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Longitudinal deteriorations in patient reported outcomes in patients with COPD

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Summary Goals of effective management of patients with chronic obstructive pulmonary disease (COPD) include relieving their symptoms and improving their health status. We examined how such patient reported outcomes would change longitudinally in comparison to physiological outcomes in COPD.

One hundred thirty-seven male outpatients with stable COPD were recruited for the study. The subjects health status was evaluated using the St. George's Respiratory Questionnaire (SGRQ) and the Chronic Respiratory Disease Questionnaire (CRQ). Their dyspnoea using the modified Medical Research Council (MRC) scale and their psychological status using the Hospital Anxiety and Depression Scale (HADS) were assessed upon entry and every 6 months thereafter over a 5-year period. Pulmonary function and exercise capacity as evaluated by peak oxygen uptake ($\dot{V}_{O_2}$) on progressive cycle ergometry were also followed over the same time.

Using mixed effects models to estimate the slopes for the changes, scores on the SGRQ, the CRQ, the MRC and the HADS worsened in a statistically significant manner over time. However, changes only weakly correlated with changes in forced expiratory volume in 1 s (FEV_1) and peak $\dot{V}_{O_2}$.

We demonstrated that although changes in pulmonary function and exercise capacity are well known in patients with COPD, patient reported outcomes such as health status, dyspnoea and psychological status also deteriorated significantly over time. In addition, deteriorations in patient reported outcomes only weakly correlated to changes in physiological indices. To capture the overall deterioration

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of COPD from the subjective viewpoints of the patients, patient reported outcomes should be followed separately from physiological outcomes.

Introduction

The goals of effective management of patients with stable chronic obstructive pulmonary disease (COPD) include relieving their symptoms and improving their health status, since none of the existing pharmacological medications for COPD has been shown to modify disease progression.[1] However, in comparison to physiological changes in pulmonary function, which is the hallmark of this disease, the progression of patient reported outcomes over time has been examined less frequently. Since the traditional test of pulmonary function as assessed by the forced expiratory volume in 1 s (FEV_1) does not necessarily correlate strongly with patient reported clinical outcomes such as health status, dyspnoea or psychological status,[2–4] a separate follow-up survey is important to capture the overall deterioration in COPD from the viewpoint of patients themselves.

Understanding the composition of patient reported outcomes versus physician centered physiological outcomes in COPD is indispensable, because patients and physicians do not always share viewpoints on what is important in this disease. As both types of outcomes reflect complementary aspects during the long-term follow-up of COPD, their assessments will enable clinicians to evaluate the overall effectiveness of the management of this disease.

In analyzing longitudinal data, how to deal with dropouts who withdraw from follow-up is a problem, because high numbers of dropouts are reported in COPD clinical trials. For example, in the Inhaled Steroids in Obstructive Lung Disease (ISOLDE) study, 46.5% of the patients dropped out at 3 years.[5] Calverley et al.[6] reported that losing these patients from the final analysis can reduce the power of the study to achieve its primary endpoint as discontinued subjects were those with the most rapidly deteriorating health status or pulmonary function. Therefore, we attempted to analyze longitudinal data in patients with COPD and asthma, including dropouts.[7–10]

We followed longitudinal changes in physiological outcomes and patient reported outcomes of health status, dyspnoea and psychological status over 5 years in patients with COPD, and partly elsewhere reported the physiological deteriorations in exercise capacity and pulmonary function.[7] We hypothesized that both types of outcomes would deteriorate over time, but that their correlations would be weak. Therefore, in the present observational study, we analyzed the 5–year longitudinal changes in patient reported outcomes in patients with COPD, and compared them with changes in physician centered physiological outcomes.

Methods

Subjects

We recruited 137 consecutive male outpatients with moderate to very severe COPD between September 1995 and April 1997, as previously reported.[7] Entry criteria included: (1) a smoking history of more than 20 pack-years; (2) maximal FEV_1/forced vital capacity ratio of less than 0.7 and postbronchodilator FEV_1 of less than 80% of the predicted normal; (3) regular attendance over 6 months; (4) no COPD exacerbations over the preceding 6 weeks; and (5) no uncontrolled comorbidities. Clinical measurements were evaluated on the same day. COPD patients meeting entry criteria were asked to have their clinical outcomes evaluated at entry and every 6 months thereafter over a 5–year period.[7] When an exacerbation of COPD requiring a change in treatment occurred within 4 weeks of a reassessment day, the evaluation was postponed for at least 4 weeks until the patient recovered. The present study was performed as part of our standard outpatient treatment and care, and verbal informed consent was obtained from all patients.

