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ORIGINAL RESEARCH

Stability of Type 2 Inflammation in a 12-Year Adult-Onset Asthma Follow-Up Study

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Purpose: To assess the stability of T2 inflammation and clinical features associated with high or low T2 markers in adult-onset asthma.

Patients and Methods: Seinäjoki Adult Asthma Study is a 12-year follow-up study including 256 patients diagnosed with new-onset adult asthma. Patients were grouped according to T2 marker status at baseline when steroid-naïve and at the 12-year follow-up after long-term inhaled corticosteroid (ICS) treatment. High T2 markers were defined at diagnosis by ≥1 of the following: blood eosinophils $\geq 0.30\times10^9$/L or positive SPT, and at follow-up by ≥1 of the following: blood eosinophils $\geq 0.30\times10^9$/L, FeNO ≥25 ppb, or specific IgE ≥0.3 ISU.

Results: At diagnosis, 109 patients (66.5%) had high and 55 (33.5%) low T2 markers. Low T2 marker patients were older, had higher BMI, and higher Airway Questionnaire 20 scores. High T2 marker patients had greater reversibility of forced expiratory volume in 1 second. At follow-up, baseline low T2 marker patients had more comorbidities, non-respiratory medications and lower Asthma Control Test scores. Of patients, 76% remained in the low T2 marker group and 24% transitioned to the high T2 marker group; those who transitioned had higher BMI. Sixty-eight percent remained in the high T2 marker group and 32% transitioned to the low T2 marker group; those who transitioned were older, had more comorbidities, and more non-respiratory medications. No significant differences were observed between patients who transitioned and those remaining stable regarding lung function, asthma severity, control, exacerbations, or ICS use.

Conclusion: T2 high and low markers of adult-onset asthma are largely stable over time. However, differences in comorbidities, non-respiratory medication, age, and BMI distinguish the groups significantly.

Keywords: adult-onset asthma, endotype, phenotype, type 2 inflammation

Introduction

Asthma is a chronic respiratory disease marked by wheezing, shortness of breath, cough, chest tightness, and variable airflow obstruction.[1] Asthma can be divided into different phenotypes and endotypes, determined by clinical characteristics and molecular mechanisms, respectively.[1] Research increasingly focuses on identifying molecular pathways that drive asthma to explain its clinical heterogeneity.

Currently, the most widely accepted classification of asthma endotypes categorizes the disease based on Type 2 (T2) inflammation into T2-high and T2-low forms.[1] T2-high asthma is driven by T helper (Th) 2 cells and group 2 innate lymphoid cells producing interleukin (IL)-4, IL-5, and IL-13, and is often associated with early-onset atopic disease, positive allergy tests, elevated levels of allergen-specific immunoglobulin E (IgE), and in late-onset cases, chronic

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rhinosinusitis with nasal polyps.[1,2] Atopy can be confirmed through skin prick testing (SPT) or allergen-specific IgE.[3] Although traditionally considered distinct, atopic and non-atopic T2-high asthma phenotypes share overlap in clinical presentation and underlying inflammatory mechanisms.[4] Airway eosinophilia is the hallmark of T2-high asthma, though peripheral eosinophils, fractional exhaled nitric oxide (FeNO), serum periostin, and allergen-specific IgEs are commonly used as surrogate markers.[1,2]

T2-low asthma lacks markers of T2-high asthma and is typically characterized by neutrophilic or paucigranulocytic airway inflammation and is often corticosteroid-resistant.[1] T2-low asthma has been linked to Th1 and Th17 activation.[1,5] Some cases may appear T2-low due to steroid-induced biomarker suppression. The drivers of neutrophilic inflammation remain poorly understood but include chronic atypical bacterial infection, obesity, smoking, and airway smooth muscle abnormalities.[1,6] Blood or sputum neutrophilia and matrix metalloproteinase 9 (MMP9) have been proposed as biomarkers, though their clinical relevance is uncertain and influenced by environmental exposures or therapy.[7]

Evaluating the stability of T2 markers over time may help establish the reliability of these biomarkers for guiding long-term clinical decisions, including treatment selection and the identification of patients who may exhibit steroid resistance. Limited studies on T2 inflammation stability have reported a consistent T2 profile.[8,9] To our knowledge, no previous study has assessed the long-term stability of T2 inflammation and clinical features associated with high or low T2 marker adult-onset asthma in steroid-naïve patients at baseline, being the aim of this study.

Methods

Study Design and Patients

This analysis is part of the Seinäjoki Adult Asthma Study (SAAS), a 12-year follow-up study including 256 patients diagnosed with new-onset adult asthma between 1999 and 2000. The diagnosis was made by a respiratory physician, based on characteristic symptoms and lung function measurements. Current and former smokers, as well as patients with comorbidities, including other lung diseases or non-respiratory conditions, were not excluded (Table E1). Exclusion criteria included age under 15 years and a prior diagnosis of asthma. All patients were steroid-naïve at diagnosis, and asthma treatment was initiated according to the Finnish Asthma Programme.[10]

A single 12-year follow-up visit was conducted in 2012–2013, with 203 patients (79%) participating. At this visit, data on asthma control, medication use, and background characteristics were collected through structured questionnaires. Lung function, blood sampling, height and weight measurements were performed. No patients showed signs of acute infection. The study protocol was approved by the Ethics Committee of Tampere University Hospital (Tampere, Finland) (R12122) and is in accordance with the Declaration of Helsinki. All participants provided written informed consent. SAAS is listed on ClinicalTrials.gov under the registration number NCT02733016. Further methodological details are described in a separate publication,[11] and a consort plot is available in the online repository (OR) (Figure E1).

T2 Inflammation

We followed a real-world data approach to include all relevant information for defining T2 inflammation.[12] High T2 markers were defined at diagnosis by ≥1 of the following: blood eosinophils $\geq 0.30\times10^9$/L or positive SPT, and at follow-up by ≥1 of the following: blood eosinophils $\geq 0.30\times10^9$/L, FeNO ≥25 ppb, or specific IgE ≥0.3 ISU. Specific IgE was assessed using the Thermo Fisher ImmunoCAP ISAC assay, which includes 112 allergen components from 48 allergen sources (see OR). Complete data to determine T2 inflammation status at baseline and follow-up were available for 164 patients (64%). Methodological details on markers of inflammation are available in the OR.

Secondary analyses were conducted using adapted criteria from the Global Initiative for Asthma (GINA) 2025 recommendations[13] for the assessment of T2 inflammation. High T2 marker status at diagnosis was reclassified as blood eosinophils $\geq 0.15\times10^9$/L or positive allergic status. At follow-up, high T2 marker status was defined by blood eosinophils $\geq 0.15\times10^9$/L, FeNO ≥ 20 ppb, or positive allergic status. Positive allergic status was defined as a positive SPT at baseline and/or positive allergen-specific IgE at follow-up.

