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Phenotypes Determined by Cluster Analysis in Moderate to Severe Bronchial Asthma

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Background: Bronchial asthma is a heterogeneous disease that includes various subtypes. They may share similar clinical characteristics, but probably have different pathological mechanisms.

Aim: To identify phenotypes using cluster analysis in moderate to severe bronchial asthma and to compare differences in clinical, physiological, immunological and inflammatory data between the clusters.

Patients and methods: Forty adult patients with moderate to severe bronchial asthma out of exacerbation were included. All underwent clinical assessment, anthropometric measurements, skin prick testing, standard spirometry and measurement fraction of exhaled nitric oxide. Blood eosinophilic count, serum total IgE and periostin levels were determined. Two-step cluster approach, hierarchical clustering method and k-mean analysis were used for identification of the clusters.

Results: We have identified four clusters. Cluster 1 (n=14) - late-onset, non-atopic asthma with impaired lung function, Cluster 2 (n=13) - late-onset, atopic asthma, Cluster 3 (n=6) - late-onset, aspirin sensitivity, eosinophilic asthma, and Cluster 4 (n=7) - early-onset, atopic asthma.

Conclusions: Our study is the first in Bulgaria in which cluster analysis is applied to asthmatic patients. We identified four clusters. The variables with greatest force for differentiation in our study were: age of asthma onset, duration of diseases, atopy, smoking, blood eosinophils, nonsteroidal anti-inflammatory drugs hypersensitivity, baseline FEV1/FVC and symptoms severity. Our results support the concept of heterogeneity of bronchial asthma and demonstrate that cluster analysis can be an useful tool for phenotyping of disease and personalized approach to the treatment of patients.

BACKGROUND

Bronchial asthma (BA) is estimated to affect 1 to 16% of the population in different countries.¹ A large-scale multicenter epidemiological study (n = 6 492) in Bulgaria found asthma morbidity to be 9%.²

Asthma is a heterogeneous disease and cluster approaches have been developed in the past years to better define phenotypes.³⁻⁸ Although variable selection and analysis methodology differ, some studies have reached comparable results.⁹ According to Wenzel, the first step to better understand asthma is to define phenotypes by cluster analysis.¹⁰

Identification of each corresponding endotype requires the definition of their clinical characteristics, biomarkers, lung physiology, genetic aspects, disease history and therapeutic response.¹¹

AIM

The aim of this study was to use cluster analysis to identify phenotypes of asthma in a population of moderate to severe bronchial asthma adult patients and then compare the differences in clinical, physiological, immunological and inflammatory parameters between the clusters.

PATIENTS AND METHODS

This study was performed after permission of the Ethics Committee on Medical Research of the Medical University - Sofia.

POPULATION

40 patients (pts) (14 men and 26 women) with moderate to severe BA were included in the study. The patients were stable, on maintenance asthma therapy in the last four weeks before inclusion in the study. The tests were conducted in the ordinary course of ambulatory practice. All patients were over 18 years old and were enrolled in the study after signing an informed consent. BA was defined according to the international guidelines – GINA, BTS/SIGN.^{1,12} The severity of BA was assessed in accordance with international recommendations of the European Respiratory Society (ERS) and the American Thoracic Society (ATS).^{1,13}

Exclusion criteria for participation were exacerbation requiring a systemic corticosteroid therapy in the last 4 weeks prior to the study, active infection, interstitial lung disease or other significant disease other than BA.

Current and ex-smokers were included if they had at least 12% improvement in FEV1 after inhalation of 400 µg of salbutamol at the time of inclusion.

METHODS

All patients completed questionnaires that assessed demographic data, medical history, use of medication, number of exacerbations during the last year, imposed intake of systemic corticosteroids, and/or hospitalization or emergency room visit due to asthma.¹⁴ Symptoms and asthma control were measured, with validated asthma questionnaires [Asthma control test (ACT), Juniper Asthma Control Questionnaire (ACQ-7)]. The Juniper score was modified to be representative of symptoms alone dividing the total score by five (ACQ-5).^{3,15} Anthropometric measurements and detailed physical examination were performed.

Baseline prebronchodilator lung function was assessed with spirometry (MiniSpir[®], software Win-spiroPRO[®] version 6.8.0; Italy). Fraction of exhaled nitric oxide (FeNO) measurement was done using a system NIOX MINO (Aerocrine, Sweden) before any forced expiratory manoeuvres.¹⁶ Total serum IgE levels (EUROIMMUN total IgE ELISA, Germany) and serum periostin levels (ELISA, Cusabio, China) were measured. Complete blood count, percentage and absolute count of eosinophils in peripheral

blood were determined. Skin prick tests (SPT) were performed with the most common aeroallergens - house dust mites, pollen, grasses, molds, weeds, cat, dog, guinea pig, feathers.

