Patient's Perception of Symptoms Related to Morning Activity in Chronic Obstructive Pulmonary Disease: The SYMBOL Study

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Background/Aims: Patients with chronic obstructive pulmonary disease (COPD) experience more problematic respiratory symptoms and have more trouble performing daily activities in the morning. The aim of this study was to assess the perception of COPD symptoms related to morning activities in patients with severe airflow limitation.

Methods: Data of 133 patients with severe airflow limitation were analyzed in a prospective, non-interventional study. A clinical symptom questionnaire was completed by patients at baseline. In patients having morning symptoms, defined by at least one or more prominent or aggravating symptom during morning activities, a morning activity questionnaire was also completed at baseline and following 2 months of COPD treatment.

Results: The most frequently reported COPD symptom was breathlessness (90.8%). Morning symptoms were reported in 76 (57%) patients; these had more frequent and severe clinical COPD symptoms. The most frequently reported morning activity was getting out of bed (82.9%). The long acting muscarinic antagonist (odds ratio [OR], 6.971; 95% confidence interval [CI], 1.317 to 11.905) and chest tightness (OR, 0.075; 95% CI, 0.011 to 0.518) were identified as significantly related to absence of morning symptoms. There was no significant correlation between the degree of forced expiratory volume in 1 second improvement and severity score differences of all items of morning activity after 2-month treatment.

Conclusions: Fifty-seven percent of COPD patients with severe airflow limitation have morning symptoms that limit their morning activities. These patients also have more prevalent and severe COPD symptoms. The results of this study therefore provide valuable information for the development of patient-reported outcomes in COPD.

Keywords: Perception; Morning; Symptoms; Activities; Chronic obstructive pulmonary disease

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a complex condition associated with long-term exposure to environmental toxic gases and particles, most often cigarette smoke, on a susceptible genetic background and is a major cause of chronic morbidity and mortality globally [1-3]. In Korea, the prevalence of COPD based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria is 17.2% among adults older than 45 years of age [4].

COPD represents a huge economic burden for the healthcare system [5-7], even though it is generally under-diagnosed and under-treated. This may be explained in part by the physician's insufficient knowledge of the patient's perception of COPD symptoms and poor adherence to COPD management guidelines [8,9]. There have been several studies [9-12] of patient perception of general symptoms, exacerbations, and treatments of COPD. In the PERCEIVE study [12], the most frequent complaint was that COPD limited daily activities. This is in part due to persistent and progressive breathlessness during daily activities or at rest, which eventually render the patient more physically passive [1].

Recent studies [13,14], based on the hypothesis that patients with COPD may have circadian variation in lung function [15-18], have shown that respiratory symptoms and the ability to perform physical activity in COPD patients were more problematic in the morning than at other times of the day. In addition, patients with severe COPD often perceive both daily and weekly variability of their symptoms in-between exacerbation periods [14]. Even though these were well-organized, multicenter, and international studies that recruited large patient populations, methodological limitations remain due to their cross-sectional design using an internet-based questionnaire survey [13] and phone interview [14], and the patient selection process.

The present study implemented a non-interventional and observational design aimed to assess patients' perception of COPD symptoms related to morning activities. Patients with severe airflow limitation were included together with a planned 2-month follow-up.

METHODS

Patients

Patients with stable COPD over 45 years old were recruited under criteria that included symptoms for at least 2 years, being current or ex-smokers with a smoking history of at least 10 pack-years, and post-bronchodilator forced expiratory volume in 1 second (FEV_1) < 50% of the predicted normal value. Exclusion criteria included on-going exacerbation of COPD or exacerbation within the previous 3 months; history of asthma or allergic rhinitis; lung cancer or any other significant respiratory disease such as bronchiectasis, lung fibrosis, interstitial lung disease, tuberculosis, or sarcoidosis; and current participation in an interventional clinical trial.

