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# Overview of asthma patients followed up in a tertiary clinic

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**Key words**

*Asthma phenotypes; asthma endotypes; asthma severity; asthma onset; obese asthma.*

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**Impact statement**

*Endotypes of asthma were examined according to asthma severity, age of asthma onset, control status and obesity subgroups in a tertiary clinic. We found that severe asthmatics were mostly eosinophilic, majority of patients with early-onset asthma were allergic, late-onset asthmatics and obese patients were mostly nonallergic and the proportion of uncontrolled patients was higher in the nonallergic-eosinophilic group.*

***Summary***

***Background.*** *Asthma is a disease that combines different biological mechanisms, inflammatory pathways, and phenotypic features. Our aim was to investigate the demographic and disease characteristics of patients with asthma and to reveal the distribution with different phenotypes according to endotype groups.* ***Methods.*** *Patients were identified as eosinophilic if the absolute eosinophil count was measured at least once ≥ 300/μL during the oral corticosteroid free period or ≥ 150/μL under oral corticosteroids. Patients sensitive to at least one inhalant allergen with skin prick test and/or spIgE measurement were defined as allergic. They were categorized into four main endotypes.* ***Results.*** *Data of 405 asthma patients with a median age of 50.9 years were analyzed. The prominent clinical and phenotypic characteristics of the study group were being obese (43.2%) or overweight (32%), severe asthma (49.6%), adult-onset (56.1%) or late-onset asthma (35.3%). The distribution of the four main endotypes according to eosinophilic and/or allergic status, is as follows: 22.7% allergic-eosinophilic (AE), 27.9% nonallergic-eosinophilic (NAE), 22.9% allergic-noneosinophilic (ANE), 26.4% nonallergic-noneosinophilic (NANE). While most severe asthma patients were in the AE and NAE groups, those with early-onset asthma were in AE and ANE, and those with late-onset asthma were in the NAE and NANE groups. The proportion of uncontrolled patients was higher in the NAE group. Among the severe asthma patients, the rate of uncontrolled disease was higher in those with NANE asthma.* ***Conclusions.*** *Different phenotypes were more closely related to some endotypes. This may allow the clinicians to identify patients and predict appropriate treatment modalities and response for individualized care.*

## Introduction

Asthma is a global problem affecting all age groups, based on the multifactorial interaction of genetic predisposition and various environmental exposures. Contrary to the old understanding, asthma is no longer considered as a single entity with increasing knowledge of the underlying heterogeneity. It is an umbrella diagnosis that includes complex biological mechanisms, inflammatory pathways, and variable phenotypic faces. As a result of many endotyping studies and cluster analysis, we now know that asthma may be of the T2 or non-T2 type (1-8). T2 type asthma is formed by the participation of Th2 lymphocytes,

which secrete cytokines such as IL-4, IL-5, IL-13, stimulate the production of IgE through the B cell and attract eosinophil, basophil, and mast cells to the airways. In addition, group 2 innate lymphoid cells (ILC2s) contribute to this process by secreting the same cytokines (6). It is now clear that patients may or may not be allergic, be eosinophilic or that eosinophils do not play a role. Studies have shown that early-onset and late-onset asthma progress differently (6, 9, 10). It is known that inflammation mechanisms show different characteristics in obese individuals and those with aspirin allergy and the clinical course is variable in these patients (6, 11, 12). Moreover, eosinophilic granulomatosis with polyangiitis (EGPA), allergic broncho-pulmonary aspergillosis (ABPA) and non-steroidal anti-inflammatory drugs-exacerbated respiratory disease (NERD) are distinct asthma-related phenotypes. However, all these different phenotypes are manifested by respiratory symptoms that may vary in intensity from time to time, such as wheezing, cough, shortness of breath, chest tightness, and variable airflow limitation (13).

Treatment and follow-up of asthma depends on whether it is mild, moderate, or severe. While, a standard treatment approach was followed for all patients in the past, nowadays, with the understanding of the complex inflammation pathways of asthma, treatment has been individualized, especially in severe asthma patients. For this reason, it is important to correctly classify patients according to endotype and phenotype and to follow up regularly in order to achieve control, which is the first goal of success in asthma.

In this study, we aimed to evaluate whether different phenotypic characteristics have different endotypes by examining the demographic and disease features of the asthma patients who applied to a private asthma outpatient clinic. The data obtained will help us develop individualized management and follow up strategies for our asthma patients in the future.

## Materials and methods

### *Study design*

This was designed as a cross-sectional observational study conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Ankara University (approval no: i7-422-20). All patients signed the written informed consent form allowing their files to be evaluated retrospectively.

### *Study group and data recording*

All patients who were diagnosed with asthma according to the GINA criteria (13) and were followed up with a diagnosis of asthma for at least one year with complete file records in our specialized asthma follow-up outpatient clinic were included in the study. Our asthma follow-up clinic is an important and experienced center in the field of asthma diagnosis and management and is one of the leading referral centers located in the capital of our country (11, 14-21).

