stages of the disease.

Keywords: COPD; comorbidity; respiratory rehabilitation; risk factors; treatment outcome

САЖЕТАК

Увод/Циљ Хронична опструктивна болест плућа (ХОБП) је примарно плућно обољење. Респираторна рехабилитација данас представља основу нефармаколошког лечења ових пацијената, са бројним потврђеним ефектима на најзначајније симптоме болести и квалитет живота. Циљ рада био је да се утврди повезаност одређених фактора ризика и исхода респираторне рехабилитације, као и да утврдимо проценат испитаника код којих је остварен позитиван исход респираторне рехабилитације.

Методе У истраживање је укључено 500 болесника са хроничном опструктивном болести плућа, утврђених према смерници *GOLD*, свих стадијума I–IV, у стабилној фази болести, који су одрадили комплетан програм амбулантне респираторне рехабилитације. Стадијум болести, придружене болести, форсирани експиријумски волумен у првој секунди, шестоминутни тест хода, *COPD Assessment Test* и *Medical Research Council dyspnea scale*, БОДЕ индекс, мерени су пре и након завршеног програма. Последња четири параметра посматрана су и као фактори ризика који утичу на исход респираторне рехабилитације, али и као параметри помоћу којих пратимо исход респираторне рехабилитације.

Резултати Успешан исход респираторне рехабилитације остварило је чак 452 (90,4%) болесника. Као независни предиктори позитивног исхода респираторне рехабилитације утврђени су: мањи број придружених болести, одсуство срчане слабости, виши *BMI* и *CAT* ≥ 10.

Закључак Респираторна рехабилитација у нашој групи болесника, доводи до статистички значајних побољшања већине испитиваних субјективних и објективних параметара, код болесника у свим стадијумима болести.

Кључне речи: хронична опструктивна болест плућа; коморбидитет; респираторна рехабилитација; фактори ризика; исход терапије

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a slow progressive, primarily lung disease, but causes significant systemic consequences [1]. According to available data, 4–15%

of the adult population in industrialized countries suffers from this disease. It is the only disease in the top ten leading causes of death in the world, in which the prevalence and number of deaths continue to grow [2]. Inflammatory changes similar to those in the lungs also occur in the systemic circulation, and are thought to occur with a simple "spill-over" phenomenon, i.e. the overflow of the mediator of inflammation into the systemic circulation. Most likely, this concept is the key to understanding the systemic effects of COPD [3].

The first problems usually appear years after the first signs of inflammation and consequent damage to the respiratory function. Most often, rapid fatigue and dyspnea bring these patients to the doctor, because they consider coughing and expectoration to be a normal consequence of cigarette smoking. When it occurs, dyspnea is usually persistent and progressive [4].

The most significant systemic disorders include: skeletal muscle dysfunction, cardiovascular disease (CVD), diabetes, osteoporosis, depression [5]. Skeletal muscle dysfunction in COPD is a common occurrence. The pathophysiological mechanisms have not been precisely determined. One of the most important is the decline due to inactivity, because these patients avoid all efforts that lead to dyspnea [6]. One of the most significant comorbidities in COPD is CVD and it is a dynamic and progressive disorder that occurs by combining endothelial dysfunction and inflammation [7]. Recent studies provide evidence that inflammatory changes may be predictors of the development of diabetes (type 2) and impaired glucose tolerance [8]. Reduced lung function, systemic inflammation, corticosteroid therapy, reduced physical activity, which in turn causes reduced mechanical load on the bones, and it is one of the most important stimuli for bone building [9], contribute to the development of osteoporosis. Depression and anxiety, have a significant impact on the course of COPD, the prognosis of the disease and the quality of life (QoL) of the patients and their families. The prevalence of depression in patients with COPD is between 10–40%, while for anxiety it is 19% [10].

