Differences between asthma–COPD overlap syndrome and adult-onset asthma

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ACOS differs from adult-onset asthma, with lower diffusing capacity, and higher serum IL-6 and blood neutrophil count http://ow.ly/Uxa030aqJAR

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ABSTRACT Differences between asthma–COPD overlap syndrome (ACOS) and adult-onset asthma are poorly understood. This study aimed to evaluate these differences in a clinical cohort of patients with adult-onset asthma, as a part of the Seinäjoki Adult Asthma Study (SAAS).

188 patients were diagnosed with adult-onset asthma and re-evaluated 12 years after diagnosis. They were divided into three groups based on smoking history and post bronchodilator spirometry values: 1) never- and ex-smokers with <10 smoked pack-years; 2) non-obstructive (forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ⩾0.7) patients with ⩾10 pack-years; and 3) ACOS patients with ⩾10 pack-years and FEV_1/FVC <0.7.

ACOS patients had lower diffusing capacity (D_{LCO}/VA 86% predicted *versus* 98 or 96% predicted; p<0.001), higher blood neutrophil levels (4.50 *versus* 3.60 or 3.85×10^9 L^{-1}; p=0.008), and higher IL-6 levels (2.88 *versus* 1.52 or 2.10 $pg\cdot mL^{-1}$, p<0.001) as compared to never- and ex-smokers with <10 pack-years, or non-obstructive patients with ⩾10 pack-years smoking history, respectively. ACOS patients also showed reduced lung function, higher remaining bronchial reversibility and a higher number of comorbidities.

This study shows distinct differences in diffusing capacity, blood neutrophil and IL-6 levels, bronchial reversibility, lung function and comorbidities between ACOS and adult-onset asthma. The present findings should be considered in the comprehensive assessment of adult asthma patients.

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Introduction

Asthma and chronic obstructive pulmonary disease (COPD) have previously been categorised as separate entities of obstructive airway disease with different clinical features [1, 2]. Recently, however, overlapping of these two diseases has been recognised, and a novel clinical phenotype, asthma–COPD overlap syndrome (ACOS) has been described. ACOS is characterised by persistent airway obstruction accompanied by several features of both asthma and COPD [3–6]. ACOS has recently been recognised by the Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD), and has been included in several national guidelines of COPD [3–5, 7]. ACOS is considered to develop mainly by two different pathways: either the patient with COPD develops asthma-like symptoms and/or typical characteristics of asthma (for example, high reversibility of the airways); or the patient with asthma continues to smoke and eventually develops non-reversible airway obstruction indicating COPD [8, 9]. There is also a third pathway suggested, in which a patient with asthma develops non-reversible airway obstruction without a smoking history [9]. However, a history of exposure to tobacco smoking (or biomass fuels) has been considered a requirement for COPD diagnosis [2]. Thus, it has been proposed that smoking is also to be regarded as a necessary factor when using the asthma–COPD overlap diagnosis [8, 10].

Previous studies on asthma have generally excluded smoking patients, and studies of COPD have mostly excluded patients with a history or diagnosis of asthma. Therefore, relatively little is known about the differences between ACOS and asthma [6, 10]. The prevalence of ACOS among patients with COPD or asthma is suggested to be 12%–61% depending on the criteria used [9], and it is reported to increase with age [11]. Previous studies on ACOS have been conducted in COPD cohorts mainly, and ACOS patients are reported to have more frequent exacerbations [12–14] and hospitalisations [11, 14], poorer quality of life [12], reduced physical activity [12] and increased dyspnoea and wheezing, as compared to patients with COPD alone [11, 12].

ACOS among asthmatic patients, remains far less frequently studied. Some epidemiological and registry-based studies on ACOS among patients with asthma have been previously published, leaving a major need for clinical studies with actual patients. However, these previous studies have reported more frequent exacerbations [14, 15], poorer asthma control, increased symptoms of dyspnoea [15], impaired lung function [14–16] and poorer quality of life [16] in ACOS patients, as compared to patients with asthma alone. Patients with ACOS are also reported to have an increased rate [14, 17] and duration of hospitalisation, as compared to patients with asthma [17]. Furthermore, the number of comorbidities [15], particularly hypertension [15, 16], has been reported to be higher among patients with ACOS as compared to those with asthma alone, and ACOS patient mortality has been suggested to be higher than that of patients with asthma [18, 19].

