Longitudinal Changes in Clinical Outcomes in Older Patients with Asthma, COPD and Asthma-COPD Overlap Syndrome

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Key Words

Asthma · Asthma-COPD overlap · Chronic obstructive pulmonary disease · Longitudinal changes · Multidimensional assessment · Obstructive airway disease

Abstract

Background: The progression of obstructive airway diseases (OADs) including asthma, chronic obstructive pulmonary disease (COPD) and asthma-COPD overlap syndrome in older adults is not well understood. **Objective:** To examine the prognosis of OADs and to identify potential determinants for longitudinal changes in clinical outcomes. **Methods:** We consecutively recruited 99 older adults (>55 years) with OADs who underwent a multidimensional assessment at baseline and 4 years which involved spirometry, 6-min walk distance (6MWD), assessments of health status (Saint George's Respiratory Questionnaire, SGRQ), comorbidity, and serum and sputum biomarkers. All-cause mortality and respiratory hospitalisation during the follow-up period were recorded. Clinical outcomes were compared between basal and final visits, and changes in clinical outcomes were compared among asthma, COPD and asthma-COPD overlap groups. Associations between clinical parameters, biomarkers and prognosis were examined. **Results:** After a median follow-up of 4.2

years, outcome data were available for 75 (75.8%) patients. There were 16 (16.2%) deaths. The BODE index predicted all-cause mortality in older people with OADs. While spirometry, 6MWD and SGRQ deteriorated significantly over the 4 years, there was significant heterogeneity in the longitudinal changes in these clinical outcomes. Participants with COPD had a significant decline in FEV₁ ($p = 0.003$), SGRQ ($p = 0.030$) and 6MWD [decline of 75.5 (93.4) m, $p = 0.024$]. The change in 6MWD was lower in the asthma-COPD overlap group. Air-flow reversibility was associated with a reduced decline in 6MWD. **Conclusion:** COPD patients had a poor prognosis compared with asthma and asthma-COPD overlap patients. The BODE index is a useful prognostic indicator in older adults with OADs. Both airway disease diagnosis and BODE index warrant specific attention in clinical practice.

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Introduction

Obstructive airway diseases (OADs) including asthma and chronic obstructive pulmonary disease (COPD) are common conditions causing significant disease burden and affecting quality of life [1, 2], but the progression of these diseases in older adults is not well understood.

As one of the most common OADs, asthma, is defined as chronic airway inflammation and airway hyper-responsiveness (AHR) that lead to recurrent episodes of respiratory symptoms [3] and typically begin in early life. AHR [4] or bronchodilator response (BDR) [3, 5] confirms the diagnosis of asthma. COPD is characterized by persistent airflow obstruction that is associated with an enhanced chronic airway inflammation [6]. However, patients with asthma or COPD can share common characteristics, e.g. incompletely reversible airflow obstruction has been observed in a proportion of asthmatics and AHR can occur in patients with COPD [7, 8]. The co-existence of these conditions is termed the asthma-COPD overlap syndrome, which is defined when an increased airflow variability occurs together with fixed airflow obstruction. Several previous studies addressed the asthma-COPD overlap and different definitions were proposed [9–15].

With age, there is an increase in the proportion of patients with an overlapping pattern of airflow obstruction. Marsh et al. [9] found that 55% of COPD patients aged >50 years had coexistence of asthma and COPD. The clinical features of the asthma-COPD overlap syndrome have been described and have included lower health-related quality of life [12, 13], an increased frequency of exacerbations [12] and potentially a reduced forced expiratory volume in 1 s (FEV₁) decline in pure asthma compared with asthma with incomplete reversibility [11].

However, little is known about prognostic indicators for mortality in older people with OADs, including asthma, COPD and the overlap pattern, and how clinical outcomes change over time. In COPD, a multidimensional index (the BODE index) [16] is a good prognostic indicator; however, its role in OADs is not characterized. Similarly, the role of comorbidity and systemic inflammation is not understood. This study aimed to examine the progression of asthma, COPD and asthma-COPD overlap syndrome in older adults by assessing mortality and performing a multidimensional assessment of the natural course of lung function, exercise capacity and quality of life over a follow-up of 4 years. We hypothesized that the prognosis may be different in the three groups of patients (and worse in COPD), who represent different clinical OADs phenotypes.

Methods

Participants

A total of 99 participants aged >55 years with OADs (according to symptoms, physician diagnosis and spirometry) were consecutively recruited from the Respiratory and Sleep Medicine Ambulatory Care Clinics at the John Hunter Hospital, Newcastle, N.S.W.,

Australia. Participants gave written informed consent. The Hunter New England Area Health Service and University of Newcastle Research Human Ethics Committees approved this study. Exclusion criteria were a current or recent smoking history or a history of other respiratory diseases. An exacerbation in the past month was cause to delay visits until recovery (4 weeks of stability).