After the diagnosis, all asthma patients who are followed up regularly in our specialized outpatient clinic are informed about their disease, action plans are given, and inhaler technique is checked by a specialist training nurse at each visit. Phenotypic and endotypic features are recorded for all of them, and patients are regularly evaluated every 3-6 months in terms of treatment steps and control status. To summarize a standardized approach is applied to asthma patients according to the individual needs. Sociodemographic features (age, gender, smoking habit, educational status), phenotypic and clinical presentations (atopy, eosinophilia, age of asthma onset, obesity), asthma severity, presence of ABPA, EGPA or NERD, presence of allergic and/or systemic comorbidities were recorded from the files. In addition, clinical assessments including spirometric measurements (minimum and maximum Forced Expiratory Volume (FEV1)), highest absolute eosinophil count, number of planned or unplanned visits, asthma exacerbations, hospitalizations, emergency admissions and oral corticosteroid use in the past year were recorded. The number of patients using one of the biologic agents (omalizumab/mepolizumab), available in the treatment of severe asthma in our country, was also noted.

Asthma control status, treatment step and asthma severity were determined based on the assessment made at the last visit between January 2019 and March 2020. Clinical assessments such as spirometry and blood eosinophil count were performed at regular intervals throughout the follow-up of the patients, but skin prick test and sIgE measurement were performed at any time during the follow-up.

### *Classification of the subjects*

During the follow-up period, asthmatic patients were defined as eosinophilic if the absolute eosinophil count was measured at least once ≥ 300/μL during the oral corticosteroid free period or ≥ 150/μL under oral corticosteroids. Patients were classified as non-eosinophilic if the absolute eosinophil count on at least three measurements did not reach 300/μL during the oral corticosteroid free period or 150/μL under corticosteroids (13). Patients who showed sensitivity to at least one inhalant allergen with skin prick test and/or spIgE measurement and whose positive test result was consistent with their history and clinical features were defined as allergic (13). Based on the data subjects were classified as allergic-eosinophilic (AE), nonallergic-eosinophilic (NAE), allergic-noneosinophilic (ANE) and nonallergic-noneosinophilic (NANE) due to endotypic specialities.

The criteria defined by the American College of Rheumatology were used in the diagnosis of EGPA (22). Accordingly, the diagnosis of EGPA is based on the presence of four or more of the following six findings at the time of the diagnosis: asthma, eosinophilia > 10% in a differential white blood cell count, mononeuropathy or polyneuropathy due to a systemic vasculitis, paranasal sinus abnormalities, migratory or transient pulmo-

nary opacities, and histologic evidence of extravascular eosinophils in a biopsy specimen.

The following criteria were used in the diagnosis of ABPA (23): bronchial asthma, *A. fumigatus* skin test positivity or elevated specific IgE levels, elevated total IgE levels, radiologic pulmonary opacities, and elevated total eosinophil count. The cut-off value for total IgE was accepted as 417 kU/ml.

According to the age of onset of asthma, early-onset was defined as under 18 years of age, adult-onset between 18-40 years, and late-onset as 40 years or older (24, 25). Patients with a body mass index (BMI) value (kg/m$^2$) of 18.5-24.9 were categorized as normal weight, 25.0-29.9 as overweight and those with a BMI of 30 and above were classified as obese (26).

Asthma control status was determined by physicians as well controlled, partly controlled, or uncontrolled based on symptom control at the last visit, and evaluation of future risks including presence of asthma exacerbation in the previous year and spirometry data. Symptom control was assessed at the last visit using the Asthma Control Test (ACT), a quantitative assessment. Accordingly, well-controlled were defined as those with an ACT score of ≥ 20, no exacerbation history in the past year and less than 12% variability in FEV1 between visits in the past year. Those who did not meet any of these three criteria were considered as partly controlled and those who meet none of these criteria were considered uncontrolled. Emergency admission, additional systemic steroid use or a history of hospitalization due to the asthma exacerbation in the last year were considered to be a factor that impairs control, even if the patient had good symptom control and these individuals were accepted as uncontrolled (13, 27). With respect to the GINA 2020 report, asthma severity was determined according to the treatment step at the last visit. Patients receiving step 1 to 2 treatment were classified as mild asthma, step-3 was classified as moderate. Patients whose asthma couldn't be controlled despite taking step 4-5 treatments or could be controlled only with these treatments were considered as difficult to treat (DTT) asthma. Patients were defined as severe asthma if they needed steps 4-5 to achieve control, or if step 4-5 treatment was not sufficient to achieve control, despite correct inhaler technique and correction of disruptive factors such as treatment of comorbidities and reduction of exposure to triggers (13, 27).

Existing comorbidities were classified as allergic and systemic. Allergic comorbidities included allergic rhinitis, food allergy, urticaria, latex allergy, atopic dermatitis. Hypertension, diabetes mellitus, coronary artery disease, thyroid diseases, anxiety-depression, migraine, renal failure, and gastroesophageal reflux, chronic sinusitis, nasal polyposis, bronchiectasis and obstructive sleep apnea (OSA) were categorized as systemic comorbidities. All comorbidities were diagnosed, treated, and followed by relevant specialist physicians.

***Measurements***

The skin prick tests were performed by using common aeroallergen extracts: *Dermatophagoides pteronyssinu, Dermatophagoides farina*, mixtures of grass pollens, weed pollens, tree pollens, and cereal pollens, molds, and animal epithelia (cat and dog) (ALK, Abello, Spain) along with appropriate positive (histamine: 10 mg/mL) and negative controls (saline) on the forearm. Prick test response to with a wheal size ≥ 3 mm in early readings at 15$^{th}$ minutes was considered as positive. CAP fluoroenzyme immunoassay was used for specific IgE measurements, in accordance with recommendation of the manufacturer (Phadia, Uppsala, Sweden). For the same allergens used in the skin prick test it was considered positive if the allergen-specific IgE levels were over 0.35 kU/L. Blood eosinophil counts were obtained from available patient records.