STATISTICAL ANALYSIS

A cluster analysis was applied to identify groups of patients with the same characteristics. Variables were selected according to previous studies, based on their considered contribution to define asthma phenotypes and their predictor importance determined by two-step cluster approach.³⁻⁶ Ward's minimum-variance hierarchical clustering method was performed using an agglomerative approach, and the linkage measure was the squared Euclidean distance with standardization in z scores, according to Moore et al.⁴ The number of likely clusters was determined by visual inspection of dendrogram (**Fig. 1**).

Clusters quality was checked by two-step cluster analysis method and K-means non-hierarchical cluster analysis was performed. The categorical variables

Figure 1. Dendrogram obtained using Ward's method.

were presented in percentages and quantitative as mean and standard deviation (SD) or median and interquartile ranges (IQR). For variables with normal distribution, differences between the clusters were analysed by analysis of variance (ANOVA) and Independent-samples T-test. Kruskal-Wallis and Mann-Whitney U tests were used for analysis of variables with distribution different from the normal. Pearson's chi-squared test (χ^2) was used for comparison of categorical variables. All statistical analyses were performed using SPSS® Software, version 19.0 (IBM, SPSS statistics Inc.) and MedCalc® statistical software for Windows version 13.0.6.0. $P < 0.05$ was considered significant.

RESULTS

Variables such as age of disease onset ($p < 0.001$), atopic status ($p < 0.001$) and nonsteroidal anti-inflammatory drugs (NSAIDs)/aspirin sensitivity ($p < 0.001$) were the most important in our cluster distinction. There were statistically significant differences between the clusters in age, onset, BA duration, atopic status, smoking history, pack-years, NSAIDs HS, FEV1/FVC, blood eosinophils, and total serum IgE (**Table 1, Fig. 2**).

Characteristics obtained for the entire group and for each of the clusters are shown in **Table 1**.

CLUSTER DESCRIPTION

Cluster 1 (C1) (n=14) (35%), late-onset, non-atopic BA with impaired lung function: This group was predominantly female – 9 pts (64.3%) with mean age of 52.36 ± 12.70 yrs, disease onset at 46 years (33.25-56.50) and average BA duration of 4.50 years (1.75-11.75). All pts showed negative SPT. The body mass index (BMI) of the group was 26.45 (23.68-30.85). Four pts (28.6%) were obese. 5 pts (35.7%) were current smokers with median pack-years of 5.00 (0.00-16.25). None of the pts reported NSAIDs hypersensitivity. According to ACQ-5, 7 pts (50%) were symptomatic and uncontrolled ($ACT < 20$). Nine pts (64.3%) have reported one or more exacerbations in the previous year. The patients had impaired lung function (FEV1 – $72.50 \pm 24.91\%$, FVC – $82.64 \pm 18.29\%$, FEV1/FVC – $69.73 \pm 13.01\%$). Median blood eosinophil count was 358.50 cells/microL (257.50-468.75) or 4.50% (2.75-6.00). Median value of FeNO was 21.50 ppb (10.75-65.00). Five pts (35.7%) showed FeNO over 50 ppb and all of them were partly uncontrolled. Total serum IgE levels were 35.40 IU/ml (12.15-130.63). Serum periostin was 1.771 ± 0.517 ng/ml (**Fig. 2**).

Cluster 2 (C2) (n=13) (32.2%), late-onset, atopic BA with high symptoms, exacerbations and smoking history: This group was predominantly female – 10 pts (76.9%), mean age of 43.15 ± 15.17 yrs, disease onset at 39 years (24.00-49.00) and average BA duration of 3.00 years (1.00-12.00). All pts showed positive SPT, of them 4 pts (30.8%) were monosensitized and 9 pts (69.2%) were polysensitized. The BMI of the group was 22.90 (20.60-26.60). One pt (7.7%) was obese. 6 pts (46.2%) were current smokers with median pack-years of 10.00 (0.00-15.00). None of these pts reported NSAIDs hypersensitivity. According to ACQ-5, 8 pts (61.5%) were symptomatic and 7 pts (53.8%) were uncontrolled ($ACT < 20$). Twelve pts (92.3%) reported one or more exacerbations in the previous year. The patients had preserved lung function (FEV1 – $85.44 \pm 20.77\%$, FVC – $93.58 \pm 18.18\%$, FEV1/FVC – $77.82 \pm 7.18\%$), despite the most pack-years in that cluster. Median blood eosinophil count was 236.00 cells/microL (147.50-426.50) or 4.00% (2.75-5.50). Median value of FeNO was 21.00 ppb (15.50-29.50). One pt (7.7%) showed FeNO over 50 ppb. Total serum IgE levels were 171.40 IU/ml (147.50-426.50). Serum periostin levels were 1.806 ± 0.460 ng/ml.

