

QUALITY OF LIFE AND OUTCOMES

Overlap Syndrome of Asthma and COPD Predicts Low Quality of Life

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Background. In clinical practice, patients whose airway disease shares features of both asthma and chronic obstructive pulmonary disease (COPD) remain poorly recognized. **Material and methods.** The study population consisted of 1546 patients with a diagnosis of asthma or COPD or both. Based on patient-reported outcomes and retrospective medical record data, the study population was divided into three groups: (1) asthma only, (2) COPD only, and (3) both asthma and COPD (overlap syndrome group). We evaluated patient characteristics associated with health-related quality of life (HRQoL). **Results.** In many respects, the overlap group fell between the asthma and COPD groups. In the overlap group, however, HRQoL was the poorest of all. In the logistic regression model, with the asthma group as the reference, both the overlap and the COPD group showed higher risk for low HRQoL [odds ratio (OR): 1.9; 95% confidence interval (CI): 1.2–3.2; and OR: 1.8, 95% CI: 1.0–3.2; respectively]. In addition, female gender, obesity, duration of disease, disability pension, and coexisting cardiovascular disease were associated with low HRQoL across the study population. **Conclusions.** Patients with overlapping asthma and COPD differed from those patients with asthma or COPD only. Overlap syndrome was associated with low HRQoL.

Keywords asthma, COPD, quality of life

INTRODUCTION

Good asthma control may be difficult to achieve among older age groups. Among elderly patients, airway variability is often accompanied by some degree of irreversible obstruction, which may be a key factor in poorer disease control (1). In adult populations, both asthma and chronic obstructive pulmonary disease (COPD) are common. In Finland, based on recent epidemiological studies, the prevalence of asthma is 5.5–11%, whereas that of chronic bronchitis is 4%, and COPD 5–9% (2–6). When the clinical criteria of both asthma and COPD are filled, the disease is known as overlap syndrome (1). According to recent cross-sectional studies, this syndrome is the most prevalent among age groups >55 years (1). No epidemiological data exist for the prevalence of overlap syndrome in Finland, and studies on how overlap syndrome predicts overall disease control, quality of life, or other variables compared with asthma only or COPD only are lacking.

Historically, long-term smoking has been linked to COPD, but among the elderly, smoking alone is insufficient to distinguish between asthma and COPD (7). Of the 469 study subjects aged >50 years derived from a random population survey, 96 were diagnosed with COPD based on a detailed questionnaire, pre- and postbronchodilation spirometry, diffusion capacity, and chest-computed tomography (CT) scanning (8). Only 18 of the patients

showed the classical phenotypes of chronic bronchitis or emphysema or both but no asthma. Asthma was the main phenotype in 53 of the patients. Emphysema differentiates COPD from asthma and can be demonstrated by impaired diffusion capacity or by low attenuation areas in high-resolution CT (9, 10). However, not all COPD patients suffer from emphysema (11).

In this study, we describe the main clinical characteristics of the overlap syndrome of both asthma and COPD compared with asthma only and COPD only. In addition, we analyzed clinical variables that explain poor health-related quality of life (HRQoL) in this hospital-based patient group. The variables used are a mixture of diagnostic data from patients' medical records covering the last 5–10 years and patients' self-reported data. We estimated the patients' HRQoL using Airway Questionnaire 20 (AQ20). The questionnaire is a modification of St. George's Respiratory Questionnaire and is designed to measure patient symptoms, limitations in daily life activities, and disease-related anxiety.

MATERIAL AND METHODS

We identified all out- and inpatients aged 18–75 years who had been discharged from the Helsinki University Central Hospital with a diagnosis of asthma or COPD (ICD10 code J44–J46) from 1995 to 2006. Without further selection, all living patients were invited to participate in the study ($N = 6676$). The recruitment was carried out with a two-phase mailing campaign. A total of 3461 patients responded to the invitation letter by providing the research consortium with their contact information.

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The subsequent letter included detailed information about the study and a consent form. Altogether 1855 patients contacted the researchers by phone to request an appointment. Nonrespondents did not differ from respondents with respect to gender in the age group ≥ 55 years. No further reminders were mailed. All participants provided their informed consent to allow the research consortium to collect, merge, and analyze their comprehensive medical history from all health-care providers who had treated them over the past 5–10 years and agreed to continue their follow-up for the next 10 years. They also donated a blood sample for DNA extraction.

