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КЛАСТЕРНЫЙ АНАЛИЗ В ФЕНОТИПИРОВАНИИ ПАЦИЕНТОВ С ТЯЖЕЛОЙ БРОНХИАЛЬНОЙ АСТМОЙ

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Cluster Analysis in Phenotyping Patients with Severe Bronchial Asthma

Резюме

Один из десяти пациентов с бронхиальной астмой имеет тяжелую астму, которая характеризуется наличием нескольких клинических фенотипов. **Цель исследования** — идентификация клинических фенотипов пациентов с трудноконтролируемой и тяжелой БА на основе кластерного анализа. **Материалы и методы.** Проведено поперечное исследование с включением 200 пациентов с трудноконтролируемой БА. Критерии включения в исследование: тяжелая и трудноконтролируемая БА, все пациенты получали лечение согласно 4-5-й ступени согласно рекомендациям GINA; возраст старше 18 лет. Критерии исключения: наличие хронической обструктивной болезни легких, активное инфекционное заболевание, в том числе инфекции респираторной системы, онкологические заболевания, беременность. Всем пациентам проводились клинико-лабораторные исследования, а также исследовались уровни лептина, адипонектина, IL-6, IL-8, IL-4 и ФНО-α. С целью фенотипирования пациентов БА тяжелого течения был проведен кластерный анализ. Статистическую обработку данных проводили с помощью программ SPSS Statistics 20.0 и StatTech v. 4.7.2 (ООО «Статтех», Россия). **Результаты.** В исследовании было включено 200 пациентов, имеющих трудноконтролируемую БА, медиана возраста участников исследования составила 53,5 (39,0-59,25) лет. В результате кластерного анализа, выполненного методом k-средних, выделено 3 кластера. Были получены значимые различия в ИМТ, уровне эозинофилии и IgE, а также лептина (p <0,001 при сравнении 3 кластеров). Также установлены различия в уровнях провоспалительных цитокинов, в первую очередь IL-4 (p=0,003 для 3 кластеров) и ФНО-α и IL-8 (p <0,001 при сравнении 3 кластеров). Установлено, что развитие гиперэозинофилии у пациентов с трудноконтролируемой БА может быть опосредовано не только уровнем ИЛ-4 (1,326, 95 %ДИ 1,132-1,554), но и ФНО-α (ОШ 1,046, 95 %ДИ 1,022-1,07) и ИЛ-8 (ОШ 1,054, 95 %ДИ 1,024-1,085). **Заключение.** Нами идентифицировано 3 кластера пациентов с трудно-контролируемой бронхиальной астмой на основе изучения клинико-лабораторных и инструментальных данных. Каждый идентифицированный кластер характеризуется специфической комбинацией лабораторных маркеров, что может учитываться при дальнейшем лечении пациентов с данным фенотипом астмы.

Ключевые слова: *бронхиальная астма, кластерный анализ, цитокины, лептин, эозинофил*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Соответствие принципам этики