Cluster 3 (C3) (n=6) (13%), late-onset, aspirin sensitivity, eosinophilic, symptomatic BA: This group was predominantly male – 4 pts (66.7%), mean age of 55.17 ± 12.94 yrs, disease onset at 32.00 years (17.75-51.25) and average BA duration of 19.50 years (10.25-33.00). Five pts (83.3%) showed positive SPT, of them 1 pt (16.7%) was monosensitized and 4 pts (66.7%) were polysensitized. The BMI of the group was 27.35 (25.10-30.52). One pt (16.7%) was obese. Current or ex-smokers were not included. These patients reported NSAIDs hypersensitivity. According to ACQ-5, 4 pts (66.7%) were more symptomatic and 2 pts (53.8%) were uncontrolled ($ACT < 20$). Three pts (50%) reported one or more exacerbations in the previous year. The patients in this cluster had the most impaired lung function (FEV1 – $80.17 \pm 24.37\%$, FVC – $97.17 \pm 14.76\%$, FEV1/FVC – $65.08 \pm 12.86\%$). Median blood eosinophil count was significantly higher 496.00 cells/microL (286.25-885.75) compared with C4 ($p = 0.028$) and C2 ($p = 0.022$). Statistically significant difference was observed between the clusters using cut off level of 250 cells/microL ($p = 0.048$). Median value of FeNO was 23.50 ppb (18.50-56.25). One pt (16.7%) showed FeNO over 50 ppb. Total serum IgE levels were 91.35 IU/ml (34.63-355.35). Serum

Table 1. Main characteristics of the study patients and of the four clusters

		Cluster 1	Cluster 2	Cluster 3	Cluster 4	
Variables	Population summary	Late-onset Non-atopic	Late-onset Atopic	Late-onset Aspirin sensitivity	Early-onset Atopic	p-value
Subjects (n, %)	40 (100%)	14 (35%)	13 (32.5%)	6 (15%)	7 (17.5%)	
Gender (female, %)	26 (65%)	9 (64.3%)	10 (76.9%)	2 (33.3%)	5 (71.4%)	p=0.310 [#]
Age (years, mean±SD)	46.37±14.77	52.36±12.70	43.15±15.17	55.17±12.94	32.86±8.47*	p=0.007
Age at onset (median, IQR)	36.50 (19.25-49.00)	46.00 (33.25-56.50)	39.00 (24.00-49.00)	32.00 (17.75-51.25)	2.00** (1.00-7.00)	p<0.001
Atopic status (positive,%)	24 (60%)	0 (0%)	13 (100%)	5 (83.3%)	6 (85.7%)	p<0.001 [#]
BMI (kg/m ²) (median, QR)	25.80 (22.75-29.55)	26.45 (23.68-30.85)	22.90 (20.60-26.60)	27.35 (25.10-30.52)	25.70 (23.50-34.70)	p=0.220
Obesity (n,%)	8 (20%)	4 (28.6%)	1 (7.7%)	1 (16.7%)	2 (28.6%)	p=0.525 [#]
Smokers (current,%)	11 (27.5%)	5 (35.7%)	6 (46.2%)	0 (0%)	0 (0%)	p=0.053 [#]
Smoking pack-years (median, IQR)	0.00 (0.00-14.25)	5.00 ^a (0.00-16.25)	10.00 ^b (0.00-15.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	p=0.008
NSAIDs HS (positive,%)	7 (17.5%)	0 (0%)	0 (0%)	6 (100%)	1 (14.3%)	p<0.001 [#]
ACQ-5 (median, IQR)	1.00 (0.00-1.80)	0.70 (0.00-2.00)	1.20 (0.00-2.40)	1.30 (0.50-2.15)	0.40 (0.00-1.80)	p=0.665
ACT score (median, IQR)	21.00 (17.30-25.00)	20.00 (17.00-25.00)	19.00 (18.00-25.00)	21.50 (17.50-25.00)	25.00 (17.00-25.00)	p=0.913
Exacerbations (yes, %)	27 (67.5%)	9 (64.3%)	12 (92.3%)	3 (50%)	3 (42.9%)	p=0.090 [#]
Baseline FEV1 (% of pred) (mean±SD)	80.99±23.17	72.50±24.91	85.44±20.77	80.17±24.37	79.80±10.28	p=0.296
Baseline FVC (% of pred) (mean±SD)	90.62±18.37	82.64±18.29	93.58±18.18	97.17±14.76	96.86±17.82	p=0.200
Baseline FEV1/FVC, % (mean±SD)	73.08±12.10	69.73±13.01	77.82 ±7.18 [§]	65.08±12.86	79.80±10.28 ^{§§}	p=0.034
Blood eosinophils, (n, %)	14 (35%)	3 (21.4%)	7 (53.8%)	0 (0%)	4 (57.1%)	p=0.048 [#]
< 250 cells/microL	26 (65%)	11(78.6%)	6 (46.2%)	6 (100%)	3 (42.9%)	
≥ 250 cells/microL						