Study Design

A 4-year prospective cohort study was conducted and involved 4 study visits, 3 at baseline and 1 follow up visit. Participants underwent a multidimensional assessment of their clinical and functional status and comorbidity at baseline [17], and then a 4-year prospective assessment of all-cause mortality, and longitudinal changes of the same clinical outcomes. The results of the baseline analysis are published elsewhere [17].

Baseline Assessments

Participants attended 3 visits within 1 month. Pre- and post-bronchodilator spirometry, symptoms, smoking status, medical history and medication use were assessed at visit 1 and a sputum induction was undertaken. At visit 2, venepuncture with blood collection and a skin allergy test [18] were performed. Sputum induction was repeated if an adequate sputum sample was not obtained at the first visit. At the 3rd visit, a hypertonic saline (4.5%) challenge was performed in those whose visit 1 FEV₁ was >1.3 litres, as previously prescribed [19].

Participant Questionnaires

The questionnaires assessed respiratory symptoms such as cough, breathlessness, wheeze and mucus production. A smoking history was taken and smoking pack-years were determined. Smoking status was reassessed at the final visit and smoking history during the follow-up period was recorded. Smoking status was validated by measurement of exhaled carbon monoxide using a piCO Smokerlyzer (Bedfont Scientific Ltd., Harrietsham, UK), and a reading of >10 parts per million was used as the cutoff for current smoking [20]. Health status was measured using Saint George's Respiratory Questionnaire (SGRQ) [21], with scores ranging from 0 to 100. A 0 score indicates no impairment in quality of life and an increasing score indicates increased impairment. The Charlson Comorbidity Index (CCI) was calculated using information collected in the medical history [22]. The Hospital Anxiety and Depression Scale was used to assess the psychological status [23].

Pulmonary Function Tests

Participants withheld bronchodilators for their duration of action before spirometry testing. Three reproducible measurements of FEV₁ and forced vital capacity (FVC) were obtained (KoKo PD Instrumentation, Louisville, Colo., USA) before and after inhalation of 400 µg salbutamol via a metered dose inhaler with valved holding chamber (Volumatic, Allen and Hanbury's, Melbourne, Vic., Australia). Predicted values were calculated according to Knudson et al. [24].

Six-Minute Walking Test

Participants were administered 400 µg salbutamol 20 min before the walking tests. The 6-min walk distance (6MWD) was measured using the best of two 6MWD tests according to American Thoracic Society guidelines [25].

Definitions of Disease Categories

Whilst participants were recruited based on physician diagnosis of OADs, a diagnostic classification was then performed using standardized objective criteria for the purposes of study analysis [10]. Asthma was defined as episodic respiratory symptoms and fully reversible airflow obstruction with a post-bronchodilator $FEV_1/FVC \geq 70\%$ and post-bronchodilator $FEV_1 > 80\%$ of predicted, together with AHR or increased BDR. AHR was defined if there was a $\geq 15\%$ FEV_1 fall from baseline after inhalation of 4.5% hypertonic saline. An increase in post-bronchodilator $FEV_1 \geq 200$ ml and 12% compared with pre-bronchodilator FEV_1 was defined as BDR [5]. Participants with COPD had incompletely reversible airflow obstruction with a post-bronchodilator $FEV_1/FVC < 70\%$ and post-bronchodilator $FEV_1 < 80\%$ of predicted and no AHR or BDR. Participants with the asthma-COPD overlap had respiratory symptoms, increased airflow variability (asthma, i.e. AHR or BDR) as well as incompletely reversible airflow obstruction (COPD; post-bronchodilator $FEV_1/FVC < 70\%$ and post-bronchodilator $FEV_1 < 80\%$ of predicted). We used hypertonic saline (4.5%) to assess AHR since it is an indirect-acting agent with high specificity for asthma and is less susceptible to the effects of baseline airflow obstruction compared to direct-acting agents (e.g. methacholine). It also had the advantage of permitting collection of induced sputum.

Sputum Induction and Analysis

Sputum induction with hypertonic saline (4.5%) or isotonic saline (0.9%) was performed as previously described [19]. Airway inflammation was assessed using induced sputum. Lower respiratory sputum portions were selected from saliva and processed using dithiothreitol, and differential cell counts were obtained as previously described [19].

