ORIGINAL ARTICLE

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The health-related quality-of-life of chronic obstructive pulmonary disease patients and disease-related indirect burdens

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Background/Aims: Many chronic obstructive pulmonary disease (COPD) patients have physical limitations. We investigated EuroQol five-dimensions five-level (EQ-5D-5L) of COPD patients to assess quality of life, and assessed indirect burden including time expenditure to visit doctor, home care rate, and caregiver related burden.

Methods: We recruited 355 COPD patients according to severity of airflow limitation that severity was set at 10% mild, 40% moderate, 30% severe, and 20% very severe in two primary and 11 secondary/tertiary hospitals. Eligible patients were aged ≥ 40 years, who have been diagnosed with COPD for more than 1 year. Patients were recruited between June 2015 and October 2016.

Results: The quality of life tended to decline with age, from mild to very severe impairment, as revealed by the EQ-5D-5L scores and the EQ visual analog scale. Family caregivers accompanied 22.6% of patients who visited outpatient clinics, and 25% of stage IV COPD patients. During emergency visits and hospitalization, this figure increased to > 60%. The home care rates were 28.5% for stage I patients, and 34.4, 31.8, and 52% for stage II to IV patients, respectively. The percentage of caregivers who stopped working was 13.6%. The EQ-5D index was strongly associated with the dyspnea scale ($r = -0.64$, $p < 0.001$). The average required time to see a doctor and visit the pharmacy was 154 minutes.

Conclusions: In patients with COPD, the EQ-5D index decreased and disease-related home caregiving increased with airflow limitation. We considered the caregiver-related burden when making a strategy for COPD management.

Keywords: Pulmonary disease, chronic obstructive; Health expenditures; Caregivers; Quality of life

Choi HS, et al. Life quality and indirect costs in COPD

KJIM

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive disease, the prevalence of which has increased over the past three decades [1,2]. The prevalence of COPD in Korea (as revealed by the Korea National Health and Nutrition Examination Survey [KNHANES]) ranged from 13.1% to 14.6% from 2010 to 2015 [3]. COPD is associated with comorbidities including muscle weakness, osteoporosis, diabetes, cardiovascular disease, hypertension, depression, and lung cancer [4]. The economic burden imposed by COPD is enormous [1,5] and will continue to rise [6]; the significance of COPD cannot be overestimated. The significant worldwide burden of COPD, and the associated economic implications triggered the creation of the global initiative for chronic obstructive lung disease (GOLD) evidence-based guidelines, which are frequently updated [7].

As is true of all chronic diseases, the economic burden of COPD is both direct and indirect. Direct costs include the healthcare resources required (drugs and medical instruments); the indirect costs include travel expenses, loss of productivity, premature retirement of patients and caregivers, and time spent in visiting healthcare institutions [8], among others. The annual COPD costs in the USA are approximately US $50 billion (40% indirect costs and 60% direct healthcare expenditures) [9]. COPD patients are associated with a reduction in workforce participation and general activity limitation than individuals without COPD reflecting increased indirect costs [10]. Many reports have explored the direct and indirect economic burdens of COPD, including productivity losses [10]. However, few studies have considered the time expenditure and lost productivity of caregivers, which are indirect costs.

Patient-reported outcomes, including the health-related quality of life (HRQL), are useful for assessing COPD severity and treatment outcomes; COPD management is largely symptomatic. The HRQL is a valuable measure of clinical trial outcomes. The EuroQol five-dimensions (EQ-5D) assesses generic HRQL via both descriptive system and visual analog scale (VAS), and is widely used to evaluate COPD outcomes [11-13]. Original EQ-5D descriptive system was redesigned with five-level response (5L) [13], which was validated in Korean people recently [14]. We hypothesized that the re-

quired time to see a doctor, severity of airflow limitation or symptom affect the HRQL.

Our objectives here were to (1) assess the HRQL using the new EQ-5D-5L; (2) measure the informal, family, and caregiver-related indirect burdens (accompanying patients to outpatient clinics and quitting jobs to deliver home care); (3) measure the time required to visit outpatient clinics/pharmacies; and (4) assess the home care rate. Also, we evaluated the relationship between the HRQL and airflow limitation, dyspnea grade, and the time required to visit clinic.