Diagnosis of ACOS is challenging, because no specific single clinical feature, spirometric finding, or biomarker has been identified to differentiate ACOS from asthma [6, 20, 21]. Differentiating ACOS from COPD has been considered important, as it affects the choice of therapy, *i.e.* the use of inhaled glucocorticoids. Differentiating ACOS from asthma, however, has received less attention, even though there are options of targeted treatment for COPD, such as long-acting muscarinic antagonists (LAMA) and roflumilast. Furthermore, ACOS is presently a phenotype with heterogenic and poorly defined clinical features. For this reason, there is an urgent need for the identification of specific characteristics and biomarkers of ACOS [20].

The aim of this study was to evaluate the differences between asthma and ACOS in a clinical cohort of patients with adult-onset asthma.

Methods

Study population and design

The Seinäjoki Adult Asthma Study (SAAS) was a 12-year follow-up study (during the years 1999–2013), in which 257 patients were diagnosed with adult-onset asthma (asthma onset at the age of ⩾15 years) in the Dept of Respiratory Medicine of Seinäjoki Central Hospital, Finland. Diagnosis of asthma was made by a respiratory physician, based on typical symptoms and was confirmed by objective lung function measurements. The study protocol and inclusion and exclusion criteria have been previously published (table S1) [22]. Smokers (current or ex-) were included. After a follow-up of 12 years, 203 patients (79%) were re-evaluated (years 2012–2013), and the data of 188 patients were included in the analysis (figure 1). During the follow-up, patients were actively treated for asthma, according to the Finnish Asthma Programme guidelines [23]. Medication use was recorded, using a structured questionnaire that included self-reported medication at the time of the follow-up visit. The present study was cross-sectional, using data mostly from the control visit (years 2012–2013). However, when assessing the use of oral corticosteroid courses, atopy or airway obstruction at baseline, longitudinal data was utilised. Written informed consent was obtained from participants and the study protocol was approved by the Ethics Committee of Tampere University Hospital, Tampere, Finland (R12122).