Spirometric measurements (forced expiratory volume in one second (FEV1), forced vital capacity (FVC), peak expiratory flow (PEF) and maximum mid expiratory flow (MMF)) were performed using a spirometry device (ZAN 100, Germany) and evaluated according to the American Thoracic Society/ European Respiratory Society (ATS/ERS) guidelines (28).

***Statistical analysis***

Statistical analysis was produced using SPSS version 21 software (SPSS Inc., Chicago, IL, USA). The conformity of the variables to normal distribution was examined by using visual (histogram and probability graphs) and analytical methods (Kolmogrov-Smirnov/Shapiro-Wilk tests). Descriptive statistics were given using mean and ± standard deviation for normally distributed variables, median and minimum-maximum for non-normally continuous distributed variables. Categorical data were evaluated using the Chi-Square test between two independent groups. The significance of the difference between the means in the normally distributed groups was calculated by ANOVA analysis of variance, and the significance of the difference between the median values in the non-normal distribution groups was calculated using the Mann-Whitney U or Kruskal-Wallis test. Values below 0.05 were considered significant for all P-values.

## Results

A total of 405 asthma patients (79.5% female, 20.5 % male) with the median disease duration of 12.2 (min-max: 1-49) years and the median follow up duration of 6.8 (min-max: 1-43) years were included in the study. The median age of the patients were 50.9 years. The majority of the group had asthma onset in adulthood and the median age of onset was 34.1 years. More than half of the patients graduated from high school. Nearly half of the study group were allergic (45.7%) and eosinophilic (50.6%). Most of the patients were overweight or obese and the median BMI of the study group was 28.9. The rate

***Table I*** *- Demographic and clinical features of the patients (n = 405).*

| Variables | |
|---|---|
| Gender % (n) | |
| Women | 79.5 (322) |
| Men | 20.5 (83) |
| Age median (min-max) | 50.9 years (18-82) |
| Education, % (n) | |
| Primary School | 45.3 (176) |
| High School | 19.9 (77) |
| University | 34.8 (135) |
| Allergy, % (n) | |
| Allergic | 45.7 (185) |
| Non-allergic | 54.3 (220) |
| Blood eosinophilia, % (n) | |
| Eosinophilic (≥ 300 cell/μL) | 50.6 (205) |
| Non eosinophilic (< 300 cell/μL) | 49.4 (200) |
| Obesity, % (n) | |
| Obese (BMI ≥ 30) | 43.2 (174) |
| Overweight (BMI = 25-29.9) | 32 (129) |
| Normal (BMI < 25) | 24.8 (100) |
| BMI, median (min-max) | 28.9 (18-49.9) |
| Age of asthma onset, median min-max) | 34.1 years (4-70) |
| Asthma onset, % (n) | 8.6 (35) |
| Early-onset | 56.1 (227) |
| Adult-onset | 35.3 (143) |
| Late-onset | |
| Disease duration, median (min-max) | 12.2 years (1-49) |
| Follow-up duration, median (min-max) | 6.8 years (1-43) |
| History of smoke, % (n) | |
| Non-smoker | 71.8 (291) |
| Smoker | 22.5 (91) |
| Ex smoker | 5.7 (23) |
| Treatment steps, % (n) | |
| Step 1 | 1.6 (7) |
| Step 2 | 5.9 (24) |
| Step 3 | 31.1 (126) |
| Step 4 | 15.3 (62) |
| Step 5 | 46.1 (186) |
| Disease severity %(n) | 7.6 (31) |
| Mild | 31.1 (126) |
| Moderate | 11.6 (47) |
| Difficult to treat | 49.6 (201) |
| Severe | |
| Biologic treatment Omalizumab/ Mepolizumab) (n) | |
| Absent | 66.2 (268) |
| Present | 43.8 (137) |

of obesity was higher in women than men (47.8% *vs* 24.1%) (p < 0.001) and in late-onset asthma compared to adult-onset or early-onset asthma (58.7%, 37%, 17%, respectively) (p < 0.0001). Three quarters of the subjects were nonsmokers and ex-smokers (**table I**).

