Multidimensional Assessment of Asthma Identifies Clinically Relevant Phenotype Overlap: A Cross-Sectional Study

Yu Yu Han, MDa,b,c,d,*, Xin Zhang, PhD, MDa,b,c,d,*, Ji Wang, MDa,b,c,d, Gang Wang, MDa,b,c,d,e, Brian G. Oliver, PhDf,g, Hong Ping Zhang, PhD, MDa,b,d, De Ying Kang, MPHh, Lei Wang, MDa,b,d, Zhi Xin Qiu, MDc, Wei Min Li, PhD, MDc, and
Gang Wang, PhD, MDc,d

BACKGROUND: Asthma is a heterogeneous disease with multiple phenotypes; however, the relevance of phenotype overlap remains largely unexplored.
OBJECTIVE: To examine the relationship between phenotype overlap and clinical and inflammatory profiles of asthma. METHODS: In this cross-sectional study, adult participants with stable asthma (n [522) underwent multidimensional assessments. The 10 most common phenotypes of asthma were defined and then classified into those commonly associated with Type (T) 2 or non-T2 inflammation. Furthermore, phenotype overlap scores (POS), representing the cumulative concomitant phenotypes, were used to analyze its association with clinical and inflammatory asthmatic profiles.
RESULTS: Among the 522 participants, 73.4% (n [383) had phenotype overlap, and mixed T2 and non-T2 inflammation coexisted in 47.5% (n [248). T2 POS was positively associated with eosinophils, IgE, and fractional exhaled nitric oxide (FeNO), and negatively with Asthma Quality of Life Questionnaire (AQLQ), sputum neutrophils, IL-17A, IL-8, and TNF-a. Non-T2 POS was positively associated with Asthma Control Questionnaire, neutrophils and sputum IL-8, and negatively with AQLQ, forced expiratory volume in 1 s, blood eosinophils, IgE, and FeNO (all P< .05). Patients with phenotypes that are associated with mixed T2 and non-T2 inflammation had elevated T2 inflammation biomarkers but worse asthma control. Both T2 (adjusted b[L0.191, P[.035) and non-T2 (adjusted b[0.310, P< .001) POS were significantly associated with severe exacerbations.
CONCLUSIONS: Phenotype overlap is extremely common in
asthmatic patients and significantly associated with clinical and inflammatory profiles. Patients with phenotypes associated with mixed T2 and non-T2 inflammation might be unresponsive to medications owing to increased non-T2 inflammation.

Asthma is a heterogeneous and common chronic airway disease,1 which is usually regarded as having multiple phenotypes based on clinical or pathophysiological features, inflammation, or unique triggers of symptoms.2 An asthma “phenotype” represents the subgrouping of asthma characteristics in patients.3 Multiple asthma phenotypes are discovered as our knowledge of disease characteristics has expanded. Different asthma phenotypes have been shown to affect asthma control or outcomes; for instance, allergic and nonallergic asthma4 respond differently to anti-IgE therapy, and noneosinophilic asthma may respond more poorly to corticosteroids.5 Identifying asthma phenotype helps clinicians predict the disease course and responsiveness to corticosteroid and biologic therapies.6

Type (T) 2 inflammation is characterized by atopy and eosinophilia and thought to be pathogenic, and it has been described or explored in several studies.7-9 Nevertheless, increasing evidence suggests the presence of non-T2emediated asthma, which may be independent of allergy and eosinophilia.3,10,11 T2 or non-T2 asthma is deemed as an

endotype that exhibits numerous distinct phenotypes based on separate immune and inflammatory processes.3,12 The role of the association between T2 and non-T2emediated inflammatory mechanisms in the occurrence and development of asthma remains unclear. Recently, the existence of phenotype overlap has gained attention from clinical researchers and physicians. Tran et al13 found the overlap of atopic, eosinophilic, and TH2-high asthma phenotypes in a general population with current asthma, but the relevance of phenotype overlap has not been explored. The National Health and Nutrition Examination Surveys investigated 5 common phenotypes (ie, blood-Eos-high, fractional exhaled nitric oxide [FeNO]-high, blood-Eos and FeNO-low, asthma with obesity, and asthma with concurrent chronic obstructive pulmonary disease [COPD]) and found that concomitant asthma phenotypes are independently related to poor lung function.14 In that study, a few patients had concomitant T2 (eg, blood-Eos-high asthma) and non-T2 (eg, asthma with obesity) phenotypes. Accordingly, it forces us to consider the clinical relevance of having 2 or more concurrent phenotypes. In this study, we addressed this gap in our knowledge. Patients who underwent multidimensional assessments were assigned to the 10 most common phenotypes of asthma described in the literature, and these were then classified as T2 or non-T2 inflammation. The associations between T2 or non-T2 inflammation and clinical and inflammatory profiles were analyzed. Some of the results from this study have been previously presented in the form of an abstract.15

METHODS

Study design and subjects

This cross-sectional study was designed to investigate the overlap of asthma phenotypes and included patients with asthma based on the Australasian Severe Asthma Network.16 We continuously assessed a total of 593 Chinese subjects who were aged 18 years with stable asthma (no respiratory tract infection and no exacerbation or systemic corticosteroid use in the previous 4 weeks) from the Asthma Clinic of West China Hospital, Sichuan University, between March 2014 and April 2019. The detailed information is described in the Methods section in this article's Online Repository at www. jaci-inpractice.org.

Clinical multidimensional assessments and data collection.

Data from participants with stable asthma, including sociodemographics, medications, atopy, asthma history, comorbidities, exacerbations in the past 12 months, sputum induction, blood sampling, spirometry, FeNO level (NIOX analyzer; Aerocrine, Solna, Sweden), Asthma Control Questionnaire (ACQ) score,17 and Asthma Quality of Life Questionnaire (AQLQ) score,18 which have been validated in the Chinese population, were analyzed. More details are described in the Methods section in this article's Online Repository at www.jaci-inpractice.org.

Definitions of asthma phenotypes

This study investigated the 10 most commonly described asthma phenotypes, which included allergic,19 early onset,20 elderly,21,22 eosinophilic,23,24 obese,25 occupational,26 smoking,27,28 aspirinsensitive,2 fixed airflow limitation,29 and neuropsychological asthma.30-33 These phenotypes are defined in Table I.

Assumptions used to classify T2 and non-T2 inflammation in asthma phenotypes

The 10 most common phenotypes were classified as T2 or non-T2 inflammation based on the literature. Allergic asthma34,35 and eosinophilic asthma36 are characterized by high immunoglobulin titers and eosinophilia and were classified as T2 inflammation. Early-onset asthma was also classified as T2 inflammation because it is related to allergic symptoms and

allergen sensitization with eosinophilic inflammation.20 Because occupational asthma is more likely to be driven primarily by CD4þ T cells and depends on the elevated expression of type 2 cytokines (IL-4 or IL-5),26,37 it was also classified as T2 inflammation. The last clinical phenotype to be categorized as T2 inflammation was aspirin-sensitive asthma, which promotes overexpression of T2 cytokines, such as IL-5, in serum38 or induced sputum.38 Thus, allergic asthma, early-onset asthma, eosinophilic

TABLE I. Definitions of the 10 common asthma phenotypes

Phenotypes	Definitions
Allergic asthma	Positive skin prick tests* and allergy symptoms19
Early-onset asthma	Age of asthma onset <12 y20
Elderly asthma	Age 65 y21,22
Eosinophilic asthma	Sputum eosinophil level 3%23 or blood eosinophil level 300 cells/mL24
Obese asthma	Body mass index25 30 kg/m2
Occupational asthma	Self-reported sensitizer-induced asthma symptoms occur or aggravate in the workplace, and remission or improvement occurs during weekends and holidays26
Smoking asthma	Asthma in current smokers or ex-smokers27,28
Aspirin-sensitive asthma	Self-reported worsening of asthma symptoms in response to nonsteroidal anti-inflammatory drugs2
Asthma with fixed airflow limitation	FEV1/FVC <70% after inhalation of bronchodilator29
Neuropsychological asthma	Hospital Anxiety and Depression Scale (HADS) anxiety symptom (HADS-A) score 8 or HADS depressive symptom (HADS-D) score 830-33

FEV1, Forced expiratory volume in 1 s; FVC, forced vital capacity.
*Skin prick tests used in this study are described in this article's Online Repository at www.jaci-inpractice.org.

asthma, occupational asthma, and aspirin-sensitive asthma were assigned to the groups often associated with T2 inflammation.

The asthma groups often associated with non-T2 inflammation comprised elderly, obese, smoking, asthma with fixed airflow obstruction, and neuropsychological groups. With increasing age, age-related inflammation in asthmas changed and differed from T2 inflammation,21,39,40 which mostly exhibited noneosinophilic or neutrophilic inflammation in induced sputum. Airway inflammation in obese asthma is predominantly noneosinophilic.25,41 Patients with smoking asthma42-44 or asthma with fixed airflow limitation45,46 also had neutrophilic inflammation mainly in the airways rather than eosinophilic inflammation. Based on our previous studies,30-32 nonT2 inflammation was shown to play a critical role in the neuropsychological asthma phenotype.

Definitions of T2 and non-T2 asthma based on biomarkers

Biomarkers, including blood eosinophil count and serum IgE and FeNO levels, were used to define T2 asthma if 2 or more of the following were present: eosinophil count 0.14 109 cells/L, IgE level 100 IU/mL, or FeNO level 30 ppb.47,48 Otherwise, it was classified as non-T2 asthma.

Analysis methodology for cumulative asthma phenotypes

Phenotype overlap scores (POS) represented the number of cumulative concomitant phenotypes. We calculated the T2 and nonT2 POS based on T2 or non-T2 inflammation status of phenotypes. That is, T2 POS reflected the number of cumulative concomitant phenotypes often associated with T2 inflammation, whereas non-T2 POS reflected the number of cumulative concomitant phenotypes often associated with non-T2 inflammation. T2 or non-T2 POS ranged from zero to the maximum number of cumulative concomitant phenotypes.

Statistical analysis

Continuous variables were expressed as means standard deviations or medians (interquartile ranges) based on distribution. Categorical variables were summarized as absolute numbers and percentages. The difference between groups for each variable was evaluated using the Kruskal-Wallis test for continuous variables and the c2 test or Fisher's exact test for categorical variables. When differences were found among groups, Bonferroni correction was used to analyze the differences. Spearman's correlation was used to explore the specific correlations between POS and clinical and inflammatory profiles. A negative binomial regression model was established to analyze correlations of POS and asthma exacerbations in the preceding year. Furthermore, subgroup analysis in patients excluding asthma and chronic obstructive pulmonary disease overlap (ACO) was performed. Two-tailed P values < .05 were considered statistically significant. Statistical analysis was performed with SPSS version 20.0 (IBM Corp., Armonk, NY), and the figure of asthma phenotypic overlap was drawn by R software version 3.5.3 ("UpSetR" packages) (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Demographic and clinical characteristics

Of the 593 adults with asthma screened for this study, 522 had complete phenotypic data and were included; 58 subjects had missing data and 13 declined to participate or had other reasons (Figure 1). The demographic and clinical characteristics of adults with asthma are presented in Table E1 (available in this article's Online Repository at www.jaci-inpractice.org). Females were predominant among the 522 subjects (n ¼ 334, 64.0%). The median age and body mass index (BMI) of participants were 45.45 (Q1, Q3: 35.91, 57.58) years and 22.87 (Q1, Q3: 20.90, 25.05) kg/m2, respectively. The most common comorbidity was rhinitis (n ¼ 279,53.4%). Amajority of patients weretreated withinhaled corticosteroids(ICS)(n¼302,57.9%).Theparticipantshadwellcontrolled asthma as shown by the ACQ scores (median [Q1, Q3]:
0.67 [0.17, 1.50]). Of all participants, 50.4% (n ¼ 263) had mild, 31.6% (n ¼ 165) had moderate, and 18.0% (n ¼ 94) had severe asthma as defined by the Global Initiative for Asthma (GINA) guidelines.29 In addition, 33.0% of these participants (n ¼ 172) had at least 1 severe exacerbation in the past 12 months.