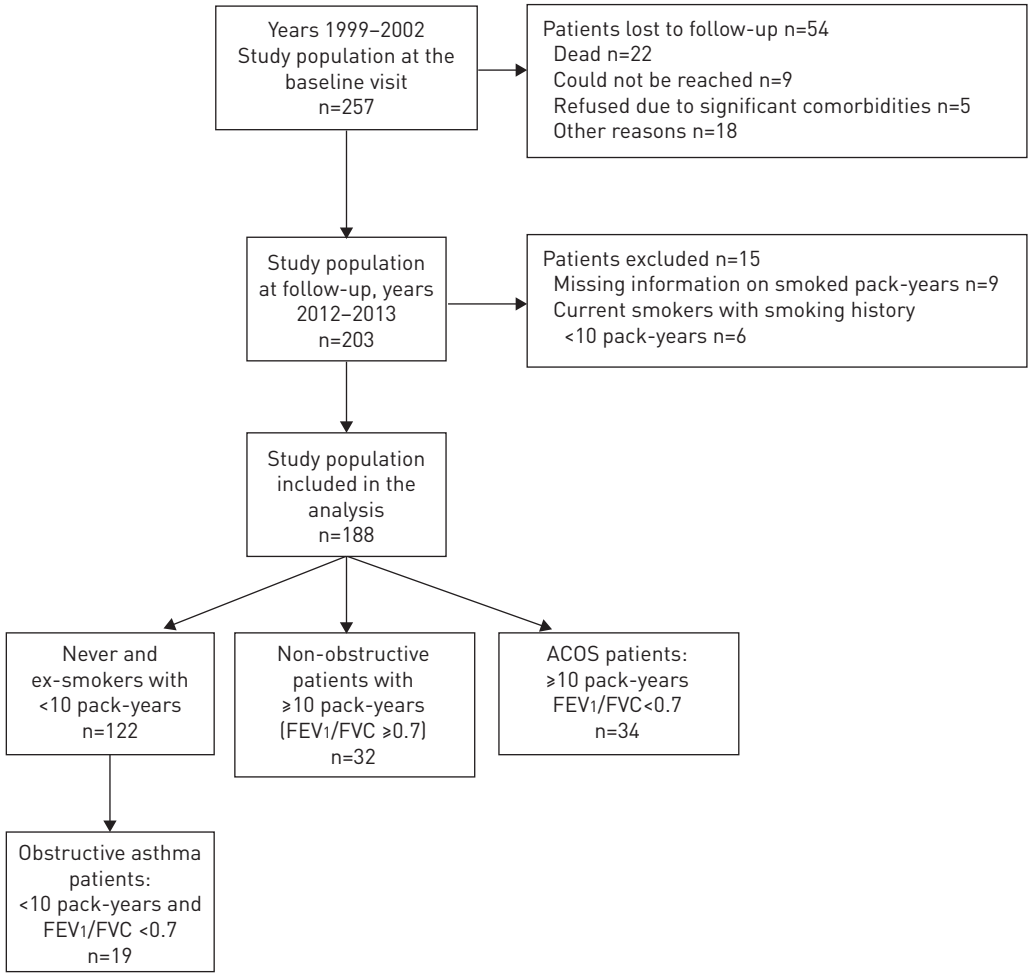

FIGURE 1 Study profile. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity.

Evaluation of smoking and lung function

Lung function measurements were performed with a spirometer (Vmax Encore 22, Viasys Healthcare, Palm Springs, CA, USA) that was calibrated daily. Finnish lung function reference values were used [24]. Lifelong cumulative exposure to tobacco was evaluated by assessing smoked pack-years (20 cigarettes per day for 1 year), and patients were divided into three groups based on smoked pack-years and lung function as follows: 1) never- and ex-smokers with <10 pack-years of smoking (current smokers excluded); 2) non-obstructive patients with ⩾10 pack-years and post-bronchodilator (BD) forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ⩾0.7; and 3) ACOS patients *i.e.* ⩾10 pack-years of smoking and post BD FEV_1/FVC <0.7 (figure 1). The differences between obstructive asthma (with <10 pack-years) and ACOS were also analysed. Patients with obstructive asthma were separated from the group of never- and ex-smokers with <10 pack-years based on post BD FEV_1/FVC; thus, patients with post BD FEV_1/FVC <0.7 were categorised as obstructive asthma patients (n=19) (figure 1). Serum interleukin-6 (IL-6), high-sensitivity C-reactive protein (hsCRP), immunoglobulin E (IgE), blood cell counts and fractions of exhaled nitric oxide (F_{ENO}) were measured as previously described [25–27], and patients completed clinical questionnaires of the Asthma Control Test (ACT), COPD Assessment Test (CAT) and Asthma Questionnaire 20 (AQ20) [28] during the visit. Asthma control was evaluated based on the recommendations of the GINA 2010 report [29].

Statistical analyses

Continuous data were expressed as mean±SD or median and interquartile range, as required. Groups were compared using the t-test, Mann–Whitney rank sum test or Chi-squared test. Comparisons between three groups were done by one-way ANOVA with Tukey's *post hoc* test, Kruskal–Wallis test or Chi-squared test. Statistical analyses were performed using the SPSS software, version 24 (IBM SPSS, Armonk, NY, USA). A p-value <0.05 was regarded as statistically significant.

Results

Out of the 188 patients analysed, 34 patients (18.1%) were classified as having ACOS and 32 patients (17.0%) belonged to the group of non-obstructive patients with ⩾10 pack-years. The mean±SD age of asthma onset in the entire cohort was 46.5±13.6 years, and in the ACOS group, it was 53.0±10.8 years. The majority of patients (122; 64.9%) were never- or ex-smokers with a smoking history less than 10 pack-years. ACOS patients were generally older as compared to the other groups, and a male predominance was observed in the two groups with a smoking history of ⩾10 pack-years. The duration of asthma was equal among all groups, owing to the 12-year follow-up period in each. Characteristics of the three groups are presented in table 1, and those of the excluded patients are presented in table S2.

The number of patients with uncontrolled asthma (55.9%) in the ACOS group was higher than that of the other groups. In addition, the percentage of patients with well-controlled asthma was lower in the two groups with a smoking history ⩾10 pack-years (table 1). Surprisingly, the use of oral steroids showed no difference among any of the groups, and equal percentages of patients among all groups were using inhaled glucocorticoids daily. However, the group of non-obstructive patients with a smoking history ⩾10 pack-years used higher doses of inhaled glucocorticoids and more frequently had long-acting beta-agonists in daily use. Daily use of LAMA, leukotriene antagonists or theophylline was similar among the groups (table 1). Prevalence of rhinitis, atopy and allergies showed no significant differences among groups (table 1).