Patient reported outcomes

Health status was measured using the disease-specific measurements: the St. George's Respiratory Questionnaire (SGRQ)[11] and the Chronic Respiratory Disease Questionnaire (CRQ)[12]; their Japanese versions have been previously validated.[3] On the SGRQ, 3 components: symptoms, activity and impacts, and the total scores were calculated, ranging from 0 to 100. On the CRQ, the patients rated 20 items on a seven-point scale, and the 4 domains of dyspnoea,

fatigue, emotional function and mastery, as well as the total scores, were calculated as the average of the sum. Increases in the scores reflect worsening of health status on the SGRQ, and the opposite holds true on the CRQ. A change in the SGRQ score of 4 units is consistent with a minimum clinically important difference (MCID) for the patient,[13] and with respect to the CRQ, a change in the score of 0.5 units is considered to be the MCID.[14]

Dyspnoea was evaluated using the Japanese version of the modified Medical Research Council (MRC) dyspnoea scale,[4,15] which is a 5–point scale based on degrees of various physical activities that precipitate dyspnoea. Higher scores indicate worse dyspnoea on the MRC.

Psychological status or mood was evaluated using the Japanese version of the Hospital Anxiety and Depression Scale (HADS),[3,16] which consists of 14 items, 7 for anxiety and 7 for depression. Each item is scored from 0 to 3, where a score of 3 represents a state corresponding to the worst anxiety or depression. The sum of these items produces 2 subscales ranging from 0 to 21.

Physiological outcomes

Pulmonary function tests were performed as previously described.[7] Subjects underwent spirometry[17] before and at 15 and 60 min after inhaling salbutamol (400 μg) and ipratropium bromide (80 μg) using a metered-dose inhaler with a spacer device. Predicted values were provided by the Japan Society of Chest Diseases.[18]

Exercise capacity was evaluated using symptom-limited progressive cycle ergometry, which was performed 60 min after bronchodilator inhalation on a calibrated, electrically braked cycle ergometer.[7] Peak oxygen uptake ($\dot{V}_{O_2}$) was calculated as the highest level reached during exercise, and was used as an index of exercise capacity.

Follow-up data

Among the 137 COPD patients enrolled, 72 patients attended the last 5–year evaluation, and only one patient was unavailable for follow-up. Twenty-five patients died during the 5–year period, 36 patients dropped out of the study due to an inability to attend the hospital for various reasons, and 3 patients skipped the last appointment.

Statistical analysis

The results are expressed as means ± SE, unless otherwise stated. Mixed effects models for the slopes were used to estimate longitudinal changes in the clinical parameters[7,8] using Statistical Analysis System PROC MIXED software.[19] In these analyses, the covariates included age and smoking status as fixed effects, whereas time was entered as a random effect.[7] By performing these analyses, all the data from the 137 patients entered in the present study were included and analyzed. Bivariate relationships between the slope changes were analyzed by Pearson's correlation coefficient tests. To compare the responsiveness between the SGRQ and the CRQ, two widely used responsiveness indices of the effect size and the standardized response mean were evaluated.[20–22] The former indicates the ratio of the mean change in the score to the SD of the baseline scores. The latter indicates the ratio of the mean change in the score to the SD of that change. Comparisons of baseline data and annual changes between survivors and non-survivors were performed with an unpaired *t*-test. *P*-values less than 0.05 were considered to be statistically significant.

Results

Patient characteristics

Baseline characteristics for 137 male patients examined are presented in Table 1. The average age was 69.0 ± 0.6 years. At baseline, 103 patients were former smokers and 34 were current smokers. Their postbronchodilator FEV_1 was 45.9 ± 1.3% predicted.