Lung Function, Asthma Control and Comorbidities

Lung function testing followed international standards (see OR).[14] Asthma symptoms were assessed using the Airways Questionnaire 20 (AQ20)[15] and Asthma Control Test (ACT).[16] Asthma control was evaluated based on the GINA 2010 report,[17] and severe asthma was defined according to the European Respiratory Society (ERS) and American Thoracic Society (ATS) 2014 guidelines[18] (see OR). Comorbidities were based on self-report and/or use of self-reported medication. Full details on included comorbidities and their prevalence have been previously published.[19]

Use of Medication, Adherence and Use of Healthcare Services

Data on prescribed inhaled corticosteroids (ICS) were gathered from asthma-related healthcare records and converted to budesonide-equivalent doses. Dispensed medication data, including ICS, oral corticosteroids (OCS), short-acting β_2-agonists (SABA), and antibiotics, were obtained from the Finnish Social Insurance Institution. Only one patient used biologic treatment. ICS adherence was defined as the proportion of dispensed ICS relative to prescribed daily dose (in micrograms) over 12 years. A detailed description of the adherence calculation is available in a separate publication,[20] and additional methodological information on medication use and adherence are available in the OR. Healthcare utilization, including asthma- and respiratory-related visits and hospitalizations, was retrieved from medical records. Unplanned respiratory visits included encounters related to upper respiratory tract infections (URTIs) and asthma exacerbations.

Data Analyses

Categorical data were expressed as population size and percentage. Continuous data were expressed as median and interquartile range (IQR) or mean and standard deviation (SD). Comparisons between T2 inflammation groups were made using one-way ANOVA for normally distributed variables, the Kruskal–Wallis test for non-normally distributed variables, and the Chi-squared test with z-test for column proportions. Linear regression analyses were applied to control for age and BMI. Results are presented as B coefficient, 95% confidence interval, and p-value. Statistical analyses were performed using SPSS version 26 (IBM SPSS Statistics, Armonk, NY). A p-value < 0.05 was considered statistically significant.

Results

Patient Characteristics

At baseline, the mean participant age was 45 years, and women accounted for 59% of the cohort. Both at baseline and at follow-up, most patients were overweight. A history of smoking or current smoking was reported by 49% of patients at baseline and 52% at follow-up. While all patients were steroid-naïve at baseline, daily use of ICS was reported by 76% of patients at follow-up. Most patients (66%) had partially controlled or uncontrolled asthma.[21]

Prevalence of T2 High and Low Marker Groups at Baseline

Patients were divided into high and low T2 marker groups based on their inflammatory status. At diagnosis, prior to ICS initiation, 66.5% presented with high and 33.5% with low T2 markers. The criteria for the classification are shown in Figure 1. In total, 23 patients showed a change in allergic sensitization status between diagnosis and 12-year follow-up: 14 lost and 9 developed sensitizations. For one patient, the only positive allergen test at baseline was for an allergen not assessed at follow-up, leaving it uncertain whether their sensitization status had changed.

Characteristics of Baseline Low versus High T2 Marker Groups

At baseline, low T2 marker patients were older, had higher BMI, and reported higher AQ20 scores than high T2 marker patients (Table 1). High T2 marker patients had higher forced expiratory volume in 1 second (FEV_1) reversibility (Table 1). At 12-year follow-up, baseline low T2 marker patients had more comorbidities, used more non-respiratory medications, and had lower ACT scores than baseline high T2 marker patients (Table 1). Differences in asthma outcomes

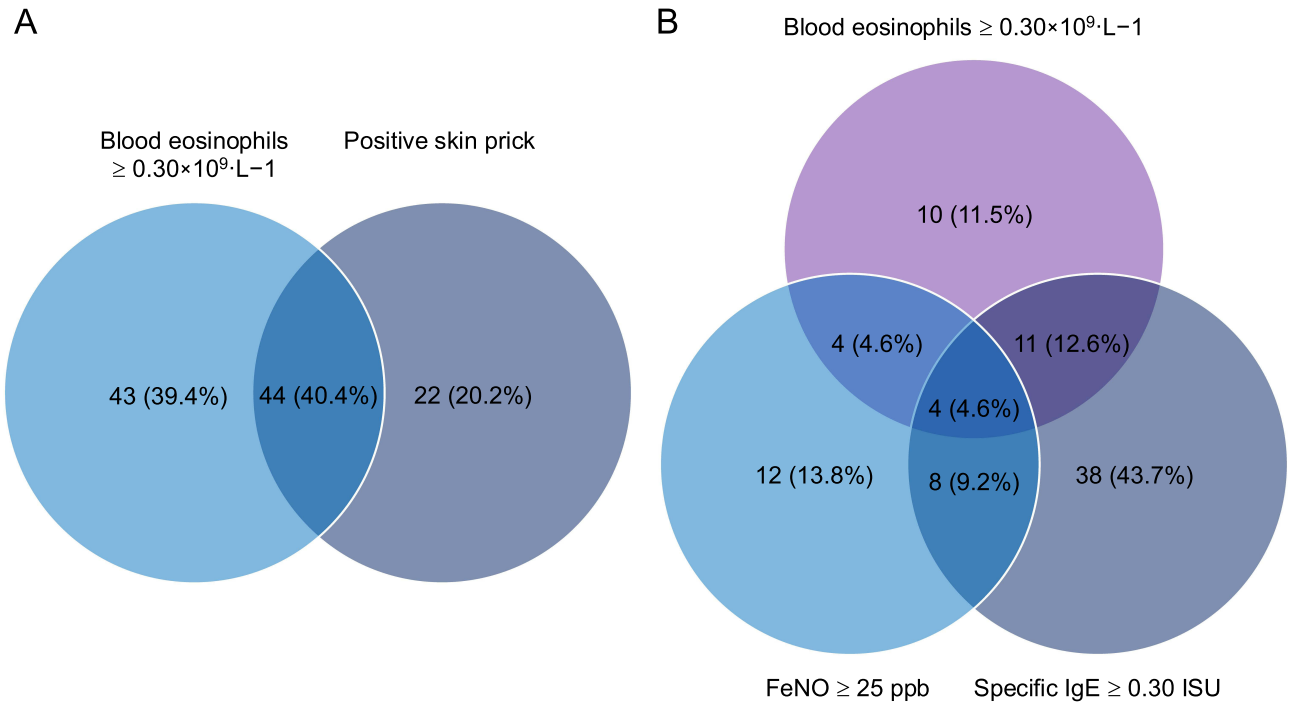

Figure 1 Venn diagram of the numbers and frequencies of individuals who fulfilled criteria for high T2 markers at baseline (**A**) and follow-up (**B**).

between the two baseline groups were otherwise minimal (Table 1). No differences were observed in 12-year adherence to ICS between patients with high versus low baseline T2 marker levels (Table 1).