We assessed whether ACOS differs from asthma, by using questionnaires that are widely validated for clinical use. The results revealed no significant differences in ACT scores or CAT scores between ACOS and non-obstructive patients with a history of ⩾10 pack-years, although ACT scores were generally lower, and CAT scores generally higher in the two groups with a smoking history ⩾10 pack-years, as compared

TABLE 1 Characteristics of the study groups

	Never- and ex-smokers with <10 pack-years	Non-obstructive patients with ⩾10 pack-years	ACOS: ⩾10 pack-years FEV_1/FVC <0.7	p-value[#]
Subjects n	122	32	34	
Age years	56.7±13.9	59.8±12.8	65.0±10.7[¶]	**0.005**
BMI kg·m^{-2}	27.9 (24.3–31.2)	30.6 (25.4–33.8)	28.1 (24.2–30.7)	0.093
Male	36 (29.5)	19 (59.4)[¶]	24 (70.6)[¶]	**<0.001**
Asthma duration years	12.3±0.6	12.4±0.7	12.0±0.7	0.091
Pack-years (of ex-/current smokers)	3 (1–5) range 0–9	21 (17–31)[¶] range 10–47	26 (15–34)[¶] range 10–68	**<0.001**
Smoking status				**<0.001**
Never-smoker	96 (78.7)	0[¶]	0[¶]	
Ex-smoker	26 (21.3)	17 (53.1)[¶]	25 (73.5)[¶]	
Current smoker	0[f]	15 (46.9)[¶]	9 (26.5)[¶]	
Asthma control according to GINA				**<0.001**
Controlled	54 (44.3)	5 (15.6)[¶]	5 (14.7)[¶]	
Partly controlled	41 (33.6)	18 (56.3)	10 (29.4)	
Uncontrolled	27 (22.1)	9 (28.1)	19 (55.9)[¶]	
ICS in daily use	96 (78.7)	26 (81.3)	27 (79.4)	0.950
ICS dose per day bud eq[§]	800 (400–1000)	1000 (763–1900)	800 (800–1200)	**0.023**
LABA in daily use	51 (41.8)	21 (65.6)[¶]	21 (61.8)	**0.016**
LAMA, LTRA or theophylline in daily use	20 (16.5)	7 (21.9)	8 (23.5)	0.575
Use of oral steroid courses ever	38 (31.7)	14 (43.8)	7 (21.2)	0.149
⩾2 oral steroid courses in 2 years	16 (13.3)	6 (18.8)	4 (12.1)	0.691
ACT score	22 (20–25)	21 (19–24)	21 (16–23)[¶]	**0.025**
CAT score	10±7	14±7[¶]	16±7[¶]	**<0.001**
AQ20 score	3 (1–7)	4 (2–7)	4 (2–8)	0.291
Post bronchodilator FEV_1/FVC <0.7 at baseline[##]	11 (9.0)	1 (3.1)	16 (47.1)[¶,+]	**<0.001**
Skin-prick positive[##]	44 (39.3)	11 (35.5)	5 (20.0)	0.191
Continuous rhinitis	44 (36.4)	13 (41.9)	8 (23.5)	0.256
Allergic conjunctivitis or rhinitis	79 (66.9)	20 (62.5)	15 (45.5)	0.079

Data are presented as n (%), mean±SD, or median (interquartile range), unless otherwise stated. Statistically significant p-values are presented in bold. [#]: p-value across all groups; [¶]: as compared to group 1 (never and ex-smokers with <10 pack-years), p<0.05; [+]: as compared to group 2 (non-obstructive patients with ⩾10 pack-years), p<0.05; [f]: excluded, [§]: budesonide equivalent, of daily users, [##]: at the moment of asthma diagnosis (1999–2002) [22]. ACOS: asthma–chronic obstructive pulmonary disease overlap syndrome; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; BMI: body mass index; GINA: Global Initiative for Asthma; ICS: inhaled corticosteroids; LABA: long-acting beta-agonists; LAMA: long-acting muscarinic antagonists; LTRA: leukotriene antagonists; ACT: Asthma Control Test; CAT: COPD Assessment Test; AQ20: Asthma Questionnaire 20.

to never- or ex-smokers with <10 pack-years of smoking (table 1). The AQ20 scores showed no significant differences among groups (table 1).

Diffusing capacity and biomarkers

ACOS patients had significantly lower diffusing capacity of the lungs for carbon monoxide (D_{LCO} % and D_{LCO}/V_A % predicted) as compared to the other groups (p=0.001). Furthermore, the blood neutrophil count and serum IL-6 levels were found to be the highest in the ACOS group (table 2). In contrast, the levels of blood eosinophils, hsCRP, IgE, and F_{eNO} showed no significant differences among any of the groups (table 2).

