Phenotypic Distribution and Cluster Analysis in Asthma Patients

Astım Hastalarında Fenotipik Dağılım ve Küme Analizleri

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ABSTRACT

Objective: Several diagnostic and treatment algorithms regarding asthma have been described in previous guidelines. Yet these descriptions fail at reflecting different phenotypes of asthma encountered in clinical practice. The purpose of this study is to retrospectively analyze the data of asthma patients that have presented to the outpatient clinic and to group the patients according to the pre-bronchodilator FEV1 value, post-bronchodilator FEV1 value, age of asthma onset while evaluating the common characteristics of the different clusters.
Methods: 246 patients that had been diagnosed with asthma and had complete data records were recruited for this study. These patients were categorized under five phenotypic clusters according to the three variables (pre-bronchodilator FEV1 value, post-bronchodilator FEV1 value, age of asthma onset) of the SARP (Severe Asthma Research Program) algorithm and were evaluated accordingly.
Results: Cluster 4 had the highest number of patients while Cluster 5 had the least number of patients within our study. Obesity and gastro-esophageal reflux was thought to be the reason behind the fixed obstruction seen in patients of Cluster 5. Multiple drug treatment regimens were also mostly used for patients in Cluster 5. This led us to think that Cluster 5 asthma was the most difficult group to obtain control. Unlike the SARP study, atopy was encountered the most in Cluster 2.
Conclusions: In conclusion, phenotypical distribution and cluster analysis using the pre-bronchodilator FEV1 value, post-bronchodilator FEV1 value and age of asthma onset is an easy and effective classification system that can both be used for the Turkish population and to set guidelines and strategies for treatment of difficult asthma cases according to different clusters.

Key Words: Asthma, cluster analysis, phenotypes

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ÖZET

Amaç: Astım ile ilgili, rehberlerde üzerinde fikir birliği bulunan tanı ve tedavi algoritmaları tanımlanmıştır. Ancak bu tanımlamaların hastalığın kliniğinde görülen farklı fenotiplerin hepsini birden yansıtması mümkün olmamaktadır. Bu çalışmanın amacı; Gazi Üniversitesi Tıp Fakültesi (GÜTF) Göğüs Hastalıkları Polikliniğine başvuran hastaların dosyalarının retrospektif incelenmesi ile pre-bronkodilatör FEV_1, post- bronkodilatör FEV_1, astım başlangıç yaşı kullanılarak hastaları kümelere ayırmak ve kümelerin ortak özelliklerini incelemektir.
Yöntem: GÜTF Göğüs Hastalıkları polikliniğine başvuran, astım tanılı ve verlieri mevcut olan 246 hasta çalışmaya alındı. Çalışmaya alınan hastalar Ağır Astım Araştırma Programı (Severe Asthma Research Program, SARP) algoritmasına göre pre-bronkodilatör FEV_1, post- bronkodilatör FEV_1 ve astım başlangıç yaşı kullanılarak beş fenotipik kümeye ayrılarak incelendi.
Bulgular: Çalışmamızda Küme 4 hasta sayısı en fazla olan en geniş küme, Küme 5 ise hasta sayısı en az olan küme olarak saptandı. Obezite ve gastro-özofageal reflü en sık Küme 5'te saptandı. Eşlik eden obezite ve gastro-özafagiyal reflünün Küme 5'teki fiks obstrüksiyondan sorumlu olabileceği düşünüldü. Kullanılan tedaviler incelendiğinde birden fazla çeşit kontrol edici ilacın en sık Küme 5'te kullanıldığı saptanmıştır. Bu durum Küme 5'te astımın kontrolünün güç olduğunu düşündürmektedir. Atopi ise SARP çalışmasından farklı olarak en sık Küme 2'de izlenmiştir.
Sonuç: Pre-bronkodilatör FEV_1, post-bronkodilatör FEV_1 ve astım başlangıç yaşı olmak üzere oldukça kolay uygulanabilecek olan fenotipik sınıflandırma ve küme analiz yöntemlerinin Türk popülasyonunda da uygulanabileceği ve astım kontrolünü güçleştiren etkenlerin bulundukları kümeye göre öngörülüp tedavi stratejisini yönlendirebileceği düşünülmektedir.