Measurement of Systemic Inflammatory Mediators

Peripheral venous blood was collected into Vacutainer® tubes (BD Worldwide, North Ryde, N.S.W., Australia). High-sensitivity C-reactive protein (CRP; MP Biomedicals Australasia, Seven Hills, N.S.W., Australia), interleukin-6 (IL-6; R&D Systems, Minneapolis, Minn., USA) and serum amyloid A (Anogen, Mississauga, Ont., Canada) levels were determined in duplicate using an enzyme-linked immunosorbent assay according to the manufacturer's instructions.

Long-Term Follow-Up

Patients were reevaluated using the same clinical protocol 4 years after the baseline visits. The clinical outcomes assessed were (1) changes in FEV_1 (ΔFEV_1), 6MWD ($\Delta 6MWD$) and SGRQ ($\Delta SGRQ$) during the follow-up period, (2) respiratory hospitalisations and emergency visits over the 4 years, and (3) all-cause deaths occurring during the follow-up.

Statistical Analysis

Data were analysed using STATA 11.2 (Stata Corp., Tex., USA). Mean (SD) or median [interquartile range (25–75%), q_1 – q_3] was used depending on the data distribution. Comparisons between two independent groups were performed using Student's *t* test or the two-sample Wilcoxon rank sum test according to the variable type and distribution. Data are summarized as relative frequencies for categorical variables and Fisher's exact test was used to estimate the difference between groups. Analyses were performed using the

Kruskal-Wallis test for more than two groups. Post hoc analyses were conducted, and an adjusted $p < 0.017$ was considered to be statistically significant to compare differences between the three groups. Univariate and multivariate logistic regression analyses were performed to investigate the impact of baseline clinical characteristics and biomarkers on mortality. Linear regression analysis was performed to assess the potential effects of baseline clinical parameters and biomarkers on the changes in clinical outcomes. Variables were included in the multivariable regression analyses if significant at $p < 0.1$ in univariable tests. A paired *t* test or Wilcoxon signed-rank test was performed to compare clinical characteristics and biomarkers at baseline to those presenting after 4 years. A $p < 0.05$ was defined as statistically significant. For the variables that were significantly different among the three groups, power analysis was performed using modules for STATA 11.2, where a type I error was set to be 0.05.

Results

The baseline assessments were performed over the period from July 2006 to December 2007, and the participants were followed up until death or December 2011. Outcome data were available for 75 (75.8%) participants. Twenty-four participants declined or were not contactable, 16 had died during the follow-up period, and 59 participants attended the follow-up assessment visits. Survival of the participants that were not contactable was confirmed by relevant medical record and database review, and death was excluded for these participants.

Spirometric Classification and Baseline Characteristics

Using the objective physiologic criteria and clinical assessment of symptoms at baseline, there were 36 (36.4%) patients with COPD alone, 55 (55.5%) patients with asthma-COPD overlap and 8 (8.1%) patients with asthma (table 1). The three groups had similar age, gender, body mass index (BMI) and atopic status. More patients in the asthma-COPD overlap group were ex-smokers than the asthma group ($p = 0.010$). Airflow obstruction, measured as FEV_1 (% of predicted) and FEV_1/FVC , was significantly greater in the COPD and overlap groups compared with the asthma group ($p < 0.001$), but no difference was found between COPD and overlap groups. Functional status (SGRQ and 6MWD), inhaled corticosteroid (ICS) treatment and comorbidity (cardiovascular dysfunction and CCI) were similar among the three groups. Levels of systemic inflammation determined by serum CRP, IL-6, serum amyloid A, and blood eosinophil and neutrophil counts were not different among the

