DOI: https://doi.org/10.36691/RJA14874

Характеристика предикторов тяжёлого течения различных фенотипов Т2-эндотипа бронхиальной астмы

М.Р. Хакимова, А.Р. Валеева, Н.Ш. Курмаева, О.В. Скороходкина

Казанский государственный медицинский университет, Казань, Российская Федерация

АННОТАЦИЯ

Обоснование. Согласно эпидемиологическим данным, тяжёлая бронхиальная астма отмечается у 5–10% пациентов и представляет собой значимое социально-экономическое бремя для системы здравоохранения.

Цель — провести сравнительный анализ клинических особенностей аллергического и неаллергического фенотипов Т2-эндотипа бронхиальной астмы и определить наиболее значимые предикторы тяжёлого течения заболевания.

Материалы и методы. Обследовано 150 больных бронхиальной астмой в возрасте от 18 до 65 лет, из них в исследование включён 61 пациент с Т2-эндотипом заболевания. Диагноз бронхиальной астмы устанавливался на основе общеклинических и аллергологических методов исследования. В качестве предикторов тяжёлого течения заболевания рассматривались фенотип бронхиальной астмы, пол, возраст (в том числе пожилой), общее количество дневных/ночных симптомов в неделю, количество обострений, требующих назначения системных глюкокортикостероидов и госпитализаций, объём форсированного выдоха за первую секунду ($ОФВ_1$, процент от должных величин), индекс массы тела (кг/м^2), наличие сопутствующей патологии, курение, сенсибилизация к неинфекционным аллергенам, абсолютное количество эозинофилов периферической крови.

Результаты. Сформированы 2 группы: пациенты с аллергическим (*n*=34; группа 1) и неаллергическим (*n*=27; группа 2) фенотипом Т2-эндотипа бронхиальной астмы. Проведённый однофакторный анализ показал, что у пациентов группы 2 шанс более тяжёлого течения был в среднем в 3,14 [95% ДИ 1,09–9,58] раза выше, чем в группе 1. Независимо от фенотипа бронхиальной астмы, увеличение общего числа дневных/ночных симптомов в неделю, числа требующих назначения системных глюкокортикостероидов обострений, числа госпитализаций из-за обострений было статистически значимо ассоциировано с более тяжёлой степенью бронхиальной астмы в среднем в 1,05 [95% ДИ 1,01–1,11], 1,21 [95% ДИ 1,05–1,45], 3,46 [95% ДИ 1,68–10,19] и 4 [95% ДИ 1,75–12,32] раза соответственно. Снижение $ОФВ_1$ являлось статистически значимым предиктором более тяжёлого течения бронхиальной астмы (ОШ 0,96 [95% ДИ 0,93–0,99]). Многофакторный анализ выявил, что только возраст пациента на момент осмотра, увеличение числа ночных симптомов и низкое значение $ОФВ_1$ ассоциированы с тяжёлым течением бронхиальной астмы.

Заключение. Аллергический и неаллергический фенотипы Т2-эндотипа бронхиальной астмы имеют определённые клинические различия, которые возможно определить на этапе анализа клинико-анамнестических данных.

Ключевые слова: бронхиальная астма; фенотипы; тяжёлая бронхиальная астма; предикторы.

Как цитировать:
Хакимова М.Р., Валеева А.Р., Курмаева Н.Ш., Скороходкина О.В. Характеристика предикторов тяжёлого течения различных фенотипов Т2-эндотипа бронхиальной астмы // *Российский аллергологический журнал*. 2023. Т. 20, № 3. С. 263–274. DOI: https://doi.org/10.36691/RJA14874

Рукопись получена: 24.07.2023 **Рукопись одобрена:** 05.09.2023 **Опубликована:** 25.09.2023

DOI: https://doi.org/10.36691/RJA14874

Severity predictors of different phenotypes of T2 asthma endotype

Milyausha R. Khakimova, Alina R. Valeeva, Naira Sh. Kurmaeva, Olesya V. Skorokhodkina

Kazan State Medical University, Kazan, Russian Federation

ABSTRACT

BACKGROUND: Epidemiological studies have showed that severe asthma is observed in 5–10% of patients. It is considered as a major social and economic burden for the healthcare system.

AIM: to perform a comparative analysis of clinical features of allergic and non-allergic phenotypes of T2 asthma and determine the most important predictors of severity.