METHODS

Study design

This study was part of a multi-center observational study of adult COPD patients. Site-based surveys were administered to patients with primary COPD diagnoses during routine visits to healthcare providers. Subjects were recruited between June 2015 and October 2016. We assigned COPD severity grades to those diagnosed in 2 primary clinics, and 11 advanced general/tertiary hospitals. Of all patients, 10% had mild, 40% moderate, 30% severe, and 20% very severe COPD.

Participants

The inclusion criteria were: (1) diagnosis of COPD by a physician more than 1 year ago; (2) age ≥ 40 years; and (3) no severe comorbidity (i.e., no malignant disease such as lung cancer). COPD severity was graded using the GOLD criteria (based on the post-bronchodilator forced expired volume in 1 second [FEV_1] as a percentage of the predicted normal value [FEV_1% predicted] in patients with FEV_1/forced vital capacity < 70%): mild, stage I, FEV_1 ≥ 80%; moderate, stage II, 50% ≤ FEV_1 < 80%; severe, stage III, 30% ≤ FEV_1 < 50%; or very severe, stage IV, FEV_1 < 30%. Respiratory specialists asked all COPD patients who met these inclusion criteria to participate in the survey. All patients who agreed underwent face-to-face interviews with their doctors, during which the questionnaire was completed; all patients gave written informed consent.

Questionnaire exploring indirect burdens

The questionnaires explored demographic character-

istics, the HRQL (as indexed by the EQ-5D), medical costs, nursing fees, absenteeism, presenteeism, productivity losses, the time required to visit outpatient clinics/pharmacies, whether a caregiver accompanied the patient, and exacerbation frequency. We collected data on age, gender, the post bronchodilator FEV_1 (% predicted), body mass index (BMI), the modified Medical Research Council (mMRC) score, the frequency of COPD exacerbation during the prior year, EQ-5D data, and indirect costs. We defined the indirect burden as: (1) a family caregiver accompanying the patient to an outpatient clinic, emergency room, or admission ward (the time from home to home); (2) the time taken to visit outpatient clinic and pharmacy (from home door to home door); (3) the home care time by a family caregiver; and, (4) work time lost by a family caregiver because of a need for home nursing (quitting a job, or transitioning from full- to part-time work). A family caregiver accompanying rate was evaluated to measure caregiver's loss of work as indirect burden. We also recorded caregiver age and gender.

HRQL assessed using the EQ-5D instrument

The EuroQol five-dimensions five-level (EQ-5D-5L) comprises a descriptive module (two pages) and the EQ-VAS (three pages). The descriptive module explores mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five-level response corresponding to no problem, slight problems, moderate problems, severe problems and extreme problems [12]. Participants tick boxes ranging from 1 (no problem) to 5 (extremely problematic); one-digit numbers yielded by the responses to the individual items are combined to give a five-digit number describing health status; the 3,125 possible outcomes range from 11111 to 55555. For example, state 11111 indicates no problems in any dimension; state 12345 indicates no problems with mobility, slight problems with washing or dressing, moderate problems with usual activities, severe pain or discomfort, and extreme anxiety or depression. The numerals 1 to 5 have no arithmetic properties and should not be used as cardinal scores. The 3,125 EQ-5D-5L health states were converted to single index values calculated using the time-tradeoff protocol [14] characteristic of the final evaluation procedure of the EuroQol Group [12]. The utility index ranges from 1.0 (best possible health, 11111)

to –0.066 (worst possible health, 55555) [14]. A higher EQ-5D-5L index value reflects better health status [12].

The EQ-5D includes the EQ-VAS, via which the respondents self-rate overall health on the interview day on a 20-cm, 0 to 100 hash-marked, vertical VAS with top and bottom endpoints of 'the worst health you can imagine' (0) and 'the best health you can imagine' (100), respectively. The respondents are instructed as follows: 'mark an X on the scale to indicate how your health is today.' Then, they are asked to 'write the number marked on the scale in the box below' [12].