Table 1. Baseline clinical characteristics by diagnostic group

	Asthma	COPD	Overlap	p value
Patients, n	8 (8.1%)	36 (36.4%)	55 (55.5%)	
Age, years	66.1±6.6	70.1±7.7	68.6±7.6	0.353
Males/females	3/5	12/24	27/28	0.317
BMI	30.3±6.5	28.6±7.1	28.8±6.4	0.794
Atopy, n	5 (62.5%)	24 (66.7%)	28 (50.9%)	0.317
Smoking, never/ex-smoker	6/2	14/22	14/41*	0.017
Pack-years	12.6 (0.1–25.0)	35.3 (17.0–51.0)	33.7 (17.1–53.8)	0.257
FEV ₁ , % of predicted	81.6±6.8	55.9±16.2*	54.6±18.2*	<0.001
FVC, % of predicted	90.7±10.4	77.5±16.1	82.9±20.2	0.133
FEV ₁ /FVC, %	73.1±3.2	57.8±14.6*	52.1±11.3*	<0.001
SGRQ score	38.9±11.8	47.6±20.9	41.7±17.3	0.248
6MWD, m	428.6±93.7	408.5±104.9	404.6±110.3	0.840
ICS use, n	7 (87.5%)	31 (86.1%)	49 (89.1%)	0.913
ICS dose, BDP equivalent, µg/day	2,000 (500–2,000)	2,000 (1,000–2,000)	2,000 (1,000–2,000)	0.835
Cardiovascular dysfunction, n	5 (52.5%)	17 (47.2%)	37 (67.3%)	0.160
CCI	3.5 (3–5)	4 (3–5)	4 (3–5)	0.828
CRP, mg/l	2.5 (2.0–9.6)	8.1 (2.4–14.6)	4.7 (1.7–8.8)	0.213
IL-6, pg/ml	1.4 (1.0–3.3)	3.0 (1.8–5.1)	2.9 (1.8–4.8)	0.207
Serum amyloid A, mg/l	5.0 (2.1–7.7)	4.8 (2.7–8.9)	4.4 (2.3–10.8)	0.928
Blood eosinophils, 10 ⁹ /l	0.2 (0.1–0.3)	0.1 (0.1–0.3)	0.1 (0.1–0.2)	0.601
Blood neutrophils, 10 ⁹ /l	5.5 (4.3–5.6)	6.7 (4.7–9.4)	5.9 (4.8–9.1)	0.493
Sputum eosinophils, %	1.9 (0.3–5.0)	1.0 (0.3–2.0)	1.3 (0.5–5.0)	0.269
Sputum neutrophils, %	38.3 (27.8–70.3)	80.5 (50.3–87.3)	62.8 (43.0–78.5)	0.041
Sputum macrophages, %	59.8 (24.1–68.6)	15.0 (8.0–47.0)	29.1 (15.0–41.8)	0.087
Sputum lymphocytes, %	0.1 (0–0.8)	0 (0–0.5)	0.3 (0–0.5)	0.517

* p < 0.05 vs. asthma. Means ± SD and medians (interquartile ranges) are shown. BDP = Beclomethasone dipropionate.

three groups. COPD patients had elevated sputum neutrophil percentage, but other markers were similar across groups.

Comparisons of Baseline Characteristics for Survivors and Non-Survivors and the Association with Mortality

There were 16 (16.2%) patients who died over a median follow-up of 4.2 (3.8–4.5) years. Baseline measurements of smoking pack-years, lung function impairment, ICS daily dose and 6MWD were significantly different between the survivors and non-survivors (table 2). Non-survivors also showed a significantly higher BODE index at baseline [median (q1–q3), 5 (3–7)] compared to survivors [2 (1–4), p < 0.001], and the non-survivors had a higher baseline SGRQ total score [mean (SD), 56.0 (16.5) for non-survivors vs. 41.2 (17.9) for survivors, p = 0.005]. Hospital admission in the previous 12 months was also greater in the non-survivors (50.0%) than the survivors (21.7%; fig. 1). Baseline

levels of blood eosinophils, neutrophils and sputum inflammatory counts were not different between the survivors and non-survivors (table 2). Survival among asthma, COPD and overlap groups was not different (p = 0.320; table 2).

Univariate logistic regression identified that the BODE index, SGRQ total score and hospital admission in the previous 12 months were significantly associated with all-cause mortality over 4 years. After adjustment in a logistic regression model, the BODE index (p = 0.004) was the only predictor that was independently associated with all-cause mortality in this population (table 3).

Changes in Clinical Parameters over the 4-Year Follow-Up

Of the participants who completed the study, none of them re-started smoking after entry into the study. Overall, there were significant deteriorations in FEV₁, 6MWD, SGRQ, BODE index and CCI over the 4-year

Table 2. Comparison of baseline clinical characteristics for survivors and non-survivors