Longitudinal changes in clinical outcomes

Changes in health status, dyspnoea, psychological status and airflow limitation are shown in Fig. 1 in 45 patients with COPD who had complete data sets of these outcomes with no missing data every 6 months over 5 years. These results enable us to compare individual changes in each measurement. Health status evaluated by the SGRQ and the CRQ total scores, and dyspnoea by the MRC scores deteriorated more prominently than the percentage of the predicted postbronchodilator FEV_1 (%FEV_1). Although psychological status evaluated by the HADS scores also tented to deteriorate, these deteriorations were not as prominent.

Results from the mixed effects models for the slopes of the longitudinal changes in the clinical parameters in all the 137 patients with COPD are presented in Table 1. Regarding health status, the activity and impact components, and total scores

Table 1 Baseline data and annual changes in 137 patients with COPD.

Characteristic	Baseline data	Annual change (/year)	*P* values
Age, years	69.0±0.6		
SGRQ symptoms (0–100)	52.9±1.6	0.83±0.43	0.054
SGRQ activity (0–100)	43.1±1.8	1.83±0.39	<0.0001
SGRQ impact (0–100)	24.3±1.4	2.24±0.37	<0.0001
SGRQ total (0–100)	36.2±1.4	1.87±0.34	<0.0001
CRQ dyspnoea (1–7)	5.28±0.09	−0.10±0.02	<0.0001
CRQ fatigue (1–7)	5.02±0.11	−0.12±0.03	<0.0001
CRQ emotional function (1–7)	5.68±0.08	−0.13±0.02	<0.0001
CRQ mastery (1–7)	5.51±0.09	−0.08±0.02	0.0022
CRQ total (1–7)	5.37±0.08	−0.12±0.02	<0.0001
MRC (0–4)	1.1±0.1	0.14±0.02	<0.0001
HADS anxiety (0–21)	4.7±0.3	0.16±0.08	0.046
HADS depression (0–21)	3.9±0.3	0.17±0.07	0.023
Postbronchodilator FEV_1, L	1.22±0.04	−0.0254±0.0059	<0.0001
Postbronchodilator FEV_1, %pred	45.9±1.3	−0.9±0.2	0.0001
Peak $\dot{V}_{O_2}$ mL/min/kg	14.8±0.3	−0.5±0.1	<0.0001

Data are presented as mean±SE. Numbers in parentheses indicate theoretical score ranges.

on the SGRQ all showed significant deterioration ($P<0.0001$), although only the change in the symptoms component score did not reach a statistically significant difference ($P=0.054$). With respect to the CRQ, all 4 domains and total scores showed statistically significant deterioration. The mean annual change in the health status scores was 1.87 units/year from the SGRQ total score, and −0.12 units/year from the CRQ total score. Therefore, the SGRQ total score took 2.14 years to deteriorate by a MCID of 4 units, as compared to 4.17 years that the CRQ total score took to decrease by a MCID of 0.5 units.

With regard to responsiveness between baseline and 5–year evaluations about the abovementioned 45 patients with COPD (Fig. 1), the effect size and the standardized response mean were 0.65 and 0.66 on the SGRQ, and 0.57 and 0.69 on the CRQ.

Dyspnoea evaluated by the MRC deteriorated significantly at 0.14±0.02 units/year ($P<0.0001$). Regarding psychological status, both anxiety and depression scores on the HADS also increased significantly by mean changes of 0.16 units/year ($P=0.046$) and 0.17 units/year ($P=0.023$), respectively; however, their statistical significances were weaker than the changes in health status and dyspnoea.

Changes in physiological outcomes are shown in Table 1. Airflow limitation evaluated by postbronchodilator FEV_1 and $\%FEV_1$ decreased over time at a rate of -25.4 ± 5.9 mL/year ($P<0.0001$) and $-0.9\pm0.2\%$ pred/year ($P=0.0001$), respectively. Exercise capacity expressed by peak $\dot{V}_{O_2}$ deteriorated at a rate of -0.5 ± 0.1 mL/min/kg/year ($P<0.0001$).