Study design

This was a non-interventional, prospective, and observational study (study NCT00894426; www.clinical-trials.gov), conducted in six out-patient care centers in southeast Korea; four centers in Daegu, one in Pohang, and one in Gyeongju. The study was conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines. Written, informed consent was obtained from all subjects, and the study protocol was approved by local hospital institutional review boards for all sites. On the baseline day, after performing the pulmonary function tests, clinical symptoms of eligible patients with post-bronchodilator FEV_1 < 50% of the predicted normal value were assessed using the clinical symptom questionnaire (CSQ). Patients who reported morning symptoms on the CSQ subsequently completed the morning activity questionnaire (MAQ). At the end of the study, after 2 months of COPD treatment, these patients completed another MAQ and underwent pulmonary function testing (Fig. 1). No standardized treatment for COPD was defined by the study protocol. The patients were treated according to routine clinical practices based on the GOLD guidelines at each study site; this treatment was maintained during the 2-month follow-up period.

Outcome measures

Spirometry was performed according to the American Thoracic Society guidelines [19] using Morris-Polgar

prediction equations [20,21]. For patient-reported outcomes, both CSQ and MAQ questionnaires were developed by the investigators using the pre-tested questions deemed relevant before the study was initiated. The CSQ consisted of four questions (Table 1). Morning symptoms were defined by prominent or aggravated clinical symptoms during morning activities compared with other times of the day. The MAQ consisted of one question specifying morning activities, such as getting out of bed, using the toilet, washing, drying, dressing, and preparing and eating breakfast (Table 1). The primary outcome variable was the patient's perception of COPD symptoms related to morning activities. The secondary outcome variables included the patient's perception of the variability of COPD symptoms, a comparison of COPD medications used at enrollment between patients with and without morning symptoms, and factors that may influence the patient's perception of symptom variability.

Statistical analysis

A descriptive analysis was made for all variables in the questionnaires. To compare the variables between patients with and without morning symptoms, t tests or Wilcoxon rank-sum tests for continuous variables and chi-square test for nominal variables were used. Logistic regression analysis was performed to investigate the factors associated with the presence of morning symptoms in patients with severe COPD. To compare changes in FEV_1 and in the severity score of morning activities at baseline and at the end of study after 2-months follow-up in patients with morning symptoms, t tests and Wilcoxon signed-rank tests were used, respectively. The Spearman correction method was used to calculate the correlation between changes in FEV_1 and in the severity score of morning activities. Statistical significance for all analysis was accepted at $p < 0.05$. All analyses were performed using the SAS version 9.2 (SAS Institute, Cary, NC, USA).
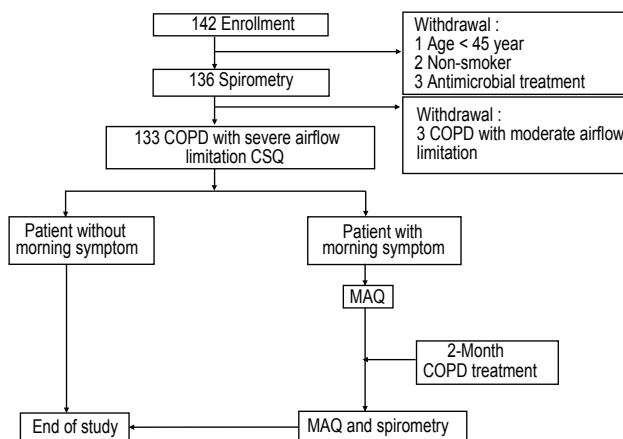

Figure 1. Study design. COPD, chronic obstructive pulmonary disease; CSQ, clinical symptom questionnaire; MAQ, morning activity questionnaire.