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Abstract

One in 10 patients with asthma suffers from severe asthma, which is characterized by the presence of several clinical phenotypes. **The aim of the study** is to identify the clinical phenotypes of patients with difficult-to-control and severe asthma based on cluster analysis. **Materials and Methods:** A cross-sectional study was conducted, including 200 patients with difficult-to-control asthma. Inclusion criteria: severe and difficult-to-control asthma, all patients received treatment according to the 4th-5th step of the provided guidelines (GINA); age over 18 years. Exclusion criteria: the presence of chronic obstructive pulmonary disease, active infectious diseases, including respiratory infections, oncological diseases, pregnancy. All patients underwent clinical and laboratory tests, and levels of leptin, adiponectin, IL-6, IL-8, IL-4, and TNF-α were measured. To phenotype patients with severe asthma, cluster analysis was performed. Statistical data processing was conducted using SPSS Statistics 20.0 and StatTech v. 4.7.2 (StatTech, Russia). **Results:** The study included 200 patients with difficult-to-control asthma, with a median age of 53.5 (39.0-59.25) years. As a result of the cluster analysis using the k-means method, 3 clusters were identified. Significant differences were found in BMI, eosinophil count, IgE levels, and leptin ($p<0.001$ when comparing the 3 clusters). Differences were also found in the levels of pro-inflammatory cytokines, primarily IL-4 ($p=0.003$ for the 3 clusters), TNF-α, and IL-8 ($p<0.001$ when comparing the 3 clusters). It was established that the development of hyper-eosinophilia in patients with difficult-to-control asthma may be mediated not only by the IL-4 level (1.326, 95 % CI 1.132-1.554), but also by TNF-α (OR 1.046, 95 % CI 1.022-1.07) and IL-8 (OR 1.054, 95 % CI 1.024-1.085). **Conclusion:** We identified 3 clusters of patients with difficult-to-control bronchial asthma based on the study of clinical, laboratory, and instrumental data. Each identified cluster is characterized by a specific combination of laboratory markers, which can be taken into account when further treating patients with this asthma phenotype.

Key words: *bronchial asthma, cluster analysis, cytokines, leptin, eosinophils*

Conflict of interests

The authors state that this work, its theme, subject and content do not affect competing interests

Sources of funding

The authors declare no funding for this study

Conformity with the principles of ethics

The study was approved by the Local Ethics Committee of Semey Medical University, Kazakhstan (extract from the protocol No. 11. September 27, 2017). Informed consent was obtained from all subjects participating in the study. Written informed consent was also obtained from patients for the publication of this article

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IL — interleukin; BMI — body mass index; WC — waist circumference; SBP — systolic blood pressure; DBP — diastolic blood pressure; FEV1 — forced expiratory volume per 1 second; FVC — forced vital capacity; TNF-α — tumor necrosis factor α; PEF — peak expiratory flow

Introduction

Asthma is a heterogenous disease associated with the chronic inflammation of the respiratory tract [1]; it is one of the most common chronic non-infectious diseases. Based on the results of large-scale epidemiological reports, its global prevalence is approximately 262 million cases [2]. With that, one of ten such patients has uncontrollable asthma despite the treatment with inhalation corticosteroids combined with one or several bronchodilators [3].

The approach recommended by GINA experts (phenotyping asthma patients) is based on the determination of associations between the specific asthma phenotype and patterns of its efficient treatment. Severe asthma (uncontrollable asthma subgroup) is one of those phenotypes. Studies arranged over the past decades have demonstrated that some of those patients have a Th2-mediated asthma endotype [4] based on hypereosinophilia with increased production of interleukins (IL) 4, 5, and 13 [5]. At the same time, the existing data confirm the non-uniform clinical patterns of patients with uncontrollable and severe asthma, while the TENOR II study demonstrated no difference in eosinophilia levels between patients with controlled and uncontrollable asthma [6]. Thus, the approach based on just assessing atopy markers is not sufficient for the efficient management of patients with the severe or uncontrollable asthma phenotype — the physician should also assess clinical and laboratory features of patients.

Our study **was aimed at** identifying clinical phenotypes of patients with uncontrollable asthma based on a cluster analysis.

Materials and Methods

We arranged a cross-sectional study that enrolled 200 patients with uncontrollable asthma. Patients were hospitalized into the inpatient department with the symptoms of exacerbation from January 2019 until January 2022. The study inclusion criteria were severe and uncontrollable asthma diagnosed based on international GINA criteria, with all patients administered treatment according to Steps 4–5 of the aforementioned guidelines; age over 18 years. Exclusion criteria: chronic obstructive pulmonary disease; active infectious diseases, including respiratory infections; malignancies; pregnancy. All patients underwent laboratory tests (including complete blood count and sputum analysis, biochemistry panel with lipid and carbohydrate metabolism parameters). Leptin, adiponectin (i.e. adipokine status markers), IL-6, IL-8, IL-4, and TNF-α levels were analyzed using available commercial kits for immunoassays according to the official instructions of manufacturers. Pulmonary function tests were also arranged in all patients using the BTL-08 Spiro Pro (UK) device; the final analysis included only results of tests conducted according to American Thoracic Society and European Respiratory Society guidelines [7].