Relationships between the changes in clinical outcomes

The relationships between the changes in clinical outcomes are presented in Table 2. The changes in health status assessed by the SGRQ and the CRQ total scores weakly correlated with the changes in $\%FEV_1$ and peak $\dot{V}_{O_2}$ (absolute correlation coefficients [r] = 0.16 to 0.44, $P<0.07$). The change in dyspnoea assessed by the MRC also significantly but weakly correlated with the changes in $\%FEV_1$ and peak $\dot{V}_{O_2}$ ($r=-0.37$ and -0.35, $P<0.05$, respectively). In comparison, changes in psychological status assessed by the HADS did not significantly correlate with changes in $\%FEV_1$ and peak $\dot{V}_{O_2}$, except for a significant but weak correlation between the HADS depression and $\%FEV_1$ ($r=-0.26$, $P=0.0022$).

The relationships between the changes in health status moderately correlated with the changes in dyspnoea and the changes in psychological status (absolute $r=0.53$–0.66, $P<0.0001$). The relationship between the changes in dyspnoea and the changes in psychological status was weak but statistically significant ($r=0.36$ and 0.46, $P<0.0001$).

Comparisons between survivors and non-survivors

In the present study, 25 study subjects died, 108 were alive at 5 years, and the living status of 4 subjects was unknown. Baseline data and annual changes were compared between 108 survivors and