	Survivors	Non-survivors	p value
Patients, n	83 (83.8%)	16 (16.2%)	
Age, years	68.6±7.6	70.8±7.1	0.270
Males/females	33/50	9/7	0.222
BMI	29.2±6.9	27.3±4.6	0.318
Smoking, never/ex-smokers	31/52	3/13	0.249
Pack-years	30.5 (15.3–46.6)	51 (41.5–63.5)	0.011
FEV ₁ , % of predicted	60.2±17.5	41.8±14.0	<0.001
FVC, % of predicted	84.2±17.6	68.0±16.9	0.002
FEV ₁ /FVC, %	57.3±13.2	48.3±12.7	0.017
ICS use	73±88.0	14±87.5	0.960
ICS dose, BDP equivalent, µg/day	2,000 (1,000–2,000)	2,000 (2,000–2,000)	0.020
Cardiovascular dysfunction, n	49 (59.0%)	10 (62.5%)	0.796
CCI	4 (3–5)	4.5 (3–5.5)	0.181
6MWD, m	429.9±94.1	297.3±97.1	<0.001
CRP, mg/l	4.8 (2.1–10.6)	6.4 (1.3–17.1)	0.947
IL-6, pg/ml	2.6 (1.7–4.8)	2.8 (1.4–16.0)	0.666
Serum amyloid A, mg/l	5.2 (2.3–9.8)	2.8 (1.9–5.7)	0.171
Blood eosinophils, 10 ⁹ /l	0.1 (0.1–0.3)	0.1 (0.1–0.1)	0.049
Blood neutrophils, 10 ⁹ /l	5.9 (4.6–8.8)	7.5 (4.7–9.9)	0.522
Sputum eosinophils, %	1.3 (0.5–3.3)	0.6 (0.3–3.3)	0.347
Sputum neutrophils, %	65.0 (43.0–85.3)	64.6 (38.0–79.5)	0.743
Sputum macrophages, %	27.8 (9.5–47.5)	24.3 (16.6–44.5)	0.743
Sputum lymphocytes, %	0 (0–0.8)	0 (0–0.3)	0.417
Asthma/COPD/overlap, n	8/31/44	0/5/11	0.320

Means ± SD or medians (interquartile ranges) are shown. BDP = Beclomethasone dipropionate.

Fig. 1. Comparisons at baseline of the BODE index (a), CCI (b), SGRQ (c) and hospital admission (HA; d) in the past year for the survivors versus non-survivors. HA = Hospital admission.

Fig. 2. Clinical outcomes deteriorated significantly over 4 years, with the comparison of FEV₁ (**a**), 6MWD (**b**), SGRQ (**c**) and CCI (**d**) between baseline visits and final visits.

Table 3. Logistic regression for all-cause mortality

Variables	Univariate logistic regression			Multivariate logistic regression		
	OR	95% CI	p value	OR	95% CI	p value
Age	1.04	0.97–1.12	0.278	1.04	0.95–1.13	0.408
Sex	0.51	0.17–1.51	0.227	0.44	0.12–1.62	0.220
BODE	1.77	1.31–2.37	<0.001	1.70	1.19–2.42	0.004
SGRQ	1.05	1.01–1.09	0.005	1.01	0.97–1.06	0.499
Hospital admission in past 12 months	3.61	1.19–10.96	0.023	2.09	0.58–7.59	0.261
Blood eosinophils	0.04	0.00–4.08	0.173	–	–	–
Blood neutrophils	1.04	0.88–1.22	0.652	–	–	–

Fig. 3. Heterogeneity in changes in FEV₁ (l/year; **a**), 6MWD (m; **b**) over 4 years and SGRQ (units; **c**) over 4 years; solid black line represents zero.

period (fig. 2). Post-bronchodilator FEV₁ decreased from 1.53 (0.56) to 1.44 (0.54) litres at the end of the study ($p < 0.001$; table 4). The decline in FEV₁ was 83 (174) ml over 4 years, and the annual rate of the FEV₁ decline was 19 (41) ml. There was no difference in the decline in FEV₁ among the three groups ($p = 0.628$; table 5). Compared to baseline visits, FEV₁ significantly declined in the COPD group at the end of the study ($p = 0.003$; table 5). Heterogeneity in the FEV₁ decline was found with the annual change ranging from a decline of 94 ml to an improvement of 107 ml (fig. 3a). FVC declined 72 (361) ml through the study period ($p = 0.038$), while no difference was found in FEV₁/FVC between basal and final visits.

6MWD decreased significantly at the end of the study [mean (SD), 441.0 (95.8) m] with a decrease of 36.7 (73.7) m less than the baseline [407.5 (114.2) m; $p < 0.001$]. There was marked variation in the change in 6MWD (fig. 3b). The change in 6MWD was significantly different among the diagnostic groups ($p = 0.010$), and the greatest decline occurred in the COPD group with a decline of 75.5 (93.4) m over 4 years ($p = 0.024$; fig. 4). Compared to the COPD group, the decline in 6MWD was less marked in the overlap group [15.7 (51.3) m; $p = 0.006$], and patients with asthma had a decline of 11.0 (41.4) m in 6MWD.

Deterioration in respiratory quality of life was observed at the endpoint of the study [mean (SD), 43.5 (18.2) units] with a 5.0 (12.8)-unit increase in the SGRQ total score compared to baseline visits [38.8 (18.1) units; $p = 0.010$]. The change was similar among the diagnostic groups ($p = 0.905$; table 5). Patients with COPD had a significantly increased SGRQ total score (worse quality of life) compared with baseline visits ($p = 0.030$). An increase in both the BODE index ($p = 0.024$) and CCI ($p =$

Fig. 4. Changes in 6MWD over 4 years by diagnostic group.

