Correlation between patient perception of the ability to perform morning activities and findings on clinical examination in COPD patients in Romania

Corelație între percepția de către pacient a capacității de a efectua activități matinale și constatările examenului clinic la pacienții cu BPOC în România

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Abstract

Physical activity level is recognized as a predictor of mortality and hospitalisation in patients with COPD. RELIEF (CorRELation Between Patlent PErception and Findings on Clinical Examination, NCT01627743) was a non-interventional, multicenter, prospective, 12-week study of patients aged at least 40 years with COPD stage C or D treated for at least 1 month previous enrollment with ICS/LABA combined therapy. The patients' perception on ability to perform morning activities, was evaluated with the CDLM (Capacity of Daily Living during the Morning) questionnaire. 505 patients were included in the final analysis. The majority of patients were male (85.1%), and the mean age of study subjects was 65 years. The average duration of COPD was 5.31 years and more than half of the patients had COPD stage C (61%). The mean duration of inhaled combined therapy before study was 36 months. Hypertension was the most frequent co-morbidity reported (38.2%), followed by coronary heart disease (20.6%). The mean CDLM score increased during the prospective follow-up from 3.68 to 3.94, as well as the percentage of patients with a general health status of 4/5 from 41.2% to 57.4%. A weak-to-moderate positive correlation was found between the CDLM total score and the general health status (Kendall tau-b values from 0.2269 to 0.3181). These results indicate a general improvement of subjective perceptions of both patients and health care providers and complete the COPD landscape research in Romania, being the first study reporting such a correlation between patient reported outcomes and clinical assessments done by specialists.

Keywords: ***COPD, ICS/LABA therapy, CDLM, quality of life***

Rezumat

Nivelul de activitate fizică este recunoscut ca un predictor de mortalitate și de spitalizare la pacienții cu BPOC. RELIEF (CorRELation Between Patlent PErception and Findings on Clinical Examination, NCT01627743) a fost un studiu non-intervențional, multicentric, prospectiv, de 12 săptămâni, care a inclus pacienți cu vârsta de cel puțin 40 de ani, cu BPOC stadiul C sau D tratati puțin cel puțin 1 lună anterior includerii cu terapie combinată ICS / LABA. Percepția pacienților asupra capacității de a efectua activități de dimineață a fost evaluată cu ajutorul chestionarului CDLM (Capacity of Daily Living during the Morning). În analiza finală au fost incluși 505 pacienți. Majoritatea pacienților au fost de sex masculin (85,1%), iar vârsta medie a subiecților studiului a fost de 65 de ani. Durata medie a BPOC a fost de 5,31 ani si mai mult de jumătate dintre pacienți au avut BPOC stadiul C (61%). Durata medie a terapiei combinate inhalatorii înainte de studiu a fost de 36 de luni. Hipertensiunea arterială a fost cea mai frecventă comorbiditate raportată (38,2%), urmată de boala coronariană (20,6%). Media scorului CDLM a crescut pe parcursul urmăririi prospective de la 3.68 la 3.94, precum și procentul de pacienți cu o stare generală de sănătate de 4/5 de la 41,2% la 57,4%. O corelație pozitivă slabă până la moderată, a fost găsită între scorul total CDLM și starea generală de sanătate (valori Kendall tau-b de la 0.2269 la 0.3181). Aceste rezultate indică o îmbunătățire generală a percepției subiective a pacienților și a furnizorilor de servicii medicale și completează cercetarea BPOC în România, fiind primul studiu care a raportat o corelatie între rezultatele raportate de pacient și evaluările clinice efectuate de către specialiști din sănătate.

Cuvinte ***cheie: BPOC, terapie ICS / LABA, CDLM, calitatea vieții***

Introduction.

Chronic obstructive pulmonary disease (COPD) is a progressive and irreversible disease with gradual debilitation over time[1]. Assessment of symptoms severity is the key to managing stable COPD patients. The impact of the symptoms and their consequences on daily function of COPD patients are often underestimated[2]. However, patients do not always report their COPD symptoms, even though these symptoms affect their quality of life to a significant extent. Daily variability of symptoms and, more specifically, the patients' perceptions regarding their symptoms in the morning, has become one of the most studied aspects of COPD impact on functionality[3].