Anahtar Sözcükler: Astım, Küme analizleri, Fenotip

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INTRODUCTION

Asthma is a reversible chronic inflammatory disease of the airways. The symptoms particularly occur at night and in the morning. These symptoms are due to diffuse airway obstruction of varying degree (1).

Various diagnostic and therapeutic algorithms have been defined in various guidelines on asthma. However, it is not possible for these definitions to cover all the different phenotypes. A phenotype is defined as "the characteristics that occur in the external appearance of the organism after the interaction of its genetic properties with the environment". Various asthma phenotypes have been identified and all these different phenotypes have been grouped under the "asthma" definition over time. Phenotypic evaluations have accelerated in asthma patients in recent years as different phenotypes have different treatment strategies and different responses to treatment. Asthma has been divided into three groups by the first few phenotypic classifications as clinical and physiological phenotypes, trigger-based phenotypes and inflammatory phenotypes (2).

Many phenotypic cluster analyses related to asthma have been performed in recent years. The first few cluster analysis studies have evaluated various treatment strategies for the inflammatory asthma phenotypes (3).

The 2009 Severe Asthma Research Program (SARP) study has divided 726 severe asthma patients into five clusters by using 34 variables and shown that the patients could also be divided into phenotypic clusters by using only three variables in the form of pre-bronchodilator FEV_1(forced expiratory volume in 1 second), post-bronchodilator FEV_1, and asthma onset age (4).

The aim of our study was to divide the patients into five phenotypic clusters with the SARP algorithm by using three variables (pre-bronchodilator FEV1 value, post-bronchodilator FEV1 value, asthma onset age), reveal the characteristics of the clusters, and evaluate the applicability of the SARP algorithm to the Turkish population.

MATERIAL and METHOD

We retrospectively reviewed the charts of the patients who presented to the Gazi University School of Medicine's Chest Diseases outpatient department between 1995 and 2013 in this study, which was evaluated and approved by the Gazi University Rectorship Clinical Research Ethics Committee under the code number of G.Ü.ET- 2013-89.

The age, gender, smoking history, body mass index, age of onset of asthma, pre-bronchodilator FEV_1 value, post-bronchodilator FEV_1 value, total immunoglobulin E(IgE) value, skin tests, blood eosinophil percentage, comorbid diseases (rhinitis, sinusitis, gastroesophageal reflux, hypertension) and the treatment data of the 246 patients included in the study were recorded. The patients were divided into five phenotypic clusters according to the SARPwhere three variables (pre-bronchodilator FEV_1, post-bronchodilator FEV_1, asthma onset age) were used (figure 1).