RESULTS

Subjects and baseline characteristics

Patients were enrolled in the study from May through

Table 1. Patient-reported outcomes questionnaires

A. Clinical symptom questionnaire
    1. During the past seven days, which of the following clinical symptoms have you suffered from?
        Breathlessness / Phlegm / Wheezing / Cough / Chest tightness / Sleep disturbance
    2. On how many days were your symptoms troublesome?
        Every day / On 4 to 6 days / On 1 to 3 days / Never
    3. On average, over the past 7 days, how your symptoms did you feel?
        Severity score: 1-10 (1, best; 10, worst)
    4. When were your symptoms the most troublesome for you?
        On waking / In the morning / In the afternoon / In the evening / At night
B. Morning activity questionnaire
    1. During the past seven days, what extent your symptoms have had an impact on each of the following activities?
        Getting out of bed / Using the toilet / Washing yourself (taking a shower or a bath) / Drying yourself / Dressing yourself /
        Preparing breakfast / Eating breakfast
        Severity score: 1-10 (1, minimal; 10, maximal)

November 2009. A total of 142 outpatients with COPD were recruited; 133 were eligible and completed the study (Fig. 1). Baseline characteristics are summarized in Table 2. The mean age was 67.5 years, 94.7% were males, and the mean post-bronchodilator FEV$_1$ was 1.0 L, 39.5% of the predicted. One hundred and twenty-seven patients (95.5%) had been prescribed at least one COPD medication. Among these, the most frequently prescribed was oral xanthine, followed by long-acting muscarinic antagonists and inhaled corticosteroids combined with long-acting β2-agonists. All patients reported experiencing at least one clinical COPD symptom in the 7 days prior to enrollment in the study. The most frequently reported symptom was breathlessness

(90.8%), followed by phlegm (77.3%), wheezing (66.1%), cough (64.6%), chest tightness (47.1%), and sleep disturbances (25%).

Patient perceptions of COPD symptoms related to morning activities

Seventy-six (57%) patients reported morning symptoms. Differences in characteristics between patients with and without morning symptoms are presented in Table 2. Among the maintenance medications used at enrollment, long-acting muscarinic antagonists and inhaled corticosteroids combined with long-acting β2-agonists were used significantly less frequently in patients with morning symptoms compared to those with-

Table 2. Baseline patient characteristics

Characteristic	Total	Patients with morning symptoms	Patients without morning symptoms	*p* value
Male/Female	126/7	72/4	54/3	0.2868
Age, yr	67.5 ± 8.8	67.4 ± 8.1	67.6 ± 9.7	0.8914
Smoking, pack-yr	44.1 ± 25.2	45.8 ± 25.8	41.7 ± 24.5	0.2198
GOLD stage				0.9715
III	120 (90.2)	69 (90.8)	51 (89.7)	
IV	13 (9.8)	7 (9.2)	6 (10.3)	
Post-bronchodilator FEV$_1$				
% pred	39.5 ± 6.7	40.0 ± 6.8	38.9 ± 6.5	0.0973
L	1.0 ± 0.22	1.01 ± 0.22	0.99 ± 0.23	0.1488
Medications used at entry				
SABA	55 (41.4)	31 (40.8)	24 (42.1)	0.8877
LABA	22 (16.5)	14 (18.4)	8 (14.0)	0.4085
SAMA	4 (3.0)	3 (3.9)	1 (1.8)	0.4287
LAMA	68 (51.1)	31 (40.8)	37 (64.9)	0.0170
ICS + LABA, fixed	68 (51.1)	32 (42.1)	36 (63.2)	0.0416
Xanthine	102 (76.7)	61 (80.3)	41 (71.9)	0.0795
Clinical symptoms				
Breathlessness	119 (90.8)	71 (93.4)	48 (84.2)	0.0043
Phlegm	102 (77.3)	64 (85.1)	38 (66.7)	0.0015
Wheezing	82 (66.1)	50 (65.8)	32 (56.1)	0.095
Cough	84 (64.6)	53 (69.7)	31 (54.4)	0.0087
Chest tightness	56 (47.1)	40 (52.6)	16 (28.1)	0.0005
Sleep disturbance	29 (25.0)	20 (26.3)	9 (15.8)	0.0531

Values are presented as mean ± SD or number (%).