MATERIALS AND METHODS: We studied 150 patients with asthma (ages 18–65). Of these, 61 were diagnosed with T2 endotype of asthma. Clinical examination and allergy testing were performed. The potential predictors of severe asthma included: asthma phenotype, gender, age (including elderly age), daytime/nocturnal symptoms per week, asthma exacerbations that required systemic corticosteroid therapy and hospitalisations, the volume of forced exhalation in the first second (FEV_1; % of predicted value), body mass index (kg/m^2), concomitant diseases, smoking status, sensitization to non-infectious allergens and blood eosinophil count.

RESULTS: Group 1 included 34 patients with allergic phenotype of asthma, group 2 — 27 patients with non-allergic phenotype of T2 endotype of asthma. Univariate analyses revealed that subjects with non-allergic asthma were likely to have severe asthma (OR=3.14 [95% CI: 1.09–9.58]. Increased daytime symptoms per week, nocturnal symptoms per week, exacerbations that require systemic corticosteroids and hospitalisation were associated with asthma severity (OR=1.05 [95% CI: 1.01–1.11], 1.21 [95% CI: 1.05–1.45], 3.46 [95% CI: 1.68–10.19], 4 [95% CI: 1.75–12.32] and 4 [95% CI: 1.75–12.32], respectively), regardless of the disease phenotype. Lower FEV_1 was associated with severe asthma (OR=0.96 [95% CI: 0.93–0.99]. Multivariate analysis showed that age, increased frequency of nocturnal symptoms, and lower FEV_1 were associated with severe asthma.

CONCLUSION: The certain clinical differences of allergic and non-allergic asthma could be revealed when analyzing anamnestic data and clinical findings. Increased frequency of nocturnal symptoms, decreased FEV_1 and age are the most significant predictors of severe T2 endotype of asthma.

Keywords: asthma; phenotypes; severe asthma; predictors.

To cite this article:
Khakimova MR, Valeeva AR, Kurmaev NSh, Skorokhodkina OV. Severity predictors of different phenotypes of T2 asthma endotype. *Russian Journal of Allergy.* 2023;20(3):263–274. DOI: https://doi.org/10.36691/RJA14874

Received: 24.07.2023 **Accepted:** 05.09.2023 **Published:** 25.09.2023

BACKGROUND

Asthma is a heterogeneous disease pathogenetically based on chronic airway inflammation [1]. Asthma endotypes are classified into two depending on the inflammation type: T2 endotype with eosinophilic inflammation development and non-T2 endotype with neutrophilic or paucigranulocytic inflammation development [2]. Asthma endotype is a disease subtype that has various phenotypes. Further, 50–80% of asthma patients have T2 endotype [3], particularly patients with severe asthma. The current Russian clinical guidelines consider severe asthma as a separate asthma phenotype. Severe asthma remains uncontrolled despite patient adherence to optimized therapy and treatment of concomitant pathologies, and high doses of corticosteroids (CS) are required to control the disease [2].

Epidemiological studies have indicated that severe asthma is observed in 5%–10% of asthma patients. However, severe asthma is the most critical socioeconomic burden for healthcare systems worldwide. Approximately 50% of the funds intended for treating asthma are generally spent on severe asthma treatment [4, 5]. Nagase et al. [6] have shown that medical expenses for the treatment of patients with severe uncontrolled asthma per year in Japan averaged US $8.346, which was significantly higher than in groups of patients with mild and moderate asthma. Furthermore, treatment costs for patients with uncontrolled severe asthma in Mexico were significantly higher compared with the treatment costs for patients with controlled asthma, with each exacerbation increasing costs by US $350 [7]. In Russia, the economic cost of asthma treatment is 13.7 billion rubles/year. This cost is associated with exacerbation treatment, accounting for the largest share of the cost to patients themselves [8].

Factors increasing the risk of asthma exacerbations have been identified: the lack of asthma control; the lack of adherence to prescribed therapy; decrease in forced expiratory volume in the first second (FEV_1 <60% of the project values); smoking; contact with trigger allergens; sputum and peripheral blood eosinophilia; one or more exacerbations over the past year; and concomitant diseases, such as rhinosinusitis, obesity, food allergies, and gastroesophageal reflux disease [2]. However, studies that aimed at identifying predictors of severe asthma are limited. Indicators, such as gender [9], old age [10], increased nitric oxide concentration in exhaled air, and absolute number of eosinophils in peripheral blood, can be predictors of severe asthma [11]. The identification of predictors of severe asthma will help clinical practitioners to timely determine the phenotype of severe asthma in a particular patient and make a personalized approach to the treatment strategy. Thus, research in this area remains relevant.