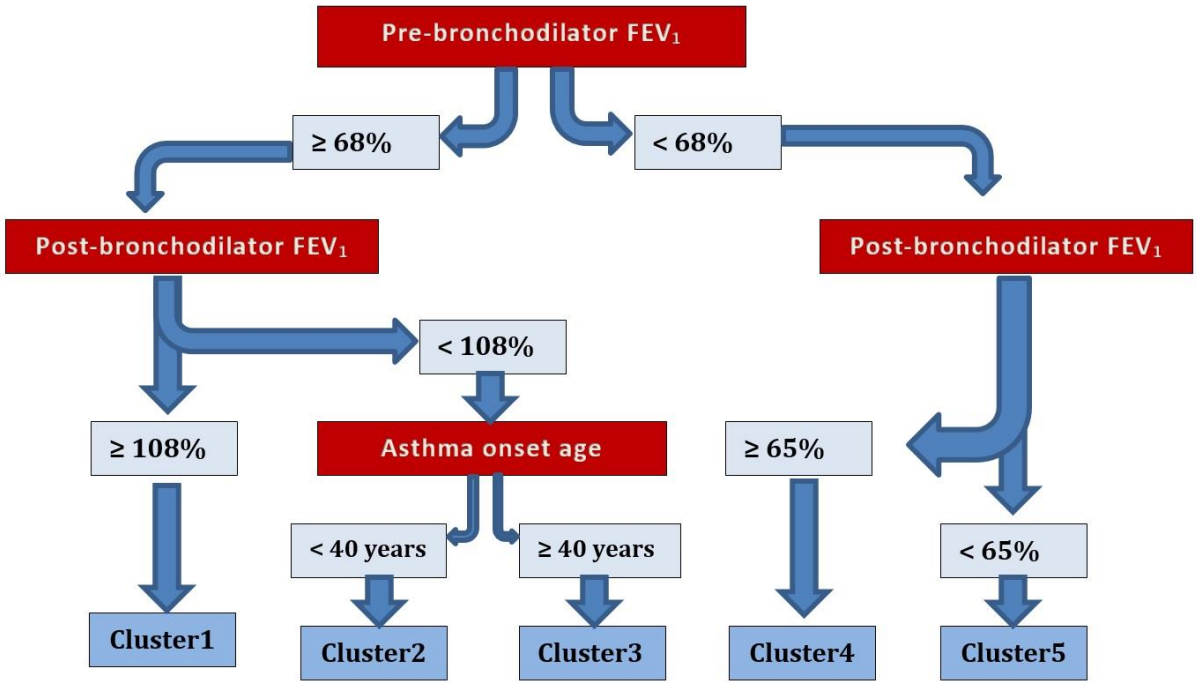

Figure 1. Clusters according to the Severe Asthma Research Program algorithm**.**

Cluster 1: Patients with a pre-bronchodilator FEV_1 value of 68% or more and a post-bronchodilator FEV_1 value of 108% or more were included in this group.
Cluster 2: Patients with a pre-bronchodilator FEV_1 value of 68% or more and a post-bronchodilator FEV_1 value of less than 108% with an asthma onset age under 40 years were included in this group.
Cluster 3: Patients with a pre-bronchodilator FEV_1 value of 68% or more and a post-bronchodilator FEV_1 value less than 108% with an asthma onset age of 40 years or more were included in this group.
Cluster 4: Patients with a pre-bronchodilator FEV_1 value of less than 68% and a post-bronchodilator FEV_1 of 65% or above were included in this group.
Cluster 5: Patients with a pre-bronchodilator FEV_1 value of less than 68% and a post-bronchodilator FEV_1 value of less than 65% were included in this group.
The files of 1621 patients who presented to the Gazi University School of Medicine's Chest Diseases Outpatient Department and were diagnosed with asthma between 1995 and 2013 were retrospectively reviewed and 246 patients with recorded data were included in the study. Data for the body mass index (BMI), pre-bronchodilator FEV1, post-bronchodilator FEV1, total immunoglobulin E (IgE), serum eosinophil percentage, drugs used for asthma treatment and the presence of any allergic rhinitis, sinusitis, gastro-esophageal reflux (GER), hypertension or heart failure accompanying the asthma were recorded.

RESULTS

The files of asthma patients who presented to the Gazi University School of Medicine's Chest Diseases outpatient department between 1995 and 2013 were retrospectively reviewed and 246 patients with complete data were included in the study.

The study group consisted of 179 (72.8%) females and 67 (27.2%) males. Nonsmokers made up 68.3% of the group with 168 subjects. The mean age was 42.5 ± 12.6 years and the mean asthma onset age was 34.1 ± 11.8 years. The mean body mass index was 28.8 ±5.8 kg/m^2 (Table 1).The demographic data characteristics according to clusters are summarized in Table 2. Evaluation of the comorbidities revealed the most common comorbidity to be allergic rhinitis (n = 126, 51.2%). In addition, the asthma was associated with sinusitis in 115 (46.7%) patients, GERin 62 (25.2%) patients, hypertension in 40 (16.3%) patients and heart failure in 12 (4.9%) patients (Figure 2).

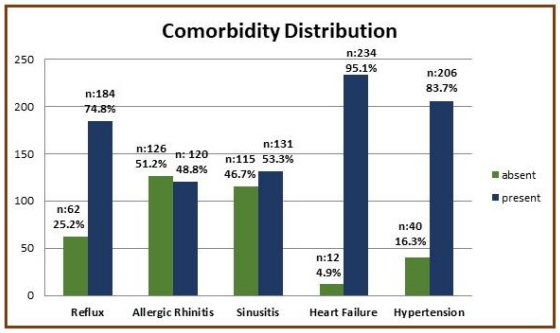

Figure 2. Comorbidity distribution.