The "gold diagnostic standard" is spirometry. Parameters necessary for the diagnosis of COPD are: forced vital capacity (FVC) and forced expiratory volume in the first second (FEV1), and FEV1/FVC ratio [11]. Postbronchodilator values are recommended for the diagnosis and assessment of COPD severity. According to the severity of the obstruction, COPD is divided into: mild (stage I), moderately severe (stage II), severe (stage III), very

severe (stage IV). A new classification of the disease was adopted: the ABCD classification, which is based on the assessment of disease symptoms, the degree of obstruction and the risk of exacerbation. The assessment of disease symptoms is performed using the "COPD Assessment Test" (CAT) and the "modified British Medical Research Council" scale (mMRC) [12].

The CAT questionnaire is a practical test consisting of 8 questions, which measure the impact of COPD on the health condition and daily life of the patient. The total score ranges 0–40, higher values indicate a worse general condition of the patient. This test has been shown to reflect the impact of PR as well as recovery after exacerbations [13]. The mMRC scale is used to assess dyspnea by gradation 0–4, in relation to effort tolerance. Grade 4 indicates the appearance of dyspnea even during the lightest physical activities. This scale correlates well with other health parameters, clinical signs and pulmonary function, and provides an estimate of future mortality [14]. The BODE index is a multidimensional index that consists of four parameters: Body Mass Index (BMI), obstruction measured via FEV1, dyspnea measured using mMRC, exercise capacity expressed over six-minute walk test (6MWT). This is an index whose values range 0–10, and the index with values ≥ 7 is an excellent predictive factor for mortality, and at the same time we can monitor the effects of PR [15].

Given that nowadays PR is a proven, very effective non-pharmacological method of treating patients with COPD, in this paper we wanted to determine whether and which risk factors affect the outcome of PR, as well as how successful the PR program is in treating patients with COPD.

METHODS

Material

A retrospective-prospective study included 500 patients diagnosed with COPD according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, stages I-IV, in the stable phase of the disease, who completed the program of outpatient PR during a two-year period. Data from associated diseases were taken from previous medical history, medical

documentation and based on the pharmacological therapy used by the patients. The PR consisted of 15 sessions, duration of each session was 45 minutes, during three weeks, and included strength exercises for the upper and lower extremities, endurance exercises on a stationary bike (symptom-limited), and diaphragmatic breathing exercises. All patients underwent pre- and post-PR: 6MWT according to guidelines issued by the American Thoracic Association, FEV1-measured on a "Master Scope PC" (spirometer, manufacturer JAEGER). Patients completed the CAT and mMRC questionnaires themselves, also before and after PR. Patients' body height and body are presented with BMI. Based on these parameters, we finally calculated the BODE index before and after the completion of the PR program. When it comes to the success of PR, our research determined the influence of individual risk factors on the successful outcome of PR (certain associated diseases, FEV1, 6MWT, CAT and mMRC questionnaire, BODE index). The assessment of rehabilitation success was done on the basis of certain parameters that were observed as risk factors (individual improvement of these factors included: increase in distance travelled during 6MWT by ≥ 54m, decrease in CAT questionnaire by 5 points, mMRC questionnaire and BODE index by 1 point). The categories of success were: excellent (improved all four parameters), very good (improved in three parameters), good (improved two parameters), sufficient (improved one parameter), and insufficient (without improvement of any parameter). The categories excellent, very good, good and sufficient were considered a successful outcome of the PR.

Statistical analysis

The study uses the measures of central tendency as methods of descriptive statistics. In this study were used methods of identification of empirical distributions, methods for assessing the significance of differences: depending on the type of data distribution t-test for independent, Mann–Whitney U test, Wilcoxon's test of equivalent pairs, χ^2 test and Spearman correlation test. To assess the significance of the relationship between input variables and outcomes, univariate as well as multivariate logistic regression analysis was used. Statistical analyses were performed using SPSS Version 22.0 with statistical significance level 0.05.

The study was approved by the Ethics Board of the Institute for Pulmonary Diseases of Vojvodina.