Therefore, this **study aimed** to conduct a comparative analysis of the clinical features of allergic and nonallergic phenotypes of T2-endotype asthma and determine predictors of severe asthma.

MATERIALS AND METHODS

Study design

An observational single-center cross-sectional case-control study was conducted.

Eligibility criteria

Inclusion criteria: patient aged 18–65 years; established clinical diagnosis of allergic or nonallergic phenotypes of T2-endotype asthma.

Exclusion criteria: allergen immunotherapy and/or biological therapy at the time of examination; medical records of these treatments received before the study.

Conditions

General clinical and allergological assessment was performed in the Republican Center for Clinical Immunology of the Republican Clinical Hospital of the Ministry of Health of the Republic of Tatarstan, Kazan.

Study duration

The study occurred from November 2019 to August 2022.

Description of medical intervention

We examined 150 patients with asthma aged 18–65 years, including 61 patients with T2-endotype asthma who enrolled in the study.

Asthma was diagnosed based on the diagnostic algorithm presented in the current clinical guidelines.

Examination included general clinical methods (general blood count with white blood cell differential and eosinophil count; spirometry with a bronchodilator test), specific allergy diagnostic methods (patient's allergy history, skin prick tests with inhalant allergens), and enzyme immunoassay to monitor total and specific IgE levels. Asthma control was assessed using the Asthma Control Test (ACT).

Main study outcomes

The study analyzed clinical symptoms and features of asthma in patients with allergic and nonallergic phenotypes of T2-endotype asthma and identified predictors of severe asthma based on the developed prognostic model.

Additional study outcomes

There were no additional study outcomes.

Subgroup analysis

Following general clinical and allergological examination, the patients were divided into two groups: group 1, 34 patients with allergic asthma phenotype, and group 2, 27 patients with nonallergic phenotype of T2-endotype asthma. Subsequently, clinical and laboratory data were analyzed, and a prognostic model of severe asthma was developed.

DOI: https://doi.org/10.36691/RJA14874

Methods for recording outcomes

To record outcomes, we developed an individual patient record, which contained data from the general clinical and specific allergological examinations.

Ethical review

The study was approved by the local ethics committee of the FSBEI HE Kazan State Medical University of the Ministry of Health of Russia (protocol no. 4; dated April 28, 2020).

Statistical analysis

Sample size was not previously calculated. Statistical analysis and visualization of the obtained data were performed using the statistical computing environment R 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) and Statistica 12.0 (StatSoft, TIBCO, USA). The normality test was conducted with the Shapiro–Wilk W-test. Descriptive analysis included calculation of median and quartiles (Me [Q_1; Q_3]) for non-normally distributed parameters. Comparative analysis was performed using the Mann–Whitney U test. p=0.05 indicated statistical significance.

Proportional odds models were used to analyze the association of asthma severity with possible predictors. Proportional odds ratio with corresponding 95% confidence intervals (95% CI) was used as an estimate of the effect size. Proportional odds models, including interactions between covariates, were utilized to establish differences in the effects of predictors on asthma severity according to asthma phenotype. The following indicators were considered as predictors of severe asthma: asthma phenotype; gender; age, including elderly age [12]; total number of daytime/nighttime symptoms per week; the number of exacerbations requiring systemic corticosteroids (CS) and hospitalizations; FEV_1 (% of the project values); body mass index (kg/m^2); concomitant pathology (allergic rhinitis, allergic conjunctivitis, rhinosinusitis with nasal polyps); hypersensitivity to nonsteroidal anti-inflammatory drugs; smoking; sensitization to the main groups of inhalant allergens; and peripheral blood eosinophil count. The association was considered statistically significant with p <0.05.

Stepwise selection (exclusion method) of variables into the multivariate prognostic model was performed using Akaike information criterion. Selected predictors were included in a proportional odds model without interactions. Multicollinearity was assessed using variance inflation factor (VIF) values. Nagelkerke's pseudo-R2, C-index, and Somers' Dxy were evaluated as model characteristics.

RESULTS

Objects (participants) of the study

The study included 61 patients aged 18–65 years with allergic and nonallergic phenotypes of T2-endotype asthma. Group 1 included 34 patients with allergic asthma, of whom 15 (44.1%) were male and 19 (55.9%) were female. The median age of group 1 was 27 [20, 43] years. Group 2 included 27 patients with nonallergic phenotype of T2-endotype asthma, of which 6 (22.2%) were male and 21 (77.8%) were female. The median age of group 2 was 53 years [39, 58]. The clinical characteristics of patients from both groups are presented in Table. 1.