All diagnostic data presented in the study were gathered retrospectively from medical records and evaluated by two pulmonary physicians. Baseline spirometry [forced expiratory flow volume in 1 second (FEV_1), forced vital capacity (FVC), peak expiratory flow (PEF)] results were available on an average of 3.8 times per patient, and after the bronchodilation test, 3.2 times per patient; these results included height, weight, and smoking status. The reference values for the spirometric test results have been validated in a large Finnish population sample (12).

Based on the given clinical diagnoses, the patients were divided into three groups: those with asthma only, those with COPD only, and those with both conditions (overlap syndrome). The diagnosis of asthma was based on the British Guidelines on Asthma Management (13), with one or more of the following findings: a postbronchodilator increase in FEV_1 of $\geq 12\%$, a bronchodilator response of $\geq 15\%$ or diurnal variation of $\geq 20\%$ in PEF recording, moderate to severe bronchial hyperreactivity, or a decrease in FEV_1 of $\geq 15\%$ in the exercise test. COPD was diagnosed according to the ATS/ERS Task Force recommendations (14–16) and defined by irreversible chronic airway obstruction ($FEV_1/FVC < 0.70$ or $FEV_1/FVC < 88\%$ of predicted reference value) in postbronchodilation spirometry related to long-term smoking (12, 17).

We also evaluated other common chronic diseases noted in the medical records. The category “coronary disease” included patients who had experienced a myocardial infarct, acute coronary syndrome, or angina pectoris diagnosed by an internist. “Cerebrovascular diseases” included patients with a stroke or a transient ischemic attack diagnosed by a neurologist. “Cardiovascular diseases” consisted of patients with one of or more of the following diseases: hypertension, coronary disease, cerebrovascular disease, or peripheral artery occlusive disease. The category “diabetes” included patients with type I or type II diabetes.

At the time of recruitment and thereafter, the participants annually reported the names of their health-care providers. In addition, the participants were asked for their work status (working, on disability pension, on old-age pension) and work-ability index on a scale from 1 (completely unable to work) to 10 (the best performance), sickness absences (no absences, 1–9 days, 10–24 days, 25–99 days, and ≥ 100 days per year for any cause), use of rescue medication [not at all, once a week, 2–4 times a week,

once a day, at least twice a day (short-acting β_2 -agonists), only long-acting β_2 -agonists (LABA) in use], smoking status (never, ex-smoker, current smoker, and pack-years), and HRQoL according to the respiratory questionnaire. The AQ20 is a unidimensional measure containing 20 items with the three responses of “yes,” “no,” and “not applicable” (18–21). “Yes” responses were scored as 1, and “no” and “not applicable” as 0. The summary score varied from 0 (no symptoms of or worries about the disease) to 20 (full range of symptoms and worries about the disease). The summary scores were normally distributed among the participants. At recruitment, all participants returned the questionnaire. Ambiguous or missing responses to questions ranged between 1% and 2%. The questionnaire has been translated into Finnish and is validated for asthma and COPD (21).

We analyzed factors associated with low HRQoL. The threshold for low HRQoL (≥ 12.1) was determined as 1 SD (4.9) above the mean of the AQ20 summary score (7.2) in the study population.

The study protocol was approved by the Coordinating Ethics Committee of the Helsinki and Uusimaa Hospital District, and permission to conduct this research was granted by the Helsinki University Central Hospital.

Statistical Analysis

We compared continuous variables using the nonparametric Mann–Whitney *U* test and categorical variables using the chi-square test. We used logistic regression to determine the factors associated with low HRQoL with the following variables: gender, age (<55 years, 55–65 years, ≥ 65 years), current smoking, pack-years (<10 years, 10–30 years, ≥ 30 years), body mass index (BMI, <19, 19–25, 25–30, ≥ 30), disease group (asthma only, COPD only, overlap syndrome), duration of disease (<5 years, 5–10 years, 11–15 years, ≥ 15 years), work status (working, on old-age pension, on disability pension), and comorbidities (cardiovascular comorbidities, diabetes). Odds ratios (ORs) were computed using 95% confidence intervals (CIs), and *p*-values $\leq .05$ were considered statistically significant in both univariate and multivariate analyses. All analyses were performed with the SPSS computer package, version 16.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient Recruitment

From 2005 to 2007, a total of 1855 patients with airway disease (asthma, COPD, or both) were recruited to the study. In this hospital-based study population, the mean age of the study subjects was 56 years (SD = 12.0).