Lung function

Post BD spirometry values of FEV_1 (p=0.002), FEV_1 % predicted (p<0.001), and FEV_1/FVC ratio (p<0.001) were found to be significantly lower in the group of patients with ACOS as compared to those of the other groups. It should be noted, however, that post BD FEV_1/FVC <0.7 was an inclusion criteria for the ACOS group. The FVC (L or % predicted) values showed no significant differences among groups (table 3). Pre-BD values are presented in table S3. We also evaluated reversibility (measurements before and after BD) of the airways at the follow-up visit, by which patients had been actively treated for asthma for 12 years. There were significantly higher levels of reversibility of the airways among patients with ACOS as compared to those of other groups. This was evident in both the FEV_1 % predicted, and the FVC mL and % predicted (table 3).

Comorbidities

The overall number of comorbidities was significantly higher in the ACOS group as compared to the other groups (p=0.008). In the ACOS group, COPD was not considered a comorbidity. Similarly, the number of medications used for the treatment of comorbidities was highest in the ACOS group. The prevalence of hypertension (p=0.029), coronary heart disease (p=0.012) and hypercholesterolaemia (p=0.023) was highest in ACOS group (table 4). In contrast, no significant differences were noted in the prevalence of diabetes, systemic rheumatoid disease, or thyroid disease. In the group of non-obstructive patients with a smoking history ⩾10 pack-years, the prevalence of obesity was higher as compared to the other groups. Moreover, the prevalence of obesity among ACOS patients was similar to that among never- or ex-smokers with <10 pack-years (table 4). In addition, no significant differences were noted in the use of antipsychotic or antidepressant medication, nor therapy for dyspepsia or pain among any of the groups (data not shown).

Differences between obstructive asthma and ACOS

Patients with obstructive asthma (FEV_1/FVC <0.7 but smoking history less than 10 pack-years) had significantly higher diffusing capacity values of the lung as compared to ACOS patients. The blood neutrophil count and serum IL-6 levels were higher in the ACOS group, as compared to the group of patients with obstructive asthma. No significant differences were found in the levels of eosinophils, IgE, hsCRP and F_{eNO} (table 5). The CAT scores in the ACOS group were higher than in the group of patients with obstructive asthma; however, no significant differences were found in the AQ20 or ACT scores (table S4). Furthermore, the use of medication was similar among patients with ACOS and those with obstructive asthma, and no

TABLE 2 Diffusing capacity and biomarker data in study groups

	Never and ex-smokers with <10 pack-years	Non-obstructive patients with ⩾10 pack-years	ACOS: ⩾10 pack-years FEV_1/FVC <0.7	p-value[#]
Subjects n	122	32	34	
D_{LCO} % pred	97±16	91±15	85±23[¶]	**0.001**
D_{LCO}/V_A % pred	98±13	96±18	86±22[¶,+]	**<0.001**
Blood neutrophils $\times 10^9$ L^{-1}	3.60 (2.70–4.60)	3.85 (2.95–4.98)	4.50 (3.50–5.53)[¶]	**0.008**
Blood eosinophils $\times 10^9$ L^{-1}	0.16 (0.09–0.28)	0.14 (0.09–0.22)	0.19 (0.10–0.29)	0.409
IgE kU·L^{-1}	59 (25–167)	95 (26–199)	59 (20–140)	0.516
F_{eNO} ppb	12 (5–21)	8 (5–13)	10 (5–15)	0.063
hsCRP mg·L^{-1}	1.24 (0.56–2.33)	1.18 (0.74–5.02)	0.93 (0.59–3.04)	0.369
IL-6 pg·mL^{-1}	1.52 (1.12–2.48)	2.10 (1.09–5.69)	2.88 (1.88–4.99)[¶]	**<0.001**

Data are presented as mean±SD, or median (interquartile range), unless otherwise stated. Statistically significant p-values are presented in bold. [#]: p-value across all groups; [¶]: as compared to group 1 (never- and ex-smokers with <10 pack-years), p<0.05; [+]: as compared to group 2 (non-obstructive patients with ⩾10 pack-years) p<0.05. ACOS: asthma–chronic obstructive pulmonary disease overlap syndrome; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; V_A: alveolar volume; IgE: immunoglobulin E; F_{eNO}: exhaled nitric oxide fraction; hsCRP: high-sensitivity C-reactive protein; IL-6: interleukin 6.