Despite the fact that several self-reporting questionnaires have been developed, research has shown a communication gap between patients and their clinicians[4]. Moreover, data indicates that patients tend to report their symptoms more accurately on self-reported questionnaires compared with responding to verbal questions from a health care professional[3].

This primary objective of RELIEF was to identify the correlation between patient perceptions of their ability to perform morning activities as measured by CDLM total score and the general health status assessed by the physician during a medical exam with the aid of a visual scale.

Main secondary objectives were to evaluate **(i)** the percentage of patients which register improvement, using CDLM and general health status visual scale; **(ii)** adherence to ICS/LABA treatment in general in patients with grade C and D COPD (according to Global Initiative for Chronic Obstructive Lung Disease [GOLD] Guidelines Revised 2011); **(iii)** the effort tolerance of patients with COPD, group C and D GOLD, by using a pedometer to measure the dynamics of daily walking distance; **(iv)** the incidence and impact of COPD exacerbations during the study.

The study was performed from July 2012 to January 2013 in Romania and Bulgaria. Here we report the results of patients enrolled in Romania.

Methods.

This was a multicenter, prospective and non-interventional 12-week study in COPD patients grades C and D (GOLD, 2011). The study consisted of a baseline visit and 3 follow-up visits, at interval of approximately 1 month. Inclusion criteria were age of 40 years or older, diagnosis of COPD grade C or D (GOLD, 2011), a current treatment with a fixed-dose ICS/LABA combination for at least 1 month prior entering in the study, and a status of current or past smokers of at least 10 pack-years. Eligible patients were enrolled in the study after having received information about the study and provided signed informed consent that allowed access to their COPD health-related data collection. The study was approved by the National Ethics Committee.

Patients were not included in the study if they had a history of COPD exacerbations within the last month before enrollment, history of asthma or allergic rhinitis, lung carcinoma or other respiratory conditions potentially limiting the airflow circulation (e.g. pulmonary fibrosis). Inability or refusal to perform study procedures (use of a pedometer, recording of values, completion of CDLM questionnaires) was also a reason to exclude patients from the study.

CDLM Questionnaire. This questionnaire was developed by AstraZeneca to evaluate the patients' perceptions of the ability to perform morning activities. Development, validation method, and score calculation were described elsewhere[5]. CDLM questionnaire evaluates 6 morning activities performed after COPD medication is administered: body washing, drying with towel, getting dressed, eating breakfast, walking around home earlier or later after taking the COPD treatment. At Visit 1, each subject was instructed as to how to complete the questionnaires, and filled the first CDLM (this constituted the baseline evaluation), and also received the questionnaires that they were to complete by the next study visit. Subjects were instructed to fill in the CDLM questionnaires at a specific time each day, preferably at about noon. In the interval between study visits, subjects completed the CDLM questionnaire on 7 consecutive days per month, specifically before the next study visit.

Registration of walking steps. The pedometers registered the total daily walking steps. The subjects were instructed how to reset the device, to attach it to their belt or their pocket, how to record the number of steps in the daily activities monitoring calendar at the end of each day. They were also instructed to register the number of steps in the same days with completion of CDLM questionnaire, in the last 7 days prior to next study visit.

Visual Analogue Scale. Based on clinical examination, the pneumologist rated the patient's general health status on a visual scale with 5 items (1-very bad; 5 – very good).

Treatment adherence. The level of patients' adherence to ICS/LABA treatment was indicated on a scale of 5 levels (from 0% to 100%) by the investigators following a discussion with the patient.

Statistical analysis. This study evaluated the potential positive correlation between improvement perceived by the patient (as measured by the CDLM total score) and improvement observed by the treating physician (as measured by the patient general health status score), using the bivariate correlation test.

The statistical analysis was mainly descriptive. No adjustment for multiple testing was done. Appropriate methods were used to derive confidence intervals, depending on the nature of the data and distribution. Continuous data were described by their mean, standard deviation (SD), median, lower and upper quartile, minimum and maximum and valid cases. Categorical data were described by absolute and percentage number of subjects per category.

Results.