Table 4. Changes in clinical outcomes over a 4-year period

Variables	Initial assessment	Final assessment	p value
BMI	28.49±7.00	29.44±8.24	0.240
FEV ₁ , litres	1.53±0.56	1.44±0.54	<0.001
FVC, litres	2.69±0.83	2.62±0.88	0.038
FEV ₁ /FVC, %	57.00±13.23	55.84±13.94	0.165
6MWD, m	441.0±95.8	407.5±114.2	<0.001
SGRQ	38.8±18.1	43.5±18.2	0.010
BODE	2 (1–4)	2 (1–4)	0.024
BODE ≥6, n	4 (6.8%)	12 (21.4%)	0.023
CCI	4 (3–4)	4 (3–5)	0.002
CCI ≥5, n	12 (20.3%)	23 (41.1%)	0.027
HADS score			
Anxiety	6 (4–9)	6 (3–8)	0.396
Depression	4 (2–7)	4 (2–7)	0.584
CRP, mg/l	4.8 (2.4–12.4)	4.3 (1.9–8.1)	0.013
IL-6, pg/ml	2.5 (1.5–4.7)	3.3 (1.7–4.5)	0.212

Means ± SD or medians (interquartile ranges) are shown. HADS = Hospital Anxiety and Depression Scale.

Table 5. Decline in clinical outcomes by different diagnostic groups (means $\pm$ SD)

	FEV ₁ , litres			6MWD, m			SGQL, units		
	initial visit	final visit	Δ	initial visit	final visit	Δ	initial visit	final visit	Δ
Asthma	2.40 $\pm$ 0.64	2.26 $\pm$ 0.54	0.14 $\pm$ 0.23	453.4 $\pm$ 90.8	442.38 $\pm$ 63.9	11.0 $\pm$ 41.4	33.2 $\pm$ 10.1	38.4 $\pm$ 17.6	-5.1 $\pm$ 20.4
COPD	1.41 $\pm$ 0.43	1.31 $\pm$ 0.43 ^a	0.10 $\pm$ 0.13	456.8 $\pm$ 79.0	381.3 $\pm$ 112.0 [*]	75.5 $\pm$ 93.4	42.2 $\pm$ 21.7	47.9 $\pm$ 19.1 [*]	-5.7 $\pm$ 11.4
Overlap	1.46 $\pm$ 0.51	1.40 $\pm$ 0.51 ^a	0.06 $\pm$ 0.19	441.5 $\pm$ 98.7	425.8 $\pm$ 116.2	15.7 $\pm$ 51.3 ^b	37.2 $\pm$ 16.2	41.3 $\pm$ 17.7	-4.1 $\pm$ 12.7

^{*} p < 0.05 vs. initial visit, ^a p < 0.05 vs. asthma at the same time point, ^b p < 0.05 vs. COPD (change in clinical outcome).

0.002) was also found over the 4-year period, but Hospital Anxiety and Depression Scale scores did not change during the study (table 4). Additionally, there was a trend towards a higher proportion of patients who had at least one hospital admission during the follow-up period in the COPD group (36.4%) than asthma and overlap groups (p = 0.053).

Associations between Baseline Characteristics and Change in Clinical Outcomes

Univariate regression that examined associations between the change in FEV₁ and baseline age, sex, BMI, smoking history, airflow reversibility, serum CRP and IL-6 level, and sputum inflammatory eosinophil and neutrophil percentages failed to identify significant predictors for FEV₁ decline (p > 0.1).

Participants without airflow reversibility had a greater decline in 6MWD of 73.9 (91.2) m compared with those with airflow reversibility [14.2 (50.0) m; p = 0.003]. In univariate regression, BMI (p = 0.670), cardiovascular dysfunction (p = 0.323), serum CRP (p = 0.139) and IL-6 (p = 0.616) at baseline were not associated with 6MWD decline; airflow reversibility was associated with less decline in 6MWD (p = 0.003). After adjustment for age and sex, it was shown that the presence of airflow reversibility at baseline was associated with a slower decline in walking distance over the 4-year period (coefficient = -65.29, p = 0.002).

Hospital admission during the follow-up period negatively correlated with the decline in the SGRQ total score (r = -0.341, p = 0.008). The score increased 13.4 (10.3) units in patients who had at least one hospital admission, which is significantly different from the 2.6 (12.5)-unit elevation in those without hospital admission (p = 0.007). The decline in FEV₁ was positively correlated with the change in 6MWD (r = 0.316, p = 0.023) but not with the SGRQ total score (r = -0.216, p = 0.111).