Regarding inflammatory biomarkers at follow-up, baseline low T2 marker patients showed higher IL-6, soluble urokinase plasminogen activator receptor (suPAR), resistin, chitinase 3-like protein 1 (YKL-40), adipsin and blood neutrophils (Table 2). Baseline high T2 marker patients had higher total IgE, FeNO, periostin and blood eosinophils (Table 2). Figure 2 shows the stability of eosinophil levels in patients with baseline high and low T2 markers over 12 years of follow-up.

Table 1 Characteristics of the Patients at Baseline and 12-year Follow-up Visit Classified According to Baseline T2 Inflammation

Variables	Baseline Low T2 Marker Group (B-Eos < 0.30×10^9/L and Negative SPT)	Baseline High T2 Marker Group (B-Eos ≥ 0.30×10^9/L or Positive SPT)	p-value
Subjects n (%)	55 (33.5)	109 (66.5)	
Baseline variables at asthma diagnosis			
Female sex n (%)	35 (63.6)	62 (56.9)	0.406
Age (y) mean (SD)	51.8 (42.4–58.2)	44.6 (32.4–52.1)	**0.001**
BMI (kg/m2) median (IQR)	27.5 (25.6–30.2)	26.1 (23.7–28.7)	**0.019**
Current/Ex-smoker n (%)	29 (52.7)	52 (47.7)	0.544
Pack-years median (IQR)[a]	10.0 (3.9–16.9)	10.8 (4.0–19.3)	0.591
AQ20 score median (IQR)[b]	7 (5–11)	6 (3–9)	**0.044**
FEV_1 reversibility (mL) median (IQR)[b]	115 (50–285)	190 (100–367)	**0.023**
Follow-up variables after 12-years of ICS therapy			
BMI (kg/m2) median (IQR)	29.1 (25.4–32.4)	27.8 (24.4–30.3)	0.099
Current/Ex-smoker n (%)	29 (52.7)	56 (51.4)	0.870
Pack-years median (IQR)[c]	15.6 (7.0–31.0)	12.1 (3.9–20.4)	0.216
Comorbidities COPD included median (IQR)	1.0 (0.0–3.0)	1.0 (0.0–2.0)	**0.020**
AQ20 score median (IQR)[d]	4 (2–8)	3 (1–6)	0.088

(*Continued*)

Table 1 (Continued).

Variables	Baseline Low T2 Marker Group (B-Eos < 0.30×10^9/L and Negative SPT)	Baseline High T2 Marker Group (B-Eos ≥ 0.30×10^9/L or Positive SPT)	p-value
Asthma control test score median (IQR)	21 (19–24)	22 (20–24)	**0.030**
FEV_1 reversibility (mL) median (IQR)	80 (50–150)	110 (20–170)	0.506
Fulfills definition of severe asthma* n (%)	5 (9.1)	4 (3.7)	0.150
Visits regarding URTIs and exacerbations median (IQR)	4 (1–10)	3 (1–9)	0.508
Average dispensed daily ICS dose (µg budesonide equivalents) median (IQR)[e]	591 (370–814)	471 (272–793)	0.258
12-year adherence to ICS (percentage) median (IQR)[f]	76.5 (42.0–99.8)	67.4 (36.8–97.5)	0.522
Dispensed prednisolone dose during entire follow-up (mg) median (IQR)	900 (0–1950)	600 (0–2400)	0.541
Daily add on medication n (%)	32 (58.2)	51 (46.8)	0.168
No. of medication other than asthma/allergy median (IQR)	2 (0–4)	1 (0–3)	**0.029**
No. of antibiotic treatments dispensed during entire follow-up median (IQR)	8 (4–15)	7 (4–13)	0.349

Notes: Data are presented as n (%), means (SDs), or medians (IQR). *Severe asthma was defined according to the European Respiratory Society and American Thoracic Society 2014 guidelines. Statistical significances were evaluated by one-way ANOVA (analysis of variance), by Pearson Chi-Square test with comparison of column proportions by z-test or by independent samples Kruskal–Wallis test. Bold text represents group names or subheadings. Bolded values represent statistically significant results. [a]Information missing from 5 patients. [b]Information missing from 6 patients. [c]Information missing from 4 patients. [d]Information missing from 1 patient. [e]Information missing from 17 patients. [f]Information missing from 17 patients.

Abbreviations: AQ20, airways questionnaire 20; B-Eos, blood eosinophil count; BMI, body-mass index; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; IQR, interquartile range; SD, standard deviation; SPT, skin prick test; URTI, upper respiratory tract infection.

Table 2 Inflammatory Parameters of the Patients at 12-year Follow-Up Visit Classified According to Baseline T2 Inflammation

Variables	Baseline Low T2 Marker Group (B-Eos < 0.30×10^9/L and Negative SPT)	Baseline High T2 Marker Group (B-Eos ≥ 0.30×10^9/L or Positive SPT)	p-value
Subjects n (%)	55 (33.5)	109 (66.5)	
Total IgE (kU/L)	33.0 (21.0–78.0)	81.0 (30.0–207.0)	**< 0.001**
FeNO (ppb)	8.0 (5.0–15.0)	12.0 (6.0–22.0)	**0.016**
IL-6 (pg/mL)[a]	2.21 (1.46–4.00)	1.46 (1.03–2.76)	**0.005**
IL-8 (pg/mL)[b]	6.4 (5.1–8.4)	5.9 (4.6–8.4)	0.147
hsCRP (mg/L)[a]	1.45 (0.81–2.40)	1.00 (0.44–2.74)	0.100
Periostin (ngmL)[a]	12.4 (10.6–15.2)	14.7 (10.9–20.9)	**0.031**
SuPAR (ng/mL)[a]	3.0 (2.6–3.4)	2.6 (2.0–3.5)	**0.010**
MMP-9 (ng/mL)[a]	65.5 (41.4–108.0)	53.4 (39.8–83.2)	0.183
Resistin (ng/mL)	14.5 (12.8–19.8)	13.3 (10.7–16.1)	**0.005**
Leptin (ng/mL)	22.2 (13.1–39.8)	20.2 (9.0–33.4)	0.183
YKL40 (ng/mL)	53.9 (36.8–85.8)	41.8 (27.0–70.2)	**0.022**
High molecular weight adiponectin (µg/mL)	4.5 (3.2–7.1)	3.8 (2.2–6.6)	0.054
Adipsin (ng/mL)	858.0 (686.2–1141.6)	749.3 (539.6–998.1)	**0.008**
Blood eosinophils (10^9/L)	0.13 (0.08–0.23)	0.19 (0.12–0.29)	**0.003**
Blood neutrophils (10^9/L)	4.4 (3.3–5.6)	3.6 (2.9–4.6)	**0.008**

Notes: Data are presented as medians (IQR). Statistical significances were evaluated by independent samples Kruskal–Wallis test. Bold text represents group names. Bolded values represent statistically significant results. [a]Information missing from 1 patient. [b]Information missing from 3 patients.