All patients signed the informed consent. The study was approved by the Local Ethics Committee of NAO Medical University Semei (Decision No. 11 dated September 27, 2017).

Statistical Analysis

Data were statistically processed using the SPSS Statistics 20.0 and StatTech v. 4.7.2 (StatTech LLC, Russia) software. Quantitative parameters were analyzed concerning the normal distribution using the Kolmogorov–Smirnov test. Normally distributed quantitative parameters were described using mean arithmetics (M) and standard deviations (SD), 95 % confidence interval (95 % CI) limits; the Student test for independent samples was used for comparison. In cases of non-normal distribution, quantitative data were described using medians (Me), lower and upper quartiles (Q1–Q3). Two groups were compared by non-normally distributed quantitative parameters using the Mann–Whitney U-test. Categorical data were described using absolute values and percentages; the Pearson χ^2 test was used to detect associations between nominal variables. Differences between the compared variables were significant at $p < 0.05$.

Cluster Analysis

The cluster analysis was arranged for phenotyping patients with severe asthma. During the first step, a hierarchic classification with the tree diagram construction using the Ward's method and the squared Euclidean distance assessment was arranged to determine the number of compared groups. The subsequent Step 2 of the classification presumed the k-mean method with the inclusion of the given amount of clusters determined using the hierarchic cluster approach. The Euclidean distance served as a measure of distance when determining both intra- and intercluster associations. The cluster analysis groups (over 2 non-associated samples) were compared using the Kruskall–Wallis test with subsequent post-hoc Bonferroni adjustment.

Results

General patient characteristics

200 patients with uncontrollable asthma were enrolled into the study; the median age of subjects was 53.5 (39.0–59.25) years, with the minimum and maximum ages of 19 and 68 years, respectively. Among patients, 80 (40 %) were males, 120 (60 %) — females; the age of males was 55 (38.75–61.0) years, that of females — 52.0 (39.75–58.0), $p = 0.354$. Clinical and functional characteristics of subjects are presented in Table 1. Based on the data obtained, among all patients with uncontrollable asthma BMI was 27.05 (23.1–28.42) kg/m^2; serum IgE levels was 107 (85.75–150.0) kU/L, FEV1 was 58.0 (55.0–65.25) %.

Cluster Analysis

During this analytical step, the hierarchic cluster analysis was arranged to verify patient phenotypes based on the isolation of occult group signs. As a result, a tree diagram was constructed that helped to visually detect 3 evident trends among all parameters (17 variables; Figure 1).

3 clusters obtained had specific differences in key aspects of severe and uncontrollable asthma. Thus, significant differences were reported for BMI ($p < 0.001$ when comparing 3 clusters) — patients from Clusters 1 and 3 had BMI corresponding to overweight, while Cluster 2 patients had normal BMI levels ($p < 0.001$ for 3 groups). Besides, Clusters 2 and 3 had higher eosinophilia levels in peripheral blood, while the IgE level over the limits of normal was reported only in Cluster 2 ($p = 0.03$ for 3 clusters) (Table 2).