Main results of the study

Our results revealed clinical and anamnestic differences between patients in two studied groups. Patients with allergic phenotype of asthma were significantly younger than those with nonallergic phenotype. The disease onset in the group with allergic phenotype was registered at an earlier age. Additionally, patients with allergic asthma were more likely to have a family history of allergic diseases and asthma (p=0.001) (Table 1).

Moreover, the groups differed in the range of comorbidities. Concomitant allergic rhinitis was diagnosed in 32 (94.1%) patients with allergic phenotype of asthma, of whom 12 patients also had allergic conjunctivitis. In turn, 11 (40.7%) patients with nonallergic asthma were diagnosed with rhinosinusitis with nasal polyps, whereas 6 patients had hypersensitivity to nonsteroidal anti-inflammatory drugs.

Allergy testing revealed sensitization to inhalant allergens in all patients with allergic asthma (Fig. 1). Monosensitization was confirmed in 11 (32.4%) patients and polysensitization in 23 (67.7%) patients (p=0.002) (Fig. 1). No allergic sensitization was found in group 2, in contrast to group 1.

In both groups, patients had high peripheral blood eosinophil count (291.8 [140.6; 516.5] and 286.0 cells/μl [170.0; 451.0], respectively), indicating eosinophilic inflammation, a characteristic of patients with T2-endotype asthma. Furthermore, high IgE in the blood serum were detected only in patients with allergic asthma phenotype (251.5 [165.2; 496.1] and 61.0 IU/ml [24.0; 84.1], respectively; p=0.0001).

Moreover, the patients in both groups had different frequencies of daytime and nighttime asthma symptoms. Patients with nonallergic phenotype had higher frequency of both daytime and nighttime asthma attacks (Table 1). However, the number of patients with exacerbations requiring the administration of systemic CS and subsequent hospitalization in the year preceding observation did not differ significantly (p=0.520). Pulmonary function tests showed significantly lower FEV_1 value (% of the project values) in patients with nonallergic phenotype of asthma than in patients with allergic phenotype of asthma. The FEV_1 median was 79.0% [62.5; 90.0] and 93.0 % [63.3; 111.0], respectively (p=0.02).

The number of patients with severe asthma was significantly higher in the group with nonallergic phenotype of T2-endotype asthma (n=13, 48.2%; p=0.039). Conversely, the number of patients with moderate asthma was higher in the group with allergic phenotype of asthma (Fig. 2).

According to clinical guidelines, anti-inflammatory therapy is crucial for asthma patients. Analysis of the

Table 1. Clinical characteristics of patients with allergic and non-allergic phenotypes of T2 endotype of asthma

Indicator	Allergic phenotype *n*=34 (%)	Nonallergic phenotype *n*=27 (%)	*p*
Sex:			
• Male, abs. (%)	15 (44.1)	6 (22.2)	-
• Female, abs. (%)	19 (55.9)	21 (77.8)	
Age, years, Me [Q_1; Q_3]	27 [20; 43]	53 [39; 58]	0.00004
Age at the time of onset of asthma, years, Me [Q_1; Q_3]	18 [9; 31]	41 [36; 50]	0.00004
Concomitant pathology (%):			
• allergic rhinitis	20 (58.8)	0 (0)	
• allergic rhinitis + allergic conjunctivitis	12 (35.3)	0 (0)	-
• chronic sinusitis with nasal polyps	0 (0)	5 (18.5)	
• chronic sinusitis with nasal polyps + hypersensitivity to NSAIDs	0 (0)	6 (22.2)	
Family history of asthma, abs. (%)	15 (44.1)	6 (22.2)	0.001
Family history of allergic diseases, abs. (%)	19 (55.9)	0 (0)	0.001
Body mass index (kg/m^2), Me [Q_1; Q_3]	23.4 [20.3; 27.1]	27.0 [23.9; 32.2]	0.0098
Total number of symptoms per week, Me [Q_1; Q_3]:			
• daytime	6.0 [1.0; 13.5]	10.5 [7,0; 20.75]	0.018
• nighttime	0 [0; 2]	3 [0; 7]	0.008
FEV_1 (% of project values), Me [Q1; Q3]	93.0 [63.3; 111.0]	79.0 [62.5; 90.0]	0.020
Number of patients who had exacerbations requiring the use of corticosteroids and were hospitalized during the previous year; abs. (%)	9 (26.5)	10 (37.0)	0.520