GOLD, Global Initiative for Chronic Obstructive Lung Disease; FEV$_1$, forced expiratory volume in 1 second; SABA, short-acting β2-agonist; LABA, long-acting β2-agonist; SAMA, short-acting muscarinic antagonist; LAMA, long-acting muscarinic antagonist; ICS, inhaled corticosteroid.

out morning symptoms. All clinical COPD symptoms were more frequent and severe in patients with morning symptoms than in those without morning symptoms. Symptom scores of breathlessness and chest tight-
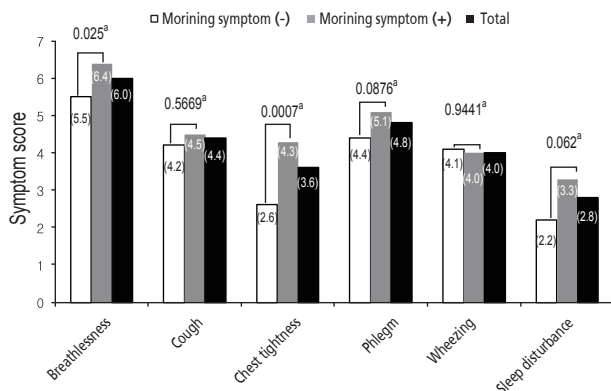

Figure 2. Comparison of clinical chronic obstructive pulmonary disease symptom severity according to the presence of morning symptoms. [a]p value by Wilcoxon's rank-sum test between patients with and without morning symptoms.

ness were significantly higher in patients with morning symptoms than in those without morning symptoms (Fig. 2). Of the morning activities limited by morning symptoms, the most frequently reported was getting out of bed (82.9%), followed by using the toilet (77.6%), drying (77.6%), and washing yourself (76.3%), and dressing yourself (70%). Washing yourself was the morning activity most severely limited by COPD symptoms (Table 3) and severity scores of all morning activities were significantly reduced after a 2-month follow-up.

Symptom variability and factors associated with the presence of morning symptoms

The two most common responses to the question, "When were your symptoms the most troublesome for you?" were on waking (35.1% to 63.6%, depending on the symptom, except sleep disturbance) and in the morning (20% to 52.1%, depending on the symptom, except wheezing and sleep disturbance). Therefore, the morning was reported as being the most troublesome

Table 3. Change in severity of morning activity after 2 months chronic obstructive pulmonary disease treatment in patients with morning symptoms (n = 76)

Morning activity	No. (%)	Visit	Mean ± SD	p value[a]
Getting out of bed	63 (82.9)	Baseline	5.2 ± 2.6	
		Endpoint	4 ± 2	
		Change	-1.2 ± 1.4	< 0.0001
Using the toilet	59 (77.6)	Baseline	4.3 ± 2.6	
		Endpoint	3.4 ± 1.9	
		Change	-0.8 ± 1.7	0.0001
Washing yourself (taking a shower or a bath)	58 (76.3)	Baseline	5.7 ± 2.4	
		Endpoint	3.8 ± 2.0	
		Change	-1.9 ± 2.0	< 0.0001
Drying yourself	59 (77.6)	Baseline	4.3 ± 2.6	
		Endpoint	3.2 ± 2.0	
		Change	-1.2 ± 1.6	< 0.0001
Dressing yourself	53 (69.7)	Baseline	3.7 ± 2.4	
		Endpoint	2.7 ± 1.8	
		Change	-1.1 ± 1.6	< 0.0001
Preparing breakfast	34 (44.7)	Baseline	2.7 ± 2.3	
		Endpoint	2 ± 1.7	
		Change	-0.7 ± 1.2	0.0021
Eating breakfast	43 (56.6)	Baseline	2.8 ± 2.2	
		Endpoint	1.8 ± 1.3	
		Change	-1 ± 1.5	< 0.0001

[a]p value by Wilcoxon's signed-rank test between baseline and end point.

time of day for experiencing COPD symptoms with the exception of except sleep disturbance (Fig. 3). When asked how many days of the previous week their symptoms were troublesome, the most common response was every day (39.3% to 66.4%, depending on the symptom), followed by 1 to 3 days and 4 to 6 days (Fig. 4). Patterns were similar in patients with and without morning symptoms. Breathlessness every day was reported by 70.4% of patients.