The **first cluster** included 67 patients with uncontrollable asthma. This patient cohort was characterized by older age and predominantly females. 85.1 % patients also had high BMI levels (Me 28.2 kg/m^2)

Table 1. *General Clinical Characteristics of Patients*

Criterion	All patients	Men, (n=80)	Women, (n=120)	p
Age, years	53,5 (39-59,25)	55 (38,75-61,0)	52,0 (39,75-58,0)	0,354[b]
Height, cm	164,6±7,68 (163,53-165,67)	168,54± 8,04 (166,75-170,33)	161,97 ± 6,20 (160,85-163,1)	< 0,001[a]
Weight, kg	78 (67,75-85,0)	80 (74,25-88,0)	74,5 (63,0-85,0)	< 0,001[b]
BMI, kg/m^2	27,05 (23,1-28,42)	27,05 (24,1-28,4)	27,1 (22,38-28,5)	0,720[b]
Waist Circumference, см	92,5 (85,0-98,0)	94,68±11,46 (89,95-99,41)	90,96±11,54 (87,05-94,86)	0,219[b]
Office SBP, mm Hg.	130 (120-140)	130 (120-140)	130 (140-140)	0,885[b]
Office DBP, mm Hg	80 (80-90)	80 (80-90)	80 (80-90)	0,709[b]
Eophinophils, %	7 (3,0-9,0)	7 (3,0-9,0)	7 (3,75-9,0)	0,693[b]
Blood glucose, mmol/L	6,0 (5,1-6,8)	5,9 (5,0-6,6)	6,0 (5,17-6,93)	0,257[b]
Total cholesterol, mmol/L	5,2 (3,3-5,9)	5,15 (3,27-5,9)	5,25 (3,3-5,9)	0,671[b]
Adiponectin, ng/mL	17,14 (14,28-31,0)	18,85 (14,76-33,93)	16,65 (14,17-28,88)	0,404[b]
Leptin, ng/mL	15,24 (5,42-21,67)	14,64 (5,56-50,1)	15,29 (5,28-22,33)	0,448[b]
Ig E, kU/L	107 (85,75-150,0)	108,0 (86,75-157,75)	105,0 (85,0-147,0)	0,661[b]
FEV1, %	58,0 (55,0-65,25)	58,0 (55,0-65,0)	60,0 (55,0-68,0)	0,220[b]
FVC, %	62,0 (60,0-70,0)	62,0 (58,0-70,0)	63,5 (60,0-70,5)	0,206[b]
TNF-α, ng/mL	34,07 (12,99-56,34)	16,79 (12,52-56,75)	35,77 (13,55-56,33)	0,495[b]
IL-8, ng/mL	59,29 (42,36-65,36)	59,94 (45,37-64,35)	58,51 (40,14-65,81)	0,703[b]
IL-6, ng/mL	8,34 (4,35-12,05)	8,48±4,88 (7,39-9,56)	8,2±4,54 (7,38-9,02)	0,68[a]
IL-4, ng/mL	10,22 (9,93-10,31)	10,22 (9,32-10,22)	10,22 (10,22-10,71)	0,709[b]

Note:
a — Parametric criteria: Student's criterion, M±SD (mean ± standard deviation);
b — Non-parametric criteria: Mann-Whitney U-test, Me(IQR), Q1-Q3

corresponding to overweight. Clinically patients were characterized by more significant obstructive respiratory patterns based on the pulmonary function tests (FVC 60.0 % (55.0–62.0), FEV1 55 % (48.0–57.0)). More severe lipid metabolism disorders with the highest leptin levels (19.18 ng/mL (14.52–22.64)) among all patients enrolled in the study were typical for patients from this cluster. At the same time, eosinophilia absence (2 (1–3)), and cytokine profile levels (mainly TNF-α and IL-4) corresponded to minimum values. Thus, this cluster was characterized by the "metabolic" type of clinical & laboratory alterations.

Cluster 2 was the smallest one and included only 34 patients. These were young (Me age 38.5 years) patients with normal BMI. This cluster was characterized by high IgE (145.5 kU/mL) levels and hypereosinophilia in peripheral blood (Me 9 % (7–11)). This cluster was also characterized by moderately altered pulmonary ventilation (with Me FVC 72.0 %). Leptin levels were minimum. At the same time TNF-α (53.05 ng/mL (15.6–62.41)) and IL-4 (10.22 ng/mL (10.22–14.02)) were the highest among the general patient cohort (n = 200), which determined a more significant level of patient hypersensitization ("allergic" type of laboratory & instrumental alterations).