Qualitative data presented as number (n) and percentage (%); Quantitative data presented as mean±standard deviation and median with interquartile range (IQR)

p-value from ANOVA, Kruskal-Wallis test or Chi-square[#] analysis between the four clusters

Abbreviations: BMI - body mass index; ACQ-5 - asthma control questionnaire 5; ACT - asthma control test; FEV1 - forced expiratory volume for the first second; FVC - forced vital capacity; FeNO - fractional concentration of nitric oxide in exhaled air; NSAIDs HS - nonsteroidal anti-inflammatory drugs hypersensitivity;

* p<0.05 comparing C4 with C1 and C3

** p<0.05 comparing C4 with C1, C2 and C3

§ p<0.05 comparing C2 with C1 and C3

§§ p< 0.05 comparing C4 with C3

^a p<0.05 comparing C1 with C3 and C4

^b p<0.05 comparing C2 with C3 and C4

Figure 2. Levels of inflammatory markers in the four clusters. *p-value determined by Kruskal-Wallis test, **p-value determined by ANOVA.

periostin was 1.404 ± 0.560 ng/ml.

Cluster 4 (C4) (n=7) (17.5%), early-onset, atopic BA: This group was predominantly female – 5 pts (71.4%), mean age of 32.86 ± 8.47 , disease onset at 2.00 years (1.00–7.00) and average BA duration of 29.00 years (20.00–39.00). Six pts (85.7%) showed positive SPT. All patients in this cluster were polysensitized. The BMI of the group was 25.70 (23.50–34.70). Two pts (28.6%) were obese. There were no current or ex-smokers in this cluster. One pt (14.3%) had reported NSAIDs hypersensitivity. According to ACQ-5, 3 pts (42.9%) were symptomatic and uncontrolled with ACT < 20. Three pts (42.9%) reported one or more exacerbations in the previous year. These patients had preserved lung function (FEV1 – $79.80 \pm 10.28\%$, FVC – $96.86 \pm 17.82\%$, FEV1/FVC – $79.80 \pm 10.28\%$). Median blood eosinophil count was 220.00 cells/microL (168.00–290.00) or 3.00% (2.00–4.00). Me-

dian value of FeNO was 40.00 ppb (16.00–46.00). Four pts (57.1%) showed FeNO over 35 ppb. Total serum IgE levels were 390.00 IU/ml (48.20–777.50). Serum periostin was 1.632 ± 0.480 ng/ml.

DISCUSSION

This study is the first in Bulgaria to apply principles of cluster analysis for the assessment of asthmatic patients. We have identified four clusters: Cluster 1 - late-onset, non-atopic asthma with impaired lung function, Cluster 2 - late-onset, atopic asthma, Cluster 3 - late-onset, aspirin sensitivity, eosinophilic asthma, and Cluster 4 - early-onset, atopic asthma.

Phenotyping in the field of bronchial asthma was initiated in 2005 by Wenzel.¹⁷ It evolved in the years defining two endotypes (Th2 and Non Th2 asthma) in 2012¹⁸ and 2013¹⁹, as well as 6 phenotypes (early-onset allergic, late-onset eosinophilic,

exercise-induced, obesity-related, neutrophilic, smoking BA).