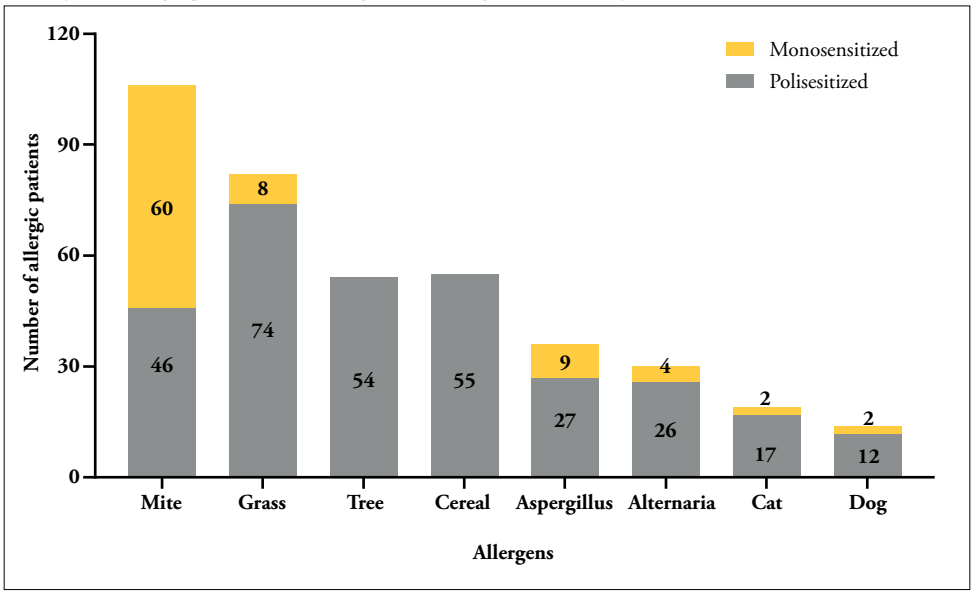
Allergy diagnosis was mostly made by skin prick tests. It was also confirmed by spIgE measurements in 52.1% of the study group, only prick test was performed in 44% of the subjects, and spIgE measurements were performed in 4% of the patients. While 85 patients were monosensitized (mostly mite), 100 patients were polysensitized. Among 185 allergic patients, 57.3% (n = 106) were sensitive to mite, 44.3% (n = 82) to grass, 29.2% (n = 54) to tree, 29.7% (n = 55) to cereal, 19.5% (n = 36) to *Aspergillus*, 16.2% (n = 30) to *Alternaria*, 10.3% (n = 19) to cat, and 7.6% (n = 14) of them were sensitive to dog (**figure 1**).

According to the asthma control evaluation in the last one year, most patients had controlled asthma and the median ACT at the last visit was 24. In general patients came to their visits regularly. In the last year, the median number of scheduled visits was 3.57 and the number of unscheduled visits, asthma attacks, emergency admissions and hospitalizations were negligible. While 63.2% of the subjects did not need systemic corticosteroids in the last year, 16.1% of them regularly used oral corticosteroids at a median dose of 3 mg (**table II**). Furthermore, 68.2% (n = 137 patients) of the severe asthma patients were using biologic treatments (omalizumab or mepolizumab).

Disease severity was divided into four groups based on the treatment steps considering the definition stated in the methods section. According to this, we had 31 mild, 126 moderate, 47 DTT and 201 severe asthma patients. When the control status of the patients was evaluated according to disease severity, it was observed that as the severity of asthma increased, the percentage of controlled patients gradually decreased (in mild asthma: 93.5%, moderate asthma: 87.3%, DTT asthma: 59.6% and severe asthma: 49.7%, respectively) (p = 0.002) (**figure 2**).

When patients were grouped according to eosinophilic and/or allergic status, there were 92 (22.7%) allergic-eosinophilic (AE), 113 (27.9%) nonallergic-eosinophilic (NAE), 93 (22.9%) allergic-noneosinophilic (ANE) and 107 (26.4%) nonallergic-noneosinophilic (NANE) patients. Severe asthma patients were mostly in eosinophilic groups including allergic and nonallergic ones (34.3% and 37.8%, respectively) (p = 0.0002). Asthma patients with early-onset were mostly distributed into allergic-eosinophilic and allergic-noneosinophilic groups (37.1%, 34.3%, respectively) and most of the late-onset patients were nonallergic-eosinophilic or nonallergic-noneosinophilic (29.4%, 31.5%) (p = 0.03). Among the obese patients, there were more nonallergic noneosinophilic subjects than allergic eosinophilic and allergic noneosinophilic

***Figure 1*** *- Distribution of the allergic patients according to the allergens which they are sensitive.*




Among patients sensitive to mite, 60/106 were monosensitized. This ratio was 8/82 for grass, 4/30 for *Alternaria*, 9/36 for *Aspergillus*, 2/19 for the cat and 2/14 for the dog sensitive patients. The grey part of the bars indicated polysensitized patients. Among mite sensitive patients, 46/106 were polysensitized. This ratio was 74/82 for grass sensitive patients, 26/30 for *Alternaria*, 27/36 for *Aspergillus*, 17/19 for the cat and 12/14 for dog sensitive patients. All the tree sensitive and cereal sensitive patients were polysensitive (n = 54, n = 55, respectively).