Note: Statistical significance of difference between groups 1 and 2 was calculated using the Mann–Whitney U test. NSAIDs: nonsteroidal anti-inflammatory drugs; FEV1: forced expiratory volume in 1 second; sCS: systemic corticosteroids.

controller therapy prescribed to the observed patients revealed that a larger number of patients with nonallergic phenotype of asthma (57.9%) received the maximum amount of drug therapy corresponding to the 4th and 5th stages of Global Initiative for Asthma owing to severe asthma. The number of patients receiving inhaled corticosteroids (iCS) in medium or high doses along with long-acting β2-agonists (LABAs) and systemic corticosteroids (sCS) or iCS along with LABAs and long-acting anticholinergics (LABAs) and sGCS was significantly higher in group 2 (*n*=5, 18.5%, versus *n*=2, 5.9%, respectively; *p*=0.001). Moreover, patients with allergic phenotype of asthma predominantly received treatment with low doses of inhaled corticosteroids/LABAs (Fig. 3).

However, in 10 (52.6%) patients in group 1 and 14 (73.7%) patients in group 2, asthma remained uncontrolled, as confirmed by ACT. Concurrently, the median in group 2 was lower than that in group 1 (7 [6; 14.5] and 18 [9.5; 23] points, respectively, *p*=0.047).

At the time of examination, 15 (44.1%) patients with allergic phenotype of asthma and 8 (29.6%) patients with nonallergic phenotype of T2-endotype asthma did not receive controller therapy (*p*=0.021), which in a significant number of cases was associated with low adherence to prescribed treatment or the fact that the diagnosis of asthma was first established during the study.

The next stage of our study was to identify predictors of severe asthma. The following parameters were considered as predictors: asthma phenotype, gender, age (including the elderly), total number of daytime symptoms per week, total number of nighttime symptoms per week, the number of exacerbations requiring the use of CS and hospitalizations, FEV_1 (% of the project values), body mass index (kg/m^2), concomitant pathology (allergic rhinitis, allergic conjunctivitis, rhinosinusitis with nasal polyps, hypersensitivity to nonsteroidal anti-inflammatory drugs), smoking, identified sensitization to the main groups of inhalant allergens, and absolute number of peripheral blood eosinophils.

A univariate analysis showed that asthma phenotype is a predictor of disease severity. For example, in patients with nonallergic phenotype of T2-endotype asthma, the chance of a more severe course was on average 3.14 [95% CI, 1.09–9.58] times higher compared to patients with allergic phenotype of asthma. Further, the identified sensitization was associated with a milder course of asthma (0.3 [95% CI, 0.1–0.85], *p*=0.026), as were concomitant diseases, such as allergic rhinitis and allergic conjunctivitis (OR, 0.29 [95% CI 0.09–0.84], *p*=0.026, and 0.16 [95% CI, 0.03–0.61], *p*=0.013, respectively). We found that an increase in patient age by each year was associated with an increase in the odds of a more severe course of asthma by an average of 1.06 times (95% CI, 1.02–1.11; *p*=0.002). Nonetheless, the older age of the patient was associated with an increase in the odds of a more severe course by 5.31 times (95% CI, 1.31–27.2; *p*=0.026). Regardless of asthma phenotype, increases in the