Abbreviations: B-Eos, blood eosinophil count; FeNO, fraction of exhaled nitric oxide; hsCRP, high-sensitivity C-reactive protein; IgE, immunoglobulin E; IL-6, interleukin 6; IL-8, interleukin 8; IQR, interquartile range; MMP-9, matrix metalloproteinase-9; SPT, skin prick test; suPAR, soluble urokinase plasminogen activator receptor; YKL40, chitinase-3-like protein.

Stability of T2 Inflammation

Among patients initially with low T2 markers, 76.4% (n=42) remained in the low T2 marker group and 23.6% (n=13) transitioned to the high T2 marker group during follow-up (Figure 3). Among the 13 transitioned, elevated FeNO was observed in four, allergic sensitization in three, high eosinophils in three, combined sensitization and eosinophilia in two,

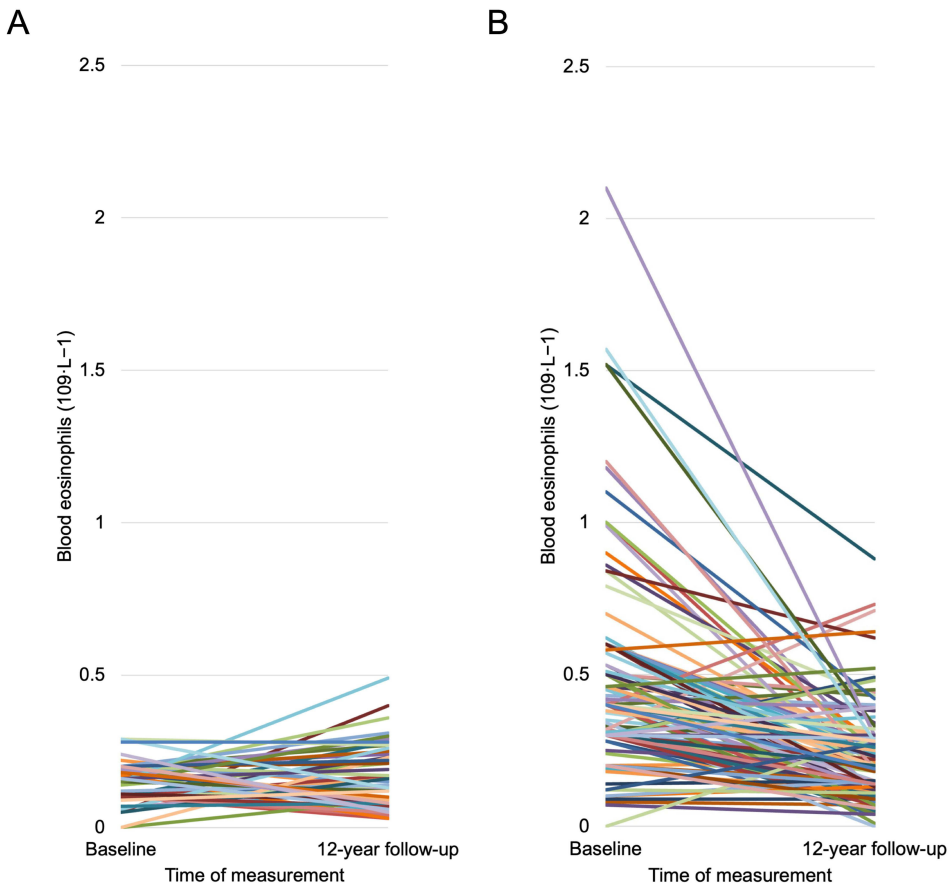

Figure 2 Stability of blood eosinophil counts for baseline low (**A**) and high (**B**) T2 marker patients during the 12-year follow-up period. At baseline, patients were steroid-naïve, whereas at the 12-year follow-up, most had been treated with ICS for 12 years, with 76% reporting daily use at follow-up.

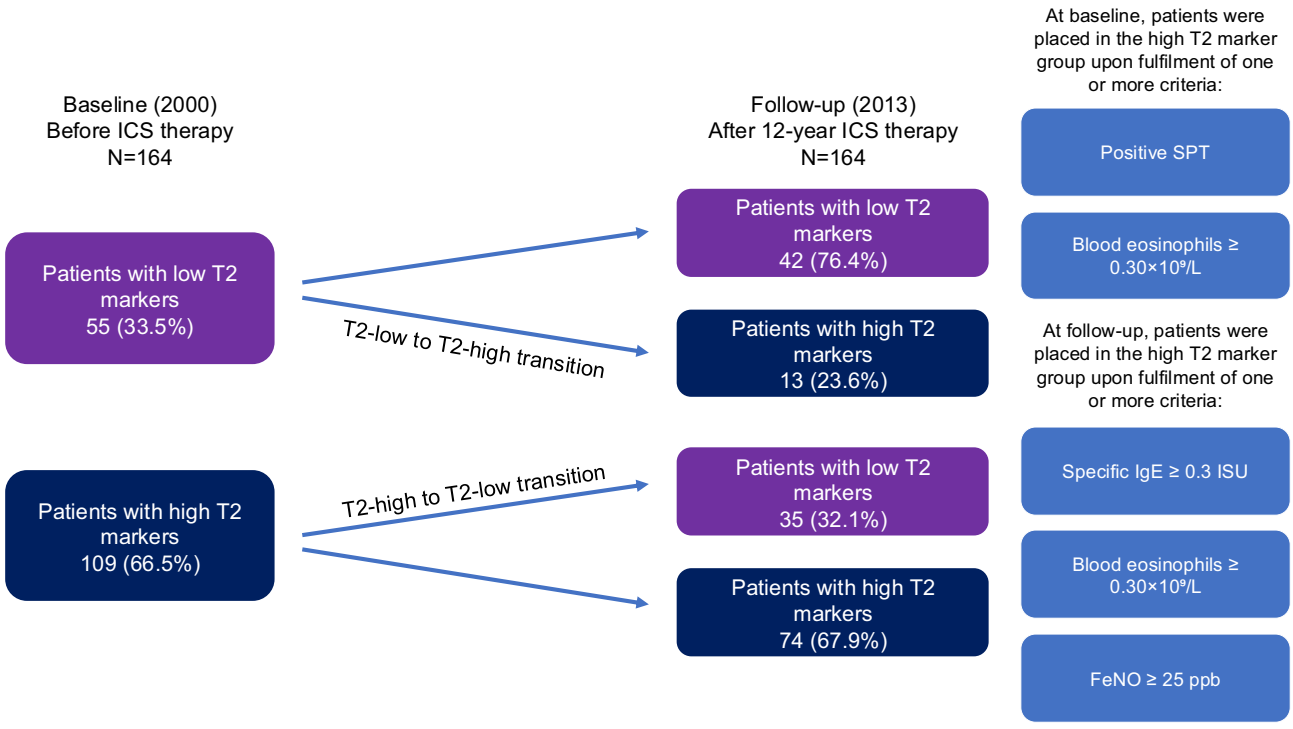

Figure 3 Transitions between groups during the 12-year follow-up period.