RESULTS

The study included 500 respondents, of whom 258 (51.6%) were male. The average age was 64.89 ± 9.02 years. The average BMI was 25.86 ± 4.25, while the average pack/years was 42.09 ± 24.52. The average duration of the disease was 7.35 ± 6.03 years (Table 1).

Three or more associated diseases were registered in 189 (37.8%) respondents, 50 patients (10%) did not have any associated diseases, while the largest number of associated diseases-7, was found in only one patient. The most common associated disease was arterial hypertension in 338 (67.6%) patients, followed by ischemic heart disease in 208 (41.6%) patients and diabetes mellitus in 143 (28.6%) patients. The rarest associated disease was lung cancer, diagnosed in only 6 (1.2%) patients (Figure 1).

The mean distance travelled during 6MWT before PR was 421.76 ± 97.75, and after PR increased on average by 64.44 ± 35.07 (p < 0.01). The increase in distance during the 6MWT > 54m was achieved by 314 (62.8%) respondents.

The mean value of FEV1 before PR was 58.15 ± 18.53, while after the PR program it increased on average by 3.05 ± 2.84 (p < 0.01).

The mean value of the CAT questionnaire before PR was 12.32 ± 6.38, and after PR it decreased by an average of 6.37 ± 3.11 (p < 0.01). The reduction of the CAT questionnaire by 5 points was achieved by 345 (69%) respondents. The mean value of the mMRC scale before PR was 1.75 ± 0.93, and after PR it decreased by an average of 0.71 ± 0.56 (p < 0.01). A decrease on the mMRC scale by 1 point was achieved by 329 (65.8%) respondents. The mean value of the BODE index before PR was 2.37 ± 2.05, and after PR it decreased by an average of 0.93 ± 0.95 (p < 0.01). The reduction of the BODE index by 1 point was achieved by 345 (69%) respondents.

When we observed these subjective parameters in relation to the proposed cut-off values for the categorization of mild and severe patients and symptoms (CAT questionnaire ≥ 10, mMRC questionnaire ≥ 2, BODE index ≥ 3) before and after PR, we obtained the following

results, which are shown in Figure 2. Further determination of the correlation of these parameters revealed the existence of a statistically significant positive correlation between the values of the CAT questionnaire (p = 0.006) and the mMRC scale (p = 0.014) at the beginning of the study and the positive outcome of PR. No statistically significant correlation was found between the BODE index values at the beginning of the study and the PR outcome (p > 0.05).

Subjects with 3 or more associated diseases had a statistically significantly lower frequency of positive PR outcome compared to subjects with less than 3 associated diseases 163 (86.2%) *vs.* 289 (92.9%) (p = 0.014). There is a statistically significant negative correlation between a number of associated diseases and a positive PR outcome (p = 0.008), as well as three or more associated diseases and a positive PR outcome (p = 0.014). It was found that subjects with heart failure had a statistically significantly lower frequency of positive PR outcome compared to subjects without heart failure (59 (83.1%) *vs.* 393 (91.6%); p = 0.024). There was no statistically significant difference in the frequency of positive PR outcome in subjects with ischemic heart disease (184 (88.5%) *vs.* 268 (91.8%); p > 0.05), arterial hypertension (302 (89.3%) *vs.* 149) (92.5%); p > 0.05), diabetes mellitus (128 (89.5%) *vs.* 324 (90.8%); p > 0.05), pulmonary tuberculosis (55 (88.7%) *vs.* 397 (90.6%); p = 0.024), lung cancer 5 (83.3%) *vs.* 447 (90.5%); p > 0.05), bronchiectasis (95 (88.8%) *vs.* 357 (90.8%); p > 0.05), osteoporosis (56 (87.5%) *vs.* 396 (90.8) %); p > 0.05) and depression (62 (86.1%) *vs.* 390 (91.1%); p > 0.05) compared to patients without these comorbidities. There is a statistically significant negative correlation between cardiac failure and a positive PR outcome (p = 0.024), while there is no statistically significant association of the other examined comorbidities with a positive PR outcome (p > 0.05) (Figure 3).