***Table II*** *- Measures of the study group in the last one-year period.*

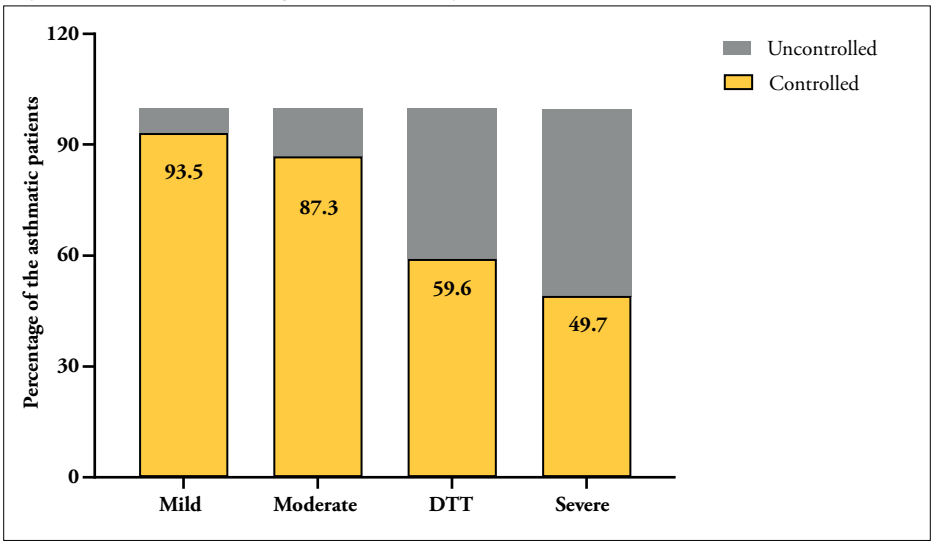
| **Variables** | |
|---|---|
| Asthma control status % (n) | |
| Well controlled | 65.9 (267) |
| Partly controlled | 4.9 (20) |
| Uncontrolled | 29.2 (118) |
| ACT, median (min-max) | 24 (5-25) |
| Pulmonary function tests, median(min-max) | |
| Min FEV1-Max FEV1 lt | 1.97 (0.35-4.96)-2.28 (0.59-5.51) |
| Min FEV1-Max FEV1 % | 83 (13-132)-96 (26-134) |
| Min FEV1/FVC-Max FEV1/FVC | 75 (35-96)-78 (42-96) |
| Number of scheduled visits, median (min-max) | 3.57 (0-24) |
| Number of unscheduled visits, median (min-max) | 0.05 (0-3) |
| Number of asthma exacerbations, median (min-max) | 0.29 (0-5) |
| Number of hospitalizations, median (min-max) | 0.09 (0-2) |
| Number of emergency visits, median (min-max) | 0.07 (0-3) |
| Need for systemic steroid treatment %(n) | |
| None | 63.2 (256) |
| 1-3 per/year | 20.7 (84) |
| Regularly | 16.1 (65) |
| Average systemic steroid dose in regular users, Median (min-max) | 3 mg (1-16 mg) |

subjects (33.3%, 18.4%, 21.8%, respectively) (p = 0.01). The percentage of patients using systemic corticosteroid approximetely 1-3 times per year during asthma attacks was similar among the four groups, but patients using continuous oral corticosteroids accumulated in allergic-eosinophilic (38.5%) and nonallergic-eosinophilic (56.9%) patient groups (p < 0.0001) (**table III**).

When the control status was evaluated according to disease endotypes, the rate of uncontrolled patients in NAE group was higher than in AE, ANE and NANE groups (44.2% *vs* 31.5%, 31.2%, 28%, respectively, p = 0.05). In severe asthma patients, the proportion of uncontrolled patients in the AE, ANE, NAE, NANE endotypic groups was 37.7%, 53.5%, 56.6%, 61.5%, respectively (p = 0.07).

These four endotypic groups were then further analyzed according to the disease onset age and obesity subgroups. Subjects in all four groups, were mostly in the adult-onset asthma subgroup. Patients in the nonallergic groups, were mostly overweight and obese. There was a significant accumulation in the adult-onset and obese asthma groups in allergic-noneosinophilic patients (p = 0.008), and in the late-onset and obese asthma groups in nonallergic-noneosinophilic patients (p < 0.0001) (**figure 3**). In terms of allergic comorbidities and endotypes, allergic rhinitis (n = 138, 34.1%) was the most common and followed by NSAID hypersensitivity (n = 76, 18.8%) and NERD (n = 63, 15.6%). Majority of the patients with

***Figure 2*** *- Evaluation of asthma control according to disease severity.*




We have 31 mild, 126 moderate, 47 DTT and 201 severe asthma patients. 93.5% of the mild asthma patients 87.3% of the moderate asthma patients, 59.6% of DTT asthma patients and 49.7% of severe asthma patients have controlled disease. The percentage of controlled subjects gradually decreased from mild asthma group to severe asthma group (p = 0.002).

***Table III*** *- Clinical characteristics of patients according to endotypic groups.*

| | AE 22.7 (n = 92) | ANE 26.4 (n = 93) | NAE 23.2 (n = 113) | NANE 26.4 (n = 107) | P-value* |
|---|---|---|---|---|---|
| Disease severity % (n) | | | | | |
| Step-1,2 (Mild) | 6.5 (2) | 51.6 (16) | 6.5 (2) | 35.5 (11) | |
| Step-3 (Moderate) | 14.3 (18) | 23.8 (30) | 18.3 (23) | 43.7 (55) | 0.0002 |
| Step-4,5 (Difficult to treat) | 6.4 (3) | 36.2 (17) | 25.5 (12) | 31.9 (15) | |
| Severe | 34.3 (69) | 14.9 (30) | 37.8 (76) | 12.9 (26) | |
| Asthma onset % (n) | | | | | |
| Early | 37.1 (13) | 34.3 (12) | 22.9 (8) | 5.7 (2) | 0.03 |
| Adult | 22.5 (51) | 23.3 (53) | 27.8 (63) | 26.4 (60) | |
| Late | 19.6 (28) | 19.6 (28) | 29.4 (42) | 31.5 (45) | |
| Obesity % (n) | | | | | |
| Normal | 26 (27) | 25 (26) | 31 (31) | 18 (18) | 0.01 |
| Overweight | 25.6 (33) | 22.5 (29) | 27.9 (36) | 24 (31) | |
| Obese | 18.4 (32) | 21.8 (38) | 26.4 (46) | 33.3 (58) | |
| Systemic CS usage % (n) | | | | | |
| None | 19.1 (49) | 27 (69) | 20.3 (52) | 33.6 (86) | < 0.0001 |
| 1-3 | 21.4 (18) | 25 (21) | 28.6 (24) | 25 (21) | |
| Continuously | 38.5 (25) | 4.6 (3) | 56.9 (37) | 0 | |
| Special diseases % (n) | | | | | |
| EGPA | 37 (10) | 0 | 63 (17) | 0 | < 0.0001 |
| ABPA | 87.5 (14) | 12.5 (2) | 0 | 0 | < 0.0001 |