Statistical analysis

All statistical analyses were performed using SPSS software version 24.0 (IBM Corp., Armonk, NY, USA). Data are presented as means or numbers with percentages. We calculated the mean or median EQ-5D-5L indices, EQ-VAS scores, and accompaniment, home care, and caregiver work loss rates, according to COPD severity. We used ANOVA to analyze EQ-5D data (i.e., the 5L indices and VAS scores) by COPD severity. The relationships between EQ-5D index score and airflow limitation (FEV_1 % predicted), dyspnea severity (mMRC grade), and indirect cost (clinic visit time) were assessed by calculating Pearson correlation coefficients. A p value < 0.050 was considered statistically significant.

Ethics statement

The study protocol was reviewed and approved by the Institutional Review Boards of all participating institutions (Konkuk University Hospital, KUH1010636; Hallym University Kangdong Sacred Heart Hospital, 2015-02-205). Written informed consent was obtained from all subjects at the time of enrolment.

RESULTS

Demographics and health status

A total of 355 COPD patients were recruited. The proportion of males was very high (91.9%) in all stages of COPD. A significantly high proportion of patients were aged > 60 years; most patients (74.4%) were aged 60 to 80 years. Among all patients, 12.1% were of GOLD I stage, 42.9% of stage II, 31% of stage III, and 14% of stage IV. Those with a severe airflow limitation had a lower BMI

Choi HS, et al. Life quality and indirect costs in COPD

KJIM

than those with a mild limitation. The mMRC grade increased by the severity of airflow limitation (Table 1). Among all patients, 53.1% had experienced exacerbations during the previous year. As airflow limitation progressed, the number of patients who experienced exacerbations increased significantly (stage I, 25.6%; stage II, 43.7%; stage III, 61.8%; and stage IV, 86%) (Table 1). Most patients (64.5%) reported mobility problems and 60% had activity problems graded as EQ-5D-5L level 2 to 5 (Table 1).

EQ-5D-5L index and EQ-VAS scores by GOLD criteria

The EQ-5D index and EQ-VAS scores by COPD severity (GOLD stage) are shown in Table 2. The mean EQ-5D-5L index of all patients was 0.74. The EQ-5D index scores of patients differed significantly among the four COPD stages ($p < 0.001$). The mean values were 0.83 for stage I, 0.79 for stage II, 0.73 for stage III, and 0.55 for stage IV patients. The mean EQ-5D-5L indexes for stage I to III patients were significantly higher than the stage IV index. The mean EQ-VAS score was 63. The EQ-VAS scores of patients of the four COPD stages differed significantly ($p < 0.001$), being 72 for stage I, 69 for stage II, 58 for stage III, and 44 for stage IV patients. The EQ-VAS scores of stage I–III patients were significantly higher than those of stage IV patients (Table 2).

Caregiver accompaniment rate by the GOLD criteria

Among all patients, 22.6% were accompanied by family caregivers when visiting outpatient clinics; 62% were accompanied when visiting emergency rooms and 62.4% were accompanied when admitted (Table 3).

Indirect burden of home care by family caregivers

Among all patients, 125 (35.2%) received home care from family caregivers. More patients with stage IV airflow limitations received home care (52%) than stage I to III patients. The family caregivers were principally female (86.4%) and had a mean age of 64 years; 13.6% of caregivers had quit their jobs to take care of patients (Table 4).

Correlations between EQ-5D index value, airflow limitation, mMRC grade, and time required to see a doctor

The EQ-5D-5L index and post-bronchodilator $FEV_1\%$ predicted were correlated (Pearson correlation coeffi-

Table 1. Demographics of study subjects (n = 355)

Variable	Value
Age, yr	
< 60	46 (12.9)
60–69	103 (29.0)
70–79	161 (45.4)
> 80	45 (12.7)
Male sex	326 (91.9)
COPD GOLD stage	
I	43 (12.1)
II	152 (42.9)
III	110 (31.0)
IV	50 (14.0)
BMI, kg/m²	
I	23.1 ± 2.8
II	24.6 ± 3.3
III	22.2 ± 3.5
IV	20.8 ± 2.9
mMRC grade	
I	0.9 ± 0.9
II	1.4 ± 1.0
III	2.1 ± 1.0
IV	2.6 ± 1.0
Exacerbation history/previous year	
I	11 (25.6)
II	66 (43.7)
III	68 (61.8)
IV	43 (86.0)
Frequency of problems reported on the EQ-5D-5L[a]	
Mobility	229 (64.5)
Self-care	122 (34.3)
Usual activity	213 (60.0)
Pain/discomfort	205 (57.7)
Anxiety/depression	181 (50.9)