TABLE 3 Lung function in study groups

	Never- and ex-smokers with <10 pack-years	Non-obstructive patients with ⩾10 pack-years	ACOS: ⩾10 pack-years FEV1/FVC <0.7	p-value#
Subjects n	122	32	34	
Post bronchodilator				
FEV1 L	2.74 (2.30–3.34)	3.08 (2.34–3.60)	2.32 (1.80–2.98)¶,+	**0.002**
FEV1 % pred	93.0 (84.0–102.0)	88.5 (81.0–95.0)	75.0 (57.5–85.5)¶,+	**<0.001**
FEV1/FVC	0.77 (0.72–0.81)	0.78 (0.72–0.81)	0.62 (0.54–0.67)¶,+	**<0.001**
FVC L	3.65 (3.07–4.36)	3.85 (3.04–4.80)	3.92 (3.41–4.47)	0.428
FVC % pred	99.0 (89.0–110.0)	93.0 (82.5–105.0)¶	98.5 (91.0–106.5)	0.080
FEV1 reversibility§				
mL	108.8±137.8	91.6±104.5	135.6±149.9	0.404
%	4.2±5.5	3.2±3.7	6.7±7.7+	**0.034**
FVC reversibility§				
mL	23.9±150.3	52.5±148.2	151.2±239.7¶	**0.001**
%	0.8±4.4	1.6±3.9	4.3±6.6¶	**0.001**

Data are presented as mean±SD, or median (interquartile range), unless otherwise stated. Statistically significant p-values are presented in bold. #: p-value across all groups; ¶: as compared to group 1 (never- and ex-smokers with <10 pack-years), p<0.05; +: as compared to group 2 (non-obstructive patients with ⩾10 pack-years), p<0.05; §: change from pre- to post-bronchodilator. ACOS: asthma–chronic obstructive pulmonary disease overlap syndrome; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity.

significant differences in lung function were observed (tables S4, S5). ACOS patients had a higher number of comorbidities, although no other differences were noted with respect to specific comorbidities (table S6).

Discussion

In this study, we evaluated the differences between ACOS and adult-onset asthma. ACOS differs from asthma most clearly by the lower levels of pulmonary diffusing capacity and higher levels of blood neutrophils and serum IL-6. ACOS patients have reduced lung function and higher reversibility of the airways as compared to those with asthma, despite the similar use of medication. ACOS patients also have a greater number of comorbidities than asthma patients without COPD. Furthermore, asthma control is significantly worse among ACOS patients, as compared to patients with asthma alone. To the best of our knowledge, this is the first study to evaluate both blood biomarkers and clinical characteristics that separate ACOS from asthma, in a cohort of clinical asthma patients, including also subjects with smoking-related ACOS.

Lower levels of pulmonary diffusing capacity among smokers have been considered an indicator of emphysema, a characteristic of COPD. However, little is known about the diffusing capacity among ACOS patients. In the present study, the diffusing capacity values of ACOS patients were found to be significantly lower than those of asthma patients without COPD. This is supported by the findings of Kitaguchi *et al.* [30], who reported lower values of *D*LCO and *D*LCO/*V*A (% predicted) among COPD patients with symptoms of asthma (defined as ACOS), as compared to those with asthma and fixed airflow limitations. Our results further

TABLE 4 Comorbidities in study groups

	Never and ex-smokers with <10 pack-years	Non-obstructive patients with ⩾10 pack-years	ACOS: ⩾10 pack-years FEV1/FVC <0.7	p-value#
Subjects n	122	32	34	
Number of comorbidities	1 (0–2)	1 (0–3)	2 (1–3)¶	**0.008**
Obesity§	37 (30.3)	19 (59.4)¶	10 (29.4)+	**0.007**
Hypertension	35 (28.7)	10 (31.3)	18 (52.9)¶	**0.029**
Coronary heart disease	7 (5.7)	6 (18.8)	7 (20.6)¶	**0.012**
Hypercholesterolaemia	18 (14.8)	8 (25.0)	12 (35.3)¶	**0.023**
Diabetes	15 (12.3)	5 (15.6)	8 (23.5)	0.264
Systemic rheumatoid disease	4 (3.3)	1 (3.1)	1 (2.9)	0.995
Thyroid disease	9 (7.4)	3 (9.4)	4 (11.8)	0.707
Number of other medications*f*	1 (0–3)	2 (1–5)	3 (1–7)¶	**0.004**

Data are presented as n (%), or median (interquartile range), unless otherwise stated. Statistically significant p-values are presented in bold. #: p-value across all groups; ¶: as compared to group 1 (never and ex-smokers with <10 pack-years), p<0.05; +: as compared to group 2 (non-obstructive patients with ⩾10 pack-years), p<0.05; §: body mass index ⩾30 kg·m^{-2}; *f*: other than medications for asthma or allergy. ACOS: asthma–chronic obstructive pulmonary disease overlap syndrome; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity.