Power Analysis

Statistical power for differences in baseline FEV₁ % of predicted and FEV₁/FVC among asthma, COPD and asthma-COPD overlap groups with respect to the α level of 0.05 was 1.00. Power for the differences in the 6MWD decline among the three groups, and the difference between COPD and overlap groups was shown to be 0.78.

Discussion

With age, an overlapping pattern of airflow obstruction and increased airflow variability is commonly present in OADs patients. While there are longitudinal studies that have reported a decline in FEV₁ [11, 26] and exacerbations related to fixed airflow obstruction due to asthma or COPD [11], to our knowledge, the current study is the first to compare disease progression in asthma, COPD and asthma-COPD overlap in an older cohort with a multidimensional assessment of lung function, exercise capacity, quality of life, inflammation and mortality. We found that the BODE index was an effective prognostic indicator for all-cause mortality in older adults with OADs, including asthma, COPD and asthma-COPD overlap, and of the three phenotypes, patients with COPD had a poor prognosis, particularly in terms of the decline in 6MWD.

Our data show that the non-survivors were different at baseline: they smoked more cigarettes, had greater lung function impairment, higher BODE index, lower 6MWD and higher SGRQ total score. These results are consistent with previous studies [27–29]. However, the logistic regression analysis of mortality demonstrated that a higher BODE index was the only covariate that was associated with an increased risk of all-cause death in patients with OADs. This suggests that the applicability of the BODE index to predict all-cause mortality is not limited to

COPD [16], making the BODE index a useful tool for OADs in general. Further study is needed to validate the use of the BODE index in asthma.

A strength of the present study is the multidimensional analyses of long-term outcomes comparing asthma, COPD and the overlap in an older cohort. It is recognized that patients with asthma tend to maintain lung function, health status and exercise capacity [30]; however, these clinical outcomes have been assessed separately in each single study and were limited to asthma [31] or COPD only [32, 33]. Heterogeneity of study participants and clinical protocols between studies may not provide robust evidence for assessing progression of asthma and COPD. In this study, we found that post-bronchodilator FEV₁, 6MWD and SGRQ were significantly decreased in the COPD group, but not in asthma and overlap groups. Remarkably, the decline in 6MWD was the greatest in the COPD group and was significantly different compared to the overlap group. These findings demonstrate the poor long-term prognosis of COPD in an older cohort. We attempted to examine the mechanisms underlying disease progression by assessing systemic inflammatory pathways. However, there was no correlation between the inflammatory markers and changes in clinical outcomes. Mechanisms of the different prognoses in older people with OADs merit further investigation.

We did not find a significant decline in FEV₁ in the overlap group, and the change in FEV₁ was not different among the three groups, which supports the data by Calverley et al. [34] and Anthonisen et al. [35], but is different from other studies [11, 26]. The conflicting results were presumably attributable to the definition of airflow reversibility and classification of disease categories. In the study by Contoli et al. [11], patients with fixed airflow obstruction due to COPD were included using the physiological definition of COPD as our study did; however, they excluded patients who had physician-diagnosed COPD with an airflow reversibility from the overlap group, which is an important subtype of the overlap syndrome. Moreover, Hardin et al. [12] reported poorer health-related quality of life and increased exacerbations in the asthma-COPD overlap than COPD groups; however, their study excluded patients with late-onset asthma, and COPD patients with <10 pack-years were also excluded. Therefore, the classification of disease categories in our study provides a more comprehensive definition and includes almost all the patients with OADs in a 'real-world' setting.

Our longitudinal data suggest that COPD patients had greater disease progression, while patients with asthma

and overlap did not have a significant decline in clinical outcomes. It is possible that the presence of the overlap syndrome has a protective effect on disease activity. One possible reason for this observation is that patients in the overlap group had predominantly physician-diagnosed asthma; however, this seems to be unlikely because 90.6% of the patients in this group were ex-smokers with a median of 33.7 (17.1–51.3) pack-years of smoking, and the median age at diagnosis of respiratory disease was 49 years. Intriguingly, the presence of airflow reversibility was shown to be associated with a slower decline in 6MWD. Another study reported that less reversibility at baseline was associated with the development of irreversible airflow obstruction [36]. The findings of the protective effects of airflow reversibility are in conflict with the traditional recognition of airflow reversibility, and should be interpreted cautiously and need to be studied further.