Asthma phenotype overlap

The distribution of the 10 most common phenotypes is shown in Figure 2. Patients with allergic asthma accounted for the largest proportion (n ¼ 311, 59.6%) of participants, and those with aspirin-sensitive asthma comprised the smallest proportion (n ¼ 8, 1.5%). Although we collected all available

FIGURE 1. Flowchart of the study. {Nonallocated phenotypes: phenotypes did not meet any criteria of the 10 predefined asthma phe-
notypes. *POS, Phenotype overlap scores.
data, 35 participants (6.7%) did not meet any criteria of the predefined phenotypes and were considered as having a “nonallocated” phenotype. Therefore, 487 participants had at least 1 asthma phenotype defined in this study (Figure 1). Of these, 310 had T2 and 177 had non-T2 asthma based on T2 biomarkers.
As shown in Figure 2, of all included participants, 383 (73.4%) had multiple (2) asthma phenotypes and 104 (19.9%) had only 1 phenotype. Finally, 120 intersecting sets of phenotypes and 9 types of single phenotypes (drawn as 9 blue bars) were identified. In addition, we found that the concomitant allergic and eosinophilic asthma (shown as a red bar) (8.2%, n ¼ 43) accounted for the most common intersecting set of

FIGURE 2. UpSetR plot of phenotypic overlap of the 10 common asthma phenotypes. UpSetR visualizes intersections of 10 sets (asthma phenotypes) as a matrix in which the rows represent the different phenotypes and the columns represent their intersections. For each phenotype that is part of a given intersection, a black-colored dot is placed in the corresponding matrix cell. If a phenotype is not part of the intersection, a light grayecolored dot is shown. Avertical black line connects the topmost black dot with the bottommost black dot in each column to emphasize the overlapping relationships. A second bar chart showing the size of each phenotype is shown to the left of
the matrix.
phenotypes. Allergic patients were responsible for more than half of instances of phenotype overlap. Besides the allergic eosinophilic asthma, another 6 sets of phenotypes were found to be the most common overlapping phenotypes (Table E18, available in this article’s Online Repository at www.jaci-inpractice.org), that is, allergic early-onset asthma (2.9%, n ¼ 15), allergic eosinophilic early-onset asthma (2.7%, n ¼ 14), allergic asthma with fixed airflow limitation (2.5%, n ¼ 13), allergic eosinophilic smoking asthma (2.5%, n ¼ 13), allergic neuropsychological asthma (2.3%, n ¼ 12), and allergic eosinophilic asthma with fixed airflow limitation (2.1%, n ¼ 11). Allergic eosinophilic asthma was also the most common overlapping phenotype in the patients with phenotypes often associated with T2 inflammation (23.2%, n ¼ 43) (Table E19, available in this article’s Online Repository at www.jaci-inpractice.org). Elderly smoking asthma with fixed airflow had the highest proportion (14.8%, n ¼ 8) in the patients with phenotypes often associated with T2 inflammation as well as the smoking asthma with fixed airflow (14.8%, n ¼ 8) (Table E19, available in this article’s Online Repository at www.jaci-inpractice.org). In the patients with phenotypes associated with mixed T2 and non-T2 inflammation, allergic asthma with fixed airflow limitation (3.2%, n ¼ 13) and allergic eosinophilic smoking asthma (3.2%, n ¼ 13) were the most common phenotypes (Table E19, available in this article’s Online Repository at www.jaci-inpractice.org). The characteristics of patients with the most common overlapping phenotypes in all participants and the characteristics of patients with the most common overlapping phenotypes in the patients with phenotypes often associated with different types of inflammation are shown in Tables E18 and E19 (available in this article’s Online Repository at www.jaci-inpractice.org), respectively.

Demographic and clinical characteristics grouped by phenotypes often associated with T2 or non-T2 inflammation

Based on phenotypes often associated with T2 or non-T2 inflammation, participants with at least 1 phenotype (n ¼ 487) were assigned into one of the 3 groups: phenotypes often associated with T2 inflammation (n ¼ 185), phenotypes often associated with non-T2 inflammation (n ¼ 54), and phenotypes associated with mixed T2 and non-T2 inflammation (n ¼ 248). Surprisingly, almost half of the participants (47.5%) had phenotypes often associated with mixed T2 and non-T2 inflammation. All demographic and clinical characteristics across the 3 groups are shown in Table II.

Participants with phenotypes often associated with T2 inflammation

Participants with phenotypes often associated with T2 inflammation had the lowest age (39.58 [30.84, 46.94] vs 64.97 [54.09, 71.03] vs 48.60 [39.80, 61.19] years, all P < .001) and lowest age of onset (29.00 [13.50, 40.00] vs 51.00 [36.50, 64.25] vs 36.00 [22.00, 47.75] years, all P < .001) in the 3 groups. There were a larger proportion of women in this group compared with those with phenotypes associated with non-T2 and phenotypes associated with mixed T2 and non-T2

TABLE II. Characteristics of patients with asthma with phenotypes often associated with T2, non-T2, and mixed T2 and non-T2 inflammation

Variables	Phenotypes associated with non-T2	Phenotypes associated with T2	Phenotypes associated with T2 and non-T2	F/c2/H	P value
N	54	185	248		
Age (y), median (Q1, Q3)	64.97 (54.09, 71.03)	39.58 (30.84, 46.94)†	48.60 (39.80, 61.19)†z	105.790	<.001x
Female, n (%)	29 (53.7)	156 (84.3)†	119 (48.0)z	61.624	<.001
BMI (kg/m2), median (Q1, Q3)	22.73 (20.68, 25.46)	22.37 (20.47, 24.17)	23.27 (21.40, 25.97)z	15.291	<.001x
Smoking history (n), current/ex/never smoker	12/12/30	0/0/185†	40/70/138z	115.737	<.001
Atopy, n (%)	0 (0.0)	141 (76.2)†	170 (68.5)†	110.020	<.001
Asthma duration (y), median (Q1, Q3)	6.13 (3.79, 15.18)	5.90 (2.58, 18.58)	8.69 (3.22, 24.74)	2.781	.249x
Age of onset (y), median (Q1, Q3)	51.00 (36.50, 64.25)	29.00 (13.50, 40.00)†	36.00 (22.00, 47.75)†z	57.093	<.001x
Asthma family history, n (%)	22 (42.3)	54 (29.8)	89 (36.8)	3.678	.159
ICS (BDP equivalent) dose (mg/d), median (Q1, Q3)	100.00 (0.00, 400.00)	400.00 (0.00, 400.00)	300.00 (0.00, 400.00)	0.479	.787x
ICS, n (%)	29 (53.7)	109 (58.9)	141 (56.9)	0.504	.777
ACQ scores, median (Q1, Q3)	0.82 (0.00, 1.33)	0.33 (0.00, 1.09)	1.00 (0.33, 1.67)z	21.638	<.001x

AQLQ scores, median (Q1, Q3) 5.89 (5.39, 6.34) 6.03 (5.44, 6.52) 5.74 (5.06, 6.31)z 9.389 .009x
Asthma severity (n), mild/moderate/ severe 27/20/7 12 (22.2) 95/57/33

122 (65.9)† 123/78/47

127 (51.4)†z 1.488

33.197 .829 <.001
Comorbidities
Rhinitis, n (%)
Bronchiectasis, n (%) 0 (0.0) 2 (1.1) 19 (7.7)z 13.926 .001
Sleep apnea, n (%) 0 (0.0) 2 (1.1) 1 (0.4) e .704k
GERD, n (%) 1 (1.9) 8 (4.3) 15 (6.1) 1.922 .383
Anaphylaxis, n (%) 8 (14.8) 62 (33.5)† 69 (27.9) 7.266 .026
Cardiovascular diseases, n (%) 10 (18.5) 7 (3.8)† 23 (9.3) 12.793 .002
Diabetes, n (%) 1 (1.9) 0.74 1.33 0 (0.0)

0.32 0.72† 12 (4.9)z

0.81 1.65z e

16.436 .003k
<.001x
Exacerbations in the past 12 mo

Frequency of severe exacerbations*

Severe exacerbation, n (%) 22 (40.7) 42 (22.7)† 97 (39.1)z 14.513 .001
Spirometry
Pre-FEV1 (L), median (Q1, Q3) 1.65 (1.34, 2.04) 2.39 (1.92, 2.83)† 1.83 (1.30, 2.43)z 58.955 <.001x
Pre-FEV1% predicted 69.16 19.06 82.12 16.51† 65.93 20.92z 70.753 <.001x
Pre-FEV1/FVC% 62.75 10.35 73.06 10.48† 60.20 13.10z 107.230 <.001x
Peripheral blood
Eosinophils (109/L), median (Q1, Q3) 0.11 (0.07, 0.17) 0.29 (0.15, 0.47)† 0.24 (0.13, 0.41)† 53.075 <.001x

Neutrophils (109/L), median 3.66 (2.91, 4.96) 3.21 (2.62, 4.20) 3.57 (2.84, 4.47) 3.011 .050{
(Q1, Q3)
Lymphocytes (109/L), median
(Q1, Q3) 1.65 (1.39, 2.01) 1.73 (1.41, 2.00) 1.68 (1.42, 2.12) 0.058 .944{
Monocytes (109/L), median
(Q1, Q3) 0.37 (0.27, 0.48) 0.31 (0.26, 0.41)† 0.36 (0.29, 0.47)z 6.809 .001{
Basophils (109/L), median
(Q1, Q3) 0.03 (0.02, 0.04) 0.04 (0.02, 0.05) 0.03 (0.02, 0.05) 2.698 .259x
IgE (IU/mL), median (Q1, Q3) 37.23 (15.81, 103.35)
0.00 (0.00, 0.32) 177.00 (69.74, 353.61)†

0.75 (0.00, 6.67)† 143.87 (55.05, 354.50)†

0.25 (0.00, 2.63)† 39.979

14.505 <.001x
.001x
Sputum
Eosinophils (%), median (Q1, Q3)

Neutrophils (%), median (Q1, Q3) 63.75 (38.63, 87.25) 26.00 (11.24, 63.25)† 37.50 (17.13, 67.88) 11.449 .003x
Lymphocytes (%), median
(Q1, Q3) 0.50 (0.25, 1.06) 0.75 (0.25, 1.50) 0.50 (0.00, 1.25) 2.780 .249x
Macrophages (%), median (Q1,
Q3) 35.77 (7.88, 60.69) 60.00 (26.75, 80.63) 46.50 (16.88, 74.75) 5.688 .058x
FeNO (ppb), median (Q1, Q3) 17.50 (13.00, 32.75) 40.00 (25.00, 81.00)†
38.00 (21.00, 68.50)† 29.716 <.001x

ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; BDP, beclomethasone dipropionate; BMI, body mass index; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroid; Q1, first quartile; Q3, third quartile.
Phenotypes associated with non-T2, phenotypes often associated with non-T2 inflammation; phenotypes associated with T2, phenotypes often associated with T2 inflammation; phenotypes associated with T2 and non-T2, phenotypes associated with mixed T2 and non-T2 inflammation.
*Shown as mean standard deviation because the median of severe exacerbations was “0”.
†Compared with phenotypes associated with the non-T2 group with P < .017 based on Bonferroni correction.
zCompared with phenotypes associated with the T2 group with P < .017 based on Bonferroni correction. xKruskal-Wallis test. kFisher’s exact probabilities.

{Data are transformed to satisfy a normal distribution.

FIGURE 3. (A) T2 and (B) non-T2 POS grouped by biomarker-defined T2 and non-T2 asthma. Individual POS are shown as red circles and blue rhombuses for T2 and non-T2 asthma, respectively. The long black horizontal bars and vertical error bars represent the mean

standard deviations. POS, Phenotype overlap scores.

inflammation (84.3% vs 53.7% vs 48.0%, P < .001). This group had the highest proportion of patients with rhinitis (65.9% vs 22.2% vs 51.4%, P < .001). As expected, these participants had greater eosinophilic inflammation with significantly increased blood eosinophil (0.29 [0.15, 0.47] vs 0.11 [0.07, 0.17] 109/L), IgE (177.00 [69.74, 353.61] vs 37.23 [15.81, 103.35] IU/mL), and FeNO (40.00 [25.00, 81.00] vs 17.50 [13.00, 32.75] ppb) levels and a greater proportion of sputum eosinophils (0.75 [0.00, 6.67] vs 0.00 [0.00, 0.32] %) compared with participants with phenotypes associated with non-T2 inflammation (all P < .001) (Table II).

Participants with phenotypes often associated with non-T2 inflammation

Participants with phenotypes often associated with non-T2 inflammation had the highest age (64.97 [54.09, 71.03] years) and the highest age of late onset of asthma (51.00 [36.50, 64.25] years) (all P < .001). Compared with participants with phenotypes associated with T2 inflammation, these participants had higher incidence of cardiovascular diseases (18.5% vs 3.8%, P ¼ .001). Furthermore, this group had a greater proportion of patients with severe exacerbations in the previous year (40.7% vs 22.7%, P ¼ .008), worse airway obstruction (forced expiratory volume in 1 s (FEV1) % predicted, 69.16 19.06 vs 82.12 16.51%; FEV1/forced vital capacity (FVC), 62.75 10.35 vs 73.06 10.48%, all P < .001), and a higher proportion of sputum neutrophils (63.75 [38.63, 87.25] vs 26.00 [11.24, 63.25] %, P ¼ .001) (Table II) and a significantly higher sputum IL-8 level (2218.00 [1094.00, 3491.00] vs 1150.00 [583.29, 2218.00] pg/mL, P ¼ .004) (Table E3, available in this article's Online Repository at www.jaci-inpractice.org). However, there were no statistically significant differences in sputum IL-1b, IL5, IL-13, IL-17A, TNF-a, and IFN-g levels among groups (Table E3, available in this article's Online Repository at www. jaci-inpractice.org).