TABLE 5 Diffusing capacity and biomarkers in the obstructive asthma and asthma–COPD overlap syndrome (ACOS) groups

	Obstructive asthma <10 pack-years and FEV1/FVC <0.7	ACOS: ⩾10 pack-years FEV1/FVC <0.7	p-value
Subjects n	19	34	
D_{LCO} % pred	103±24	85±23	**0.011**
D_{LCO}/V_A % pred	100±17	86±22	**0.018**
Blood neutrophils $\times 10^9$ L^{-1}	3.68±1.33	4.54±1.37	**0.033**
Blood eosinophils $\times 10^9$ L^{-1}	0.16 (0.08–0.20)	0.19 (0.10–0.29)	0.217
IgE kU·L^{-1}	77 (29–198)	59 (20–140)	0.399
F_{ENO} ppb	11 (5–24)	10 (5–15)	0.524
hsCRP mg·L^{-1}	0.94 (0.49–1.57)	0.93 (0.59–3.04)	0.475
IL-6 pg·mL^{-1}	1.64 (1.12–2.21)	2.88 (1.88–4.99)	**0.001**

Data are shown as mean±SD, or median (interquartile range), unless otherwise stated. Statistically significant p-values are presented in bold. FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; V_A: alveolar volume; IgE: immunoglobulin E; F_{ENO}: exhaled nitric oxide; hsCRP: high-sensitivity C-reactive protein; IL-6: interleukin 6.

suggest that measurement of the diffusing capacity could be considered a useful tool with clinical applications, when differentiating ACOS patients from those with asthma alone. In addition, a lower diffusing capacity among ACOS patients might contribute to the increased disease burden and lower quality of life suggested by the present study and previous studies [14–17]. Patients with ACOS had significantly lower lung function as compared to patients with asthma alone, as measured by the FEV1 (mL and % predicted) and FEV1/FVC ratio. This finding is consistent with those of previous studies [14–16, 31], and is feasible, as a FEV1/FVC <0.7 was an inclusion criterion for the ACOS group in the present study. Furthermore, our study shows that the reversibility of the airways was significantly higher in the ACOS group as compared to groups with asthma alone, at a point when the patients had been already treated for asthma for 12 years. These findings are supported by those of KITAGUCHI *et al.* [30], who reported a greater increase in FEV1 after the bronchodilator test in the ACOS group (*i.e.* those with COPD and asthmatic symptoms), as compared to the group of asthma patients with airflow limitation. Our finding of higher levels of remaining reversibility in ACOS patients, who were similarly medicated for asthma, further suggests the involvement of steroid resistance [32] in ACOS.

In the present study, we found the blood neutrophil count to be significantly higher in ACOS patients than in patients with asthma. Previous studies have reported higher levels of sputum neutrophils in patients with ACOS [33, 34]. Given the fact that inhaled glucocorticoids are known to inhibit apoptosis of neutrophils [35, 36], the possibility of iatrogenic neutrophilia in ACOS exists. However, in the present study, the dosages of daily inhaled glucocorticoids were not any higher in the ACOS group, in which neutrophil levels were the highest, suggesting that blood neutrophilia among ACOS patients might be derived from the actual inflammatory pathway rather than the purely iatrogenic result of the use of glucocorticoids. For example, it has been previously suggested that IL-6, being higher in ACOS patients, might promote neutrophilic inflammation in asthma [25].

Among the obstructive airway diseases, systemic inflammation has previously been typically associated with COPD. However, more recently, a similar prevalence of systemic inflammation has been reported among patients with ACOS [33]. The most widely studied biomarkers of systemic inflammation have been IL-6 and CRP [37], with which elevated levels of IL-6 and less favourable outcomes of asthma are associated [25]. We evaluated whether the assessment of blood biomarkers would help to distinguish ACOS from asthma. Our results revealed significantly higher levels of IL-6 in ACOS patients as compared to patients with asthma. This finding is supported by similar results of FU *et al.* [33], whose definition of ACOS was however, not based on smoking history. Another recent study showed significantly higher concentrations of sputum IL-6 in ACOS, as compared to asthma [34]. Systemic inflammation in ACOS, including elevated CRP levels, has been proposed to resemble that in COPD [38]. In our study, the levels of hsCRP showed no significant difference among groups; an unexpected finding, considering the existence of systemic inflammation in COPD and ACOS. However, FU *et al.* [33] reported similar findings in their study, and reported no significant differences in CRP levels between the ACOS and asthma groups. Thus, the results of the present study suggest that IL-6, but not hsCRP, distinguishes ACOS from asthma.