Table 1. The demographic data of the patients

Demographic Data	General distribution	
	N	%
Gender		
Female	179	72.8%
Male	67	27.2%
Smoking status		
Smoker	78	31.7%
Non-smoker	168	68.3%
Age		
Mean	42.5 years	
Minimum	17 years	
Maximum	83 years	
Asthma onset age		
Mean	34.1 years	
Minimum	10 years	
Maximum	82 years	
Body mass index		
Mean	28.8 kg/m^2	
Minimum	16.9 kg/m^2	
Maximum	56.4 kg/m^2	

Table 2. Demographic Data Characteristics According to Clusters

	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5
n,%	65,26.4%	50,20.3%	49,19.9%	66,26.8%	16, 6.5%
Age (years)	41,4±11.7	31.6±7.7	48.7±8.2	44.2±13.1	54.9±12.8
Asthma onset age	35.3±10.5	26.2±2,9	39.5±11,1	34,9±12,9	34,2±15,3
BMI (kg/m^2)	28.1±5.6	28.3±5.7	29.2±5.3	28.8±5.0	32.6±9.5
Hypertension (n,%)	11, 16.9%	0, 0%	13, 26.5%	10, 15.2%	6, 37.5%
GER (n,%)	15,23.1%	7, 14%	11,22.4%	19, 28.8%	10, 61.5%
Heart Failure (n,%)	4, 6.2%	0, 0%	4, 8.2%	2, 3%	2, 12.5%
Allergic rhinitis(n,%)	39, 60%	29, 58%	26, 53,1%	24, 36,4%	8, 50%
ICS (n,%)	26, 40%	14, 28%	14, 28.6%	11, 16.7%	1, 6.3%
ICS+LABA (n,%)	38, 58.5%	33, 66%	32, 65.3%	35, 53%	7, 43.8%
ICS+LABA+LTRA (n,%)	1, 1.5%	3, 6%	2, 4.1%	16, 24.2%	8, 50%
ICS+LTRA (n,%)	0, 0%	0, 0%	1, 2%	4, 6.1%	0, 0%

The type of control drugs of the patients was reviewed and an inhaler corticosteroid (ICS) + long-acting β_2 agonist (LABA) combination was the most commonly used type of control drug (n = 145, 58.9%). None of the patients used only anti-IgE drugs or leukotriene receptor antagonists (LTRA).

The patients included in the study were divided into five clusters using three variables (pre-bronchodilator FEV_1, post-bronchodilator FEV_1 and asthma onset age) with the SARP algorithm. Cluster 1 consisted of patients with a pre-bronchodilator FEV_1 value of 68% or more and a post-bronchodilator FEV_1 value of 108% or more; Cluster 2 consisted of patients with a pre-bronchodilator FEV_1 value of 68% or more, a post-bronchodilator FEV_1 value of less than 108%, and an asthma onset age under 40 years; Cluster 3 consisted of patients with a pre-bronchodilator FEV_1 value of 68% or more, a post-bronchodilator FEV1 value of less than 108%, and an asthma onset age of 40 years or more; Cluster 4 consisted of patients with a pre-bronchodilator FEV_1 value of less than 68% and a post-bronchodilator FEV_1 value of 65% or more; and Cluster 5 consisted of patients with a pre-bronchodilator FEV_1 value of less than 68% and a post-bronchodilator FEV_1 value of less than 65%. Cluster 4 had the highest (n=66, 26.8%) and Cluster 5 the lowest (n=16, 6.5%) number of patients (Figure 3) in this distribution.

Patients included in the study were evaluated in terms of comorbidity distribution by cluster. There was no statistically significant difference between the clusters in terms of allergic rhinitis distribution (p>0.05). However, allergic rhinitis was more common in Clusters 1 (n=39, 60%) and 2 (n=29, 58%).

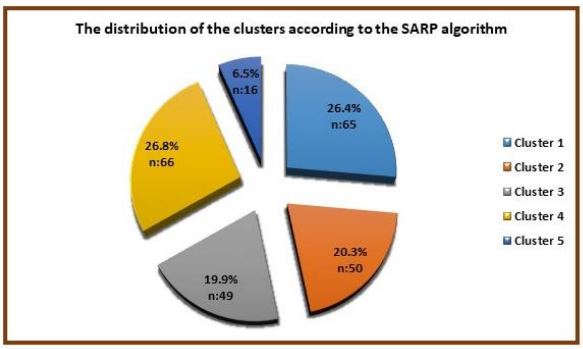

Figure 3. The distribution of the clusters according to the SARP algorithm.