Participants with phenotypes associated with mixed T2 and non-T2 inflammation

This group had the largest number of patients (n ¼ 248, 50.9%) with increased BMI (23.27 [21.40, 25.97] vs 22.37 [20.47, 24.17] kg/m2, P < .001) and higher incidence of bronchiectasis (7.7% vs 1.1%, P ¼ .002) and diabetes (4.9% vs 0.0%, P ¼ .002) than the group with phenotypes associated with T2 inflammation. Moreover, these participants had the worse asthma control level (ACQ scores, 1.00 [0.33, 1.67] vs 0.33 [0.00, 1.09], P < .001), worse asthma quality of life (AQLQ scores, 5.74 [5.06, 6.31] vs 6.03 [5.44, 6.52], P ¼ .002), and more severe exacerbations in the past 12 months (39.1% vs 22.7%, P < .001) and worse airway obstruction (FEV1% predicted, 65.93 20.92 vs 82.12 16.51%; FEV1/FVC, 60.20 13.10 vs 73.06 10.48%, both P < .001) than those with phenotypes associated with T2 inflammation. They also had greater eosinophilic inflammation in the blood (0.24 [0.13, 0.41] vs 0.11 [0.07, 0.17] 109/L, P < .001) and sputum (0.25 [0.00, 2.63] vs 0.00 [0.00, 0.32] %, P ¼ .006), and increased IgE (143.87 [55.05, 354.50] vs 37.23 [15.81, 103.35] IU/mL, P < .001) and FeNO (38.00 [21.00, 68.50] vs 17.50 [13.00, 32.75] ppb, P < .001) levels than those with phenotypes associated with non-T2 inflammation (Table II).

Biomarker-defined inflammatory phenotypes

Based on biomarkers of blood eosinophil count, serum IgE level, and FeNO level, participants with at least one of the most common phenotypes (n ¼ 487) were classified as the those with T2 (n ¼ 310) and non-T2 (n ¼ 177) inflammation, whose characteristics are shown in Table E13 (available in this article's Online Repository at www.jaci-inpractice.org). Characteristics of different asthma phenotypes in patients grouped by biomarkerdefined T2 and non-T2 inflammation are shown in Table E2 (available in this article's Online Repository at www.jaciinpractice.org). T2 POS in the T2 inflammation group was significantly higher than that in the non-T2 inflammation group (1.68 0.80 vs 1.02 0.75, P < .001), and non-T2 POS in the non-T2 asthma group was significantly higher than that in the T2 inflammation group (1.24 0.99 vs 0.84 0.96, P < .001) (Figure 3). The relationship of phenotypes often associated with T2 or/and non-T2 inflammation with biomarker-defined inflammatory phenotypes is presented in Figure 4. We further explored the accuracy of T2 POS in diagnosing T2 inflammation. The area under the curve was 0.713 with the sensitivity of 55.8% and the specificity of 77.4% (data not shown).

Correlations of T2 or non-T2 POS with clinical and inflammatory profiles

We explored the correlations between T2 or non-T2 POS and clinical and inflammatory profiles. T2 POS was positively

FIGURE 4. Relationship of phenotypes often associated with T2 or/and non-T2 inflammation with biomarker-defined inflammatory phenotypes. The intersecting zones represent overlap. Blue downward arrows and red upward arrows indicate a decrease and increase of different characteristics, respectively. BMI, Body mass index; FeNO, fractional exhaled nitric oxide.

TABLE III. Correlations of T2 or non-T2 POS representing cumulative concomitant phenotypes with clinical and inflammatory characteristics in asthma

	T2 POS		Non-T2 POS	
Variables	rs	P value	rs	P value
Asthma-related questionnaires			0.058	
.185				
0.208				
<.001				
ACQ scores				
AQLQ scores	0.098	.026	0.120	.006
Spirometry				
Pre-FEV1% predicted	0.005	.912	0.465	<.001
Pre-FEV1/FVC%	0.015	.733		
<.001	0.533			
0.170	<.001			
<.001				
Peripheral blood	0.474			
Eosinophils (109/L)				

Neutrophils (109/L)			0.021		.640		0.111	.011
IgE (IU/mL)	0.398	<.001						
<.001	0.109							
0.093	.013							
.101								
Sputum		0.325						
Eosinophils (%)								
Neutrophils (%)			0.208		<.001		0.152	.007
IFN-g (pg/mL)	0.083	.240	0.060	.399				
IL-13 (pg/mL)		0.005		.949		0.044	.537	
IL-17A (pg/mL)		0.139	.048	0.110	.120			
IL-1b (pg/mL)		0.117		.097		0.095	.177	
IL-5 (pg/mL)	0.127	.072	0.064	.361				
IL-8 (pg/mL)		0.193		.006		0.184	.008	
TNF-a (pg/mL)	0.148	.035	0.090	.201				
FeNO (ppb)		0.289		<.001		0.147	.002	

ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; POS, phenotype overlap scores; rs, Spearman's rank correlation coefficient.
associated with eosinophil, IgE, and FeNO levels, and negatively with AQLQ scores, sputum neutrophils percent, IL-17A and IL-8, and TNF-a levels. Non-T2 POS was positively associated with ACQ scores, neutrophil and sputum IL-8 levels and negatively with AQLQ scores, pre-FEV1% predicted, and blood eosinophil, IgE, and FeNO levels (all P < .05, Table III), which are described in the Results section in this article's Online Repository at www.jaci-inpractice.org. The additional analysis of clinical outcomes in participants with overlapping phenotypes based on different inflammation statuses also showed that, as the number of phenotypes increased, the clinical outcomes worsened (Tables E4-E12 and Figure E1, available in this article's Online Repository at www.jaciinpractice.org).

The univariate analysis found that T2 (b ¼0.183, 95% confidence interval [CI] ¼ [0.343, 0.023], P ¼ .025) or non-T2 (b¼ 0.278, 95% CI ¼ [0.137, 0.419], P < .001) POS was correlated with the frequency of asthma severe exacerbations in the past 12 months. The multivariable negative binomial regression model was established to further explore the relationships of T2 and non-T2 POS with the frequency of severe asthma exacerbations in the previous year when adjusted for sex, ICS (beclomethasone dipropionate equivalent) dose, family history, asthma duration, and comorbidities (Table IV). Therefore, it indicated that T2 POS (adjusted b [ab] ¼0.191, 95% CI ¼ [0.368, 0.013], P ¼ .035) or non-T2 POS (ab ¼ 0.310, 95% CI ¼ [0.135, 0.485], P < .001) was significantly associated with the frequency of severe asthma exacerbations in the past 12 months. It revealed that, in the real-world setting, the higher the T2 POS, the lower the frequency of asthma severe exacerbations, but the higher the non-T2 POS, the higher the frequency of severe asthma exacerbations.

Subgroup analysis when excluding participants with ACO

The characteristics of participants with ACO and asthma without COPD were compared (Table E14, available in this article's Online Repository at www.jaci-inpractice.org), and

phenotype overlap was analyzed after excluding patients with ACO (Figure E2 and Tables E15-E17, available in this article's Online Repository at www.jaci-inpractice.org). As a result, we found that these phenotype overlaps were roughly similar to the results from all patients (Tables II-IV). The detailed results are provided in this article's Online Repository at www.jaciinpractice.org.

DISCUSSION

To the best of our knowledge, few studies have examined asthma phenotype overlap. This study using multidimensional assessment has shown that 73.4% of patients have at least 2 of 10 common phenotypes concurrently with stable asthma, which indicated that asthma phenotypes overlap, including phenotypes often associated with T2 and/or non-T2 inflammation, was extremely common in the real-world setting. Among the patients with phenotypes often associated with T2 and/or non-T2 inflammation, there were differential demographic and clinical characteristics. Intriguingly, the patients with phenotypes associated with mixed T2 and non-T2 inflammation had similar levels of T2 inflammatory biomarkers to those with phenotypes often associated with T2 inflammation but had worse asthma control and outcomes that were comparable to those with phenotypes often associated with non-T2 inflammation. Furthermore, POS associated with T2 or non-T2 inflammation was associated with clinical profiles, such as asthma symptoms and exacerbations, and inflammatory biomarkers, which implicates that it is important to assess phenotype overlaps using multidimensional assessment in clinical practice (Figure 4).

Participants with asthma were consecutively recruited in this study; thus, patients with asthma with varying severities were included. The proportion of patients with diverse severities of asthma (50.4% with mild asthma, 31.6% with moderate asthma, and 18.0% with severe asthma) (Table E1, available in this article's Online Repository at www.jaci-inpractice.org) defined using GINA29 guidelines in this study is similar to those in other observational studies.49-51 In this study, almost half of patients had mild asthma (50.4%, n ¼ 263), most of whom did not use ICS (83.3%, n ¼ 219) (data not shown). That might account for low rates of ICS use (n ¼ 302, 57.9%) in these included participants in this study. This rate of ICS use is still higher than that in a recently published epidemiological study in China showing that the proportion of respondents with asthma who received ICS therapy was only 5.6% to 10.2%,52,53 although this proportion was much lower than the proportions reported in some developed countries (17% to 49%).54 This could be partly explained by a reduced pooled adherence on daily ICS therapy (37.6%, 95% CI ¼ [33.1, 42.2])55 in the real-world setting, which indicated that some patients in this study would be undertreated.

TABLE IV. Variables associated with the frequency of severe exacerbations in the past 12 months using negative binomial regression models

Independent variables	Univariable models		Multivariable model	
	Regression coefficient (b) [95% CI]	P value	Adjusted regression coefficient (ab) [95% CI]	P value
T2 POS	0.183 [0.343, 0.023]	.025	0.191 [0.368, 0.013]	.035
Non-T2 POS	0.278 [0.137, 0.419]	<.001	0.310 [0.135, 0.485]	.001
ICS (BDP equivalent) dose	0.001 [0.000, 0.001]	<.001	0.000 [0.000, 0.001]	.002

Sex	0.018 [0.307, 0.272]	.904	0.379 [0.736, 0.022]	.037
Asthma family history	0.244 [0.547, 0.060]	.116	0.187 [0.514, 0.140]	.263
Asthma duration	0.004 [0.006, 0.013]	.473	0.004 [0.007, 0.015]	.457
Bronchiectasis	1.184 [0.665, 1.702]	<.001	1.169 [0.620, 1.719]	<.001

BDP, Beclomethasone dipropionate; CI, confidence interval; ICS, inhaled corticosteroid; POS, phenotype overlap scores.

Our findings indicate that the complexity and unique features of asthma phenotypes overlap when categorizing individuals with asthma, supporting the view that asthma is a heterogeneous disease.56 First, our study showed the highest proportion of participants with concurrent allergic and eosinophilic phenotypes, illustrating the classical concept that asthma is mainly mediated by allergic eosinophilic inflammation.1 Second, our study found that the proportion of current smokers with asthma (9.96%) was lower than that in the general population in China (25.2%; 95% CI, 25.1-25.4)57 or other countries (United States, approximately 15%58). However, this study was supported by a multicenter cross-sectional survey59 based on patients with asthma enrolled consecutively in China or urban areas in China (7.7%),60 which would be attributed to the self-management of smoking cessation under asthma education provided by GINA guidelines.29 Third, the prevalence of obese phenotype in this study was significantly lower than that in Caucasian individuals, which could be explained by race. Ng et al61 estimated the global, regional, and national prevalence of overweight and obesity during 1980 to 2013, which showed a lower rate of obesity (approximately 3.8% to 5.0%) in Chinese adults. A further study found that the prevalence of obesity in a crosssectional survey of 15,364 participants in China was 7.9%,62 which was similar to our prevalence of obesity (8.8%) in this study. Fourth, there was a large subset of patients with asthma with fixed airflow limitation (31.8%, n ¼ 166), which reflected some features of asthma-COPD overlap (ACO).29 Inclusion of ACO could be because of broader inclusion/exclusion criteria in a real-world study, but it would result in external validity and strong generalization of our findings. In addition, the extremely few patients with aspirin-sensitive asthma (1.5%) in this study were consistent with the low proportion (1.2%) reported in an earlier study by Hedman et al.63 Furthermore, 6.7% of subjects with asthma (n ¼ 35) could not be allocated as having any of the 10 common phenotypes, which was similar to the findings by Amaral et al.14 This supports the fact that there are a small number of patients with asthma whose phenotype is not easily allocated, suggesting the possible presence of subphenotypes or endotypes that have not been recognized until now.2-4,64

Our study found that patients with phenotypes often associated with T2 inflammation were characterized by higher T2 inflammation (ie, increased blood and sputum eosinophil, IgE, and FeNO levels), but the participants with phenotypes often associated with non-T2 inflammation had airway neutrophilia, elevated IL-8 levels, and worse clinical outcomes. It has been previously validated that T2 and non-T2 inflammation processes are the main difference in the inflammation-immune mechanisms of asthma, which could explain the disease manifestations and therapeutic response differentiated by separate pathways.3,65 Accordingly, the responsiveness of T2 inflammation to therapy might lead to reduced exacerbations in patients with greater T2 inflammation.