→

| | AE 22.7 (n = 92) | ANE 26.4 (n = 93) | NAE 23.2 (n = 113) | NANE 26.4 (n = 107) | P-value* |
|---|---|---|---|---|---|
| NERD | 33.3 (21) | 7.9 (5) | 44.4 (28) | 14.3 (9) | < 0.0001 |
| Allergic comorbidities % (n) | | | | | |
| AR | 37.7 (52) | 38.4 (53) | 12.3 (17) | 11.6 (16) | < 0.0001 |
| NSAID hypersensitivity | 28.9 (22) | 13.2 (10) | 40.8 (31) | 17.1 (13) | 0.003 |
| Urticaria | 13.5 (5) | 40.5 (15) | 18.8 (7) | 27 (10) | 0.04 |
| Systemic comorbidities % (n) | | | | | |
| Chronic sinusitis | 32.4 (24) | 13.5 (10) | 44.6 (33) | 9.5 (7) | < 0.0001 |
| Nasal polyposis | 40.9 (36) | 9.1 (8) | 38.6 (34) | 11.4 (10) | < 0.0001 |
| Bronchiectasis | 60 (15) | 12 (3) | 16 (4) | 12 (3) | < 0.0001 |
| Osteoporosis | 38.5 (10) | 7.7 (2) | 46.2 (12) | 7.7 (2) | 0.005 |

*Chi-Square test; AE: allergic-eosinophilic; ANE: allergic-non eosinophilic; NAE: nonallergic-eosinophilic; NANE: nonallergic-non eosinophilic; EGPA: Eosinophilic Granulomatosis with Polyangiitis; NERD: NSAID-exacerbated respiratory disease; ABPA: allergic broncho-pulmonary aspergillosis; AR: allergic rhinitis; CS: Corticosteroid.

NSAID hypersensitivity (n = 76) were nonallergic-eosinophilic (40.8%) (p = 0.003). For NERD (n = 63), 44.4% of the patients were nonallergic-eosinophilic, 33.3% were allergic eosinophilic (p < 0.0001). Among the special asthma profiles, as expected in EGPA, all patients (n = 27) were in eosinophilic group and most of them were in the nonallergic-eosinophilic group (n = 17, 63%), but the majority of patients with ABPA (n = 16) were allergic-eosinophilic (n = 14, 87.5%) (p < 0.0001). Systemic comorbidities include GERD (n = 107, 26.4%), hypertension (n = 95, 23.5%), nasal polyposis (n = 88, 21.7%) and chronic sinusitis (n = 74, 18.3%) were the most common. Patients with chronic sinusitis or nasal polyposis were mostly allergic-eosinophilic (32.4%, 40.9%, respectively) or nonallergic eosinophilic (44.6%, 38.6%, respectively) (p < 0.0001). We have 25 asthmatic patients with bronchiectasis and 60% of them were allergic-eosinophilic (p < 0.0001). Osteoporosis was seen in 26 patients and 46.2% of them were in the nonallergic- eosinophilic and 38.5% of them were in the allergic-eosinophilic groups (p = 0.005) (**table III**). Among overall group, four asthmatic patients had OSA. All four patients had adult-onset or late-onset asthma and were overweight or obese. Three of them were nonallergic-eosinophilic and one patient was nonallergic-noneosinophilic.

## Discussion

This study showed that patients followed up in our specialized out-patient clinic were mostly women, overweight or obese, adult-late onset and generally well-controlled asthmatics. Half of the patient population were either allergic or eosinophilic, and a quarter of them were both allergic and eosinophilic. A significant number of patients had severe asthma, mostly eosinophilic and more than half of them were under biologic therapy (either mepolizumab or omalizumab). Disease control was worse in the severe group than in moderate or mild asthma. It was observed that, the later the disease started, the less likely it was to be allergic. The allergic-eosinophilic endotype was predominant among early-onset asthmatics, while nonallergic-noneosinophilic endotype was common in late-onset asthma. Among the obese patients, nonallergic-noneosinophilic ones were in the majority. Moreover, as expected, patients with bronchiectasis and ABPA generally had an allergic-eosinophilic endotype whereas NSAID hypersensitive, NERD and EGPA patients were mostly nonallergic-eosinophilic. Additionally, patients with sinusitis or nasal polyposis were evenly distributed in allergic-eosinophilic or nonallergic-eosinophilic endotypes.