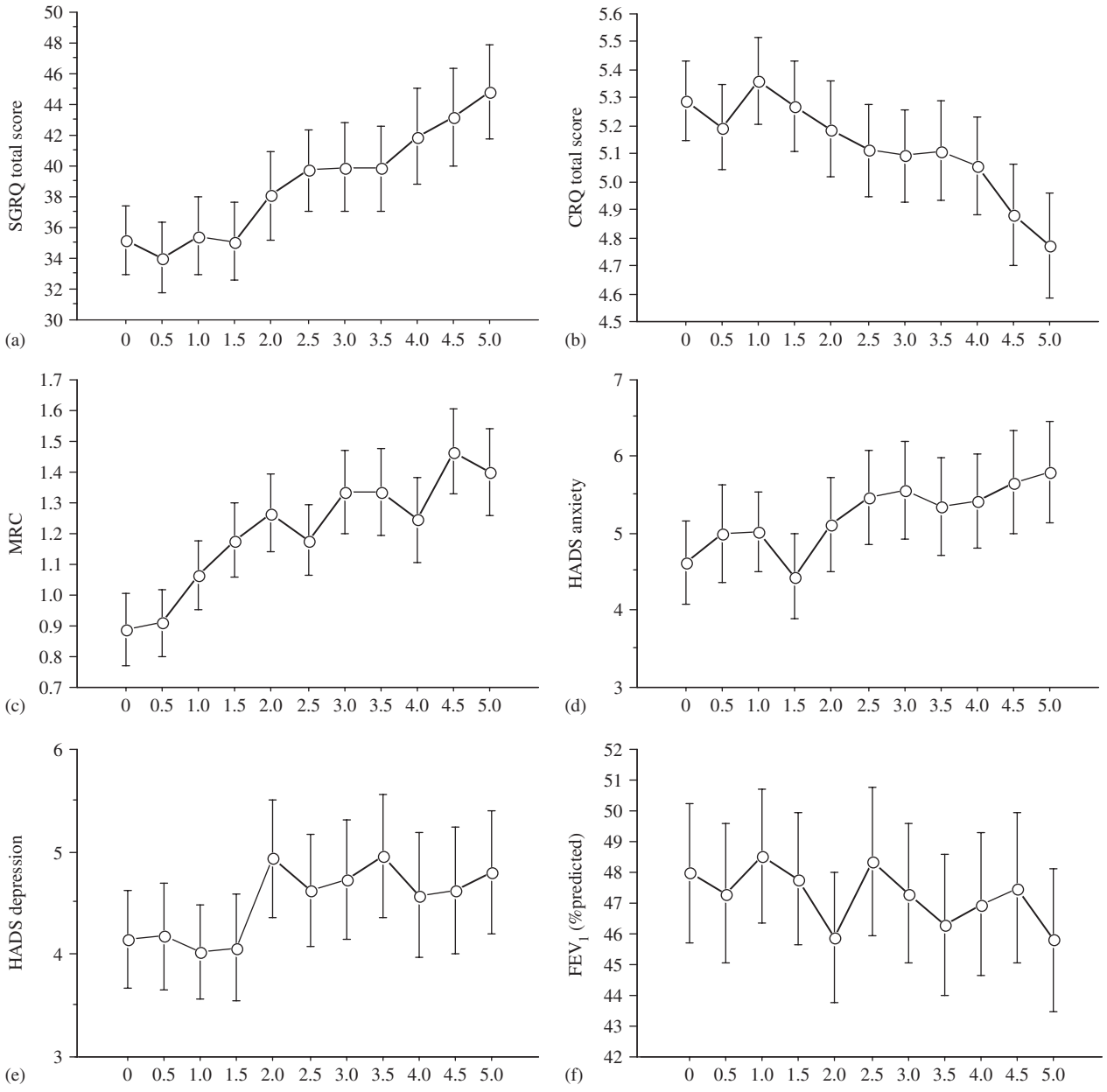

Figure 1 Longitudinal changes in the SGRQ (a), the CRQ (b), the MRC (c), the anxiety (d) and depression (e) of the HADS, and postbronchodilator FEV_1 (f) in 45 patients with COPD who had complete data sets with no missing data every 6 months over 5 years. Higher scores indicate worse status on the SGRQ, the MRC, and the HADS, and the opposite is true on the CRQ.

Table 2 Correlation coefficients between annual changes in various clinical parameters.

Variable	SGRQ total	CRQ total	MRC	HADS anxiety	HADS depression	%FEV_1	Peak $\dot{V}_{O_2}$
SGRQ total	1						
CRQ total	−0.77*	1					
MRC	0.59*	−0.53*	1				
HADS anxiety	0.55*	−0.64*	0.36*	1			
HADS depression	0.56*	−0.66*	0.46*	0.80*	1		
%FEV_1	−0.44*	0.33*	−0.37*	−0.12	−0.26*	1	
Peak $\dot{V}_{O_2}$	−0.20*	0.16	−0.35*	−0.08	−0.13	0.21*	1

*Statistically significant relationships ($P<0.05$).

Table 3 Comparisons of baseline data and annual changes between the 108 survivors and 25 non-survivors.

Characteristic	Baseline data		Annual changes (/year)	
	Survivors	Non-survivors	Survivors	Non-survivors
Age, years	68.0±0.6	72.7±1.5*		
SGRQ total	34.2±1.5	43.3±2.4*	2.00±0.19	1.33±0.41
CRQ total	5.45±0.09	5.17±0.14	−0.13±0.01	−0.10±0.02
MRC	0.9±0.1	1.6±0.1*	0.14±0.01	0.14±0.02
HADS anxiety	4.3±0.3	5.7±0.8	0.16±0.04	0.13±0.06
HADS depression	3.7±0.3	4.2±0.7	0.17±0.04	0.15±0.06
FEV_1, %pred	47.8±1.4	35.9±2.8*	−0.9±0.1	−0.7±0.2
Peak $\dot{V}_{O_2}$, mL/min/kg	15.5±0.3	11.5±0.6*	−0.6±0.0	−0.4±0.1

Data are presented as mean±SE.
*Statistically significant differences between survivors and non-survivors ($P<0.01$).

25 non-survivors in Table 3. Regarding the baseline data, non-survivors were significantly older and worse as rated by the SGRQ and MRC scores, FEV_1 levels and peak $\dot{V}_{O_2}$. However, there were no significant differences between annual changes in outcomes between survivors and non-survivors.

Discussion

We followed 5–year longitudinal changes in patient reported outcomes versus physiological outcomes in patients with COPD. We demonstrated that both types of outcomes deteriorated significantly over time, and deteriorations only weakly correlated with one another.

Although COPD has its primary effect in the lungs, structural and functional changes also take place in other organs, which causes multisystem symptoms.[2] Therefore, COPD is regarded as a systemic disorder, and a multidimensional assessment is needed. However, the progression and patterns of multiple COPD measurements over time have not been followed simultaneously. We demonstrated that although deteriorations in physiological outcomes as evaluated by pulmonary function and exercise capacity were confirmed,[7] patient reported outcomes as evaluated by health status, dyspnoea and psychological status also deteriorated significantly and these deteriorations only weakly correlated to physiological deteriorations. This indicates that patient follow up with FEV_1 alone leads to overlooking deteriorations in patient reported outcomes, and it scientifically shows the deteriorative characteristics of COPD.