Intriguingly, we found that a third group of patients with asthma had phenotypes associated with mixed T2 and non-T2 inflammation who were clinically different from those in the previous 2 groups with phenotypes often associated with T2 or non-T2 inflammation. To the best of our knowledge, these patients might indeed be a unique population that has not been previously reported. Compared with patients with phenotypes associated with T2 inflammation, these patients had poorer symptom control and quality of life, worse airway obstruction, and more severe exacerbations, although they were characterized by higher levels of inflammatory biomarkers, such as blood and sputum eosinophils, IgE, and FeNO. The following issues would account for these features: First, the intermediate age or age of onset in the groups with phenotypes associated with mixed T2 and non-T2 inflammation might reflect a transitional state from T2 to non-T2 of immune inflammation with increasing age.66 Aging was the potential factor that led to worse asthma outcomes in this group. Second, these patients with phenotypes of mixed inflammation with greater eosinophilic inflammation seemed to have an obvious disposition to T2 inflammation. For example, Calixto et al67 found that obesity, as a non-T2 inflammatory feature, enhanced eosinophilic inflammation in an allergic mouse model. Lastly, more comorbidities, such as bronchiectasis and diabetes, in these patients would lead to adverse asthma outcomes.68,69 Therefore, worse outcomes in patients with phenotypes associated with mixed T2 and non-T2 inflammation would be explained by their non-T2 phenotypes modifying the T2-existing inflammation-immune process.70-73 These findings propose a challenge that only defining T2 inflammatory phenotype in asthma is insufficient to predict asthma symptom control and exacerbations in the real-world setting. Furthermore, it would provide important information and direction for precise treatment of asthma in clinical practice,74,75 but its interaction of T2 and non-T2 inflammation needs to be further explored.

This study used POS (ie, T2 or non-T2) to represent the presence of concomitant diverse phenotypes. To investigate the association of phenotype overlap with clinical and inflammatory characteristics and severe exacerbations in stable asthma, we separately analyzed T2 or non-T2 POS based on phenotypes often associated with T2 or non-T2 inflammation. Intriguingly, it indicated that the number of concomitant phenotypes was distinctly correlated with the intensity of inflammation, such as sputum blood eosinophil, IL-17A, and TNF-a levels for T2 POS; blood neutrophil level for non-T2 POS; and blood eosinophil, IgE, FeNO, sputum neutrophil, and IL-8 levels for both T2 and non-T2 POS. First, our study supports the previously existing concept that blood eosinophils, IgE, and FeNO are the signature biomarkers in defining T2 or non-T2 asthma76,77 because of the relationships between these biomarkers and T2 or non-T2 POS. Second, neutrophils in sputum, but not peripheral blood, and IL-8 in sputum would be potential signature biomarkers in defining T2 or non-T2 asthma because either one was significantly associated with both T2 and non-T2 POS. Their cutoff values need to be further determined, although neutrophilic asthma has been well defined.78,79 Third, the number of phenotypes associated with non-T2 inflammation was significantly correlated with neutrophil level in both blood and sputum, which indicated that patients with these phenotypes have a low grade of systemic inflammation. It would account for worse airway obstruction or possible airway remodeling. Last, the lack of significant associations between T2 POS and type 2 cytokines (ie, IL-13, IL-5) may be explained by anti-asthma therapies, such as the prescribed medication (ICS) that effectively suppresses type 2 cytokines but is less effective against non-T2 cytokines (eg, IL-17A, and TNF-a).80

There are several limitations of this study that need to be addressed. First, we could not analyze the effects of integrated T2 and non-T2 inflammation in overlapping phenotypes on asthma control and airway obstruction because of the different types of inflammation, although we have observed asthma heterogeneity explained by phenotype overlap in this study. Second, definitions of these common phenotypes in this study were based on guidelines or previously published studies,23,29-31,33 which are often not precisely defined.27,36,81,82 Lastly, this study initially found significant relationships between POS and demographic and clinical profiles in stable asthma but did not determine their causes and effects because of its cross-sectional design.

CONCLUSION

This study found that phenotype overlap was extremely common in patients with asthma, which additionally accounted for asthma heterogeneity. The number of cumulative concomitant phenotypes often related to T2 or non-T2 inflammation being represented as POS was associated with asthma symptoms and exacerbations. Furthermore, there was a third group of patients with asthma with phenotypes associated with mixed T2 and non-T2 inflammation who had distinctive clinical and inflammatory characteristics, which seemed to have similar elevated biomarkers of T2 inflammation to those with phenotypes often associated with T2 inflammation but had worse asthma control and more exacerbations that were comparable to those in patients with phenotypes often associated with non-T2 inflammation. It proposed a challenging question in clinical practice that, although it had elevated T2 signature biomarkers, patients might have an insensitive response to asthma medications because of increased non-T2 POS representing cumulative concomitant phenotypes often associated with non-T2 inflammation.

Prospective longitudinal studies would be required to assess the value of multidimensional asthma assessment in clinical practice, and to validate our findings and explore whether targeting treatable traits of these overlapping phenotypes could improve asthma control and future risk.

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ONLINE REPOSITORY

METHODS

Subjects

Asthma was diagnosed in accordance with American Thoracic Society (ATS)E1 and Global Initiative for Asthma (GINA) guidelines,E2 which were defined as a history of respiratory symptoms (ie, wheeze, shortness of breath, chest tightness, cough) that vary over time and in intensity and reversible airflow limitation. The variable airflow limitation was confirmed by either positive bronchial provocation test or bronchodilator responsiveness with improvement in forced expiratory volume in 1 s (FEV1) > 12% and 200 mL from the baseline. We defined asthma chronic obstructive pulmonary disease overlap (ACO) as having current asthma, post-bronchodilator FEV1/forced vital capacity (FVC) <0.70 in individuals 40 years of age or older and at least 10 pack-years of tobacco smoking OR equivalent indoor or outdoor air pollution exposure.E2 This study excluded the subjects with incomplete asthma phenotypic data, rheumatoid arthritis, severe unstable heart disease, and other severe unstable chronic diseases. We also excluded those who were pregnant or were breastfeeding and those who were unable to accomplish spirometry and other required study procedures. This study was reviewed and approved by the institutional review board of West China Hospital, Sichuan University (Chengdu, China) (No. 2014-30), and all subjects provided written informed consent.

Clinical multidimensional assessments and data collection

Atopy was defined as a positive skin prick test result for at least 1 or more allergens, as described in our previous studies.E3,E4 Psychological dysfunction was assessed using the Hospital Anxiety and Depression Scale (HADS), which contains 7 questions specially designed for depressive or anxiety symptoms, with a total score of 21. HADS has different sensitivities and specificities in different populations, and a cutoff score of 8 could mostly achieve the

optimal balance between sensitivity and specificity as approximately 0.90 for each subscale.E5 Furthermore, we also collected comorbidities (self-reported but required from specialists) and asthma-related exacerbations in the past 12 months. Asthma-related exacerbations were defined based on the use of systemic corticosteroids for acute asthma for at least 3 days according to the ATS/European Respiratory Society (ERS) guidelines. The criteria for severe exacerbations also included hospitalization or emergency room or intensive care unit visits requiring systemic corticosteroids for asthma.E6 All subjects underwent sputum induction, blood sampling, and spirometry.E1 Spirometry was performed according to the ATS/ERS guidelines,E7 and FEV1 and FVC were measured (MedGraphics Corp., Saint Paul, Minn) before and 15 minutes after administration of 400 mg salbutamol (GSK, Avda de Extremadura, Spain) through a metered-dose inhaler and spacer (150 mL; Vanbo Technology Corp., Shanghai, China). The best of the 3 reproducible maneuvers was used in the analysis.

Skin prick tests

As previously described,E3,E4 atopy was defined as a positive skin prick test result (3 mm wheal diameter above the negative control) for at least 1 or more allergens, including house dust mites (Dermatophagoides pteronyssinus, Dermatophagoides farinae), mold (Alternaria tenuis, Aspergillus species), dog hair, cat hair, pollen (ragweed, birch, London plane), and cockroach, in addition to positive (histamine) and negative (saline) controls.

Peripheral blood collection and detection

Fasting intravenous blood samples were collected (with 1 untreated tube and with 1 tube for ethylenediaminetetraacetic acid anticoagulation) for blood cell counts (Sysmex XN-9000 hematology analyzer; Sysmex Corporation, Kobe, Japan) using standard morphological criteria and analysis of total serum IgE levels (Beckman Immage 800 immunology analyzer; Beckman Coulter Inc., Brea, Calif), and 5.0 IU/mL was the minimum detectable level.

Sputum induction and airway inflammatory cytokine assay

We performed sputum induction based on the standardized operation process as described in our previous studies.E8 We collected the sputum supernatant and counted sputum differential cells. Sputum was induced after pretreatment with 400 mg salbutamol (GSK) using 4.5% saline atomized with an ultrasonic nebulizer (Cumulus; HEYER Medical AG, Bad Ems, Germany). If preorpost-FEV1 was<40%predicted,sputumwasinducedwith0.9% saline after it was deemed safe by the supervising physician. The sputum supernatantwasstored at80C untilassessment. Selected sputum plugs were used for inflammatory cell counts. Sputum supernatant cytokines, regarded as airway inflammatory biomarkers, including IL-1b, IL-5, IL-8, IL-13, IL-17A, IFN-g, and TNF-a, were detected using a Luminex-based MILLIPLEX MAP Human Cytokine/Chemokine Magnetic Bead Panel Kit (EMD Millipore Corporation, Billerica, Mass) with the MILLIPLEX Analyst 5.1 software. The minimum detectable levels of these cytokines in sputum supernatant were 0.8, 0.5, 0.4, 1.3, 0.7, 0.8, and 0.7 pg/mL, respectively. Spiking experiments on cytokines in sputum supernatants showed that recovery ranged from 70% to 130% in all detectable analyses.E9,E10

RESULTS

Overlapping phenotypes of asthma

Simply based on statistical description but not comparison, patients with allergic asthma with fixed airflow limitation seemed to be the oldest (51.84 8.17 years) and have the largest proportion of women (92.3%, n ¼ 12), severe asthma (38.5%, n ¼ 5), and sputum neutrophils (37.25 [27.25, 89.38] %). There was no woman (0.0%, n ¼ 0) in patients with allergic eosinophilic smoking asthma. This group seemed to have the largest proportion of

patients with severe exacerbations in the previous year (53.8%, n ¼ 7) and the greatest eosinophilic inflammation in the sputum (69.50 [4.25, 78.00] %) and FeNO (95.00 [35.50, 165.50] ppb) levels. The allergic eosinophilic early-onset asthma group had the longest duration (28.73 [16.90, 39.90] years) and highest blood eosinophil level (0.50 [0.38, 0.59] 109/L). And the patients with allergic neuropsychological asthma had the worst asthma quality of life (AQLQ scores, 5.45 [5.14, 6.49]). Allergic eosinophilic asthma with the fixed airflow limitation group seemed to have the latest asthma onset (40.82 13.77 years), worst asthma control level (ACQ scores, 1.17 [0.33,
2.00]), worst airway obstruction (FEV1% predicted, 62.89 11.59%; FEV1/FVC, 57.11 5.38%), highest blood neutrophil (4.12 [3.39, 4.95] 109/L), and IgE (463.45 [227.00, 625.06] IU/mL) levels (Table E18).

Correlations of T2 or non-T2 phenotype overlap scores (POS) with clinical and inflammatory profiles

T2 POS positively correlated with blood and sputum eosinophil (rs ¼ 0.474, P < .001 and rs ¼ 0.325, P < .001, respectively), IgE (rs ¼ 0.398, P < .001) and FeNO (rs ¼ 0.289, P < .001) levels but not with ACQ scores (rs ¼ 0.058, P ¼ .185), pre-FEV1% predicted (rs ¼0.005, P ¼ .912), preFEV1/FVC (rs ¼ 0.015, P ¼ .733), sputum IL-13 and IL-5 levels (rs ¼ 0.005, P ¼ .949 and rs ¼ 0.127, P ¼ .072, respectively). Furthermore, T2 POS was negatively correlated with AQLQ scores (rs ¼0.098, P ¼ .026), percentage of sputum neutrophils (rs ¼0.208, P < .001), and sputum IL17A, IL-8, and TNF-a levels (rs ¼ 0.139, P ¼ .048; rs ¼0.193, P ¼ .006; and rs ¼0.148, P ¼ .035, respectively). In contrast, non-T2 POS was positively associated with ACQ scores (rs ¼ 0.208, P < .001), sputum and blood neutrophil levels (rs ¼ 0.152, P ¼ .007 and rs ¼ 0.111, P ¼ .011, respectively), and sputum IL-8 level (rs ¼ 0.184, P ¼ .008), rather than with sputum IFN-g (rs ¼ 0.060, P ¼ .399), IL-1b (rs ¼ 0.095, P ¼ .177), IL-17A (rs ¼ 0.110, P ¼ .120), and TNF-a (rs ¼ 0.090, P ¼ .201) levels. Non-T2 POS was negatively correlated with AQLQ scores (rs ¼0.120, P ¼ .006), pre-FEV1% predicted (rs ¼0.465, P < .001), preFEV1/FVC (rs ¼0.533, P < .001), and blood eosinophil (rs ¼ 0.170, P < .001), IgE (rs ¼0.109, P ¼ .013), and FeNO (rs ¼0.147, P ¼ .002) levels.

Clinical outcomes in participants with overlapping phenotypes

Based on the phenotypes often associated with T2 inflammation, for the extremely small sample size of participants with 4 phenotypes (often associated with T2 inflammation) (n ¼ 4), this group was excluded from the statistical analysis (Tables E4E6). There were statistically significant differences in AQLQ scores (6.29 [5.52, 6.67] vs 6.00 [5.49, 6.34] vs 5.59 [5.22, 6.40], P ¼ .040) among participants with different numbers of phenotypes, but we did not find any significant difference in other clinical outcomes including ACQ scores, severe exacerbations in the past 12 months, pre-FEV1% predicted, and preFEV1/FVC among participants with phenotypes often associated with T2 inflammation. We further analyzed the linear trend of clinical outcomes in participants with an overlap of phenotypes and found a decreasing linear trend of AQLQ scores with the number of phenotypes often associated with T2 inflammation (P for trend ¼ .012) (Table E5). Moreover, the correlation analysis found that the number of phenotypes often associated with T2 inflammation was significantly associated with ACQ scores (rs ¼ 0.15, P ¼ .046) and AQLQ scores (rs ¼0.19, P ¼ .012)
(Table E6).