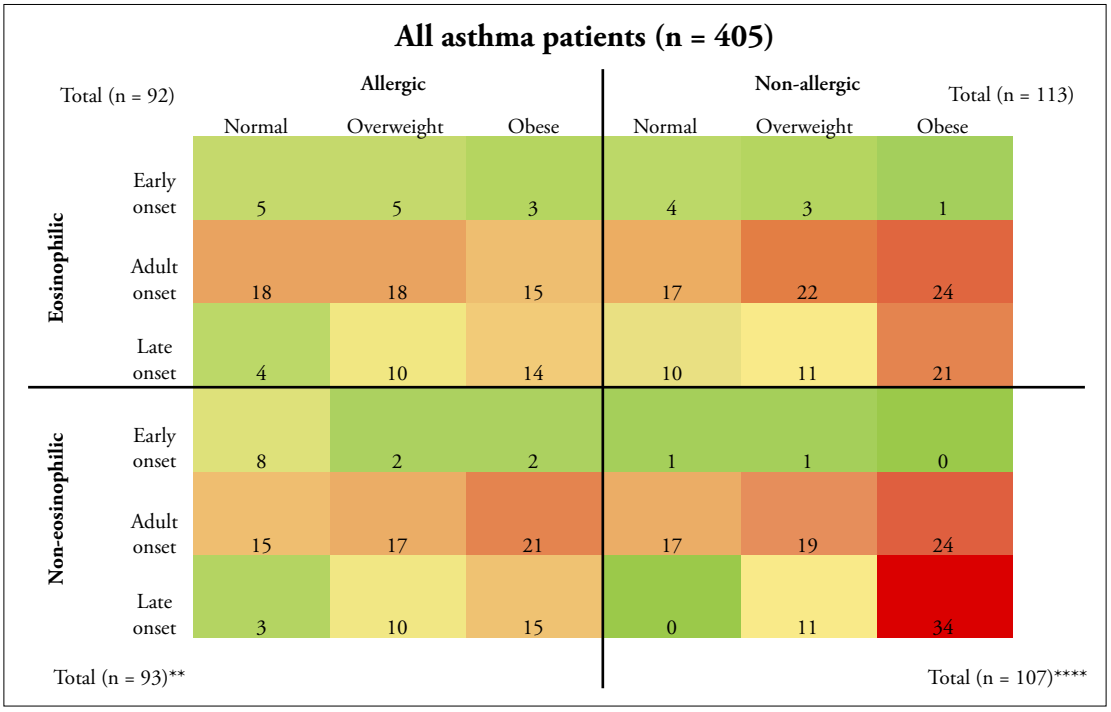
In our study, the rate of being allergic was high in early-onset asthmatics, regardless of whether they were eosinophilic or noneosinophilic. Since the phenotyping of asthma as extrinsic (allergic) and intrinsic (non-allergic) is a historical study (29), similar results have been obtained in many studies parallel with our findings (2, 4, 6, 30). For this reason, the terms of "early-onset" and "allergic" are often used together. In our entire patient population, the distribution was balanced between eosinophilic and noneosinophilic endotypes, favoring the nonallergic side. This slight excess in the nonallergic subjects was thought to be secondary to the predominance of patients in the group with asthma onset over 18 years of age. Adult-onset asthmatics predominated both in the whole group and in each of the four phenotypic subgroups. This situation was thought to be secondary to the low transfer rate of early asthmatics to adult outpatient clinics due to remission in early-onset asthma (9). Additionally, the high number of severe asthma patients in our group may be another explanation for the high number of patients with adult-onset asthma, which is in line with the results of the previous studies documenting the association between adult-onset asthma and disease severity (9, 31).

Consistent with the previous reports, severe asthma was found to be associated with the eosinophilic endotype in our patients. Furthermore, different studies have documented that patients

with adult-late onset asthma tend to be more frequently eosinophilic than those with early-onset asthma (31, 32). Although the prevalence of eosinophilic asthma is not known exactly, it was reported as 40% in a multicenter study conducted in Brazil and 20-40% in the literature especially in severe asthma patients (2, 32-34). In a recent study that included 4,990 patients worldwide, and revealed the characteristics of severe asthmatics, it was reported that 48.5% of the patients had a blood eosinophil count above 300/μL (35). In our group this ratio was about 50% for entire group and 72% for severe asthmatics. These are reasonable findings for a specialized asthma outpatient clinic where most patients have severe asthma. In addition, ABPA, EGPA, NERD, nasal polyposis, and chronic sinusitis, which are adult-onset airway diseases of the eosinophilic spectrum, were in considerable numbers in our group and were most frequently observed with severe asthma. The fact that our EGPA, NERD and chronic sinusitis patients are usually NAE endotype and our ABPA patients show AE endotypic features due to sensitivity to fungal allergens supports the argument that there are some common genetic, immunological, and pathological conditions among these adult-onset eosinophilic diseases (32). Unlike allergen induced IgE-mediated early-onset allergic asthma, adult-onset eosinophilic diseases are not necessarily IgE-mediated but are often accompanied by marked peripheral blood eosinophilia that develops simultaneously or sequentially. In addition to the specific pathophysiological mechanisms exhibited for each disease in this group, these diseases have been reported to share a common pathophysiology such as eosinophil extracellular trap cell death (EETosis), increased IL-33 and thymic stromal lymphopoietin (TSLP) receptor gene expression, increased recruitment of ILC2s and mucus plug formation (36-40).