Multivariate logistic regression analysis was performed to investigate the factors associated with the presence of morning symptoms. Treatment with a long-acting muscarinic antagonist was a preventive factor for the presence of morning symptoms, while chest tightness was a strong predictive factor for the presence of morning symptoms (Table 4). Significantly greater improvement in FEV_1 was demonstrated after 2 months of COPD treatment in patients with morning symptoms

(Fig. 5). However, there were no significant correlations between the degree of improvement of FEV_1 and the changes in severity scores for all morning activities, except dressing (Table 5).

DISCUSSION

Our data demonstrate that 57% of COPD patients with severe airflow limitation have morning symptoms that limit their morning activities. Several previous studies [15-18] have reported that patients with COPD may experience diurnal variation in lung function. These studies determined that spirometry results over 24 hours, FEV_1, forced vital capacity, and inspiratory capacity exhibited circadian variation with maximum values at ap-
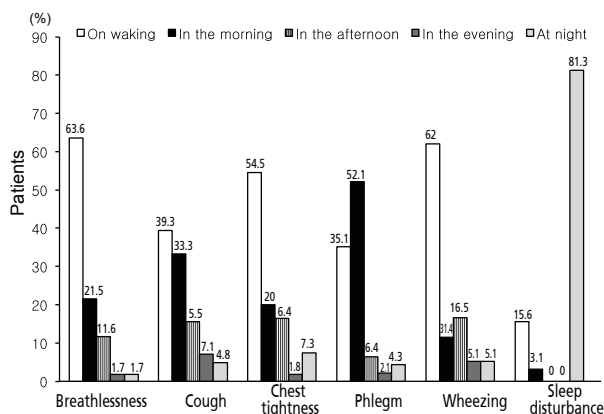

Figure 3. Patients who had reported chronic obstructive pulmonary disease symptoms in the past 7 days were asked during what times of the day the symptoms were most troublesome.
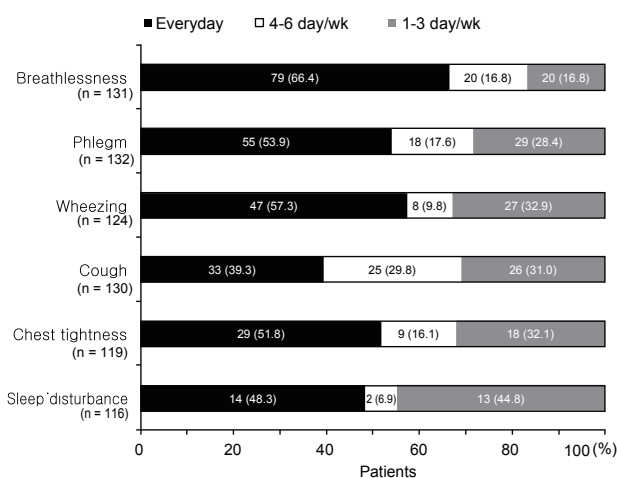

Figure 4. Patients who had reported chronic obstructive pulmonary disease symptoms in the past 7 days were asked for how many days the symptoms were troublesome.