In 2008, Haldar et al.³ used cluster analysis to define different phenotypes in a population of 371 mild to severe refractory AP. They described 3 clusters (C1 – early-onset atopic asthma, C2 – obese non-eosinophilic asthma, C3 – benign asthma) in primary care, and 4 clusters (C1 – early-onset, atopic BA, C2 – obese, non-eosinophilic BA, C3 – early symptom predominant BA, C4 – inflammation predominant BA) in secondary care.

Moore et al.⁴ identified 5 groups in the Severe Asthma Research Program (n=726) using unsupervised hierarchical analysis. C1 was early - onset atopic asthma with normal lung function and minimal controller medication and health care utilization, C2 – also early-onset of atopic asthma and preserved lung function, but with increased medication requirements and health care utilization, C3 – late-onset, non-atopic asthma with predominantly obese older women and moderate reduction in FEV1 and frequent exacerbations, C4 and C5 were AP with severe airflow obstruction but differences in age of onset, atopic status and use of oral corticosteroids.

In 2014, Newby et al.⁵ have performed cluster analysis of 349 patients from British Thoracic Society Severe Refractory Asthma Registry. They identified 5 clusters. C1 were atopic with early-onset disease, C2 were obese with late-onset of BA, C3 had the least severe disease, C4 were eosinophilic, late-onset AP, and C5 had significant fixed airflow obstruction. In Haldar, Moore and Newby's studies, smokers were excluded. However, cigarette smoking is one of the most important environmental risk factors for asthma.²⁰ Cigarette smoking is now recognized to contribute to severe asthma, aggravate asthma symptoms, accelerate decline of lung function²¹, and limit responses to corticosteroids.²² Excluding smokers would not reflect the real world.

Schatz et al.⁶ use cluster analysis in 3612 patients with severe and difficult to treat asthma (TENOR study). Smokers were included. They have identified 5 clusters. The most common cluster C1 included white female patients most likely to have adult onset, without aspirin sensitivity, who had lower total IgE levels. Other clusters were distinguished by the highest atopy, especially atopic dermatitis C2, male sex – C3, non-white race C4, and aspirin sensitivity in C5.

Cluster analysis in Portuguese population of 57 AP⁷ is similar.

Cluster 1 in our study partially corresponds

to the previously defined late-onset eosinophilic, inflammatory predominant clusters, but to some extent also with the characteristics of obese non-atopic clusters. We have observed obesity in 8 pts (20%) of the studied population. They were distributed in the clusters as follows: C1 - 4 pts, C2 - 1 pt, C3 - 1 pt, C4 - 2 pts. Perhaps the 4 patients with obesity in C1 could become part of a separate cluster after increasing the number of cases. Cluster 1 corresponds to C2 and partially to C4 of Haldar second care clusters, C3 of Moore and C2 and C4 of Newby with some differences. In our study, all C1 pts were non-atopic and in Haldar, Moore and Newby all clusters included some rate of atopic patients.

Cluster 2 appears to overlap with C3 of Haldar, C4 (difference in lung function) and C2 (difference in age of onset) of Moore. Compared with Newby data C2 mostly overlaps C3, although atopy is less presented in Newby's cluster. C2 corresponds to C2 of Schatz by atopic status and smoking history.

Cluster 3 pts demonstrated late-onset, aspirin sensitive asthma. In this cluster, 5 pts (83.3%) were represented with allergy to common aeroallergens. Depending on the case series, between 30 and 70% of the pts with aspirin-exacerbated respiratory disease (AERD) were atopic.²³⁻²⁶ Cluster 3 corresponds to C4 of Haldar and C5 of Moore, although aspirin sensitivity was not described in these studies. C3 appears to overlap with C4 and C5 of Newby. C3 is similar to a great extent to C5 of Schatz - also 100% of the pts with aspirin sensitivity and comparable characteristics and C5 of Loureiro.

Cluster 4 is the most recognisable cluster. It matches the Wenzel phenotype – early-onset, allergic asthma corresponding to Th2 endotype. C4 is also described by Haldar as C1, Moore as C1 and partially as C2, Newby as C1, Loureiro as C1 and partly as C3.