When it comes to the success of PR, we must note that the evaluation of the success of rehabilitation was done on the basis of certain parameters that were observed as risk factors (6 MTH, "CAT" questionnaire, "mMRC" questionnaire and BODE index). Of the 500 patients included in the study, as many as 452 (90.4%) subjects achieved a successful PR outcome, while only 48 (9.6%) subjects were without improvement and one test parameter. Within the successful outcomes of PR, most respondents 142 (28.4%) were in the category very good, followed by the categories good with 129 respondents (25.8%), sufficient with 102 respondents (20.4%), and finally categories excellent with a total of 79 (15.8%) respondents.

In our research, we tried to determine the predictive values of pre-determined risk factors. The results obtained by univariate logistic regression analysis showed that statistically significant univariate predictors of a positive PR outcome are: lower number of associated diseases (PR 0.74 95% IP (0.59–0.93); p = 0.011); absence of heart failure (PR 0.45 95% IP (0.22–0.92); p = 0.027); higher BMI (PR 1.84 95% IP (0.87–3.87); p = 0.03); mMRC ≥ 2 (PR 2.73 95% IP (1.47–5.08); p = 0.002); CAT ≥ 10 (PR 3.23 95% IP (1.74–6.02); p < 0.001).

Age, sex, smoking, "pack years", duration of illness, number of exacerbations during the past year, ischemic heart disease, diabetes mellitus, arterial hypertension, osteoporosis, pulmonary tuberculosis-TB, lung cancer, bronchiectasis, depression, 6MWT, BODE, FEV1 and "GOLD" stages are not statistically significant predictors of a positive PR outcome. Further data processing, multivariate logistic regression analysis showed that the independent predictors of a positive outcome are PR: lower number of associated diseases (PR 0.67 95% IP (0.52–0.88); p = 0.004), absence of heart failure (PR 0.42 95% IP (0.19–0.93); p = 0.033); higher BMI (PR 1.15 95% IP (1.05–1.25); p = 0.002); CAT ≥ 10 (PR 4.99 95% IP (2.51–9.91); p < 0.001).

DISCUSSION

In our study, 500 patients with COPD were analyzed, with 258 being male (51.6%). Today, it is known that comorbidities have a very significant impact on the health status of patients with COPD, but they also have a great impact on the burden on the entire health system. Comorbidities significantly worsen the patient's QoL and prognosis. The second revision of GOLD, for the first time, included comorbidities and exacerbations in the definition of COPD, thus confirming their importance. The prevalence of comorbidities is quite diverse, the most common data that indicate that about 2/3 of patients with COPD have one or two comorbidities, although the results range from 50–98, 5%. Divo et al. found in one of the largest comorbidity studies, which included 1,969 patients with COPD and 316 patients without COPD, they found that patients with COPD were more likely to have a larger number of comorbidities than patients without COPD [16].

In our study, 50 patients did not have comorbidities (10%), patients with comorbidities had a share of 90%. The number of comorbidities in the remaining 450 patients ranged from 1–7, and the average number of comorbidities was 2.1 ± 1.3. As a risk factor that can negatively affect the outcome of PR, we took the limit of ≥ 3 comorbidities, and a total of 189 patients had ≥ 3 comorbidities (37.8%). This factor proved to be statistically significant to the successful outcome of PR. In the group with ≤ 2 comorbidities, there were 311 patients, of which 289 had successful PR (92.9%), while in the group of patients with more then 3 comorbidities successful rehabilitation was reported in 86% of cases. These data correlate with the results from the references, even our prevalence of comorbidities is at the upper limit, compared to the results in the research published so far.