There was no statistically significant difference between the clusters for sinusitis distribution (p>0.05). Sinusitis was most commonly observed in Cluster 2 (n=31, 62%).GERwas most commonly found in Cluster 5 (n = 10, 61.5%) and statistical analysis revealed that this difference was significant (p=0.003). GER was least common in Cluster 2 (n=7, 14%).Hypertension was most commonly found in Cluster 5 (n=6, 37.5%) and this difference in prevalence was found to be statistically significant (p=0.001). No hypertension was found in the asthma patients in Cluster 2.There was no statistically significant difference between the clusters regarding the distribution of heart failure (p>0.05)There was also no statistically significant difference between the clusters for BMI (p>0.05). However, the highest mean BMI was found in Cluster 5 (32.6 ± 9.5).The mean peripheral blood eosinophil percentages were within normal limits in all the clusters.TotalIgE value was found to be above the normal limits (0-100 IU/mL) in all clusters.

The patients were divided into groups according to the number of positive allergens in the skin test and the distribution of these groups by cluster was investigated. A status of no allergen positivity on the skin test was most commonly found in Cluster 5 (n=12, 75%). Skin test positivity was most commonly found in Cluster 2 (n=30, %60).

The distribution of the treatments used by the patients was also evaluated by cluster. There was no patient using an anti IgE drug or LTRA alone in the study. Multiple control drugs were most commonly used in Cluster 5 (n=15, 93.8%) (p=0.0001). Only one patient in Cluster 5 was using a single control drug type (ICS).

Our patients were divided into clusters according to the three basic criteria (pre-bronchodilator FEV_1 value, post-bronchodilator FEV_1 value and asthma onset age) recommended by the SARP, and cluster analysis revealed the following information:

Cluster 1: Patients with pulmonary function test (PFT) values within normal limits were included in this cluster. Females made up the majority. The cluster included patients with asthma onset at an advanced age (mean 35.3 ± 10.5 years) and a shorter duration of asthma (mean 6 years). Rhinitis was the most common comorbidity (p>0.05).

Cluster 2: Patients with a post-bronchodilator FEV_1 value lower than Cluster 1 on PFT and an asthma onset age under 40 years were included in this cluster. Cluster 2 had a majority of females again together with a shorter duration of asthma (mean 5 years). It was also found to be the cluster with the youngest patients (mean age 31.6±7.7 years).
Skin test positivity accompanied by increased total IgEwas also most commonly found in Cluster 2. Sinusitis was the most common comorbidity (p>0.05).
Cluster 3: Patients whose PFT values were similar to Cluster 2 but where the asthma onset age was 40 years or more were included in this cluster. The cluster consisted of older patients (mean age 48.7 ± 8.2 years) with a majority of females and comorbidities were not common.
Cluster 4: Patients whose PFT values were lower than in the first three clusters but had no fixed obstruction were included in this cluster. Cluster 4 was found to contain the highest number of patients (n=66, 26.8%). This cluster consisted of mostly female patients where comorbidities were not common and the PFT values were low, unlike Cluster 3.
Cluster 5: Patients who were found to have fixed obstruction on PFT were included in this cluster. Cluster 5 consisted of an equal proportion of females and males with asthma onset at an advanced age (mean age 54±12.8 years) and the longest mean duration of asthma (10 years). GER (p=0.003) and hypertension (p=0.001) was most commonly observed in Cluster 5. The highest mean BMI value was also found in this cluster (mean 32.6±9.5 kg/m^2) (p>0.05). In addition, the highest number of control drug types were used in Cluster 5 (p<0.05) and a negative skin test was also most commonly found here (p>0.05).

DISCUSSION

The idea of treatment according to phenotype has emerged in recent years and resulted in more detailed phenotyping studies and various phenotypic classifications. The aim of these classifications is to predict the common prognostic evaluation groups with similar clinical findings in addition to the treatment protocol and response to treatment (2).

Several cluster analysis studies have been conducted with such phenotypic evaluations in recent years. Cluster analysis is concerned with "identifying similarities according to a large number of variables predetermined in a population".