Cluster 3 was the most numerous one, enrolling 99 patients. Two thirds of patients in this group were females, with 55.6 % patients having a metabolic syndrome. This cluster was characterized by moderate hypereosinophilia (7 % (5–9)) and normal IgE levels. Clinically patients had significantly impaired pulmonary ventilation with Me FVC 64.0 %, as well as increased pro-inflammatory cytokine leves (especially IL-8 and TNF-α). This cluster was characterized by an "intermediate" type of disorders corresponding to Clusters 1 and 2.

Accounting for the established differences in pro-inflammatory cytokine levels, primarily IL-4 and TNF-α among Cluster 1 and 2 patients, as well their moderate increases in Cluster 3 patients combined with moderate hypereosinophilia, we arranged a binary regression analysis evaluating an association of hypereosinophilia

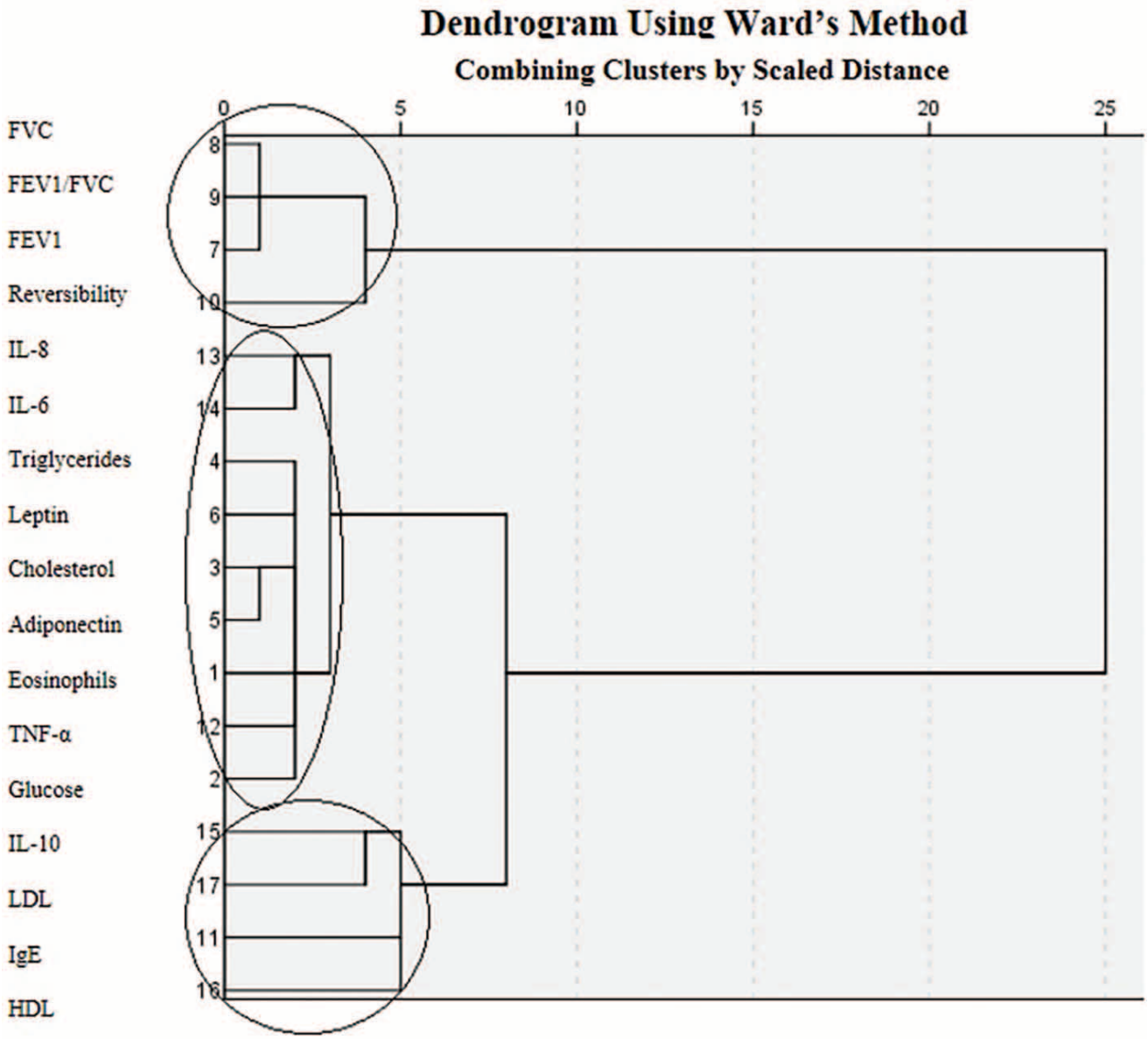

Figure 1. *Dendrogram showing three main trends in the studied parameters*

with the aforementioned pro-inflammatory cytokines (Figure 2). Thus, we have demonstrated that hypereosinophilic response in patients with asthma may be mediated not only by IL-4, but also TNF-α and IL-8 levels.

Discussion

The clinical approach to the classification of patients with severe or uncontrollable asthma has dominated recently in literature. Thus, the following patient cohorts were defined: childhood-onset asthma, allergic asthma with or without eosinophilia, asthma in patients with obesity, and asthma in smokers [8–11]. Later the results of classification for this patient category were presented based on the cluster analysis; according to one of those, 2 patient phenotypes were identified — the first class with eosinophilic asthma characterized by later symptom manifestation, combination with rhinosinusitis, and frequent exacerbations, and the second class with non-eosinophilic inflammation, typical early onset, commonly detected in patients with obesity [12,13]. Thus, 2 main asthma endotypes were formed [4]. Besides, the possibility of combination of several phenotypes in one patient, as well as their transformation during the disease course have been proven extensively [14].