Patient Characteristics

The study subjects were categorized into asthma-only, COPD-only, and overlap groups based on the clinical diagnoses. The evaluation of medical records, however, led to the exclusion of patients due to fragmented or insufficient documentation of the disease (*N* = 206). In addition, patients tested for asthma or COPD/chronic

bronchitis-like symptoms, but who did not fulfill the diagnostic criteria at any point in time, were excluded ($N = 103$). After the evaluation, a total of 1546 eligible patients were included: for these patients, all relevant clinical data and spirometry results were available (Tables 1 and 2). The largest group consisted of patients diagnosed with asthma only ($N = 1084$). As expected, this group was significantly younger, predominantly women, and differed in many other respects from patients with COPD only ($N = 237$). The overlap group consisted of 225 patients diagnosed with both asthma and COPD (Tables 1 and 2). Spirometry findings were available for all included patients.

In the overlap group, the mean age was 61 years. These patients were significantly older than those with asthma only (mean age = 54 years, $p < .001$) and significantly younger than those with COPD only (mean age = 64 years, $p \leq .001$) (Tables 1). Of those with overlap syndrome, 75.5% had been smoking for at least 10 years; the respective value for those with asthma only was 25.8% and for those with COPD only was 72.2%. With regard to several other clinical characteristics, such as gender, duration of disease, mean of pack-years of smoking, lung function parameters, and prevalence of common comorbidities, the overlap group fell between the asthma-only and the COPD-only group.

The proportion of disability pensioners and patients with ≥ 10 days of sickness absence during the past year was higher in the overlap group than in the other two groups. Similarly, the work-ability index (compared to their best) was the lowest in the overlap group. However, these differences were significant only between the overlap and asthma groups. The trends were the same in comparison with COPD, but insignificant due to the small number of patients still active in the workforce.

Health-Related Quality of Life

In the overlap group, the mean AQ20 summary score was 8.8 at the 1-year follow-up, which was significantly higher (patients reporting more symptoms) than in the asthma-only (6.8, $p \leq .001$) or the COPD-only group (7.4, $p \leq .05$) (Table 2). To further analyze the patients' characteristics associated with low HRQoL, we performed uni- and multivariate regression analyses (Table 3). The threshold for the low HRQoL (≥ 12.1) was defined as 1 SD above the mean AQ20 score of the study population. Patients with a low HRQoL represented 22% of the study population who reported the most symptoms, signs, and worries about the disease. When each clinical variable was analyzed separately, age > 55 years, BMI ≥ 30 , overlap syndrome and COPD-only groups, duration of the disease > 10 years, old-age and disability pensions, and coexisting cardiovascular diseases all increased the patient's risk for low HRQoL. In the multivariate model, both overlap syndrome (OR = 1.9, 95% CI: 1.2–3.2) and COPD only (OR = 1.8, 95% CI: 1.0–3.2) remained independent factors associated with low QoL when compared with the asthma group. In addition, female gender, BMI ≥ 30 , duration of disease > 10 years, disability pension, and cardiovascular

diseases as comorbidity remained determinants associated with low QoL across the study population (Table 3). We also performed the analysis using age, pack-years, and duration of the disease as continuous variables, but this did not change the results (data not shown). In multivariate analysis, prolongation of the disease by 1 year resulted in an OR of 1.02 (95% CI: 1.007–1.031, $p = .002$).

DISCUSSION

Our findings show that patients with overlap syndrome form a clinically separate group from asthma-only and COPD-only patients, and in many respects, this group falls between the two. The differences between these groups in such clinical features as age, lung function, and cardiovascular comorbidity profile were significant. Therefore, the discovery that respiratory-specific HRQoL in the overlap syndrome group was significantly the poorest of all was somewhat surprising. This finding was, however, consistent with the results among those patients still active in the working life ($N = 584$). In this group, the work-ability index was the lowest in the overlap syndrome group. In addition, the proportion of patients reporting ≥ 10 days/year of sickness absences and the proportion of those on disability pension were the largest in the overlap syndrome group. Factors associated with low HRQoL included overlap syndrome, COPD only, obesity, duration of disease > 10 years, disability pension, and cardiovascular diseases.