The comorbidity study within our paper included the following diseases: heart failure (present in 14.2%), ischemic heart disease (41.6%) and hypertension (67.7%), diabetes (28.6%), bronchiectasis (21.4), TB (12.2) lung cancer (1.2%); osteoporosis (12.8) and depression (14.4%). The examination of the prevalence of comorbidities showed what is stated in the references, that CVD have the highest prevalence in people with COPD, and these values are compared with the results from the references. Prevalence values for other diseases also range within the references, with the exception of lung cancer, where we had a much lower prevalence compared to data from the refernces, perhaps due to somewhat weaker screening in that direction, then osteoporosis whose prevalence in the references is up to 35%, and depression with the same slightly lower prevalence compared to the references (about 25%). Only heart failure has a statistically significant impact on the success of PR. Its presence was more significant in the group with "insufficient" PR success compared to all other success categories. These results also coincide with the results from the references. In addition to the impact of these comorbidities on the course and prognosis of COPD, they may also affect the success of PR. Studies indicate that patients with comorbidities, especially ≥ 2, have a higher degree of dyspnea, less tolerance to exertion, and a poorer QoL. Patients with CVD and COPD, according to Hornikx et al. [17] do not have worse values either before or after the PR program, when it comes to the assessment of dyspnea, but they have worse results related to the exercise tolerance and QoL.

In contrast, Carreiro et al. as well as Tunsupon et al., in patients with this type of comorbidity received numerous positive changes in terms of symptoms, but also in terms of QoL, after completing the PR program [18, 19]. PR in these patients is more complex, difficult

and more individual, but these patients have more chances to progress and achieve better results. And just as these two views are opposed, so are the results of the studies that have been done on this topic in recent years.

The results of PR on the influence of CAT test are very positive, and for these reasons it is used today as one of the main parameters for monitoring the effects of PR. Our results confirmed that PR significantly improved the values of the CAT questionnaire, by far more than 2 points of value MCID (minimum clinically important difference) stated in the references. Also, the value of CAT showed that it has a statistically significant correlation with the success of PR, namely the initially worse the values of the CAT questionnaire are, the better the results of rehabilitation. For example, we must note that the group of patients with "excellent" success had the highest mean CAT before the program (17.14 points), while the average correction for all categories of success was slightly more than 6 points. These results are in complete agreement with what Dodd et al. officially confirmed in their prospective multicenter study, pointing out that it is a simple test which responds well to PR and that can very well distinguish categories in relation to the effects of this program. This author further examined the duration of changes in the values of the CAT and found that the CAT questionnaire responds immediately to the PR program, and that these effects last up to 6 months after PR [20].

Our work confirmed and pointed out the significant effect of PR to dyspnea. After PR, there was a statistically significant improvement of mMRC, and its statistically significant correlation with PR success was confirmed. In the case of mMRC, as well as in the case of CAT questionnaire, this correlation is negative, i.e., the higher the values of mMRC before PR, the better the success. The category with "excellent" success initially had the highest values of mMRC (2.65 points), and the average improvement was by 1 point. Previous study has shown that PR leads to the improvement of dyspnea in all patients, although it is recommended that only patients with mMRC ≥ 2 should be included in the program. Rugbjerg et al. found that all categories of patients, in relation to mMRC, have some improvement, and that it is weak in patients with mild symptoms, while in patients with more pronounced symptoms this improvement is statistically significant [21]. Betancourt-Peña et al. [22] also contributed to this topic. They concluded that patients with mMRC 2 have the same improvement after the PR, when it comes to 6mwd and VO2, as well as patients with mMRC ¾, and also concluded that all persons regardless of the degree of dyspnea should be referred to the PR.