The clinical outcomes in participants with phenotypes associated with mixed T2 and non-T2 inflammation and non-T2 inflammation were also analyzed. First, when we excluded the patients with 6 phenotypes associated with mixed T2 and nonT2 inflammation for a limited

sample size (n ¼ 2), there were statistically significant differences in FEV1% predicted (73.23 21.39 vs 65.64 18.98 vs 59.66 21.38 vs 58.17 18.29%, P ¼ .001) and FEV1/FVC (64.20 12.84 vs 61.05 11.84 vs 54.96 14.35 vs 56.24 9.15%, P < .001) among participants with different numbers of phenotypes associated with mixed T2 and non-T2 inflammation (Table E7). Furthermore, a linear trend of FEV1% predicted (P for trend ¼ .006) and FEV1/ FVC (P for trend ¼ .011) with the number of phenotypes associated with mixed T2 and non-T2 inflammation was shown (Table E8 and Figure E1, D and E). It was found that, in the patients with phenotypes often associated with mixed T2 and non-2 inflammation, non-T2 POS defined by the number of phenotypes often associated with non-T2 inflammation was negatively correlated with pre-FEV1% predicted (rs ¼0.319, P < .001) and FEV1/FVC (rs ¼0.328, P < .001) (Table E9).

Second, in patients with phenotypes often associated with non-T2 inflammation, there were statistically significant differences in FEV1% predicted (77.04 17.42 vs 66.92 18.00 vs 52.94 16.04%, P ¼ .005) and FEV1/FVC (67.37 9.65 vs 60.79 9.60 vs 55.13 8.94%, P ¼ .006) across the different numbers of phenotypes (Table E10). Although severe exacerbations in the past 12 months in patients with 3 phenotypes often associated with non-T2 inflammation were markedly increased compared with those in patients with 1 or 2 phenotypes (1.38 1.30 vs 0.57 0.95 vs 0.70 1.64), they did not reach a statistically significant difference (P ¼ .064). Moreover, a linear trend in FEV1% predicted (P for trend ¼ .001) and FEV1/FVC (P for trend ¼ .003) with the number of phenotypes associated with non-T2 inflammation was shown (Table E11). In addition, it was found that non-T2 POS defined by the number of phenotypes often associated with non-T2 inflammation was negatively correlated with pre-FEV1% predicted (rs ¼0.382, P ¼ .004) and FEV1/FVC (rs ¼0.407, P ¼ .002) (Table E12).

Clinical and inflammatory outcomes grouped by biomarker-determined T2 and non-T2 inflammation

The T2 asthma group had the worse asthma control level (ACQ scores, 0.83 [0.17, 1.67] vs 0.50 [0.00, 1.25], P ¼ .004), worse asthma quality of life (AQLQ scores, 5.81 [5.24, 6.34] vs 6.02 [5.35, 6.47], P ¼ .002), and greater T2 inflammation, including higher blood eosinophil (0.32 [0.19, 0.51] vs 0.11 [0.08, 0.17] 109/L, P < .001), sputum eosinophil (0.32 [0.19, 0.51] vs 0.11 [0.08, 0.17] %, P < .001), sputum IL-5 (1.56 [0.96, 4.16] vs 1.16 [0.84, 2.17] pg/mL, P ¼ .031), serum total IgE (0.32 [0.19, 0.51] vs 0.11 [0.08, 0.17] IU/mL, P < .001), and FeNO (36.00 [18.00, 56.00] vs 18.00 [13.50, 24.50] ppb, P < .001) levels compared with the non-T2 asthma group. However, the non-T2 asthma group had higher sputum neutrophil (43.00 [19.25, 76.50] vs 31.50 [13.00, 64.80] %, P ¼ .038), IL-8 (2027.50 [1101.00, 3649.25] vs 1108.00 [579.67, 2105.00] pg/mL, P < .001), and TNF-a (14.43 [7.05, 32.52] vs 8.10 [3.26, 23.20] pg/mL, P ¼ .012) levels compared with the T2 asthma group. No statistically significant difference was found in spirometry (FEV1% predicted or FEV1/FVC), exacerbations in the past 12 months, and cytokine levels (IFN-g, IL-13, IL-17A, IL-1b) between the 2 groups.

Subgroup analysis when excluding participants with ACO

We analyzed the differences of characteristics between patients with ACO (n ¼ 55) and only asthma (n ¼ 467). Compared with the asthma group, the ACO group were older (61.30 [49.94, 69.91] vs 44.33 [34.71, 54.96] years, P < .001), late-onset (47.00 [35.00, 64.00] vs 32.00 [19.00, 44.00] years, P < .001), had a lower proportion of women (1.8% vs 71.3%, P < .001), more severe asthma exacerbations in the past 12 months (50.9% vs 30.8%, P ¼ .003),

worse airway obstruction (FEV1% predicted, 53.27 [38.24, 69.40] vs 77.30 [62.34, 90.14] %, P < .001; FEV1/FVC, 51.30 11.72 vs 67.71 12.35%, P < .001), a lower proportion of patients with atopy (43.6% vs 61.5%, P ¼ .011) and rhinitis (29.1% vs 56.4%, P < .001). And these participants had greater neutrophilic inflammation with significantly increased blood neutrophils (3.73 [2.93, 4.98] vs 3.44 [2.73, 4.33] 109/L, P ¼ .044) and higher proportion of sputum neutrophils (56.50 [31.75, 89.38] vs 36.63 [15.00, 66.50] %, P ¼ .008) (Table E14). After excluding patients with ACO, we further analyzed phenotypic overlap of the 10 common asthma phenotypes (Figure E2), the characteristics of patients with asthma with phenotypes often associated with different inflammation (Table E15), and correlations of T2 or non-T2 POS with clinical and inflammatory profiles (Tables E16 and E17). We found that these results were roughly similar to the previous results that patients with ACO were included (Tables II-IV). However, the multivariable negative binomial regression analysis indicated that T2 POS (b ¼0.184, 95% confidence interval ¼ [0.371, 0.003], P ¼ .054) was not statistically associated with the frequency of asthma severe exacerbations in the past 12 months, which would be explained by the reduced sample size for excluding patients with ACO.

TABLE E1. Characteristics of study participants

Variables	Characteristics
n	522
Age (y), median (Q1, Q3)	45.45 (35.91, 57.58)
Female, n (%)	334 (64.0)
BMI (kg/m2), median (Q1, Q3)	22.87 (20.90, 25.05)
Smoking history (n), current/ex/never smoker	52/82/388
Smoking* (pack-years), median (Q1, Q3)	18.02 (5.60, 32.00)
Atopy, n (%)	311 (59.6)
Asthma duration (y), median (Q1, Q3)	7.14 (2.97, 20.43)
Age of onset (y), median (Q1, Q3)	34.00 (20.00, 46.00)
Asthma (family history), n (%)	173 (33.1)
ACQ scores, median (Q1, Q3)	0.67 (0.17, 1.50)
AQLQ scores, median (Q1, Q3)	5.88 (5.27, 6.38)
Asthma-related medication	200.00 (0.00, 400.00)
ICS (BDP equivalent) dose (mg/d), median (Q1, Q3)	
ICS, n (%)	302 (57.9)
OCS, n (%)	17 (3.3)
Reliever medication, n (%)	60 (11.5)
Leukotriene modifier, n (%)	178 (34.1)
Theophylline, n (%)	85 (16.3)
Asthma severity (n), mild/moderate/severe	263/165/94
Comorbidities	279 (53.4)
Rhinitis, n (%)	
Bronchiectasis, n (%)	24 (4.6)
Sleep apnea, n (%)	4 (0.8)
GERD, n (%)	26 (5.0)
Anaphylaxis, n (%)	148 (28.4)
Cardiovascular diseases, n (%)	43 (8.2)
Diabetes, n (%)	14 (2.7)

Exacerbations in the past 12 mo	0.62	1.38
Frequency of severe exacerbations†		
Severe exacerbation, n (%)	172 (33.0)	

ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; BDP, beclomethasone dipropionate; BMI, body mass index; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroid; OCS, oral corticosteroid; Q1, first quartile; Q3, third quartile.
*Never smokers are excluded from the analysis of pack-years.
†Shown as mean standard deviation because the median of severe exacerbations was “0”.

TABLE E2. Characteristics of different asthma phenotypes in patients grouped by biomarker-defined T2 and non-T2 inflammation

Phenotypes	T2 asthma	Non-T2 asthma	c2	P value
N	310	177	e	e
Allergic asthma, n (%)	220 (71.0)	91 (51.4)	18.669	<.001
Early-onset asthma, n (%)	55 (17.7)	31 (17.5)	0.004	.949
Elderly asthma, n (%)	27 (8.7)	44 (24.9)	23.594	<.001
Eosinophilic asthma, n (%)	192 (61.9)	24 (13.6)	106.833	<.001
Obese asthma, n (%)	30 (9.7)	16 (9.0)	0.054	.817
Occupational asthma, n (%)	49 (15.8)	30 (16.9)	0.108	.742
Smoking asthma, n (%)	81 (26.1)	53 (29.9)	0.822	.365
Aspirin-sensitive asthma, n (%)	4 (1.3)	4 (2.3)	e	.470*
Asthma with fixed airflow limitation, n (%)	83 (26.8)	83 (46.9)	20.297	<.001
Neuropsychological asthma, n (%)	40 (12.9)	23 (13.0)	0.001	.977

*Fisher’s exact probabilities.

TABLE E3. Sputum cytokines in patients with asthma with phenotypes often associated with T2, non-T2, and mixed T2 and non-T2 inflammation

Sputum cytokines	Phenotypes associated with non-T2	Phenotypes associated with T2	Phenotypes associated with T2 and non-T2	F/c2/H	P value
IFN-g (pg/mL)	0.54 (0.43, 0.58)	0.55 (0.48, 0.70)	0.55 (0.46, 0.66)	1.220	.298†
IL-13 (pg/mL)	2.65 (2.20, 3.39)	3.04 (1.96, 5.20)	2.74 (2.16, 4.70)	0.666	.777z
IL-17A (pg/mL)	3.11 (1.79, 4.27)	2.21 (1.60, 3.29)	2.38 (1.70, 3.37)	1.135	.324†
IL-1b (pg/mL)	15.20 (8.64, 72.34)	16.20 (6.85, 38.58)	19.45 (7.34, 44.05)	0.773	.679z
IL-5 (pg/mL)	0.92 (0.74, 1.91)	1.55 (0.96, 2.75)	1.49 (0.94, 3.82)	5.413	.067z
IL-8 (pg/mL)	2218.00 (1094.00, 3491.00)	1150.00 (583.29, 2218.00)*	1406.00 (813.98, 3491.00)	8.759	.013z

TNF-a (pg/mL)	12.94 (5.07, 36.69)				8.64 (3.50, 21.64)				12.59 (4.85, 26.71)		0.536	.586†

Phenotypes associated with non-T2, phenotypes often associated with non-T2 inflammation; phenotypes associated with T2, phenotypes often associated with T2 inflammation; phenotypes associated with T2 and non-T2, phenotypes associated with mixed T2 and non-T2 inflammation.
*Compared with phenotypes associated with the non-T2 group with P < .017 based on Bonferroni correction.
†Data are transformed to satisfy a normal distribution.
zKruskal-Wallis test.
TABLE E4. Clinical outcomes in participants with phenotypes often associated with T2 inflammation

Clinical outcomes	One	Two	Three	Four	H/F	value					
n	81			74			26			4	e	e
ACQ scores, median (Q1, Q3)	0.33 (0.00, 0.92)				0.50 (0.17, 1.00)				0.59 (0.00, 1.67)		1.00 (0.71, 2.30)	3.983 .137x
AQLQ scores median (Q1, Q3)				6.29 (5.52, 6.67)†					6.00 (5.49, 6.34)			
	5.59 (5.22, 6.40)			5.45 (4.58, 6.38)					6.419			
.040x												
Severe exacerbations in the past 12 mo*	0.42	0.88		0.22	0.56		0.31	0.55				
0.25	0.50		2.987	.225x								
Pre-FEV1% predicted, median (Q1, Q3)				84.87 (71.10, 95.64)					83.34 (73.01, 92.22)			
86.19 (71.34, 94.17)				76.86 (65.22, 92.65)					0.338			
.713												
Pre-FEV1/FVC%, median (Q1, Q3)	74.29 (67.92, 81.67)				71.57 (67.11, 80.97)				73.06 (65.85, 81.58)			
66.65 (60.53, 77.01)			0.420	.658								
z	P											

ACQ, Asthma control questionnaire; AQLQ, asthma quality of life questionnaire; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; Q1, first quartile; Q3, third quartile.
*Shown as mean standard deviation because the median of severe exacerbations was “0”.
†Compared with the group of 3 phenotypes with P < .005 based on Bonferroni correction.
zThis group was excluded from the statistical analysis. xKruskal-Wallis test.
TABLE E5. Linear trend analysis of clinical outcomes in participants with phenotypes often associated with T2 inflammation

Clinical outcomes	F	P for trend
ACQ scores	2.101	.149
AQLQ scores	6.407	.012
Severe exacerbations in the past 12 mo	0.479	.490
Pre-FEV1% predicted	0.008	.929
Pre-FEV1/FVC%	0.454	.501

ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity.