Previous population-based studies have suggested that half of elderly people with airway disease show airflow variability together with some degree of irreversible airway obstruction (1, 8). In our study, 15% (225/1546) of all patients, 17% (225/1309) of asthma patients, and 49% (225/462) of COPD patients belonged to the overlap syndrome group. One limitation of our study is its low overall participation rate. In addition, the hospital-based study population was biased toward elderly, predominantly female, and severe cases requiring specialist care. For these reasons, our findings may not reflect the true prevalence figures for overlap syndrome in Finland. In the asthma-only group, the nonrespondents were younger than the respondents. In the age group ≥ 55 years, the respondents and the nonrespondents showed no differences with respect to gender. Unfortunately, we were unable to include further analysis between respondents and nonrespondents.

Some have suggested that the GOLD criteria (the Global Initiative for Chronic Obstructive Lung Disease) based on a fixed FEV₁/FCV ratio, overestimate the prevalence of COPD among elderly patients because they fail to take into account the natural decline in lung function with age (22). Contrary to many studies, our diagnostic criteria do not rely on only one cross-sectional spirometry value and self-reported asthma/COPD diagnosis. One strength of our study is its design, with both self-reported data and retrospective information from medical records for each participant. This allows us to simultaneously examine multiple, clinically valid variables affecting HRQoL

TABLE 1.—Comparison of the clinical characteristics of the overlap syndrome group with those in the asthma-only and in the COPD-only groups.

Clinical characteristics	Asthma only (<i>N</i> = 1084)	Overlap syndrome (<i>N</i> = 225)	COPD only (<i>N</i> = 237)
Age, mean $\pm$ SD (years)	53 $\pm$ 13*	61 $\pm$ 7	64 $\pm$ 7*
<i>N</i> of study subjects			
≤40 years of age	182 (16.7%)	1 (0.4%)	2 (0.8%)
41–55 years of age	359 (33.1%)	48 (21.3%)	22 (9.2%)
>55 years of age	543 (50.0%)	176 (78.2%)	213 (89.8%)
Duration of disease, mean $\pm$ SD (years)	13 $\pm$ 12*	10 $\pm$ 10	6 $\pm$ 4*
Proportion (%) of women	73.7*	51.6	36.3*
Pack-years, mean $\pm$ SD	6 $\pm$ 12*	36 $\pm$ 21	46 $\pm$ 22*
Smoking status, <i>N</i> (%)			
Current smoker	98 (48.5%)	110 (10.9%)*	97 (48.0%)
Ex-smoker	96 (47.5%)	354 (35.2%)*	103 (51.0%)
Never	8 (4.0%)	543 (53.9%)*	2 (1.0%)
BMI, mean	27.2 $\pm$ 5.5	27.3 $\pm$ 5.8	26.7 $\pm$ 5.1
Baseline spirometry (% predicted, mean $\pm$ SD)			
FEV ₁	85.7 $\pm$ 16.8*	62.9 $\pm$ 18.4	59.5 $\pm$ 19.6
FVC	90.1 $\pm$ 14.8*	78.0 $\pm$ 18.1	73.5 $\pm$ 19.0**
FEV ₁ /FVC	78.0 $\pm$ 9.3*	65.4 $\pm$ 13.4	65.3 $\pm$ 13.6
PEF	92.7 $\pm$ 19.3*	70.2 $\pm$ 20.7	66.1 $\pm$ 22.9
Postbronchodilation spirometry (% of predicted, mean $\pm$ SD)			
FEV ₁	86.5 $\pm$ 15.6*	67.4 $\pm$ 18.0	61.4 $\pm$ 19.4**
FVC	90.5 $\pm$ 14.8*	83.1 $\pm$ 17.4	76.1 $\pm$ 18.3*
FEV ₁ /FVC ratio	78.5 $\pm$ 9.3*	65.8 $\pm$ 13.2	65.3 $\pm$ 14.6
PEF	93.5 $\pm$ 18.5*	75.1 $\pm$ 19.5	67.6 $\pm$ 23.6*
Proportion (%) of patients with concomitant			
Hypertension	32.3**	41.3	44.7
Coronary disease	7.7*	19.1	25.3*
Diabetes	6.8*	12.9	19.8*
Cerebrovascular disease	3.2**	7.1	10.1*
Peripheral vascular disease	0.6*	3.6	7.2**

Notes: BMI = body mass index; **p* ≤ .001, ***p* ≤ .05. In statistical comparisons, the overlap group was compared with the asthma-only or the COPD-only groups.