Values are presented as number (%) or mean ± SD.
COPD, chronic obstructive pulmonary disease; GOLD, global initiative for chronic obstructive lung disease; BMI, body mass index; mMRC, modified Medical Research Council; EQ-5D-5L, EuroQol five-dimensions five-level questionnaire.
[a]The numbers of patients reporting at least one problem on the EQ-5D.

cient, $r = 0.47$, $p < 0.001$). The relationship between the EQ-5D-5L index value and the mMRC was also strong ($r = -0.64$, $p < 0.001$), as was the relationship between the EQ-VAS score and the mMRC grade ($r = -0.55$, $p < 0.001$). We found no relationship between the EQ-5D index score and the time required to see a doctor at outpatient clinics (Table 5).

Required time to visit outpatient clinics
The average time required to visit an outpatient clinic including the pharmacy was 154 minutes. Patients of stages III (172 minutes) and IV (162 minutes) required more time than stage I (153 minutes) and II (138 minutes) patients (Fig. 1).

Table 2. EQ-5D-5L index and EQ-VAS scores according to the GOLD stage

	Mean	Median	p value[a]
EQ-5D-5L index, total	0.74	0.80	< 0.001
I	0.83	0.86	
II	0.79	0.83	
III	0.73	0.76	
IV	0.55	0.57	
EQ-VAS score, total	63	70	< 0.001
I	72	75	
II	69	70	
III	58	60	
IV	44	50	

EQ-5D-5L, EuroQol five-dimensions five-level questionnaire; EQ-VAS, EuroQol visual analog scale; GOLD, global initiative for chronic obstructive lung disease.
[a]A p values were derived using analysis of variance.

DISCUSSION

We found that the HRQL of COPD patients, as measured by the EQ-5D, deteriorated as the COPD stage and dyspnea severity worsened. The disease-related indirect burden (home caregiving) increased as airflow limitation increased. Previous reports on the EQ-5D status of Korean COPD patients evaluated KNHANES data [15] or COPD patients treated in a single center [16]; both reports used the EQ-5D-3L [15,16]. COPD patients from KNHANES IV to V (2007 to 2010) data were diagnosed via pulmonary function test of on-site national survey [15]. However, uniquely, we gathered data from symptomatic COPD patients formally diagnosed and had ongoing treatment for COPD in several centers. For the first time, we used the EQ-5D-5L to measure quality of life of COPD patients in Korean setting. The EQ-5D utility index of COPD patients from KNHANES data [15] was higher than our utility index (0.89 vs. 0.74). We could not compare of both, because data from KNHANES did not showed severity of airflow limitations and used three leveled EQ-5D. The three leveled EQ-5D utility index of COPD patients from single center [16] was higher than our utility index (0.84 vs. 0.74). The EQ-5D indexes were decreased according to the severity of airflow limitation [16], which was similar with our study.

The EQ-5D was developed in 1987 by the EuroQol Group, involving five European countries. This instrument is self-completed, and is thus ideal for use in postal surveys and clinics, or during face-to-face interviews. The EQ-5D is simple and can be completed rapidly. Each dimension features three levels of response (no problem, some problems, and extreme problems; EQ-5D-3L) [11,12]. To improve sensitivity and reduce ceiling

Table 3. Indirect burdens on family caregivers accompanying patients visiting healthcare resources according to the GOLD stage

GOLD criteria	Total subjects, no. (caregiver accompanying rate, %)		
	Outpatient clinic visit	Emergency room visit	Hospitalization
I	39 (20.3)	3 (33.3)	1 (0)
II	141 (23.5)	16 (68.8)	17 (82.4)
III	95 (21.2)	20 (67.5)	28 (54.7)
IV	45 (25.0)	15 (53.3)	19 (59.2)
Total	320 (22.6)	54 (62.0)	65 (62.4)

GOLD, global initiative for chronic obstructive lung disease.