Our research confirmed that the PR leads to a statistically significant improvement in 6MWT values and one of the best things about this test is that it reflects pulmonary and extrapulmonary manifestations of COPD. This improvement averaged 64.4 ± 35.1m in our study, which is far more than all the mentioned values, which are referred to in the references as MCID (14–30.5 m). Today, it is assumed that the improvement in the 6MWT value could be clearly reflected in the increase in physical activity of the daily life of patients, measured by the number of steps taken during the day [23]. As with the aforementioned CAT and mMRC questionnaires, the lowest test values were in the group of patients with "excellent" PR success (354.9 m). All this clearly indicates a good correlation of CAT, mMRC and 6MWT parameters before and after PR, suggesting that patients who initially have worse results of these parameters achieve better PR results.

CONCLUSION

Based on our results, we can conclude that PR should be a mandatory part of the treatment of patients with COPD, regardless of the stage of the disease. It can also be performed in patients with numerous comorbidities, although we must note that a smaller number of associated diseases and the absence of heart failure in our work have been proven as independent predictors of a positive PR outcome. Patients with initially poorer CAT and mMRC questionnaire values had better PR scores. Baseline values ≥ 10 for the CAT questionnaire, in our study, also proved to be an independent predictor of a positive PR outcome. We proved that this program leads to statistically significant improvements in both subjective and objective parameters of the disease, and a successful outcome after the PR program was achieved by 90% of our patients.

Conflict of interest: None declared.

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**Table 1.** Descriptive parameters of patients in total and according to the outcome of pulmonary rehabilitation

| Variables	Sum	Outcome of PR		p
		Successful	Unsuccessful	
Sex male (n, %)	258 (51.6)	231 (89.5%)	221 (91.3%)	0.498
Age (X ± SD)	64.89 ± 9.02	64.76 ± 9.04	66.10 ± 8.82	0.326
BMI (X ± SD)	25.86 ± 4.25	26.00 ± 4.26	24.59 ± 3.96	0.029
Pack/years (X ± SD)	42.09 ± 24.52	41.60 ± 24.81	46.73 ± 21.16	0.168
Length of disease years (median)	7.35 ± 6.03	6	3	0.103

BMI – Body Mass Index; SD – standard deviation; X – mean
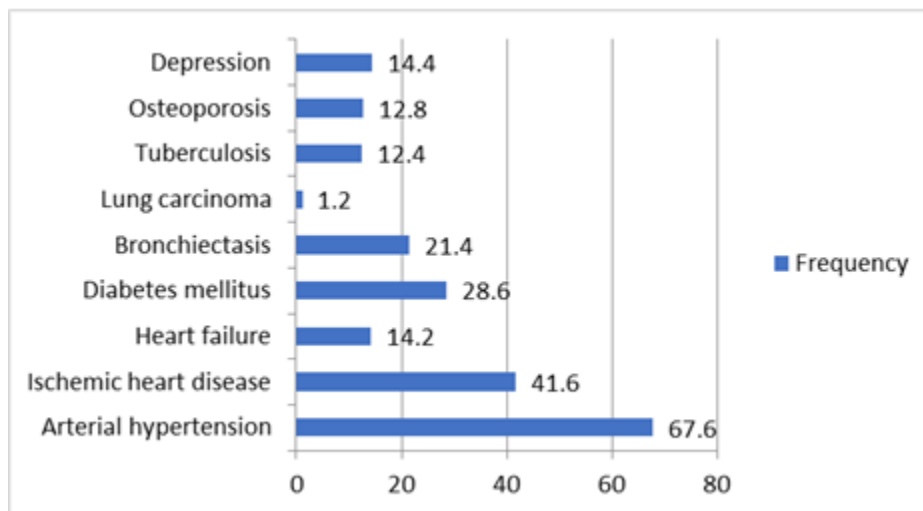
Figure 1. Frequency of comorbidities of respondents
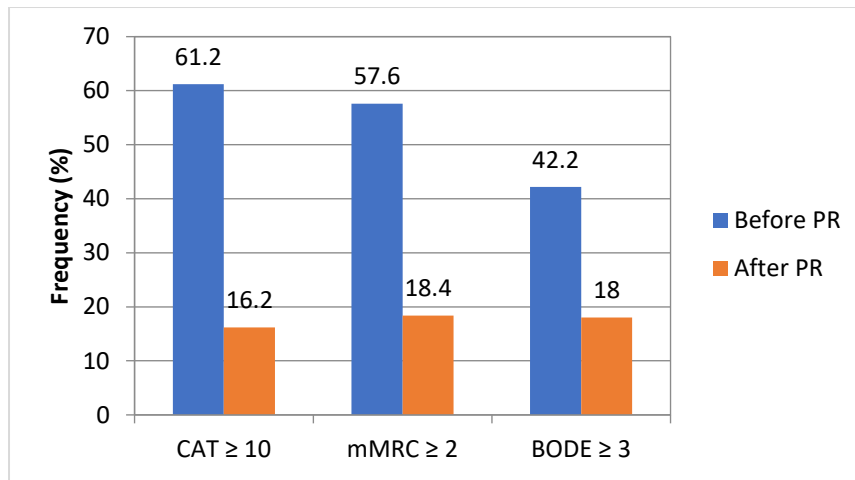
Figure 2. Frequency of cut-off values for CAT, mMRC, and BODE questionnaires before