According to Wenzel, presence of the Th2 signature was associated with increased eosinophilic inflammation, expression of Th2 cytokines, and atopy.⁷ Thus, even the molecular phenotype of Th2-high asthma appears to identify a widely heterogeneous group of patients ranging from mild allergic to severe adult onset eosinophilic asthma.⁷ Therefore, we suggest that Clusters 1, 2 and 4 in our study be matched to some of Wenzel Th2 high asthma endotypes. Cluster 3 - AERD is a good example of the complex overlap between the various phenotypes of severe asthma. Peripheral blood eosinophilia occurs in approximately 50% of patients with AERD²⁷,

although not all patients with eosinophilic asthma have AERD. In addition, different rates of patients with AERD are atopic. Although the underlying pathophysiology of AERD is baseline dysregulation of arachidonic acid metabolism, agents targeting Type-2 lymphocyte inflammation may also have a role in treating nasal polyposis and AERD.²⁸⁻³⁰ Moreover, serum periostin levels (emerging biomarker of Th-2 high asthma)³¹ and FeNO did not show statistically significant differences between the clusters.

Our study is limited by the small sample size and should be tested in larger datasets. Further, the cross-sectional nature of the study does not allow us to assess the cluster stability over time. The choice of variables has been generally limited to consideration of expert opinion based on previous studies.

Discrepancies between the levels of FeNO and the data for eosinophilic inflammation, atopy and presumed Th2 inflammation may be explained with the maintenance ICS therapy and possibly different level of patient compliance to therapy. Unfortunately, we have no objective method in ambulatory practice to assess the patients' adherence to treatment, but that was not the purpose of the study.

This research advances our understanding of asthma, but clinical data is insufficient to present all the subtypes and endotypes under the umbrella of bronchial asthma. Clusters in various studies may differ due to variation in methodology, applied variables and encoding or transformation of data. More variables are needed (mostly genetic, molecular and inflammatory biomarkers) for identification of those phenotypes, which could give us information about the underlying pathogenesis of this heterogeneous disease.

Future challenges for the clustering methodologies include development of standardized approach that will allow to use phenotyping in daily routine practice.

CONCLUSIONS

Our study is the first in Bulgaria in which cluster analysis is applied to asthmatic patients. We identified four clusters. The variables with greatest force for differentiation in our study were: age of asthma onset, duration of diseases, atopy, smoking, blood eosinophils, nonsteroidal anti-inflammatory drugs hypersensitivity, baseline FEV1/FVC and symptoms severity. Our results support the concept of heterogeneity of bronchial asthma and demonstrate that cluster analysis can be a useful tool for phenotyping of disease and personalized approach to

the treatment of patients.

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Фенотипы, установленные методом кластерного анализа при бронхиальной астме в умеренной и тяжёлой форме

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Введение: Бронхиальная астма является гетерогенным заболеванием, включающим в себя различные подтипы. У них могут проявляться сходные клинические характеристики, но вероятно имеют различные патологические механизмы.

Цель: Идентификация фенотипов с применением кластерного анализа в случаях бронхиальной астмы в умеренной и тяжёлой форме и сравнение различий в клинических, физиологических, иммунологических и воспалительных результатах между кластерами.

Пациенты и методы: В исследовании приняли участие сорок взрослых пациентов с бронхиальной астмой умеренной и тяжёлой формы в неострой фазе. Все они прошли клиническую оценку, антропометрические измерения, накожные пробы, стандартную спирометрию и измерение фракционного выдыхаемого оксида азота. Было исследовано количество эозинофилов в крови, общий сывороточный IgE и уровни периостина. Были использованы двухшаговая кластеризация, метод иерархической кластеризации и анализ К-средних для идентификации кластеров.

Результаты: Нами была проведена идентификация четырёх кластеров. Кластер 1 (n=14) - неатопическая астма с поздним началом и нарушением функции лёгких. Кластер 2 (n=13) – atopическая астма с поздним началом. Кластер 3 (n=6) – эозинофильная астма с поздним началом и чувствительностью к аспирину. Кластер 4 (n=7) - atopическая астма с ранним началом.

Заключение: Наше исследование является первым в Болгарии с применением кластерного анализа в отношении пациентов с астмой. Нами была проведена идентификация четырёх кластеров. Наиболее весомыми переменными для дифференциации в нашем исследовании являются: возраст пациента при возникновении астмы, длительность заболевания, атопия, курение, эозинофилы в крови, чувствительность к нестероидным противовоспалительным средствам, ОФВ 1/ФЖЕЛ исходного уровня и тяжесть симптомов. Наши результаты подтверждают идею о гетерогенности бронхиальной астмы и показывают, что кластерный анализ может стать полезным инструментом для фенотипирования заболевания и индивидуальным подходом к лечению пациентов.