TABLE E6. Correlations of clinical outcomes with the number of phenotypes often associated with T2 inflammation

No. of phenotypes (T2 POS)		
Clinical outcomes	rs	P value
ACQ scores	0.149	.046
AQLQ scores	0.186	.012
Severe exacerbations in the past 12 mo	0.071	.343
Pre-FEV1% predicted	0.034	.652
Pre-FEV1/FVC%	0.062	.407

ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; POS, phenotype overlap scores; rs, Spearman's rank correlation coefficient.

TABLE E7. Clinical outcomes in participants with phenotypes associated with mixed T2 and non-T2 inflammation

Clinical outcomes	Two	Three	Four	Five	Six	H/F	value
n	75	95	63	13	2	e	
ACQ scores, median (Q1, Q3)	1.00 (0.33, 1.50)		0.83 (0.17, 1.50)		1.33 (0.33, 2.33)		
	0.83 (0.42, 1.83)	e	7.080	.069k			
AQLQ scores median (Q1, Q3)	6.00 (5.10, 6.40)		5.88 (5.25, 6.38)				
	5.56 (4.64, 6.06)	5.50 (4.91, 6.35)		e			
	5.760	.124k					
Severe exacerbations in the past 12 mo*	0.97 1.96	0.75 1.63	0.68 1.34				
	1.08 1.26	e	2.987	.394k			
Pre-FEV1% predicted	73.23 21.39	65.64 18.98	59.66 21.38†				
	58.17 18.29	e	5.815	.001			
Pre-FEV1/FVC%	64.20 12.84	61.05 11.84	54.96 14.35†z	56.24 9.15	e		
	6.568	<.001					
	x	P					

ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; Q1, first quartile; Q3, third quartile.

*Shown as mean standard deviation because the median of severe exacerbations was "0".

†Compared with the group with 2 phenotypes with P < .005 based on Bonferroni correction.

zCompared with the group with 3 phenotypes with P < .005 based on Bonferroni correction.

xThe group was excluded from the statistical analysis. kKruskal-Wallis test.

TABLE E8. Linear trend analysis of clinical outcomes in participants with an overlap of phenotypes (associated with mixed T2 and non-T2 inflammation)

Clinical outcomes	F	P for trend
ACQ scores	0.541	.463
AQLQ scores	0.176	.675
Severe exacerbations in the past 12 mo	0.026	.871
Pre-FEV1% predicted	7.537	.006
Pre-FEV1/FVC%	6.612	.011

ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity.

TABLE E9. Correlations of clinical outcomes and the number of phenotypes associated with mixed T2 and non-T2 inflammation

Clinical outcomes	No. of phenotypes (T2 POS or non-T2 POS)			
	T2 POS		Non-T2 POS	
	rs	P value	rs	P value
ACQ scores	0.040	.536	0.062	.329
AQLQ scores	0.125	.050	0.001	.982
Severe exacerbations in the past 12 mo	0.045	.479	0.044	.495
Pre-FEV1% predicted	0.019	.769	0.319	<.001
Pre-FEV1/FVC%	0.050	.435	0.328	<.001

ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; POS, phenotype overlap scores; rs, Spearman's rank correlation coefficient.

TABLE E10. Clinical outcomes in participants with phenotypes often associated with non-T2 inflammation

Clinical outcomes	One	Two	Three	H/F	value
n	23	23	8	e	e
ACQ scores, median (Q1, Q3)	0.67 (0.00, 1.17)		0.83 (0.17, 1.33)		1.08 (0.70, 1.71)
	1.951	.377z			
AQLQ scores	5.97 0.61		5.65 0.65		5.97 0.62
	1.711	.191			
Severe exacerbations in the past 12 mo*	0.57 0.95		0.70 1.64		1.38 1.30
	5.503	.064z			
Pre-FEV1% predicted	77.04 17.42†		66.92 18.00		52.94 16.04
	5.961	.005			
Pre-FEV1/FVC%	67.37 9.65†	60.79 9.60	55.13 8.94	5.740	.006
P					

ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; Q1, first quartile; Q3, third quartile.

*Shown as mean standard deviation because the median of severe exacerbations was "0".

†Compared with the group with 3 phenotypes with P < .017 based on Bonferroni correction.

zKruskal-Wallis test.

TABLE E11. Linear trend analysis of clinical outcomes in participants with phenotypes often associated with non-T2 inflammation

Clinical outcomes	F	P for trend
ACQ scores	0.766	.385
AQLQ scores	0.000	.985

Severe exacerbations in the past 12 mo 2.196 .145
Pre-FEV1% predicted 11.266 .001
Pre-FEV1/FVC% 9.777 .003

ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity.

TABLE E12. Correlations of clinical outcomes with the number of phenotypes often associated with non-T2 inflammation

No. of phenotypes (non-T2 POS)
Clinical outcomes rs P value
ACQ scores 0.189 .172
AQLQ scores 0.104 .452
Severe exacerbations in the past 12 mo 0.166 .229
Pre-FEV1% predicted 0.382 .004
Pre-FEV1/FVC% 0.407 .002

ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; POS, phenotype overlap scores; rs, Spearman's rank correlation coefficient.

TABLE E13. Clinical and inflammatory outcomes in patients with asthma grouped by biomarker-defined T2 and non-T2 inflammation

Variables T2 asthma Non-T2 asthma t/c2/U P value
Asthma-related questionnaires
0.83 (0.17, 1.67)
0.50 (0.00, 1.25)
2.916 .004†
ACQ scores, median (Q1, Q3)
AQLQ scores, median (Q1, Q3) 5.81 (5.24, 6.34) 6.02 (5.35, 6.47)
2.329 .020†
Exacerbations in the past 12 mo
Frequency of severe exacerbations* 0.65 1.48 0.55 1.08
0.317 .751†
Severe exacerbation, n (%) 104 (33.5%)

75.29 (60.21, 88.31) 57 (32.2%)

69.86 (53.87, 85.07) 0.092

1.893 .762
.058†
Spirometry
Pre-FEV1% predicted, median (Q1, Q3)
Pre-FEV1/FVC%, median (Q1, Q3) 65.85 12.95 64.56 13.93
1.244 .214†
Peripheral blood

Eosinophils (109/L), median (Q1, Q3)	0.32 (0.19, 0.51)	0.11 (0.08, 0.17)	12.719	<.001†
Neutrophils (109/L), median (Q1, Q3)	3.43 (2.66, 4.34)	3.53 (2.87, 4.52)	1.225	.221z
IgE (IU/mL), median (Q1, Q3)	226.50 (117.27, 482.50)	49.39 (24.53, 87.21)	12.345	<.001†
Sputum				
Eosinophils (%), median (Q1, Q3)	1.25 (0.00, 8.63)	0.00 (0.00, 0.50)	6.724	<.001†
Neutrophils (%), median (Q1, Q3)	31.50 (13.00, 64.80)	43.00 (19.25, 76.50)	2.074	.038†
IFN-g (pg/mL), median (Q1, Q3)	1.85 (1.49, 2.30)	1.74 (1.51, 2.00)	1.669	.097z
IL-13 (pg/mL), median (Q1, Q3)	3.04 (2.13, 5.20)	2.72 (1.99, 3.85)	1.410	.160z
IL-17A (pg/mL), median (Q1, Q3)	2.43 (1.62, 3.53)	2.44 (1.65, 3.14)	0.158	.875†
IL-1b (pg/mL), median (Q1, Q3)	16.01 (6.08, 53.34)	19.20 (9.51, 42.80)	1.263	.207†
IL-5 (pg/mL), median (Q1, Q3)	1.56 (0.96, 4.16)	1.16 (0.84, 2.17)	2.153	.031†
IL-8 (pg/mL), median (Q1, Q3)	1108.00 (579.67, 2105.00)	2027.50 (1101.00, 3649.25)	4.216	<.001†
TNF-a (pg/mL), median (Q1, Q3)	8.10 (3.26, 23.20)	14.43 (7.05, 32.52)	2.506	.012†
FeNO (ppb), median (Q1, Q3)	36.00 (18.00, 56.00)	18.00 (13.50, 24.50)	8.221	<.001†

ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; FeNO, fractional exhaled nitric oxide.

*Shown as mean standard deviation because the median of severe exacerbations was “0”.

†Mann-Whitney test. zData are transformed to satisfy a normal distribution.

TABLE E14. Characteristics of patients with asthma-COPD overlap and asthma only

Variables	Asthma-COPD overlap	Asthma only	t/c2/U	P value
n	55	467	e	e
Age (y), median (Q1, Q3)	61.30 (49.94, 69.91)	44.33 (34.71,54.96)	7.190	<.001†
Female, n (%)	1 (1.8)	333 (71.3)	103.102	<.001
BMI (kg/m2), median (Q1, Q3)	23.23 (21.96, 25.84)	22.79 (20.86, 24.87)	1.379	.168†
Smoking history (n), current/ex/never smoker		27/28/0	25/54/388	188.677
Atopy, n (%)	24 (43.6)	287 (61.5)	6.488	.011
Asthma duration (y), median (Q1, Q3)		7.81 (2.97, 21.97)	6.91 (2.97, 20.10)	0.092
Age of onset (y), median (Q1, Q3)	47.00 (35.00, 64.00)	32.00 (19.00, 44.00)	5.634	<.001†
Asthma family history, n (%)	23 (42.6)	150 (33.0)	1.993	.158

ICS (BDP equivalent) dose (mg/d), median (Q1, Q3) 400.00 (0.00, 400.00) 200.00 (0.00, 400.00) 0.300 .764†
ICS, n (%) 29 (52.7) 273 (58.5) 0.663 .416
ACQ scores, median (Q1, Q3) 1.00 (0.33, 1.67) 0.67 (0.00, 1.50) 1.908 .056†
AQLQ scores, median (Q1, Q3) 5.73 (5.40, 6.38) 5.91 (5.25, 6.38) 0.356 .715†
Asthma severity (n), mild/moderate/severe) 27/16/12

16 (29.1) 236/149/82

263 (56.4) 0.639

14.790 .726 <.001
Comorbidities
Rhinitis, n (%)
Bronchiectasis, n (%) 4 (7.3) 20 (4.3) e .497z
Sleep apnea, n (%) 0 (0.0) 4 (0.9) e 1.000z
GERD, n (%) 2 (3.6) 24 (5.2) e 1.000z
Anaphylaxis, n (%) 5 (9.1) 143 (30.7) 11.281 .001
Cardiovascular diseases, n (%) 7 (12.7) 36 (7.7) e .198z
Diabetes, n (%) 4 (7.3)

0.78 1.08 10 (2.1)

0.60 1.41 e

2.710 .050z
.007†
Exacerbations in the past 12 mo
Frequency of severe exacerbations*
Severe exacerbation, n (%) 28 (50.9) 144 (30.8) 8.975 .003
Spirometry
Pre-FEV1 (L) 1.64 0.60 2.18 0.78 6.119 <.001
Pre-FEV1% predicted, median (Q1, Q3) 53.27 (38.24, 69.40) 77.30 (62.34, 90.14) 5.123 <.001x
Pre-FEV1/FVC% 51.30 11.72 67.71 12.35 9.364 <.001
Peripheral blood
Eosinophils (109/L), median (Q1, Q3) 0.15 (0.09, 0.30) 0.23 (0.12, 0.40) 2.916 .004†
Neutrophils (109/L), median (Q1, Q3) 3.73 (2.93, 4.98) 3.44 (2.73, 4.33) 2.020 .044x
Lymphocytes (109/L), median (Q1, Q3) 1.58 (1.35, 2.29) 1.71 (1.42, 2.06) 0.430 .667†

Monocytes (109/L), median (Q1, Q3) 0.43 (0.34, 0.59) 0.33 (0.26, 0.43) 5.149 <.001x
Basophils (109/L), median (Q1, Q3) 0.03 (0.02, 0.05) 0.03 (0.02, 0.05) 0.881 .378†
IgE (IU/mL), median (Q1, Q3) 53.87 (36.20, 179.70)

0.25 (0.00, 1.00) 138.00 (46.77, 306.02)

0.25 (0.00, 3.00) 2.656
0.804 .008†
.421†
Sputum
Eosinophils (%), median (Q1, Q3)
Neutrophils (%), median (Q1, Q3) 56.50 (31.75, 89.38) 36.63 (15.00, 66.50) 2.646 .008†
Lymphocytes (%), median (Q1, Q3) 0.50 (0.25, 0.75) 0.50 (0.25, 1.31) 1.233 .217†
Macrophages (%), median (Q1, Q3) 42.75 (8.88, 67.06) 53.00 (20.69, 77.81) 1.442 .149†
FeNO (ppb), median (Q1, Q3) 24.00 (13.50, 45.50) 37.00 (21.00, 70.00) 2.610 .009†
ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; BDP, beclomethasone dipropionate; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroid; Q1, first quartile; Q3, third quartile.
*Shown as mean standard deviation because the median of severe exacerbations was “0”.
†Mann-Whitney test.
zFisher’s exact probabilities. xData are transformed to satisfy a normal distribution.