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and both FeNO and sensitization in one patient. Those who transitioned had higher BMI, FeNO, and blood eosinophils counts, and lower high molecular weight adiponectin at follow-up (Tables 3 and 4).

Among patients initially with high T2 markers, 67.9% (n=74) remained in the high T2 marker group, while 32.1% (n=35) transitioned to the low T2 marker subtype (Figure 3). Among the 35 transitioned, eight were initially atopic by SPT but did not show allergic sensitization at follow-up. Patients transitioning to the low T2 marker group were older, had more comorbidities, used more non-respiratory medications, had lower IgE, FeNO, and blood eosinophils, but higher adipsin levels compared with patients who were in the high T2 marker group both at baseline and follow-up (Tables 3 and 4).

No significant differences were observed between patients who transitioned between groups and those who remained stable regarding lung function, asthma severity, control, exacerbation frequency, or use of ICS, add-on therapy, OCS, or antibiotics (Table 3). Adherence was similar between patients who transitioned between T2 marker groups and those who remained stable (Table 3). Comorbidity results are shown in Tables E2 and E3.

Secondary Analyses

In analyses using criteria adapted from the GINA 2025 recommendations,[13] 87.2% of patients were classified as having high and 12.8% as having low T2 markers at diagnosis (Figure 4). During follow-up, baseline low T2 marker patients received more prescribed antibiotic treatments (Table E4). Among baseline low T2 marker patients, 61.9% (n=13) remained with low T2 markers and 38.1% (n=8) transitioned to the high T2 marker group (Figure 4). Patients who remained with low T2 markers were more frequently current smokers at both baseline and follow-up (Table E5). Among baseline high T2 marker patients, 85.3% (n=122) maintained this classification, while 14.7% (n=21) transitioned to the low T2 marker group during follow-up (Figure 4). Individuals who transitioned to low T2 markers were older, more likely to be a current smoker, and more frequently diagnosed with COPD at follow-up (Table E5).

Patients who remained with high T2 markers demonstrated greater reversibility in FEV_1 at baseline and were more frequently daily users of ICS (Table E5). In addition, IgE, FeNO, and blood eosinophil levels were higher among patients who remained in the high T2 marker group (data not shown). By contrast, levels of high–molecular weight adiponectin were elevated among those who transitioned from the high T2 marker group to the low T2 marker group (data not shown).

Regression Analyses

As baseline high and low T2 marker groups differed in BMI and age, we carried out linear regression analyses to determine whether the observed associations remained independent of these covariates. Independent associations with high T2 markers at diagnosis were observed for periostin, FeNO, and eosinophils, whereas independent associations with low T2 markers at diagnosis were found for resistin and neutrophils. Among baseline low T2 marker patients, those who transitioned to the high T2 marker group had higher eosinophil counts and higher FeNO compared with those who remained in the low T2 marker group. Among baseline high T2 marker patients, those who remained in the high T2 marker group had significantly higher FeNO and eosinophils compared with those who transitioned to the low T2 marker group. Other variables were no longer significant. (Table E6)

Discussion

In this real-life study, most patients with adult-onset asthma maintained a stable T2 inflammatory profile over treatment, with 71% showing no change. Grouping patients into high and low T2 marker groups did not reveal significant differences in asthma outcomes but highlighted differences in demographics, comorbidities, non-respiratory medication use, and inflammatory parameters.

The baseline distribution of high (66.5%) and low (33.5%) T2 marker patients in our cohort mirrored a previous cross-sectional study of 503 patients with mild-to-severe adult-onset asthma.[22] T2 inflammation was defined by ≥1 of the following: blood eosinophils $\geq 0.30\times10^9$/L, FeNO ≥30 ppb, or allergy confirmed by SPT and/or serum IgE assays — criteria closely aligned with ours. Consistent with that study, our baseline data showed that low T2 marker patients were older and had higher BMI. Our findings also align with a Finnish study showing persistence of T2-low status in severe, uncontrolled asthma.[8] Over 4 years, 72% of patients with baseline blood eosinophils $< 0.30\times10^9$/L and FeNO < 25 ppb

Table 3 Characteristics of the Patients at Baseline and 12-year Follow-Up Visit Classified According to T2 Inflammation and Transitions Between Groups During the 12-year Follow-Up Period