Choi HS, et al. Life quality and indirect costs in COPD

KJIM

Table 4. Indirect burdens of home care and home caregiver work loss according to the GOLD stage

GOLD stage	Home care	Home caregiver		
		Female sex	Age, yr	Quit working
I	12 (28.6)	12 (100)	69.3 ± 8.3	2 (16.7)
II	52 (34.4)	46 (88.5)	64.9 ± 13.5	7 (13.5)
III	35 (31.8)	29 (82.9)	64.1 ± 17.2	4 (11.4)
IV	26 (52.0)	21 (80.7)	61.5 ± 10.9	4 (15.4)
Total	125 (35.2)	108 (86.4)	64.4 ± 13.2	17 (13.6)

Values are presented as number (%) or mean ± SD.
GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Table 5. Correlations between EQ-5D index scores and airflow limitation, mMRC grade, and indirect costs

Variable	EQ-5D-5L index		EQ-VAS	
	Pearson coefficient	p value	Pearson coefficient	p value
Post-bronchodilator FEV_1, % predicted	0.47	< 0.001	0.39	< 0.001
mMRC grade	−0.64	< 0.001	−0.55	< 0.001
Time required to see a doctor at the outpatient clinic, min	−0.11	0.03	−0.09	0.06

EQ-5D-5L, EuroQol five-dimensions five-level questionnaire; mMRC, modified Medical Research Council; EQ-VAS, EuroQol visual analog scale; FEV_1, forced expiratory volume in 1 second.
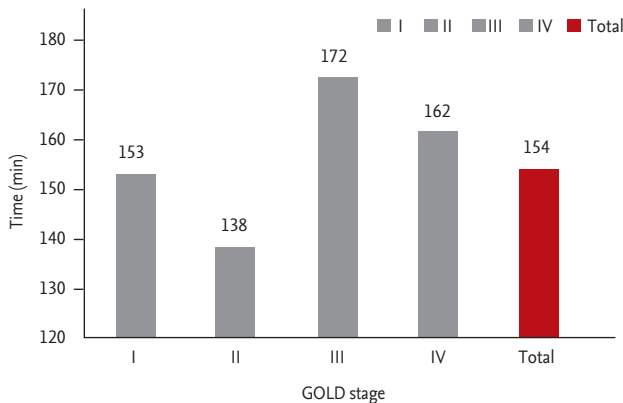

Figure 1. The time required to visit outpatient clinics and pharmacies according to the global initiative for chronic obstructive lung disease (GOLD) stage. Values are means.

effects, the EQ-5D-5L was introduced by the EuroQol Group in 2009 [13]. The EQ-5D-5L has been widely tested and used (in both general and patient populations) to describe and evaluate general health status. The instrument has been translated into over 130 languages and has been employed in clinical trials, observational studies, and health surveys [12]. The Korean version was validated by Kim et al. [14].

We found that the mean EQ-5D-5L index and the EQ-VAS score fell significantly as COPD became more severe, particularly in patients with advanced airflow limitations, as previously reported [17]. Approximately 60% of COPD patients experienced limitations in usual activities; 64% reported limited mobility. Lin et al. [17] found that about 64% of COPD patients reported mobility problems and about 55% had problems in the performance of daily activities. Thus, many COPD patients cannot work. Patel et al. [10] reported COPD patients were less likely to be working than non-COPD subjects. The most common problem revealed by the EQ-5D was in the mobility domain; 25% of patients were accompanied by family caregivers when visiting outpatient clinics/pharmacies. One-third of all patients received in-home care from family caregivers. COPD (with or without comorbidities) imposes a high economic burden not only on healthcare systems, but also on society in general, being associated with disability, loss of productivity, and premature mortality. The true burden of a disease is not reflected in the direct medical costs alone; indirect costs constitute a substantial proportion of the burden. No prior Korean report on the burden imposed

on family caregivers has appeared. We measured the time contributed by family caregivers to assist COPD patients in accessing medical treatment.