TABLE E15. Characteristics of patients with asthma with phenotypes often associated with T2, non-T2, and mixed T2 and non-T2 inflammation excluding patients with asthma-COPD overlap
Variables Phenotypes associated with non-T2 Phenotypes associated with T2 Phenotypes associated with T2 and non-T2 F/c2/H P value
n 40 185 207 e e
Age (y), median (Q1, Q3) 62.49 (49.97, 70.59) 39.58 (30.84, 46.94)† 46.32 (37.87, 59.41)†z 73.749 <.001x
Female, n (%) 28 (70.0) 156 (84.3) 119 (57.5)z 33.593 <.001
BMI (kg/m2), median (Q1, Q3) 22.73 (20.74, 26.50) 22.37 (20.47, 24.17) 23.27 (21.26, 25.89)z 12.888 .002x
Smoking history (n), current/ex/never smoker 5/5/30 0/0/185† 20/49/138z 76.510 <.001
Atopy, n (%) 0 (0.0) 141 (76.2)† 146 (70.5)† 88.667 <.001
Asthma duration (y), median (Q1, Q3) 5.91 (3.40, 13.70) 5.90 (2.58, 18.58) 8.92 (3.32, 26.62) 4.117 .128x

Age of onset (y), median (Q1, Q3) 51.00 (39.25, 63.50) 29.00 (13.50, 40.00)† 34.00 (19.00, 44.00)†z 44.944 <.001x
Asthma family history, n (%) 14 (36.8) 54 (29.8) 74 (36.6) 2.156 .340
ICS (BDP equivalent) dose (mg/d), median (Q1, Q3) 100.00 (0.00, 400.00) 400.00 (0.00, 400.00) 200 (0.00, 400.00) 0.646 .724x
ICS, n (%) 21 (52.5) 109 (58.9) 120 (58.0) 0.557 .757
ACQ scores, median (Q1, Q3) 0.83 (0.00, 1.29) 0.33 (0.00, 1.09) 1.00 (0.17, 1.67)z 17.953 <.001x
AQLQ scores, median (Q1, Q3) 5.89 (5.29, 6.33) 6.03 (5.44, 6.52) 5.76 (4.84, 6.31)z 10.431 .005x
Asthma severity (n), mild/moderate/severe 20/16/4

10 (25.0) 95/57/33

122 (65.9)† 103/66/38

113 (54.9)† 2.316

23.115 .678

<.001
Comorbidities
Rhinitis, n (%)
Bronchiectasis, n (%) 0 (0.0) 2 (1.1) 15 (7.3)z 11.701 .003
Sleep apnea, n (%) 0 (0.0) 2 (1.1) 1 (0.5) e .705k
GERD, n (%) 0 (0.0) 8 (4.3) 14 (6.8) 3.601 .165
Anaphylaxis, n (%) 8 (20.0) 62 (33.5) 64 (31.1) 2.803 .246
Cardiovascular diseases, n (%) 8 (20.0) 7 (3.8)† 18 (8.7) 12.885 .002
Diabetes, n (%) 1 (2.5)

0.68 1.40 0 (0.0)

0.32 0.72 8 (3.9)z

0.83 1.74z e

12.264 .014k

.002x
Exacerbations in the past 12 mo
Frequency of severe exacerbations*

Severe exacerbation, n (%) 14 (35.0) 42 (22.7) 77 (37.2)z 10.000 .007
Spirometry
Pre-FEV1 (L), median (Q1, Q3) 1.63 (1.34, 2.05) 2.39 (1.92, 2.83)† 1.91 (1.36, 2.52)z 43.864 <.001x
Pre-FEV1% predicted 73.26 19.06 82.12 16.51† 68.68 20.21z 48.150 <.001x
Pre-FEV1/FVC% 64.89 10.08 73.06 10.48† 62.33 12.23z 44.728 <.001
Peripheral blood
Eosinophils (109/L), median (Q1, Q3) 0.11 (0.07, 0.17) 0.29 (0.15, 0.47)† 0.25 (0.13, 0.42)† 41.901 <.001x
Neutrophils (109/L), median (Q1, Q3) 3.40 (2.75, 5.04) 3.21 (2.62, 4.20) 3.57 (2.83, 4.38) 1.845 .159{
Lymphocytes (109/L), median (Q1, Q3) 1.65 (1.36, 1.97) 1.73 (1.41, 2.00) 1.71 (1.45, 2.11) 0.700 .497{
Monocytes (109/L), median (Q1, Q3) 0.37 (0.25, 0.47) 0.31 (0.26, 0.41) 0.35 (0.27, 0.44) 2.830 .060{
Basophils (109/L), median (Q1, Q3) 0.03 (0.02, 0.05) 0.04 (0.02, 0.05) 0.03 (0.02, 0.05) 1.388 .499x
IgE (IU/mL), median (Q1, Q3) 37.23 (13.96, 112.45)

0.00 (0.00, 0.25) 177.00 (69.74, 353.61)†

0.75 (0.00, 6.67)† 152.69 (65.90, 367.82)†

0.25 (0.00, 3.97) 30.307

10.140 <.001x

.006x
Sputum
Eosinophils (%), median (Q1, Q3)
Neutrophils (%), median (Q1, Q3) 57.25 (39.25, 86.00) 26.00 (11.24, 63.25)† 35.00 (15.81, 67.44) 6.859 .032x
Lymphocytes (%), median (Q1, Q3) 0.50 (0.25, 1.75) 0.75 (0.25, 1.50) 0.50 (0.00, 1.25) 2.001 .368
Macrophages (%), median (Q1, Q3) 42.50 (8.00, 60.00) 60.00 (26.75, 80.63) 50.50 (17.44, 75.25) 3.747 .154
FeNO (ppb), median (Q1, Q3) 17.50 (13.00, 38.50) 40.00 (25.00, 81.00)† 39.00 (22.00, 70.75)† 21.831 <.001x
ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; BDP, beclomethasone dipropionate; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroid; Q1, first quartile; Q3, third quartile.

Phenotypes associated with non-T2, phenotypes often associated with non-T2 inflammation; phenotypes associated with T2, phenotypes often associated with T2 inflammation; phenotypes associated with T2 and non-T2, phenotypes associated with mixed T2 and non-T2 inflammation.
*Shown as mean standard deviation because the median of severe exacerbations was “0”.
†Compared with phenotypes associated with the non-T2 group with P < .017 based on Bonferroni correction.
zCompared with phenotypes associated with the T2 group with P < .017 based on Bonferroni correction. xKruskal-Wallis test. kFisher’s exact probabilities.
{Data are transformed to satisfy a normal distribution.

TABLE E16. Correlations of T2 or non-T2 POS representing cumulative concomitant phenotypes with clinical and inflammatory characteristics in asthma when excluding asthmaCOPD overlap

	T2 POS		Non-T2 POS				
Variables	rs	P value	rs	P value			
Asthma-related questionnaires				0.069			
.135							
0.199							
<.001							
ACQ scores							
AQLQ scores	0.106		.022		0.157		.001
Spirometry							
Pre-FEV1% predicted		0.065		.159		0.378	<.001
Pre-FEV1/FVC%	0.045	.337	0.447	<.001			
.006							
Peripheral blood							
Eosinophils (109/L)	0.470	<.001	0.126				
Neutrophils (109/L)		0.009		.854		0.084	.069
IgE (IU/mL)	0.388	<.001					
<.001	0.058						
0.085	.208						
.162							
Sputum	0.331						
Eosinophils (%)							
Neutrophils (%)		0.188		.002		0.090	.139
IFN-g (pg/mL)	0.087	.247	0.057	.445			
IL-13 (pg/mL)		0.036		.633		0.007	.924
IL-17A (pg/mL)		0.101	.179	0.044	.554		
IL-1b (pg/mL)		0.105		.162		0.044	.563
IL-5 (pg/mL)	0.088	.242	0.016	.830			
IL-8 (pg/mL)		0.204		.006		0.123	.101
TNF-a (pg/mL)	0.170	.023	0.082	.274			

FeNO (ppb)	0.278	<.001	0.108	.028

ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; FeNO, fractional exhaled nitric oxide; POS, phenotype overlap scores; rs, Spearman's rank correlation coefficient.

TABLE E17. Variables associated with the frequency of severe exacerbations in the past 12 months using negative binomial regression models when excluding asthma-COPD overlap

Independent variables	Univariable models		Multivariable model	
	Regression coefficient (b) [95% CI]	P value	Adjusted regression coefficient (ab) [95% CI]	P value
T2 POS	0.164 [0.332, 0.004]	.055	0.184 [0.371, 0.003]	.054
Non-T2 POS	0.376 [0.188, 0.564]	<.001	0.368 [0.158, 0.578]	.001
ICS (BDP equivalent) dose	0.000 [0.000, 0.001]	.001	0.000 [0.000, 0.001]	.008
Sex	0.114 [0.446, 0.219]	.504	0.340 [0.716, 0.037]	.077
Asthma family history	0.281 [0.610, 0.048]	.094	0.176 [0.532, 0.180]	.333
Asthma duration	0.003 [0.008, 0.013]	.623	0.003 [0.009, 0.014]	.665
Bronchiectasis	1.342 [0.785, 1.899]	<.001	1.308 [0.714, 1.901]	<.001

BDP, Beclomethasone dipropionate; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; POS, phenotype overlap scores.

TABLE E18. Characteristics of patients with most common overlapping phenotypes in all participants

Most common overlapping phenotypes	Allergic eosinophilic asthma	Allergic early-onset asthma	Allergic eosinophilic early-onset asthma	Allergic asthma with fixed airflow limitation	Allergic eosinophilic smoking asthma	Allergic neuropsychological asthma	Allergic eosinophilic asthma with fixed airflow limitation
n	43	15	14	13	13	12	11
Age (y)	39.16 10.07	32.55 9.14	33.68 10.06	51.84 8.17	44.15 11.85	36.41 11.12	51.06 8.48
Female, n (%)	36 (83.7)	13 (86.7)	11 (78.6)	12 (92.3)	0 (0.0)	9 (75.0)	7 (63.6)
BMI (kg/m2)	22.20 2.45	21.68 2.62	22.74 2.27	22.80 2.26	22.49 2.59	21.82 2.74	22.49 1.59

Smoking history (n), current/ex/never smoker 0/0/43 0/0/15 0/0/14 0/0/13 2/11/0 0/0/12 0/0/11
Atopy, n (%) 43 (100.0) 15 (100.0) 14 (100.0) 13 (100.0) 13 (100.0) 12 (100.0) 11 (100.0)
Asthma duration (y), median (Q1, Q3) 4.15 (1.68, 10.12) 28.27 (18.76, 33.15) 28.73 (16.90, 39.90) 17.08 (9.01, 26.84) 3.76 (1.33, 5.10) 2.81 (1.06, 5.79) 6.00 (3.35, 15.04)
Age of onset (y) 32.56 10.63 5.67 3.11 5.29 2.34 34.08 11.36 38.62 12.37 32.25 12.94 40.82 13.77
Asthma family history, n (%) 9 (20.9) 6 (40.0) 6 (42.9) 5 (38.5) 3 (23.1) 4 (33.3) 5 (45.5)
ICS (BDP equivalent) dose (mg/d), median (Q1, Q3) 0.00 (0.00, 400.00) 0.00 (0.00, 400.00) 0.00 (0.00, 400.00) 400.00 (200.00,1000.00) 0.00 (0.00, 400.00) 300.00 (0.00, 400.00) 400.00 (0.00, 400.00)
ICS, n (%) 20 (46.5) 9 (60.0) 7 (50.0) 11 (84.6) 6 (46.2) 8 (66.7) 8 (72.7)
ACQ scores, median (Q1, Q3) 0.50 (0.17, 1.00) 0.17 (0.17, 0.50) 0.59 (0.25, 1.30) 0.83 (0.50, 1.33) 0.67 (0.09, 1.84) 0.92 (0.00, 1.46) 1.17 (0.33, 2.00)
AQLQ scores, median (Q1, Q3) 5.97 (5.58, 6.34) 6.06 (5.71, 6.61) 5.58 (5.26, 5.88) 6.10 (5.10, 6.25) 5.87 (5.29, 6.46) 5.45 (5.14, 6.49) 6.19 (5.25, 6.45)
Asthma severity (n), mild/ moderate/severe 28/11/4

0.14 0.35 8/4/3

e 9/4/1

0.36 0.50 2/6/5

0.38 0.51 10/2/1

1.54 3.23 5/7/0

0.92 1.44 3/6/2

0.36 0.81
Exacerbations in the past 12 mo
Frequency of severe exacerbations*

Severe exacerbation, n

(%) 6 (14.0) 0 (0.0) 5 (35.7) 5 (38.5)
7 (53.8) 6 (50.0) 2 (18.2)
Spirometry

Pre-FEV1 (L), median
(Q1, Q3) 2.26 (1.94, 2.69) 2.64 (1.95, 3.03) 2.57 (1.84,
2.77) 1.53 (1.29, 1.91) 3.27 (1.94, 3.68) 2.41 (1.93, 3.08)
1.67 (1.26, 2.02)
Pre-FEV1% predicted 79.06 19.41 81.57 13.44 78.83 13.30 65.53
16.86 78.03 19.05 85.07 18.93 62.89 11.59
Pre-FEV1/FVC% 71.32 10.36 71.56 10.51 72.79 10.91
57.77 9.57 66.07 11.01 74.52 10.79 57.11 5.38
Peripheral blood