Table 4. Multivariate logistic regression analyses of parameters that discriminated the absence of morning symptoms

Variable	OR (95% CI)	p value
LAMA	6.971 (1.317–11.905)	0.0143
ICS + LABA, fixed	0.333 (0.065–1.716)	0.1888
Breathlessness	0.661 (0.050–8.659)	0.7522
Phlegm	0.661 (0.053–1.483)	0.1347
Cough	1.606 (0.302–8.555)	0.5787
Chest tightness	0.075 (0.011–0.518)	0.0086

OR, odds ratio; CI, confidence interval; LAMA, long-acting muscarinic antagonist; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist.

proximately noon and minimum values during the early morning [16,17]. This supports the observation that most COPD patients report more severe symptoms in the morning. In the internet-based questionnaire survey by Partridge et al. [13], 46% of patients with severe COPD reported that the morning was the worst time of day for COPD symptoms. However, this value may not represent the true prevalence of symptoms in severe COPD patients since spirometry data was not reported and severity was assessed according to regular use of COPD medication, dyspnea level, and exacerbation frequency. Therefore, our study provides valuable information on the prevalence of morning symptoms in COPD patients with severe airflow limitation, as defined by GOLD. The high frequency of awakenings in our patient population supports the perception that the morning is the most troublesome time of the day for experiencing
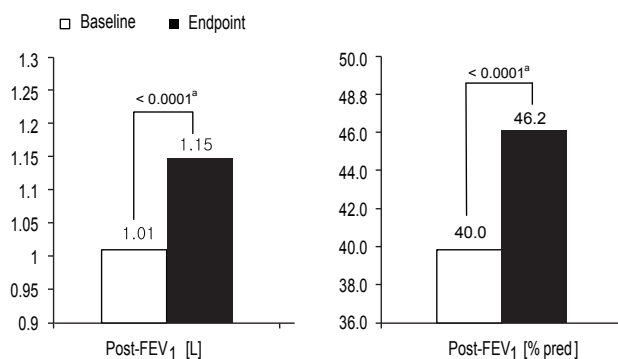
COPD symptoms, as reported by Kessler et al. [14]. In general, co-morbid depressive symptoms and depressive disorders in COPD are associated with a negative course of disease, including increases in mortality and symptom burden, as well as decreases in functional status, quality of life and activities [22]. Disruptions to circadian rhythms, such as early morning waking, diurnal mood changes, and changes in sleep architecture have been found among patients with major depression [23]. For these reasons, we hypothesize that the high prevalence of depression in COPD may also be associated with the high prevalence of morning symptoms. However, this hypothesis in patients with COPD needs to be substantiated by further research.

Breathlessness, which was the most common COPD symptom in this study, is a hallmark symptom of COPD and is characteristically persistent and progressive [1,24]. According to a telephone survey of patients with COPD living in North America and in Europe [11], dyspnea was common and was more prevalent in older COPD subjects, over 65 years of age. This supports our results since all of the patients in our study were older and had severe or very severe end airflow limitations. In addition, respiratory conditions can limit many fundamental physical activities in COPD subjects of all ages [11,12]. For example, morning activities such as getting out of bed, using the toilet, washing, drying, dressing, and preparing or eating breakfast are essential to start the day. Limitations on these activities can greatly impact behavioral and psychosocial aspects of COPD patients. The present study showed that all COPD symptoms were more frequent and severe in patients

Figure 5. Change in post-bronchodilator forced expiratory volume in 1 second (FEV_1) after 2 months of chronic obstructive pulmonary disease treatment in patients with morning symptoms. [a]p value by Student's t test between baseline and end point.

Table 5. Correlation between changes in post-bronchodilator FEV_1 and severity of morning activities after 2-month chronic obstructive pulmonary disease treatment[a]

Morning activity	Changes in post-bronchodilator FEV_1			
	% pred	p value	L	p value
Getting out of bed	-0.1506	0.2592	-0.1170	0.3820
Using the toilet	-0.0490	0.7250	-0.0660	0.6354
Washing yourself (taking a shower or a bath)	-0.1982	0.1549	-0.1247	0.3737
Drying yourself	-0.1808	0.1907	-0.1141	0.4116
Dressing yourself	-0.3349	0.0200	-0.2532	0.0825
Preparing breakfast	-0.1496	0.4139	-0.1149	0.5313
Eating breakfast	-0.1178	0.4813	-0.0761	0.6498

FEV_1, forced expiratory volume in 1 second.