A total of 505 subjects were enrolled in 24 study sites in Romania and 489 (96.8%) completed the study. The majority of patients were male (85.1%). Overall, 61% of patients had COPD grade C and 39% COPD grade D. Mean age of participants was 65 years (range: 40 to 88 years). The majority of them (74.7%) were ex-smokers, with a mean of 1 pack per day (20 cigarettes) and the mean number of pack-years of 34.69 (range: 10 to 300). COPD had a mean duration of 5.31 years. Most of the subjects (363, 71.9%) had experienced at least 1 exacerbation of their COPD within the previous 12 months, and the mean number of exacerbations was 2 (range: 1 to 12).

With regards to COPD ICS/LABA combination, the majority of subjects (54.3%) were using salmeterol/fluticasone, while 45.7% were taking budesonide/formoterol. The mean duration of combined inhaled therapy was 36 months. Other COPD medications in addition to combined inhaled therapy are summarized in **Table 1**.

The comorbidities in COPD grade C and D patients are summarized in **Table 2**, hypertension (38.2%), coronary heart disease (20.6%) and *cor pulmonale* (10.5%) being the most frequently reported.

CDLM total score change from Visit 1 to Visit 4 (end of study) was 0.16 (**Table 3**). The improvement was considered statistically significant (p=0.0015, Per Protocol [PP] population). Similarly, patients' general health status significantly

Table 1 Respiratory medication administered at baseline in addition to ICS/LABA fixed dose combination

Other COPD medication at baseline	N (%)
Long acting anticholinergic	199 (39.4)
Short-acting beta2-agonist	142 (28.1)
Methylxanthines	131 (25.9)
Short acting beta2– agonist/anticholinergic fixed combination	28 (5.5)
Short acting anticholinergic	12 (2.4)
Phosphodiesterase-4 inhibitor	10 (2)
Long-acting beta2-agonist	8 (1.6)
Inhaled corticosteroids	1 (0.2)

Table 2 Comorbidities found in evaluated COPD grade C and D patients

Characteristics	N (%)
No comorbidity	162 (32.1)
Current comorbidities	343 (67.9)
Hypertension	193 (38.2)
Myocardial ischemia	104 (20.6)
Cor pulmonale	53 (10.5)
Diabetes	32 (6.3)
Hypercholesterolemia	20 (4)
Atrial fibrillation	18 (3.6)
Cardiac failure	16 (3.2)

improved from Visit 1 to Visit 4 (**Table 4**), based on the Wilcoxon signed rank test. The correlation between CDLM total score and the 5-scale general health status score was investigated at every visit using the Kendall tau-b correlation test. A significant positive correlation was identified at every visit, with a range from 0.2269 to 0.3181 of Kendall tau-b values, implying a weak-to-moderate positive connection between these 2 parameters ($p<0.001$ for each evaluation).

Patients used a pedometer to measure their daily walking distance on 7 consecutive days between the visits. The mean of the daily averages of number of steps at Visit 2 was 3,014.65 and decreased to 2,695.26 on Visit 4. The difference of daily averages of number of steps between the visits was significant (based on Wilcoxon signed rank test).

At baseline, 93.1% of subjects (Full Analysis Set [FAS] population) were considered to be adherent to their treatment (75% - 100% level of adherence). At Visit 4, this proportion had increased to 98.2%. Results were similar for the PP population analysis, with 95.8% of patients considered adherent at Visit 1, increasing to 98.5% by Visit 4. The analysis of the changes at each visit (by number and % of subjects) showed a significant improvement for the PP population based on the Wilcoxon signed rank test.

The change in incidence and impact of COPD exacerbations was small, with the percentage of subjects with exacerbations ranging from 8% to 9.6% across all visits. Less than 1.5% of subjects required hospitalization because of a COPD exacerbation or visited a physician due to a COPD exacerbation.

Discussions.

This is the first study to evaluate patient reported outcomes in COPD patients in Romania. One of the inclusion criteria was current treatment with fixed dose ICS/LABA combination. A previous international study [6] showed that budesonide/formoterol or salmeterol/fluticasone treatment was effective in improving lung function, symptoms and morning activity in patients with severe COPD.

The profile of COPD patients of our study showed that they are elderly, mainly men, usually presenting multiple comorbidities. These results are consistent with data from published literature[7]. Our study also highlighted the high incidence of arterial hypertension (32.2%), a condition with prevalence increasing linearly with age. The most frequent comorbidities in RELIEF study are from cardiovascular spectrum, a result consistent with data from literature.