and after pulmonary rehabilitation
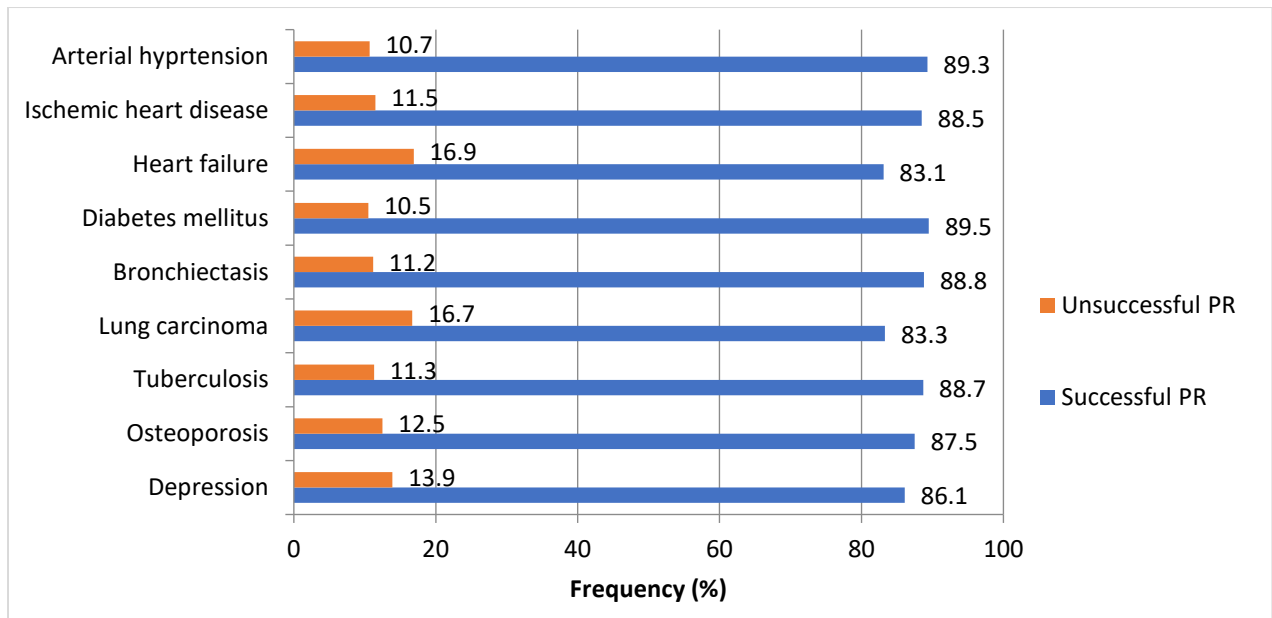
Figure 3. Pulmonary rehabilitation (PR) success rate by comorbidities