[a]Spearman correction and p value.

with morning symptoms than in those without morning symptoms. Furthermore, getting out of bed, using the toilet, drying, and washing were the most frequent morning activities limited by morning symptoms. In an internet-based questionnaire survey by Partridge et al. [13], morning activities most affected by COPD were walking up and down stairs, putting on shoes and socks, making the bed, showering or bathing, drying their body with a towel and dressing. Even though some disparity in the frequency or severity of activities between the two studies is noted, likely resulting from differences in patient selection and life styles, it is clear that in patients with severe COPD, the disease has a considerable impact on morning activities.

There have been two interventional studies [25,26] using a MAQ as a clinical outcome assessment. That by Partridge et al. [25] showed that short-term budesonide/formoterol dry powder inhaler (DPI) or salmeterol/fluticasone DPI treatment was effective in improving lung function, symptoms, and morning activity in patients with severe COPD. Budesonide/formoterol, in particular, had a more rapid onset of effect compared with salmeterol/fluticasone and resulted in greater improvements in the ability to perform morning activities despite the lower inhaled corticosteroid dose. The CLIMB study [26] showed that budesonide/formoterol added to tiotropium versus tiotropium alone provides rapid and sustained improvements in lung function, health status, morning symptoms and activities, and reduces severe exacerbations. In this present study, long-acting muscarinic antagonists or inhaled corticosteroids combined with long-acting β2-agonists were used significantly less frequently in patients with morning symptoms than in patients without morning symptoms. Furthermore, treatment with a long-acting muscarinic antagonist was a preventive factor for the presence of morning symptoms. Collectively, these results suggest that morning symptoms in severe COPD patients can be improved by treatment based on the COPD guidelines and monitoring morning symptoms can provide useful clinical parameters for evaluating the effectiveness of COPD therapy. Although the present study was not of an interventional design, the severity of pulmonary function and morning activities were improved after a 2-month follow-up. This may be explained in part by physician adherence to COPD guidelines or increased patient self-awareness and compliance to COPD management following enrollment.

It is important to note that there was no significant correlation between the degree of improvement of FEV_1 and the changes of severity scores of all morning activities. The airflow limitation in COPD did not correlate well with patient-reported outcomes such as symptoms, exercise capacity, activities of daily living and health-related quality of life [27-31]. Moreover, as the disease severity increases, patients with COPD develop more co-morbid conditions compromising patient-reported outcomes [32,33]. Therefore, it seems likely that changes in these extrapulmonary conditions after treatment should influence improvement of morning activities in our COPD patients. Although spirometry is the most frequently recommended monitoring routine in clinical practice guidelines [34], useful information about lung function decline is unlikely to be provided from spirometry measurements performed more than once a year [1]; this is even more pronounced in severe COPD. Frequent check-ups of patient-reported outcomes is a more practical way to monitor disease progression and development of exacerbations and to evaluate the effectiveness of therapy [35,36]. Accordingly, our results provide additional valuable information for development of patient-reported outcomes related to morning activities [37].

This study has some limitations. Since we did not assess the health-related quality of life as an outcome measurement from the beginning of study, the relationship between quality of life and severity of morning activity remains to be determined. In addition, due to a lack of patient co-morbidity information, we could not evaluate the factors affecting morning symptoms in detail. Further research should be directed towards answering these questions.

In conclusion, 57% of COPD patients with severe airflow limitation have morning symptoms that limit their morning activities. These patients had more prevalent and severe COPD symptoms than those without morning symptoms. The results reported here provide additional valuable information necessary for development of patient-reported outcomes for evaluating the effectiveness of COPD therapy.

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