Eosinophils (109/L), median (Q1, Q3) 0.45 (0.34, 0.68) 0.11 (0.08, 0.17)
0.50 (0.38, 0.59) 0.11 (0.08, 0.18) 0.41 (0.33, 0.55)
0.12 (0.07, 0.22) 0.42 (0.33, 0.62)
Neutrophils (109/L), median (Q1, Q3) 3.19 (2.60, 4.51) 3.12 (2.13, 3.55)
3.09 (2.68, 4.35) 3.37 (2.34, 5.58) 3.51 (2.72, 5.55)
3.39 (2.68, 4.19) 4.12 (3.39, 4.95)
(continued)
TABLE E18. (Continued)
Most common overlapping phenotypes Allergic eosinophilic asthma Allergic
early-onset asthma Allergic eosinophilic early-onset asthma Allergic asthma
with fixed airflow limitation Allergic eosinophilic smoking asthma Allergic
neuropsychological asthma Allergic eosinophilic asthma with fixed airflow
limitation
Lymphocytes (109/ L), median (Q1, Q3) 1.93 (1.41, 2.19) 1.80 (1.33,
1.93) 2.01 (1.83, 2.26) 1.43 (0.99, 1.72) 1.72 (1.61, 2.39)
1.65 (1.43, 1.71) 1.87 (1.62, 2.14)
Monocytes (109/L), median (Q1, Q3) 0.32 (0.25, 0.43) 0.27 (0.22, 0.33)
0.32 (0.30, 0.36) 0.29 (0.22, 0.38) 0.49 (0.29, 0.61)
0.29 (0.24, 0.36) 0.37 (0.30, 0.62)
Basophils (109/L), median (Q1, Q3) 0.05 (0.03, 0.06) 0.02 (0.01, 0.03)
0.05 (0.04, 0.06) 0.02 (0.02, 0.04) 0.04 (0.03, 0.07)
0.03 (0.02, 0.03) 0.04 (0.03, 0.09)
IgE (IU/mL), median
(Q1, Q3) 234.76 (148.00,
608.04)

3.00 (0.88, 8.04) 167.00 (95.72,
339.45)

0.00 (0.00, 0.25) 398.48 (137.25,
2034.81)

10.50 (2.13, 19.38) 179.55 (72.61,

613.30)

0.00 (0.00, 0.25) 207.13 (159.50, 413.41)

69.50 (4.25, 78.00) 125.10 (103.78, 240.02)

0.00 (0.00, 0.63) 463.45 (227.00, 625.06)

0.50 (0.00, 36.50)
Sputum

Eosinophils (%), median (Q1, Q3)

Neutrophils (%), median (Q1, Q3) 24.50 (10.24, 71.88) 18.88 (7.63, 83.06) 17.50 (11.25, 24.75) 37.25 (27.25, 89.38) 16.00 (6.50, 53.25) 17.75 (5.25, 57.25) 31.50 (20.50, 99.00)
Lymphocytes (%), median (Q1, Q3) 0.50 (0.25, 1.36) 0.63 (0.00, 1.63) 1.75 (0.63, 2.63) 1.75 (0.50, 3.13) 0.00 (0.00, 0.00) 0.75 (0.63, 1.50) 0.25 (0.25, 1.50)
Macrophages (%), median (Q1, Q3) 63.75 (23.00, 80.25) 80.00 (16.75, 90.06) 61.25 (50.13, 78.13) 59.25 (10.00, 70.38) 24.00 (6.00, 42.50) 81.50 (40.88, 93.88) 6.00 (0.75, 73.00)
FeNO (ppb), median (Q1, Q3) 65.00 (33.50, 104.50) 36.00 (24.75, 51.25) 68.50 (43.75, 147.50) 35.00 (20.75, 43.75) 95.00 (35.50, 165.50) 40.50 (17.50, 94.50) 44.00 (31.50, 56.75)
Phenotypes associated with non-T2, n (%) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0)
Phenotypes associated with T2, n (%) 43 (100.0) 15 (100.0) 14 (100.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0)
Phenotypes associated with T2 and non-T2, n (%) 0 (0.0) 0 (0.0) 0 (0.0) 13 (100.0) 13 (100.0) 12 (100.0) 11 (100.0)

ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; BDP, beclomethasone dipropionate; BMI, body mass index; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; ICS, inhaled corticosteroid; Q1, first quartile; Q3, third quartile.
Phenotypes associated with non-T2, phenotypes often associated with non-T2 inflammation; phenotypes associated with T2, phenotypes often associated with T2 inflammation; phenotypes associated with T2 and non-T2, phenotypes associated with mixed T2 and non-T2 inflammation.
*Shown as mean standard deviation because the median of severe exacerbations was “0”.
Most common overlapping phenotypes Smoking asthma with fixed airflow Elderly smoking asthma with fixed airflow Allergic eosinophilic asthma

	Allergic asthma with fixed airflow limitation				Allergic eosinophilic asthma					
N	8		8		43		13		13	
Age (y)	58.20	7.09	71.57	2.33	39.16	10.07	51.84	8.17	44.15	11.85
Female, n (%)	1 (12.5)		1 (12.5)		36 (83.7)		12 (92.3)		0 (0.0)	
BMI (kg/m2)	21.49	3.11	23.33	2.79	22.20	2.45	22.80	2.26	22.49	2.59
Smoking history (n), current/ex/never smoker	5/3/0		3/5/0		0/0/43		0/0/13		2/11/0	
Atopy, n (%)	0 (0.0)		0 (0.0)		43 (100.0)		13 (100.0)		13 (100.0)	
Asthma duration (y), median (Q1, Q3)	35.32 (6.18, 11.90)		6.06 (2.45, 19.49)		4.15 (1.68, 10.12)		17.08 (9.01, 26.84)		3.76 (1.33, 5.10)	
Age of onset (y), median (Q1, Q3)	42.50 (25.75, 57.50)		66.00 (51.50, 69.50)		34.00 (25.00, 40.00)		37.00 (24.50, 40.50)		37.00 (31.00, 49.50)	
Asthma family history, n (%)	4 (50.0)		5 (62.5)		9 (20.9)		5 (38.5)		3 (23.1)	
ICS (BDP equivalent) dose (mg/d), median (Q1, Q3)	0.00 (0.00, 0.00)		400.00 (100.00, 1000.00)		0.00 (0.00, 400.00)		400.00 (200.00, 1000.00)		0.00 (0.00, 400.00)	
ICS, n (%)	2 (25.0)		7 (87.5)		20 (46.5)		11 (84.6)		6 (46.2)	
ACQ scores, median (Q1, Q3)	0.50 (0.08, 1.25)		1.08 (0.70, 1.71)		0.50 (0.17, 1.00)		0.83 (0.50, 1.33)		0.67 (0.09, 1.84)	
AQLQ scores	5.60	0.61	5.97	0.62	5.88	0.65	5.82	0.73	5.76	0.92
Asthma severity (n), mild/moderate/ severe	7/1/0									
	0.25	0.46	2/3/3							
	1.38	1.30	28/11/4							
	0.14	0.35	2/6/5							
	0.38	0.51	10/2/1							
	1.54	3.23								
Exacerbations in the past 12 mo										

Frequency of severe exacerbations*

Severe exacerbation, n (%) 2 (25.0) 6 (75.0) 6 (14.0) 5 (38.5) 7 (53.8)

Spirometry

Pre-FEV1 (L), median (Q1, Q3) 1.83 (1.55, 2.12) 1.32 (1.17, 1.81) 2.26 (1.94, 2.69) 1.53 (1.29, 1.91) 3.27 (1.94, 3.68)

Pre-FEV1% predicted 60.01 9.59 52.94 16.04 79.06 19.41 65.53 16.86 78.03 19.05

Pre-FEV1/FVC% 56.84 9.22 55.13 8.94 71.32 10.36 57.77 9.57 66.07 11.01

Peripheral blood

Eosinophils (109/L), median (Q1, Q3) 0.09 (0.06, 0.17) 0.11 (0.04, 0.18) 0.45 (0.34, 0.68) 0.11 (0.08, 0.18) 0.41 (0.33, 0.55)

Neutrophils (109/L), median (Q1, Q3) 4.60 (3.25, 6.95) 3.54 (3.13, 4.12) 3.19 (2.60, 4.51) 3.37 (2.34, 5.58) 3.51 (2.72, 5.55)

Lymphocytes (109/L), median (Q1, Q3) 1.62 (1.41, 2.61) 1.75 (1.43, 2.83) 1.93 (1.41, 2.19) 1.43 (0.99, 1.72) 1.72 (1.61, 2.39)

TABLE E19. Characteristics of patients with most common overlapping phenotypes in the patients with phenotypes often associated with T2, non-T2, and mixed T2 and non-T2

(continued)

TABLE E19. (Continued)

Group Phenotypes associated with non-T2 T2 Phenotypes associated with T2 and non-T2

Most common overlapping phenotypes Smoking asthma with fixed airflow Elderly smoking asthma with fixed airflow Allergic eosinophilic asthma Allergic asthma with fixed airflow limitation Allergic eosinophilic smoking asthma

Monocytes (109/L), median (Q1, Q3) 0.40 (0.35, 0.72) 0.39 (0.31, 0.69) 0.32 (0.25, 0.43) 0.29 (0.22, 0.38) 0.49 (0.29, 0.61)

Basophils (109/L), median (Q1, Q3) 0.03 (0.02, 0.05) 0.03 (0.02, 0.03) 0.05 (0.03, 0.06) 0.02 (0.02, 0.04) 0.04 (0.03, 0.07)

IgE (IU/mL), median (Q1, Q3) 37.20 (28.45, 118.92)

0.13 (0.00, 0.81) 44.34 (21.43, 53.32)

0.00 (0.00, 0.44) 234.76 (148.00, 608.04)

3.00 (0.88, 8.04) 179.55 (72.61,

613.30)

0.00 (0.00, 0.25) 207.13 (159.50, 413.41)

69.50 (4.25, 78.00)
Sputum
Eosinophils (%), median (Q1, Q3)

Neutrophils (%), median (Q1, Q3) 76.00 (45.81,
96.06) 73.19 (29.44, 91.69) 24.50 (10.24,
71.88) 37.25 (27.25,
89.38) 16.00 (6.50, 53.25)
Lymphocytes (%), median (Q1,
Q3) 0.25 (0.19,0.56) 0.50 (0.19, 1.56) 0.50 (0.25, 1.36)
1.75 (0.50, 3.13) 0.00 (0.00, 0.00)
Macrophages (%), median (Q1,
Q3) 22.50 (3.56,
53.56) 25.32 (7.44, 69.88) 63.75 (23.00,
80.25) 59.25 (10.00,
70.38) 24.00 (6.00, 42.50)
FeNO (ppb), median (Q1, Q3) 14.00 (5.00,
26.00) 20.00 (14.00, 31.00) 65.00 (33.50,
104.50) 35.00 (20.75,
43.75) 95.00 (35.50, 165.50)
Phenotypes associated with non-T2, n
(%) 8 (100.0) 8 (100.0) 0 (0.0) 0 (0.0) 0
(0.0)
Phenotypes associated with T2, n (%) 0 (0.0) 0 (0.0) 43 (100.0)
0 (0.0) 0 (0.0)
Phenotypes associated with T2 and non-T2, n (%) 0 (0.0) 0 (0.0) 0
(0.0) 13 (100.0) 13 (100.0)

ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; BDP, beclomethasone dipropionate; BMI, body mass index; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; ICS, inhaled corticosteroid; Q1, first quartile; Q3, third quartile.
Phenotypes associated with non-T2, phenotypes often associated with non-T2 inflammation; phenotypes associated with T2, phenotypes often associated with T2 inflammation; phenotypes associated with T2 and non-T2, phenotypes associated with mixed T2 and non-T2 inflammation.
*Shown as mean standard deviation because the median of severe exacerbations was “0”.

FIGURE E1. Linear trend of clinical outcomes in participants with overlapping phenotypes. (A) ACQ scores; (B) AQLQ scores; (C) severe exacerbations in the past 12 months; (D) pre-

FEV1% predicted; (E) pre-FEV1/FVC. The error bars represent the mean standard error of the mean. ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity.

FIGURE E2. UpSetR plot of phenotypic overlap of the 10 common asthma phenotypes excluding patients with asthma-COPD overlap. UpSetR visualizes intersections of 10 sets (asthma phenotypes) as a matrix in which the rows represent the different phenotypes and the columns represent their intersections. For each phenotype that is part of a given intersection, a black-colored dot is placed in the corresponding matrix cell. If a phenotype is not part of the intersection, a light grayecolored dot is shown. A vertical black line connects the topmost black dot with the bottommost black dot in each column to emphasize the overlapping relationships. A second bar chart showing the size of each phenotype is shown to the left of the matrix. COPD, Chronic obstructive pulmonary disease.

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