Compared to previous longitudinal studies, our data show a relatively smaller decline in clinical outcomes, in particular in terms of FEV₁ decline [26, 37, 38]. This may be attributed to active pharmacotherapy [39]. In our study, 84.7% of the patients were using a combination of ICS and long-acting β_2 -agonist therapy with a median ICS dose of 2,000 μ g beclomethasone dipropionate equivalent daily, and 49.2% of the patients were using long-acting anti-cholinergics. In previous studies, fewer participants were using ICS [37], or the dose of ICS was not documented [26, 40]. Although the average 6MWD decline in our study was less compared with other studies [41], the decrease in the COPD group of 75.5 (93.4) m was greater than the minimum clinically important difference of 25 m [42, 43] and a noticeable difference in perceived walking ability of 54 m [44]. The average increase in SGRQ in each group was greater than the minimum clinically important difference of 4 units [45], indicating a decrease in quality of life with clinical significance over the 4 years.

In COPD, traditional notions of gradual decay in clinical outcomes have been challenged by a series of recent studies [26, 38, 40]. Our data also demonstrate heterogeneity in the progression of patients with OADs in terms of changes in FEV₁, 6MWD and SGRQ. We failed to identify any baseline clinical characteristic or inflammatory marker that may relate to future changes in FEV₁ and SGRQ. In the context that most of these participants were taking high-dose treatment, it is possible that specific groups of patients present different phenotypes, or have an altered disease pathobiology and response to treatment. Further studies are worthwhile to address the het-

erogeneity within the three disease groups and the mechanisms of this heterogeneity.

Some limitations of the present study need to be considered. At present, there are different definitions used for the diagnosis of the asthma-COPD overlap. We used physiological lung function criteria with the presence where possible of AHR [10]. Other definitions have been proposed based on the presence of a specific inflammatory pattern [14], but these are unfortunately not specific for asthma and COPD [46, 47]. We used hypertonic saline as the bronchial provocation agent, since it is highly specific for asthma [48, 49], and is an indirect-acting agent, making it less susceptible to the spurious effects of baseline reduction in airflow [50]. In patients whose lung function was too low to undergo a hypertonic saline challenge, we used the presence of BDR in the definition of overlap. In the absence of better diagnostic criteria, we urge that this is justified as the overlap group had clinical symptoms and physiological changes of asthma and COPD. Additionally, the concordance of the proportion of the asthma-COPD overlap group with other studies [7, 9] may also indicate the rationality of this definition. Moreover, the definition given in this study delimits patients with different phenotypes that may be excluded by previous studies [11, 12]. Consensus on the definition of the asthma-COPD overlap among the respiratory community is required. In addition, the overlap group may consist of two subtypes: asthmatics, non-smokers with persistent airflow obstruction and COPD patients with a partial response to bronchodilators. Whether the clinical characteristics and changes in those clinical parameters are different between the two groups, and also compared with asthma or COPD alone, is unknown. Our study is not powered to further subtype the overlap group into these subcategories, but future studies are required to address the phenotypes within the overlap group.

The changes in clinical outcomes, in particular FEV₁, were assessed at baseline visits and at the end of the study. Extra time points during the 4 years monitoring the consecutive changes in these clinical outcomes would help to improve our understanding on disease progression. We did not assess the severity of airflow reversibility, and a dose-response relationship would strengthen the finding of the association between airflow reversibility and the change in 6MWD.

A further limitation of the study is the small sample size in the asthma group. It is known that asthma is a potential risk factor for developing COPD, and an incomplete reversible airflow obstruction can be seen in patients with long-term asthma [51]. Since this may represent the

natural history of asthma physiologically, fewer patients were identified as pure asthmatics in this older population, rather than because of selection bias. Additionally, the proportion of patients in each group, which is consistent with previously published studies [7, 9], reflects the distribution of older people with OADs rather than an intentional selection. To lower the impact of unequal sample sizes on study power, the Kruskal-Wallis test was used to compare differences among the three groups. Furthermore, despite the unequal sample size, the power calculation for the clinical parameters that were significantly different among groups showed that the statistical power of those comparisons was still acceptable. Finally, our study is under-powered to further examine the heterogeneity within the three phenotypes; future studies addressing this question are required.

In conclusion, we have shown that the BODE index is a significant predictor for all-cause mortality in older patients with OADs not only COPD. This makes the BODE index a useful tool for the assessment of older patients with OADs. We confirmed heterogeneity in the progression of OADs and also demonstrated that patients with COPD had a poor prognosis compared to those with the asthma-COPD overlap. The presence of airflow reversibility was shown to be associated with a reduced decline in 6MWD. These findings have increased our understanding on the diversity of OADs, and therefore we propose that enhanced recognition, monitoring and management would lead to an improvement in the progression of OADs. Further studies in larger sample sizes are needed to confirm these study findings, as well as to explore the pathogenesis of disease progression.

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