Our study is characterized by a specific concordance of results with articles published earlier [9,13,15]. Thus, we also identified two evident immune reaction variants in patients with uncontrollable asthma. However, another (intermediate) phenotype was determined during the cluster analysis described. A study published

Table 2. *Characteristics of patients in the 3 clusters*

Parameter	Cluster 1, n=67	Cluster 2, n=34	Cluster 3, n=99	p
Age, years	56 (42,5-61,0)	38,5 (32,5-51,0)	55,0 (44,0-60,0)	<0,001*
Sex:				
Male	32 (47,8 %)	15 (44,1 %)	33 (33,3 %)	0,153**
Female	35 (52,2 %)	19 (55,9 %)	66 (66,7 %)	
MS, %	57 (85,1 %)	0 (0 %)	55 (55,6 %)	<0,001**
BMI, kg/m2	28,2 (27,3-29,75)	21,25 (20,12-22,3)	26,4 (23,11-28,35)	<0,001*
Eosinophils, %	2 (1-3)	9 (7-11)	7 (5-9)	<0,001*
Adiponectin, ng/ml	15,6 (14,4-19,45)	32,47 (23,3-54,3)	16,61 (13,05-28,4)	<0,001*
Leptin, ng/ml	19,18 (14,52-22,64)	4,53 (3,2-6,5)	15,26 (5,52-22,3)	<0,001*
AST test	10 (9-12)	15 (12-16)	12 (10-14)	<0,001*
FEV1, %	55 (48,0-57,0)	68,5 (65,0-71,5)	61,0 (55-66)	<0,001*
FVC, %	60,0 (55,0-62,0)	72,0 (68,0-77,75)	64,0 (60,0-70,0)	<0,001*
FEV1/FVC	58,0 (52-59)	71,0 (63,5-75,0)	62,0 (58,0-68,0)	<0,001*
Pre-Sample Peak Expiratory Flow Rate	200,0 (195-220)	300,0 (300-320)	250,0 (230-280)	<0,001*
Post-Sample Peak Expiratory Flow Rate	260,0 (250-280)	380 (362,5-395)	320,0 (300-350)	<0,001*
IgE, kU/l	105,0 (101,5-115,1)	145,5 (94,5-168,7)	88 (74-102)	<0,001*
TNF-α, нг/мл	11,98 (6,42-13,57)	53,05 (15,6-62,41)	49,56 (14,57-56,41)	<0,001*
IL-8, нг/мл	63,45 (61,24-66,22)	33,46 (22,17-45,73)	58,45 (43,01-65,73)	<0,001*
IL-6, нг/мл	11,31 (9,04-12,95)	5,08 (2,09-6,15)	8 (3,79-11,6)	<0,001*
IL-4, нг/мл	9,2 (9,37-10,1)	10,22 (10,22-14,02)	10,1 (8,84-10,44)	0,03*