About 25% of COPD patients visited outpatient clinics accompanied by family caregivers, and > 50% were accompanied when visiting emergency rooms or during admission. However, no linear relationship between the accompaniment rate and COPD severity was apparent. Gautun et al. [18] reported that about 70% of COPD patients had informal caregivers and 67% of caregivers accompanied patients to healthcare facilities. COPD patients often require continuous care; the EQ-5D showed that this may be attributable to limitations in mobility or usual activities. A previous report found that up to 66% of COPD patients received informal home care [19]. We found that 33% of patients were supported by family caregivers at home, as were 50% of those with advanced airflow limitation. The indirect costs increase as airflow limitation deteriorates [5]; we found that the in-home care rate increased as airflow limitation progressed. Of all caregivers, 13.6% quit their jobs to stay home. The proportion of home care increased with COPD severity, but caregiver work loss was not associated with the severity of airflow limitation. A previous study found that 7% of caregivers quit their jobs [20]. Family-related caregivers are at high risk of such loss; they perform housework, arrange transportation, and accompany patients to healthcare services. In one study, 43% of informal caregivers were employed, but 44% took time off from work and 4% quit working to care for COPD patients [18]. Indeed, the work loss is greater than reported. Caregivers take days off, leave the office earlier, or are late to work. This compromises financial security, in turn reducing the availability of care resources.

Most family caregivers had mood- and health-related problems [19], emphasizing the need to improve support. Effective strategies assisting caregivers to deliver usual care, providing emotional and psychosocial support, and enhancing adherence to treatment, are required. Almost all caregivers in the present study were females > 60 years of age, as in a previous report [19]. The principal caregivers were relatives or friends in 88.6% of cases [19]. The most common caregiver was the patient's spouse (70%) or an adult child (21%) [18]. Caregivers greatly influence the well-being of COPD patients. The availability of an informal caregiver (compared to no caregiver) was associated with better adherence to treatment [21], a reduced rate of smoking [21], and less frequent emergency room visits [22]. Interventions for patients with and without caregivers are required to optimize COPD management. Both clinicians and researchers are increasingly studying informal COPD caregiving; the prevalence of severe disease continues to rise, associated with substantial health, social, and economic impacts [23]. Healthcare systems must economically optimize the quality of life of COPD patients. Thus, a shift from hospital to home care may be inevitable; patients will increasingly rely on informal caregivers [24]. Informal family caregiver status is not evaluated by the GOLD guideline [7]; no validated questionnaire explores this topic. COPD management must focus not only on optimal therapy, but also on home management, including the role of the informal caregiver. Such caregiving is complex [24]. Caregivers may lack knowledge on COPD and be unaware that palliative care is available. Informal caregivers play critical roles; most COPD home care is provided by family and friends, not healthcare professionals [25].

Most COPD-associated expenditures are incurred when complications require hospitalization; many complications are preventable. As is true of other chronic diseases, improved healthcare management improves COPD outcomes and lowers costs. Better care and treatment adherence lowers avoidable costs and improves health; productivity increases and absenteeism falls [26]. We found that COPD was associated with substantial indirect costs (the time required to visit outpatient clinics, the extent of home care, time required by caregivers to accompany patients to outpatient clinics, and caregiver work loss). Thus, apart from COPD prevention, patient activity levels must be improved to reduce indirect COPD costs. The time required to visit outpatient clinics/pharmacies was > 2 hours, associated with both patient and caregiver work loss. This lost time constitutes part of the COPD economic burden. Rapid and more appropriate medical treatments are required to reduce costs, increase productivity, and decrease absenteeism.

Our study had several limitations. First, our sample size was small. However, we recruited patients from primary clinics through to tertiary hospitals. Second, almost all subjects (91%) were male, although this reflects the COPD demographic in Korea [27]. Third, although

Choi HS, et al. Life quality and indirect costs in COPD

KJIM

we explored job quitting or changing, we did not explore absenteeism; thus, the work loss of caregivers may have been underestimated. Fourth, we did not investigate caregiver/patient relationships, but all caregivers were family members. Our results cannot be generalized to countries with different healthcare systems and/or workplace illness policies.

In conclusion, the EQ-5D revealed that higher COPD severity was associated with a lower quality of life, and major indirect burdens in terms of family caregiver work loss and home caring, and the time required for medical treatment. Our findings will inform COPD management strategies.

KEY MESSAGE

1. This is the first report to assess EuroQol five-dimensions five-level (EQ-5D-5L) in chronic obstructive pulmonary disease (COPD) patients in Korea.
2. EQ-5D-5L is valuable tool to assess quality of life in COPD patients.
3. Indirect costs including caregiver accompanying rate and time to visit hospitals, home caregiving rate, work loss of caregivers are high in COPD patients.
4. Severe airflow limitations induce a lower quality of life, and higher care-related indirect burdens.

Conflict of interest

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