Variable	Low T2 Markers at Asthma Diagnosis (B-Eos < 0.30×10^9/L and Negative SPT)		p-value[x]	High T2 Markers at Asthma Diagnosis (B-Eos ≥ 0.30×10^9/L or Positive SPT)		p-value[y]
	Low T2 markers at follow-up (B-Eos < 0.30×10^9/L, FeNO < 25 ppb, and specific IgE < 0.3 ISU)	High T2 markers at follow-up (B-Eos ≥ 0.30×10^9/L, FeNO ≥ 25 ppb, or specific IgE ≥ 0.3 ISU)		High T2 markers at follow-up (B-Eos ≥ 0.30×10^9/L, FeNO ≥ 25 ppb, or specific IgE ≥ 0.3 ISU)	Low T2 markers at follow-up (B-Eos < 0.30×10^9/L, FeNO < 25 ppb, and specific IgE < 0.3 ISU)	
Subjects n (%)	42 (76.4)	13 (23.6)		74 (67.9)	35 (32.1)	
Baseline variables at asthma diagnosis						
Female sex n (%)	29 (69.0)	6 (46.2)	0.134	40 (54.1)	22 (62.9)	0.386
Age (y) mean (SD)	51.1 (40.6–57.2)	56.2 (49.2–58.9)	0.148	40.6 (13.6)	47.3 (13.1)	**0.016**
BMI (kg/m2) median (IQR)	27.6 (4.4)	30.2 (3.6)	0.054	25.4 (23.6–28.4)	27.8 (24.0–29.1)	0.067
Current/Ex-smoker n (%)	24 (57.1)	5 (38.5)	0.238	13 (17.6)	4 (11.4)	0.409
Pack-years median (IQR)[a]	8.5 (3.1–15.0)	21.8 (10.3–27.8)	0.069	10.0 (3.8–17.0)	15.0 (7.0–21.0)	0.193
AQ20 score median (IQR)[b]	7.5 (3.9)	8.2 (4.8)	0.583	5.5 (3.0–9.0)	7.0 (2.0–10.0)	0.958
FEV_1 reversibility (mL) median (IQR)[b]	110 (35–270)	140 (80–365)	0.341	225.0 (110.0–447.5)	160.0 (62.5–267.5)	0.061
Follow-up variable after 12-years of ICS therapy						
BMI (kg/m2) median (IQR)	26.9 (24.1–31.5)	30.8 (27.9–34.6)	**0.022**	27.7 (24.1–30.5)	28.1 (24.8–30.1)	0.465
Current/Ex-smoker n (%)	24 (57.1)	5 (38.5)	0.238	36 (48.6)	20 (57.1)	0.407
Pack-years median (IQR)[c]	17.2 (13.7)	25.9 (15.7)	0.258	10.0 (3.0–18.8)	18.0 (8.0–25.0)	0.067
Comorbidities COPD included median (IQR)	1.0 (0.0–2.0)	2.0 (0.5–3.5)	0.137	0.0 (0.0–1.3)	1.0 (0.0–2.0)	**0.008**
AQ20 score median (IQR)[d]	4 (2–8)	5 (1–9)	0.889	2 (1–7)	4 (1–6)	0.646
Asthma control test score median (IQR)	21 (19–23)	21 (17–24)	0.772	23 (20–25)	22 (20–24)	0.309
FEV_1 reversibility (mL) median (IQR)	80 (48–143)	90 (15–215)	0.572	120.0 (27.5–170.0)	100.0 (10.0–170.0)	0.743
Fulfills definition of severe asthma* n (%)	3 (7.1)	2 (15.4)	0.366	3 (4.1)	1 (2.9)	0.756
Visits regarding URTIs and exacerbations median (IQR)	4.5 (1.8–10.0)	4.0 (0.0–6.5)	0.198	2.5 (0.8–9.0)	4.0 (1.0–9.0)	0.621
Average dispensed daily ICS dose (μg budesonide equivalents) median (IQR)[e]	601 (385–790)	520 (348–953)	0.982	470 (271–773)	478 (283–802)	0.872
12-year adherence to ICS (percentage) mean (SD)[f]	68.9 (38.4)	78.1 (46.0)	0.489	68.4 (36.2)	62.8 (36.7)	0.470
Dispensed prednisolone dose during entire follow-up (mg) median (IQR)	600 (83–1827)	1200 (0–2700)	0.865	600 (0–2257)	600 (0–3150)	0.234
Daily add on medication n (%)	25 (59.5)	7 (53.8)	0.717	33 (44.6)	18 (51.4)	0.504
No. of medication other than asthma/allergy median (IQR)	1.5 (0.0–4.0)	4.0 (1.0–5.0)	0.168	1.0 (0.0–2.0)	2.0 (0.0–4.0)	**0.024**
No. of antibiotic treatments dispensed during entire follow-up median (IQR)	8.0 (3.8–16.3)	7.0 (4.5–13.5)	0.627	7.5 (4.0–13.3)	6.0 (4.0–11.0)	0.619

Notes: Data are presented as n (%), means (SDs), or medians (IQR). p-value[x]: p-value between baseline low T2 marker patients who remained with low T2 markers and baseline low T2 marker patients who transitioned to having high T2 markers. p-value[y]: p-value between baseline high T2 marker patients who remained with high T2 markers and baseline T2 high marker patients who transitioned to having low T2 markers. *Severe asthma was defined according to the European Respiratory Society and American Thoracic Society 2014 guidelines. Statistical significances were evaluated by one-way ANOVA (analysis of variance), by Pearson Chi-Square test with comparison of column proportions by z-test or by independent samples Kruskal–Wallis test. Bold text represents group names or subheadings. Bolded values represent statistically significant results. [a]Information missing from 5 patients. [b]Information missing from 6 patients. [c]Information missing from 4 patients. [d]Information missing from 1 patient. [e]Information missing from 17 patients. [f]Information missing from 17 patients.

Abbreviations: AQ20, airways questionnaire 20; B-Eos, blood eosinophil count; BMI, body-mass index; COPD, chronic obstructive pulmonary disease; FeNO, fraction of exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IQR, interquartile range; SD, standard deviation; SPT, skin prick test; URTI, upper respiratory tract infection.

Table 4 Inflammatory Parameters of the Patients at 12-year Follow-Up Visit Classified According to T2 Inflammation and Transitions Between Groups During the 12-year Follow-Up Period

Variable	Low T2 Markers at Asthma Diagnosis (B-Eos < 0.30×10⁹/L and Negative SPT)		p-value[x]	High T2 Markers at Asthma Diagnosis (B-Eos ≥ 0.30×10⁹/L or Positive SPT)		p- value[y]
	Low T2 markers at follow-up (B-Eos < 0.30×10⁹/L, FeNO < 25 ppb, and specific IgE < 0.3 ISU)	High T2 markers at follow-up (B-Eos ≥ 0.30×10⁹/L, FeNO ≥ 25 ppb, or specific IgE ≥ 0.3 ISU)		High T2 markers at follow-up (B-Eos ≥ 0.30×10⁹/L, FeNO ≥ 25 ppb, or specific IgE ≥ 0.3 ISU)	Low T2 markers at follow-up (B-Eos < 0.30×10⁹/L, FeNO < 25 ppb, and specific IgE < 0.3 ISU)	
Subjects n (%)	42 (76.4)	13 (23.6)		74 (67.9)	35 (32.1)	
Total IgE (kU/L)	31.5 (21.8–76.0)	50.0 (14.0–259.5)	0.953	114.0 (40.8–362.0)	48.0 (25.0–110.0)	**0.003**
FeNO (ppb)	6.0 (5.0–11.0)	15.0 (8.5–37.0)	**0.002**	15.0 (7.0–30.3)	9.0 (5.0–13.0)	**0.002**
IL-6 (pg/mL)[a]	1.9 (1.4–3.7)	3.2 (1.6–6.0)	0.172	1.3 (1.0–2.5)	2.0 (1.0–4.9)	0.167
IL-8 (pg/mL)[b]	6.2 (5.1–8.4)	7.1 (5.9–8.7)	0.284	5.7 (4.5–8.2)	6.2 (4.9–8.4)	0.333
hsCRP (mg/L)[a]	1.4 (0.4–2.5)	1.7 (0.8–2.7)	0.422	1.0 (0.4–2.3)	1.6 (0.4–4.4)	0.230
Periostin (ng/mL)[a]	12.3 (10.7–14.7)	13.0 (10.0–18.8)	0.759	14.8 (10.9–20.8)	14.6 (10.8–21.1)	0.914
SuPAR (ng/mL)[a]	3.0 (2.6–3.3)	3.3 (2.8–3.4)	0.190	2.6 (2.1–3.2)	2.6 (2.0–3.6)	0.545
MMP-9 (ng/mL)[a]	57.9 (41.4–102.8)	84.4 (38.1–137.5)	0.303	51.9 (38.8–71.2)	55.6 (40.0–93.8)	0.301
Resistin (ng/mL)	14.6 (12.3–19.4)	14.3 (13.2–23.7)	0.383	13.2 (10.0–15.7)	13.7 (11.8–18.2)	0.215
Leptin (ng/mL)	21.5 (14.7–39.5)	23.8 (9.5–45.8)	0.937	20.1 (8.8–34.3)	21.3 (11.9–30.2)	0.846
YKL40 (ng/mL)	50.8 (36.3–80.8)	59.4 (44.4–92.3)	0.367	40.4 (26.0–64.4)	45.5 (33.3–91.0)	0.092
High molecular weight adiponectin (µg/mL)	5.7 (3.3–7.2)	3.9 (2.8–4.3)	**0.028**	3.3 (2.1–6.4)	5.0 (2.8–7.3)	0.130
Adipsin (ng/mL)	823.1 (684.5–1029.8)	1141.6 (771.8–1332.5)	0.055	713.4 (491.3–907.0)	789.4 (695.1–1086.6)	**0.027**
Blood eosinophils (10^9/L)	0.12 (0.07–0.21)	0.21 (0.12–0.34)	**0.009**	0.22 (0.13–0.35)	0.15 (0.11–0.23)	**0.005**
Blood neutrophils (10^9/L)	4.6 (3.3–5.6)	4.3 (3.4–4.8)	0.572	3.6 (2.9–4.6)	3.6 (3.0–4.6)	0.847