Note: *Kruskal-Wallis test; *Pearson's chi-square test; quantitative variables: Median (Q1-Q3); nominal variables: number (%)

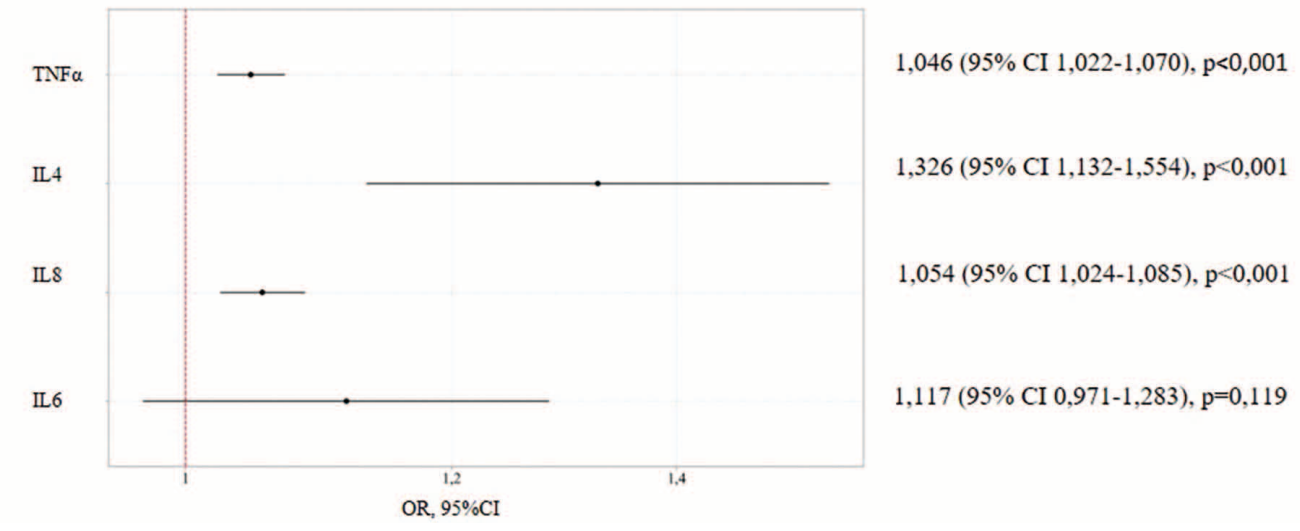

Figure 2. *Estimated odds of developing hypereosinophilia as a function of pro-inflammatory cytokine levels in patients with difficult-to-control asthma*