The prevalence of ACOS among patients with asthma in the present study was 18.1%, which is consistent with the results of previous studies [9, 16]. Over half of the ACOS patients had uncontrolled asthma, representing a significantly higher proportion of patients than in any other group. However, asthma

control was assessed according to the GINA 2010 report [29]; thus, impaired lung function might partially explain the poor control of asthma in the present study. Previously, it has been suggested that ACOS patients might have higher CAT scores than patients with asthma [39]. Therefore, we evaluated whether ACOS can be distinguished from asthma, using questionnaires that have been validated for clinical use. We found that ACT scores, CAT scores and AQ20 questionnaires could not distinguish ACOS from asthma, even though CAT scores were higher and ACT scores were lower among patients with a history of heavier smoking (⩾10 pack-years). Thus, ACT, CAT and AQ20 questionnaires might not be useful in the diagnosis of ACOS among patients with asthma in clinical practice.

Moreover, our results showed a higher number of comorbidities among ACOS patients as compared to patients with asthma. Cardiovascular morbidity in particular, was found to be higher, as the prevalence of hypertension and coronary heart disease was higher in the ACOS group. This finding is supported by those of previous studies [15, 16].

Fixed airflow obstruction due to asthma or COPD has been widely studied. Reports suggest that lower diffusing capacity, lower F_{ENO} levels, higher levels of neutrophils and lower eosinophil counts are evident among patients with fixed obstruction caused by COPD, as compared to those induced by asthma [40–42]. However, the differences between ACOS and obstructive asthma have been far less identified [42]. When comparing obstructive asthma (with a smoking history <10 pack-years) and ACOS in the present study, the results reveal that ACOS most clearly differs from obstructive asthma by a lower diffusing capacity, higher number of comorbidities, and higher levels of neutrophils and IL-6 in the blood. Levels of eosinophils, IgE, F_{ENO} and hsCRP could not distinguish obstructive asthma from ACOS.

The present study has several strengths. In our real-life clinical cohort, the diagnosis of adult-onset asthma was made by a respiratory physician, and the diagnosis was based on typical symptoms and objective lung function measurements, showing reversibility of airway obstruction [22]. The diagnosis of ACOS among our patients with asthma was based on a significant history of smoking (⩾10 pack-years) combined with post BD FEV_1/FVC <0.7. The duration of asthma was equal among all groups, making it possible to compare variables reliably without bias from differences in duration of the disease. However, some limitations remain in the interpretation of our results. The number of patients in the two groups of ⩾10 pack-years were somewhat low (n=32 and 34, respectively), which might lead to a loss of power in the analyses. Thus, further clinical studies with larger study cohorts are still needed. We did not have a control group of healthy persons, which could also be considered a limitation of the study. We acknowledge that a recent consensus definition of ACOS has been published, in which a key suggested feature of ACOS should be the diagnosis of asthma or atopy before 40 years of age [10]. However, another recent study has shown that the majority of adult-onset asthma is actually diagnosed at an older age [43], which makes the proposed age limit of 40 somewhat low. The present study cohort included only patients with adult-onset asthma, and the age of onset of asthma in our cohort was on average 46.5 years, and in the ACOS group, 53.0 years. The diagnosis of asthma was based on established guidelines, taking into account typical symptoms and objective lung function measurements showing bronchial variability. Therefore, possible bias due to incorrect categorisation of ACOS was unlikely in the present study, despite the higher age of asthma onset. However, given the fact that some of the subjects with COPD may have significant reversibility of obstruction, and some subjects with a history of smoking and asthma may have only partially reversible airway obstruction, there is no exact method by which these patients could be diagnostically categorised. Therefore, we acknowledge the possibility of misclassification, although diagnoses were made by carefully following the existing guidelines.

In conclusion, ACOS most clearly differs from adult-onset asthma by lower levels of pulmonary diffusing capacity, and higher levels of blood neutrophils and serum IL-6. Patients with ACOS have reduced lung function, greater reversibility of the airways (despite equal medication for asthma), and a greater number of comorbidities than asthmatic patients without COPD. Measurements of the diffusing capacity could be considered a useful clinical tool to facilitate the identification of ACOS patients among those with asthma alone.

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