Notes: Data are presented as medians (IQR). p-value[x]: p-value between baseline low T2 marker patients who remained with low T2 markers and baseline low T2 marker patients who transitioned to having high T2 markers. p-value[y]: p-value between baseline high T2 marker patients who remained with high T2 markers and baseline T2 high marker patients who transitioned to having low T2 markers. Statistical significances were evaluated by independent samples Kruskal–Wallis test. Bold text represents group names. Bolded values represent statistically significant results. [a]Information missing from 1 patient. [b]Information missing from 3 patients.

Abbreviations: B-Eos, blood eosinophil count; FeNO, fraction of exhaled nitric oxide; hsCRP, high-sensitivity C-reactive protein; IgE, immunoglobulin E; IL-6, interleukin 6; IL-8, interleukin 8; IQR, interquartile range; MMP-9, matrix metalloproteinase-9; SD, standard deviation; SPT, skin prick test; suPAR, soluble urokinase plasminogen activator receptor; YKL40, chitinase-3-like protein.

maintained a stable T2-low profile.[8] A Spanish study reported no significant changes in T2 stability among patients with mild-to-moderate asthma; however, follow-up lasted only one year, and lower eosinophil cut-offs were applied.[9]

At follow-up, patients with low T2 markers at diagnosis exhibited elevated systemic inflammatory markers, including IL-6, suPAR, resistin, YKL-40, and adipsin. Many of these inflammatory markers have been associated with higher BMI and aging, which were also features in the group with low T2 markers.[23–25] After adjusting for age and BMI, most inflammatory differences disappeared. Independent associations with low T2 markers remained for resistin and neutrophils. Still, all the BMI- and aging-related inflammatory mediators may be relevant in mediating T2-low asthma. Elevated IL-6 and suPAR levels have been linked to neutrophilic asthma, while resistin has been associated with neutrophilic and mixed granulocytic phenotypes.[26] Evidence regarding resistin remains inconsistent: one study reported higher levels in steroid-treated patients with moderate-to-severe disease, increasing with severity,[27] whereas another reported lower levels in atopic asthmatic children, inversely associated with atopy and bronchial responsiveness.[28] YKL-40 has been found elevated across asthma severities[29] and suggested as a biomarker of non-T2 inflammation.[30] Surprisingly, those who transitioned from low to high T2 marker group had higher BMI, despite previous studies associating obesity with lower FeNO,[31–33] blood eosinophils,[31] and IgE.[31] A Japanese study suggested BMI correlates positively with eosinophils when counts are $< 0.20\times10^{9}\cdot L^{-1}$, but negatively at higher levels.[34]

Patients with high T2 markers at diagnosis had higher FeNO, blood eosinophils, and periostin at follow-up, even after adjusting for age and BMI. Serum periostin has been proposed as a predictor of T2 eosinophilic inflammation in uncontrolled moderate-to-severe asthma.[35] Those transitioning from high to low T2 markers were older, had more comorbidities, and used more non-respiratory medications. After adjustment for age and BMI, these associations were no longer significant.

In our analyses using adapted GINA cut-points, the baseline proportions of patients with high and low T2 markers were comparable to those reported in a Swedish cross-sectional asthma study of 896 patients.[36] The previous study