TABLE 2.—Comparison of self-reported patient outcomes in the overlap syndrome group with those in the asthma-only and COPD-only groups.

Self-reported outcomes	Asthma only (<i>N</i> = 1084)	Overlap syndrome (<i>N</i> = 225)	COPD only (<i>N</i> = 237)
AQ20 summary score (mean $\pm$ SD)	6.8 $\pm$ 4.8*	8.8 $\pm$ 5.1	7.4 $\pm$ 5.2**
Proportion (%) of patients who have used rescue medication in the last year			
No use	16.2	14.1	23.9**
On average once a week	36.5	34.1	26.9
On average two to four times a week	12.0	16.8	9.3
On average once a day	7.8	3.8	12.1
On average at least twice a day	14.0	16.8	17.0
Only long-acting β 2-agonists in use	13.5	14.6	11.0
Work-ability index ^a (mean $\pm$ SD)	8.18 $\pm$ 1.52*	6.87 $\pm$ 2.02	7.10 $\pm$ 1.39
Proportion (%) of patients who had sickness absences for any cause during the past year ^a			
None	88 (17.6%)**	4 (11.1%)	7 (20.6%)
A total of 1–9 days	194 (38.7%)	9 (25.0%)	13 (38.2%)
A total of 10–24 days	107 (21.4%)	11 (30.6%)	4 (11.8%)
A total of 25–99 days	98 (19.6%)	8 (22.2%)	8 (23.5%)
A total of ≥100 days	14 (2.8%)	4 (11.1%)	2 (5.9%)
Proportion <i>N</i> (%) of patients in			
Active workforce	627 (62.3%)*	61 (30.5%)	53 (26.0%)
Old-age pension	255 (25.3%)	84 (42.0%)	98 (48.0%)
Disability pension	125 (12.4%)	55 (27.5%)	53 (26.0%)

Notes: ^aComputed among the employed study subjects who had answered the questions. Work-ability index *N* (total) = 582, *N* (asthma only) = 504, *N* (COPD only) = 40, *N* (overlap group) = 38. Sickness absences *N* (total) = 571, *N* (asthma only) = 498, *N* (COPD only) = 34, *N* (overlap group) = 36.

p* ≤ .001, *p* ≤ .05. In statistical comparisons, the overlap group was compared with the asthma-only or COPD-only subgroups.

TABLE 3.—Factors associated with low HRQoL in the univariate and multivariate analyses.

Gender	Number of patients analyzed (N)	Patients with low HRQoL ^a (%)	Crude OR	95% CI	<i>p</i>	Adjusted OR	95% CI	<i>p</i>
Male	495	20.6	1.00			1.00		
Female	946	23.3	1.17	0.90–1.52	NS	1.56	1.12–2.18	.008
Recruitment age								
<55 years	570	16.5	1.00	–	–	1.00	–	
55–65 years	539	27.5	1.92	1.43–2.56	<.001	1.14	0.76–1.71	NS
≥65 years	332	24.1	1.61	1.15–2.25	.005	1.19	0.67–2.11	NS
Current smoking								
No	1106	21.3	1.00			1.00		
Yes	205	25.2	1.25	0.93–1.67	NS	0.98	0.66–1.75	NS
Pack-years								
<10	751	19.0	1.00			1.00		
10–30	270	20.4	1.09	0.77–1.54	NS	0.83	0.54–1.29	NS
≥30	294	28.9	1.73	1.27–2.36	.001	1.01	0.60–1.72	NS
BMI								
<19	41	22.0	1.31	0.61–2.84	NS	0.85	0.32–2.22	NS
19–25	527	17.6	1.00			1.00		
25–30	479	21.1	1.25	0.91–1.71	NS	1.37	0.95–1.97	NS
≥30	380	30.3	2.03	1.48–2.77	<.001	1.82	1.25–2.64	0.002
Disease group								
Asthma only	1024	19.3	1.00			1.00		
COPD only	212	27.4	1.57	1.12–2.21	.009	1.81	1.01–3.23	0.047
Overlap syndrome	205	32.2	1.98	1.42–2.76	<.001	1.93	1.16–3.22	0.011
Duration of the airway disease								
<5 years	324	17.3	1.00			1.00		
5–10 years	589	20.7	1.25	0.88–1.78	NS	1.33	0.89–2.00	NS
11–15 years	236	26.7	1.74	1.16–2.62	.008	1.97	1.23–3.16	0.005
≥15 years	291	27.8	1.85	1.26–2.71	.002	2.30	1.44–3.68	<0.001
Work status								
Working	741	15.1	1.00			1.00		
On old-age pension	437	21.1	1.50	1.10–2.03	.010	1.08	0.66–1.75	NS
On disability pension	233	46.4	4.85	3.50–6.73	<.001	3.39	2.24–5.12	<0.001
Comorbidities								
Cardiovascular diseases ^b	587	29.8	2.04	1.59–2.63	<.001	1.45	1.06–1.98	0.021
Diabetes	133	32.3	1.76	1.20–2.59	.004	1.10	0.68–1.77	NS