COPD may have circadian variations in lung function and ability to perform physical activities is more problematic in the morning than at other times of the day[3,8]. The results of RELIEF study suggest that morning functionality in COPD grade C and D patients can be improved with treatment based on COPD guidelines. The observational nature of the investigation increases the applicability to clinical practice, where clinical exam should include quality of life assessment and monitoring of morning symptoms which can provide useful clinical parameters for evaluating the effectiveness of COPD therapy.

COPD is an incurrable and progressive disease, with a considerable impact on daily functioning[4]. More than 80% of COPD patients report difficulties in climbing stairs and the majority of patients need help in performing activities of daily living[4]. Literature indicates that physical activity level is reduced in patients with moderate to severe COPD compared to healthy subjects. Thus, step counts were reported 40 to 60% lower and walking time was 55% lower in patients with moderate to severe COPD compared to the healthy control subjects[9,10], with a proportional decline in steps for the more severe stages[9]. For healthy subjects, preliminary pedometer-determined physical activity cut-points were determined, with values of less than 5,000 steps/day defining the sedentary activity, which includes two sub-categories: basal activity for < 2,500 steps/day and limited activity for a level of 2,500 – 4,999 steps/day[11]. The first studies in the field of physical activity focusing on older adults and special populations, including those with heart and vascular diseases, COPD, diabetes and dyalisis,

Table 3 CDLM score at each study visit (Per Protocol [PP] population)

	Visit 1	Visit 2	Visit 3	Visit 4
n	259	259	259	259
Mean (SD)	3.79 (0.93)	3.94 (0.86)	3.96 (0.93)	3.95 (0.92)
Median	4	4.04	4.06	4.03
Q1, Q3	3, 4.5	3.33, 4.74	3.33, 4.85	3.33, 4.83
Min, Max	1.17, 5	1.05, 5	0.6, 5	0.48, 5

SD – Standard Deviation, Q1 – 1st quartile, Q3 – 3rd quartile, Min – minim, Max - maxim

Table 4 General health status score change between study visits

Change in each score category [N (%)]	Visit 1 to Visit 2	Visit 2 to Visit 3	Visit 3 to Visit 4	Visit 1 to Visit 4
1	0 (0)	0 (0)	0 (0)	0 (0)
2	-3 (1.2)	-5 (1.9)	1 (0.4)	-7 (2.7)
3	-17 (6.6)	0 (0)	-12 (4.6)	-29 (11.2)
4	1 (0.4)	4 (1.5)	8 (3.1)	13 (5)
5	19 (7.3)	1 (0.4)	3 (1.2)	23 (8.9)
p-value	<.0001	0.5488	0.0654	<.0001

breast cancer etc., have shown that older adults with disabilities took the lower number of steps/day (1,214 steps/day) followed by individuals with COPD (2,237 steps/day) [12]. Normative data from these studies reported that one can expect special populations to take 3,500 – 5,500 steps/day[12]. In our study, the number of steps/day was consistent to the ones previously reported in other studies for patients with severe COPD[9,10,13]. In RELIEF study, the number of daily steps performed for the last 7 consecutive days before Visits 2, 3, and 4 slightly decreased from one visit to another. One possible explanation would be that most of Visits 2 occurred in one month after enrolment had been performed in the summer time and at the beginning of the autumn, while most of Visits 4 occured at the end of autumn and during winter time. This result needs further investigation for a possible correlation with weather conditions. Preliminary data of a study assessing the influence of weather on physical activity in patients with COPD[14] indicated that inactivity is greatest during cold, overcast, and rainy weather. Most likely, the same explanation related to the time when the study was performed might be used for the low rate of exacerbation reported in RELIEF study.

Although the present study was not of interventional design, an improved capacity to perform morning activities was noted at the three-month follow-up.. This may be partially explained by increased patient self-awareness and high adherence rates to treatment after enrollment. Another plausible explanation is that clinical research in general, including non-interventional studies, is associated with an educational approach[4]. In our case, patient education consisted in increasing their ability to better understand their condition, the changes over the evolution of the disease and the correct management of symptoms and exacerbations. ■

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