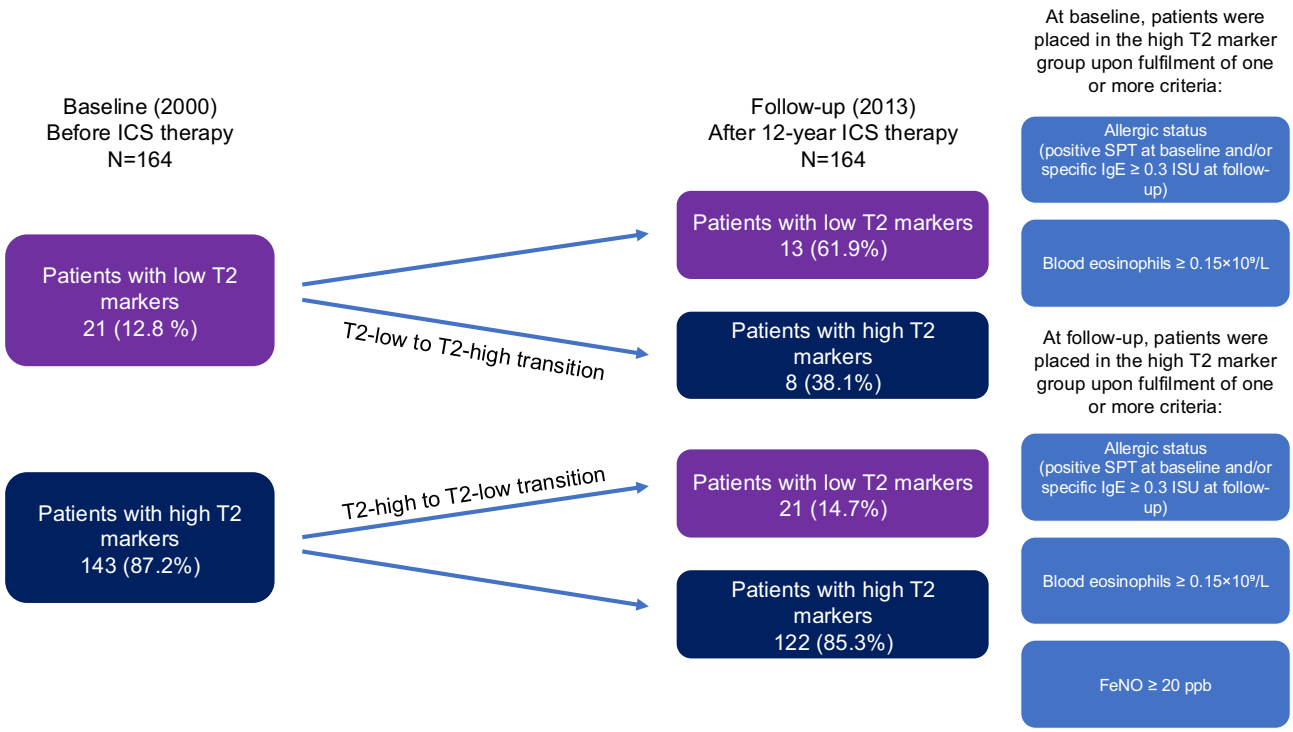

Figure 4 Transitions between groups during the 12-year follow-up period according to secondary analyses using criteria adapted from the GINA 2025 recommendations[13].

included both childhood-onset and adult-onset asthma patients, consisting of both ICS users and non-users, and found that 85.7% had high and 14.3% had low T2 markers.[36] In addition to differences in study design, the methods used to diagnose asthma differed between our study and the previous study. In our study, asthma was physician-confirmed based on characteristic symptoms and lung function measurements, whereas in the earlier study, asthma was self-reported as physician-diagnosed. High T2 markers in the previous study were defined as blood eosinophils $\geq 0.15 \times 10^9$/L, FeNO ≥20 ppb, or allergen-driven asthma. Patients with low T2 markers had a greater risk of exacerbations, which were assessed through clinical interviews.[36] In our cohort, there were no differences in OCS use, URTIs, exacerbations, or hospitalizations; however, patients with low T2 markers received more antibiotics. Healthcare utilization in our study was retrieved from medical records. In the current study, smoking was more common among patients with low T2 markers, as reported in other earlier studies.[22,37] Interpretation, however, is limited by the small size of the low T2 marker group.

This study offers several strengths. It reflects real-world asthma, as patients with comorbidities and current or former smoking were included. Unlike many studies, ours mirrors the clinical reality that adult asthma is often accompanied by other chronic conditions. Asthma diagnosis was thorough, made by a respiratory physician using characteristic symptoms and lung function measurements. The non-invasive biomarkers may allow broad implementation. The 12-year follow-up is a particular strength, and, to our knowledge, no previous study has examined long-term stability of T2 inflammation in steroid-naïve patients at baseline.

Limitations include modest sample size and differences in how T2 marker groups were defined at baseline versus follow-up, reflecting changes in clinical practice. We followed real-world data analysis principles to include all relevant data.[12] This approach contrasts with rigorous trial settings, where most of these comparisons would not have been possible. Applying this method allows us to provide evidence on the stability of high and low T2 marker groups, as well as on changes between steroid-naïve and steroid-treated states, previously unreported. Due to the nature of the analysis, our results should be considered hypothesis-generating rather than conclusive. SPT, used at baseline, remains the most common method for detecting IgE antibodies and demonstrates high sensitivity and specificity when conducted appropriately.[38] For respiratory and food allergies, SPTs have sensitivity equivalent to specific IgE.[38] However, negative results may miss IgE-mediated sensitization due to absent allergens in commercial extracts.[38] Our results suggest allergic

status may vary over time; therefore, baseline SPT and follow-up allergen-specific IgE levels were analysed as distinct variables. Unfortunately, we lack information on whether allergens producing positive results caused clinical symptoms of asthma, as in many other asthma studies.[39,40] Biomarkers of T2 inflammation were measured only once at each visit. GINA 2025 recommends repeating blood eosinophil and FeNO measurements up to 3 times before defining asthma as T2-low.[13] Thus, this study may overestimate low T2 status. Ongoing ICS treatment can mask T2 inflammation at follow-up. All the above could cause small errors in group sizes. Despite variation in T2 criteria across time points, this research remains valuable, as no previous longitudinal studies have examined T2 parameters both before and after ICS initiation.

Environmental exposures and smoking represent potential confounders in T2 inflammation. The study area is predominantly rural, with low traffic and no major industrial pollution, and overall air quality is generally very good, reducing the likelihood that air pollution substantially influenced T2 marker patterns. Although smoking can affect T2 inflammation, we observed no significant differences in smoking history or pack-years between high and low T2 marker groups. There were minor trends toward higher cumulative smoking exposure among patients who changed T2 status over time, but these did not reach statistical significance. Given the small number of smokers in subgroup analyses, these findings should be interpreted cautiously and are recognized as a potential limitation.

Conclusion

In conclusion, our findings suggest that most individuals with adult-onset asthma maintain a consistent T2 profile throughout ICS treatment. While dividing patients into high and low T2 marker groups does not highlight major differences in asthma outcomes, it uncovers distinct patterns in comorbidities, non-respiratory medication use and inflammatory parameters. These features are associated with BMI and aging and may be relevant in the mechanisms of low T2 marker asthma and useful for distinguishing patients with T2-low status. These findings may also open new avenues for research on molecular mechanisms and use of biomarkers in treatment strategies for patients with adult-onset asthma. Future research should focus on evaluating the stability of T2 inflammation status in large real-life population cohorts using biomarker sets that are as comprehensive and comparable as possible across asthma endotypes over long follow-up periods. This is central to improving our understanding of the disease and determining whether treatment responses, for example to corticosteroids, can be expected at various phases of the disease.

Previous Presentation

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Abbreviations

ACT, Asthma Control Test; AQ20, Airways Questionnaire 20; B-Eos, blood eosinophil count; BMI, body-mass index; COPD, chronic obstructive pulmonary disease; FeNO, fraction of exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; GINA, Global Initiative for Asthma; hsCRP, high-sensitivity C-reactive protein; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IL-6, interleukin 6; IL-8, interleukin 8; IQR, interquartile range; MMP-9, matrix metalloproteinase 9; OCS, oral corticosteroid; SAAS, Seinäjoki Adult Asthma Study; SABA, short-acting beta$_2$-agonists; SD, standard deviation; SPT, skin prick test; suPAR, soluble urokinase plasminogen activator receptor; T2, type 2; Th, T helper cell; URTI, upper respiratory tract infection; YKL40, chitinase-3-like protein.

Data Sharing Statement

The authors do not plan to make individual deidentified participant data or related study documents available.

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