Notes: ^aLow HRQoL was defined as the mean of the AQ20 summary score + 1 SD; in this study group ≥12.1.

^bIncludes hypertension, coronary disease, cerebrovascular and peripheral artery occlusive disease. BMI, body mass index.

within each disease group. Due to the reimbursement policy of the Finnish Social Insurance Institution, the diagnostic criteria are uniform and diagnostic procedures are homogeneous and well documented for patients requiring regular medication and who are thus entitled for reimbursement.

Overlap syndrome was not the only factor associated with low HRQoL. Obesity (BMI ≥30, OR = 1.8, 95% CI: 1.3–2.6) also increased the risk for low QoL across the patient group. This finding is in agreement with those of a recent report on the increased incidence and severity of asthma in the Danish population. The increase was at least partially attributed to simultaneously increased obesity (23). In addition to low HRQoL, obesity has been associated with poor asthma control and asthma-related hospitalizations (24, 25). Age ≥55 years, ≥10 pack-years of smoking, and old-age pension did not remain independent risk factors, but clearly showed a significant risk in univariate analysis. Actually, low QoL was associated

with several factors in addition to diagnostic group and BMI, such as female gender, duration of the disease (≥10 years), disability pension, and cardiovascular diseases as comorbidity.

Chronic pulmonary disease, especially among elderly populations, stems from a group of disorders that differ significantly with regard to their etiology, clinical features, prognosis, and response to treatment (26). The current taxonomy may not reflect the phenotypes of clinical importance. To some extent, differential diagnostics are often artificial due to multiple overlapping sub-phenotypes (7). The first attempt to reclassify the sub-phenotypes used cluster analysis and identified five groups: (1) severe and markedly variable airflow obstruction with features of atopic asthma, chronic bronchitis, and emphysema; (2) emphysema alone; (3) atopic asthma with eosinophilic airways inflammation; (4) mild airflow obstruction without other dominant phenotypic features; and (5) chronic bronchitis in nonsmokers (11, 27). In

the future, the most interesting classifications of chronic airway obstruction will be those that show predictive value in clinical practice. Overlap syndrome in our study design most resembles the first cluster and proved to be of clinical importance.

A Dutch hypothesis suggests that asthma, chronic bronchitis, and emphysema are different expressions of one disease entity (28, 29). Later, researches viewed asthma and COPD as distinct clinical entities with different inflammatory mediators and different causal mechanisms (30). Others have criticized this, however, stating that the prevalence of those with overlap syndrome (both asthma and COPD) is higher than it should be than expected if the diseases were unrelated (31). In our study, the overlap syndrome group fell between the asthma and COPD groups in many aspects. The future follow-up of this study population will show whether overlap syndrome is predictive for the development of COPD. This study does not reflect the prevalence of overlap syndrome in Finland but does reflect its prevalence in a hospital-based patient population.

Even though the current treatment protocols fail to recognize overlap syndrome, the scientific community has recently become conscious of the clinical relevance of overlap syndrome (1). Based on the ATS/ERS Task 365 Force report, prebronchodilator FEV¹ is a good predictor of exacerbations, whereas postbronchodilator FEV¹ best predicts the long-term decline in lung function (32). In addition, low postbronchodilator FEV¹ is associated with serious adverse events, such as pneumonia (33). Overlap 370 syndrome represents patients with combined lung function defects: constant airway obstruction accompanied by day-to-day variability. Our findings further suggest that these combined defects have clinical implications, thus differentiating these patients from others. Further studies 375 are therefore needed to explore the role of overlap syndrome in patients' prognoses and to prevent exacerbations and hospitalizations.

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DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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