Asthma patients were evaluated after dividing them into five different clusters by using the 34 variables in the SARPstudy conducted with a large patient population consisting of 726 participants (4). Despite the 34 variables used in that study, we found that it was possible to include 80% of the subjects in the correct cluster by using only three variables: pre-bronchodilator FEV_1, post-bronchodilator FEV_1, and asthma onset age. According to the analysis based on the SARP, Cluster 1 consisted of young, atopic, female asthmatics with asthma onset at an early age and 40% of these patients were not using medication. Cluster 2 consisted of patients who were atopic and mostly female, who were somewhat older than in Cluster 1, and with earlier onset of asthma and normal PFT values. No medication was being used by 26% of the patients in Cluster 2. Cluster 3 consisted of obese female patients of an advanced age with asthma onset at a young age, low degree of atopy, and moderate obstruction on PFT. Cluster 4 consisted of an equal proportion of females and males with asthma onset at an early age, most of whom were atopic and required high medication doses. Cluster 5 consisted of obese female patients with asthma onset at an advanced age and who suffered from atopy less commonly. According to the distribution by SARP category, Cluster 2 had the highest and Cluster 3 the lowest number of patients.

The aim of our study was to divide the study subjects into clusters using the three variables and evaluate their characteristics as in the SARP study. It is known that allergic rhinitis is present in 75% of asthma cases and conversely asthma is present in 10-40% of allergic rhinitis cases (5). The physician should be aware that asthma and allergic rhinitis affect each other's course negatively and the treatment should take this into account (1,5). Sinusitis is also frequently concurrent with asthma and can make its control difficult (5). The patients were evaluated under "sinus diseases" in the SARP study. Accordingly, the incidence of sinus diseases in our entire patient population was found to be 45% and these were most commonly observed in Cluster 3. Allergic rhinitis was seen in 51.2% and sinusitis in 46.7% of all patients in our study. No statistical difference was found between the clusters in terms of allergic rhinitis and sinusitis.

However, allergic rhinitis was most commonly seen in Clusters 1 and 2, and sinusitis in Cluster 2. Based on our patient population, we believe that allergic rhinitis and sinusitis should especially be investigated in patients with the phenotypic characteristics of Clusters 1 and 2.

Asthma is more common and more difficult to control in obese patients (body mass index > 30 kg/m^2) (6-8). Asthma control can be provided more easily in obese patients who lose weight thanks to the relevant decrease in the accompanying reflux and elimination of the negative effects on lung mechanics (5). The review of the treatments used by the patients in Cluster 5, which was the cluster where obesity was most common in our study, revealed this cluster to most commonly include patients requiring multiple types of control drugs. Weight loss could have positive effects on asthma in this cluster where asthma control could have been difficult judging by the variety of drugs used.

GERhas been reported to aggravate asthma findings (9). The disorder may play a role in patients whose asthma is difficult to treat and cannot be controlled. The asthma can be controlled and the quality of life improved by adding a proton pump inhibitor to the treatment in these patients (9-12). Similar to the SARP study, gastro-esophageal reflux was most commonly found in Cluster 5 in our study. GER and obesity associated with asthma could therefore be responsible for the fixed obstruction in Cluster 5 and make asthma control difficult. When the treatments used were investigated, it was found that multiple control drug types were most commonly used in Cluster 5, suggesting that asthma was difficult to control in this group. The addition of proton pump inhibitors to the treatment could possibly improve asthma control in this group of patients.

Unlike the SARP study, the skin test negativity rate was found to be high in Cluster 5 in our study. However, similar to the SARP study, total IgE values were found to be high in Cluster 2, and skin test positivity was also most commonly seen in Cluster 2 in our study. Atopy was therefore thought to be common in Cluster 2.
Hypertension was most commonly found in Cluster 5 in this study, similar to the SARP study. We believe that hypertension occurring most commonly in Cluster 5 may be related to the older age of Cluster 5 patients.
Evaluation of the comorbidities revealed that obesity and reflux were mostly seen in Cluster 5 with fixed obstruction. These two factors were thought to make it difficult to control asthma and may be the reason multiple types of control drugs were required in the relevant cluster in this study where phenotypic evaluation and cluster analysis were investigated by using pre-bronchodilator FEV_1, post-bronchodilator FEV_1 and asthma onset age in patients with asthma. Allergic rhinitis and sinusitis were found to be particularly common in Clusters 1 and 2.

CONCLUSION

We believe that the phenotypic classification and cluster analysis methods that can be applied easily using the criteria of pre-bronchodilator FEV1, post-bronchodilator FEV1 and asthma onset age values can also be useful in the Turkish population and the factors that make it difficult to control asthma can be predicted by cluster to guide the treatment strategy. This issue should be further clarified by future studies and increasing clinical experience.

Conflict of interest
No conflict of interest was declared by the authors.

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