Especially late-onset asthma without eosinophilia, is thought to be associated with age-related changes in the immune system, obesity, smoking, and occupational exposure rather than atopy (4, 41-47). From the obesity perspective, studies classify obese asthma patients as a distinct phenotype (48-50). Considering that the majority of the cases in our group were obese, it is clear that the obesity-asthma phenotype is a common condition in our clinical practice. Several reports have documented an increased risk of asthma in obese patients particularly those who are nonallergic and/or noneosinophilic (51-54). Concordantly,

***Figure 3*** *- Heat map graphic of the allergic-eosinophilic (n = 92), allergic noneosinophilic (n = 93), nonallergic-eosinophilic (n = 113) and nonallergic-noneosinophilic (n = 107) endotype groups according to age of onset and obesity subgroups.*




The majority of patients in allergic-eosinophilic group were overweight or obese and had adult onset asthma. Similarly, most nonallergic-eosinophilic patients were overweighted or obese and had adult-onset asthma. However, patients with late onset were more common especially in obese subgroups. There was significant accumulation in the adult-onset and obese asthma groups among allergic-noneosinophilic patients ($p = 0.008$), and in the late-onset and obese asthma groups among nonallergic-noneosinophilic patients ($p < 0.0001$).

in our study obese patients was found to be mostly in non-allergic and noneosinophilic subgroups. Previous studies have reported that obesity-asthma association was divided into two separate groups. The first is defined as late-onset, nonallergic, non-T2 endotypic asthma that develops as a result of obesity, and the second is defined as obesity secondary to early-onset, allergic and T2 endotypic asthma (11, 48, 50, 53). Obese asthmatics in our study group are thought to be in the first group with non-T2 inflammation, because of their late-onset and mainly noneosinophilic and nonatopic features.

The majority of patients (65.9%) in this study were evaluated as having well controlled asthma during the study period. In recent years, despite the availability of effective treatments, it has been documented that the level of asthma control achieved is below the goals of long-term asthma management. Several surveys from different parts of the world reported that nearly half of their study population had uncontrolled asthma (7, 34, 41-43, 55).

Compared with these data, the level of asthma control was higher in our study population and the proportion of controlled patients was even higher than in tertiary care hospitals in our country (20). The reason for this may be due to regular follow up of patients in an outpatient clinic specialized in asthma.

However, it is not unexpected that the rate of controlled patients is the lowest in severe asthma subjects. Although two thirds of the patients with severe asthma were under treatment with biologic drugs, half were still uncontrolled. It can be speculated that the frequency of uncontrolled asthma would have been higher if this group did not receive biological treatment. The proportion of uncontrolled patients was higher in NAE subjects than in other three endotypes.

However, it is known that eosinophilia is associated with poor asthma control and frequent exacerbations in adult-onset severe asthma, but not in patients with mild to moderate disease (32).

When the severe asthma group was evaluated in this regard, we found that the rate of uncontrolled asthma was higher in non-allergic endotype than the allergic group and surprisingly, the non-eosinophilic asthma group was more prone to uncontrolled disease than the eosinophilic subjects. In addition, the rate of uncontrolled asthma was highest among the severe NANE asthma patients.

Taken together, these findings may reflect the fact that majority of the severe asthma patients in our study were treated with omalizumab or mepolizumab.

The results of our study once again reinforced the heterogeneity of asthma and provided some clues for management in clinical practice. Since those with severe asthma and those with uncontrolled disease are more likely to be eosinophilic, it may be advisable to consider T2 inflammation-targeted therapy earlier. On the other hand, the fact that obese asthmatics are mostly non-allergic and non-eosinophilic made us think that this patient group may not benefit from current treatment options and should turn to non-T2 inflammation-targeted treatment.

Our study has some strengths and limitations. First, this study had a large sample of diverse endo-phenotypes from a single tertiary care center experienced in asthma management. Second, patients had long follow up duration of up to 40 years, regular and complete file records. The retrospective pattern of the study can be seen as a limitation but can be ignored due to the long follow-up period and full patient records of the study population.

As another limitation, it can be mentioned that fractional exhaled nitric oxide (FeNO) evaluation and induced sputum analysis were not performed for endotyping. If this could be done, type 2 inflammation and eosinophilic asthma could be more precisely defined. However, blood eosinophil count correlates with sputum and tissue eosinophilia and as well as FeNO. It is a useful marker in prediction of asthma exacerbations and in identifying responders to biologics, and it is widely used in clinical practice to assess type 2 inflammation.

Endotype and phenotype determination is needed in asthma, which is a heterogeneous disease. This study demonstrated that different clinical phenotypes have endotypes ranging from NAE to NEA to NANE. We suggest that the rate of asthma control can be increased even in severe asthmatic cases with correct endotyping and accordingly the use of the appropriate individualized treatment modalities.

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None.

**Contributions**

ZCS: study design, data collection and analysis, writing - original draft, writing - review & editing. BÖÖ: study design, data collection, writing - original draft, writing review & editing. ÖA: study design, writing - original draft, writing review & editing. SB: conceptualization, study design, writing - original draft, writing review & editing. DM: conceptualization, study design, writing - original draft, writing review & editing.

**Conflict of interests**

The authors declare that they have no conflict of interests.

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