earlier that enrolled over 1,500 patients and was based on the discrete cluster analysis with the evaluation of specific biomarkers (IgE, eosinophil count in peripheral blood, NO fraction in exhaled air) determined 5 patient phenotypes, stressing out various endotype combinations among the clusters formed [16]. Thus, the first cluster defined by authors was mainly presented by older females with elevated BMI and rather low eosinophil counts. This cluster almost completely corresponded to the phenotype identified by us ("metabolic" Cluster 1). We also demonstrated a syndemic of asthma and metabolic syndrome typical for the cluster — that manifested as increased leptin levels among patients (Me leptin level was 19.18 ng/mL (14.52–22.64)). Besides, we additionally analyzed pro-inflammatory interleukins — those demonstrated low impact, primarily IL-4 in this cluster. Our Cluster 2 ("allergic" phenotype) had similar laboratory signs to those in the aforementioned study, i.e. increased IgE levels and hypereosinophilia. At the same time, in our study this cluster was characterized by less severe obstructive respiratory alterations, which may probably help to identify only several features of Clusters 4 and 5 in it [16]. Cluster 3 ("intermediate" phenotype) included overweight patients with a slight predominance of females, moderate hypereosinophilia, and increased IgE levels — this fact helped to identify Cluster 4 features in it. This aspect significantly expands our understanding of pathogenetic associations in severe and uncontrollable asthma, in particular in the context of target biological therapy.

However, this is not the only study that evaluated biomarkers among patients with asthma. Thus, an article recently published by Japanese authors defined 3 clusters of patients with asthma [17]. The following 3 patient phenotypes were analyzed: Cluster 1 with late onset and low-granulocytic blood type; Cluster 2 with obesity and neutrophilia; Cluster 3 with early disease onset, atopy, and eosinophilia. Besides, authors tried to identify all three clusters after dividing patients into 2 groups (> 65 and < 65 years), thus demonstrating not only the clinical asthma phenotype, but also the risk of asthma exacerbations among 3 established clusters with their age associations.

One of the factors reflecting pathogenetic mechanisms of severe asthma is the cytokine patient status. Several cytokines with very important roles in asthma pathogenesis have been identified. Thus, Th2 asthma is associated with the enhanced production of IL-5, IL-4, and IL-13 produced by these cells [18]. IL-5 promotes hypereosinophilia maintenance in lungs, including its increased levels in the sputum [19]. On the other hand, non-Th2 asthma is mainly caused by neutrophilic inflammation, which mechanisms are still not clear [11]. Neutrophilia detected in this asthma endotype may be also mediated by the administration of corticosteroids, but on the other hand it may act as a factor of treatment resistance. Tumor necrosis factor α (TNF-α) is one of the cytokines playing a role in non-Th2 asthma. TNF-α interacts with IL-17, enhances neutrophilic migration, and also stimulates the production of IL-4, IL-5, and IL-13 [18,20]. Thus, TNF-α may be considered one of the key factors in severe and uncontrollable asthma. In our study the increased levels of this cytokine were detected among Cluster 2 and (to a lesser extent) Cluster 3 patients. Its increased levels among Cluster 2 patients ("allergic variant") was also combined with higher IL-4 levels. Besides, IL-8, an active neutrophil chemoattractant, was also analyzed in our study. Several studies have demonstrated that specifically IL-8 analyzed in blood and respiratory secretions is a key factor of neutrophilic inflammation in patients with severe asthma [21, 22]. Besides, IL-8 may be probably considered a predictor of response to the future corticosteroid therapy [23]. We also demonstrated that the increased level of this cytokine was associated with severe asthma phenotypes, with its largest values observed among Cluster 1 patients having more significant metabolic disorders.

Conclusion

Thus, the analysis presented demonstrated a pathophysiological non-uniformity of patients with uncontrollable and severe asthma, manifesting as several phenotypes. This fact underscores the need for personalized approach to the patient management, which is especially important when recommending biological therapy in asthma patients. Thus, the approach based on the analysis of only threshold levels of specific laboratory parameters is not suitable in this variable patient category. At the same time, the strategy based on the combined analysis of pro-inflammatory markers with the adipokine status assessment using three clusters presented by us may form the basis for the personified treatment strategy in patients with uncontrollable and severe asthma.

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