Although health status deterioration in COPD over 3 years has been previously demonstrated using the SGRQ[23] or the CRQ,[9] to our knowledge, this is the longest study to follow it over 5 years. The present study shows that health status continues to deteriorate over time, and tends to be steep after 3 years as shown in Fig. 1. Although COPD patients could maintain their health status by using additionally bronchodilators or changing their lifestyle at first, they may gradually begin to become unable to adapt themselves to worsening situations.

We evaluated health status using the most widely used disease-specific instruments of the SGRQ and the CRQ to compare responsiveness. Health status measurements generally possess 3 properties[24]; a discriminative property, an evaluative property and a predictive property. We previously reported that although both had similar discriminative properties,[3] the SGRQ had a stronger ability to predict mortality.[25] Regarding responsiveness, although 3 rehabilitation studies[26–28] reported conflicting results, the present study indicates that the SGRQ and the CRQ were similarly responsive, judging from the effect size and the standardized response of the mean, except for the SGRQ symptom component.

Dyspnoea is an important outcome in COPD, because it is the most frequent symptom that COPD patients complain about, and it is strongly related to mortality.[29,30] However, its longitudinal change has rarely been analyzed. Mahler et al.[31] demonstrated that while pulmonary function improved in patients with COPD, their dyspnoea score worsened over 2 years. Lareau et al.[32] showed that although 34 COPD patients experienced varying degrees of airflow limitation over 5 years, their dyspnoea scores did not differ from the beginning to the end of the study. We demonstrated a deterioration in dyspnoea with a larger sample size and a longer observational period. In addition, weak correlations between changes in dyspnoea and declines in

pulmonary function and exercise capacity indicate that worsening dyspnoea may also be affected by deteriorations in other important factors such as cardiovascular fitness or muscular weakness. Therefore, although measuring dyspnoea is recommended as an indicator of disease severity in recent guidelines,[33,34] its longitudinal follow-up is also necessary.

Psychological problems such as anxiety and depression are common in patients with COPD although they are not often addressed.[35] Although we demonstrated significant deteriorations in these psychological indices over time, they were less prominent than health status or dyspnoea deteriorations as shown in Fig. 1. A greater variability in psychological status changes among patients may exist judging from the large SE values as compared to the means. Therefore, it is important to find patients who show a faster deterioration in psychological status, as anxiety and depression are reported to be related to frequent hospitalization for acute exacerbations[36] or the outcomes of emergency treatment in COPD,[37] and their progression may inhibit the patient's ability to manage the disease in itself.

Unexpectedly, we did not find significant differences in annual changes in clinical outcomes between survivors and non-survivors. This may be partly because non-survivors already had a significantly worse status in airflow limitation, exercise capacity, health status and dyspnoea than survivors. In addition, the aforementioned result reveals that even outcomes in survivors deteriorated longitudinally in patients with COPD. Although we anticipated that non-survivors had steeper declines in clinical measurements, worse baseline data seemed to have contributed more to the mortality in the present study. This theme should be studied in the future.

Recently, the MCID is an important emerging concept in addition to the statistically significant difference. Regarding some commonly used outcome measures, the MCID has begun to suggest; 100 mL on FEV_1, 10 W on maximal exercise tests, and so on.[38] Although, considering the MCID ideology, the SGRQ reached the MCID faster than the CRQ in the present study, MCID values represent only empirically derived estimates,[39] and it is difficult to compare one MCID with another. How to reach a common interpretation across the different MCID on some outcomes is a problem that needs to be resolved.

Some limitations of this study should be discussed. Firstly, the present study did not investigate longitudinal changes in healthy subjects. Therefore, although it is difficult to evaluate the relative deteriorations of these outcomes, one should pay attention to relationships between these changes. Secondly, we did not count the number of exacerbations during the study period, and therefore we could not evaluate their impact on clinical outcomes although frequent exacerbations have been reported to be related to health status and other COPD parameters.[40,41]

In conclusion, we demonstrated that patient reported outcomes as well as physiological outcomes deteriorated over time in patients with COPD, and scientifically cleared the deteriorative characteristics of COPD. In addition, correlations between both types of outcomes were relatively weak. To capture the overall deterioration of COPD from the perspective of patients and physicians, these outcomes should be followed separately and with caution.

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