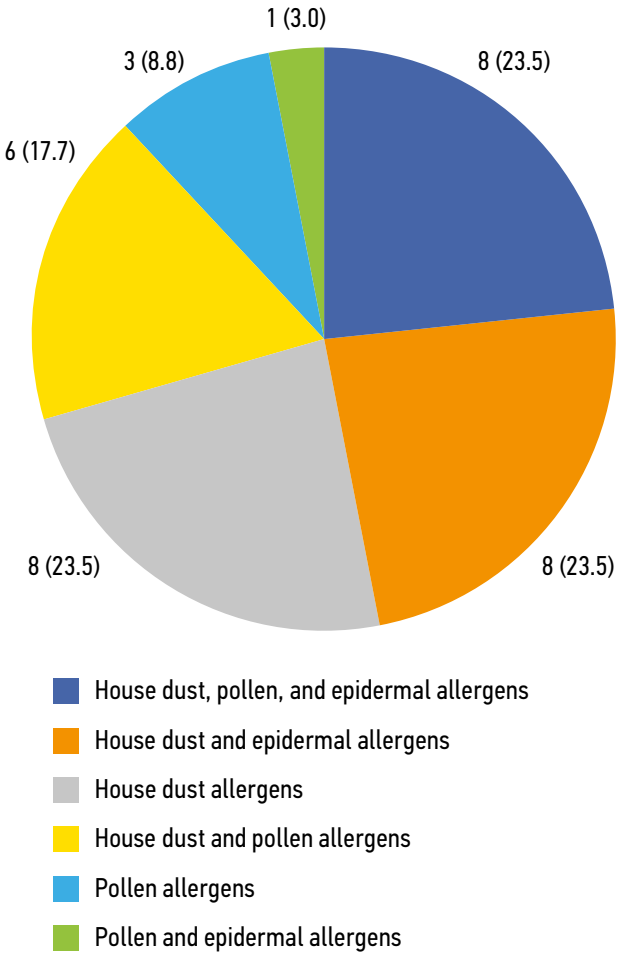

Fig. 1. Sensitization profile in patients with allergic asthma, *n* (%).

total number of daytime symptoms per week, total number of nighttime symptoms per week, number of exacerbations requiring the use of CS, and number of hospitalizations because of exacerbations were associated with more severe asthma by an average of 1.05 (95% CI, 1.01–1.11), 1.21 (95% CI, 1.05–1.45), 3.46 (95% CI, 1.68–10.19), and 4 [95% CI, 1.75–12.32] times, respectively. In addition, a decrease in FEV_1 was a predictor of a more severe disease (OR, 0.96 [95% CI, 0.93–0.99]).

Subsequently, we compiled a multifactorial model of predictors of severe asthma. This model showed that variables such as the patient's age at the time of examination, an increase in the number of nighttime symptoms, and a low FEV_1 value are associated with severe asthma (Table 2).

Adverse events

No adverse events were observed.

DISCUSSION

Summary of the main outcome of the study

We performed a comparative analysis of the clinical features of allergic and nonallergic phenotypes of T2-endotype asthma. Significant predictors of severe asthma were identified using the proportional odds model.

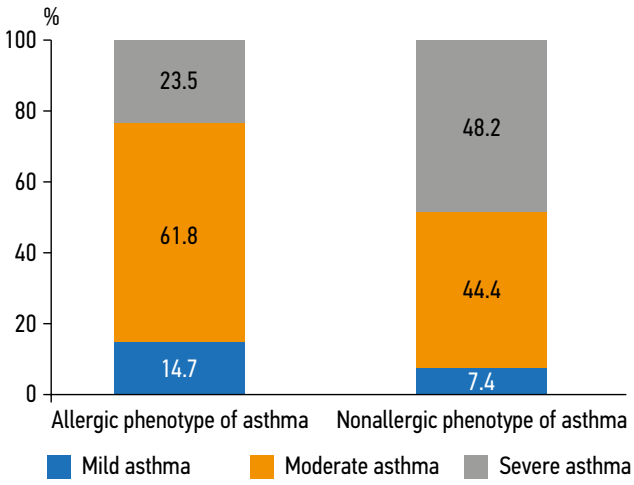

Fig. 2. Asthma severity in the studied groups.

Discussion of the main outcome of the study

Clinical and anamnestic differences were found between the allergic and nonallergic phenotypes of T2-endotype asthma. Patients with an allergic phenotype of asthma were younger at the time of disease onset compared to those with nonallergic phenotype of asthma. Similar results were reported by Pakkasela et al. [13], who in a cross-sectional study showed that patients with nonallergic phenotype of asthma were older than patients with allergic phenotype of asthma at the time of diagnosis. Additionally, only patients with allergic phenotype of asthma had a family history of atopic diseases in our study, which is consistent with literature data [14, 15].

A family history of asthma and other allergic diseases is directly linked to the development of asthma in patients [1, 16]. While the probability of asthma in a child is 25%, if one of the parents has an allergic disease, it increases to 40% in children whose parents both have allergic diseases [15]. Moreover, in patients with allergic phenotype of asthma polysensitization to inhalant allergens prevails (67.7%; p=0.002). Similar data were revealed by Burte et al. [17], who have reported polysensitization in 65% of patients with asthma and allergic rhinitis. Considering the pathogenesis of chronic inflammation in the bronchial mucosa in allergic phenotype of asthma, increased IgE was noted only in group 1 patients. This finding was consistent with that of other studies [18, 19].

Furthermore, patients in groups 1 and 2 differed by the range of concomitant pathologies. In patients with allergic phenotype of asthma, allergic rhinitis and its combination with allergic conjunctivitis prevailed, which is fully consistent with the results of epidemiological studies, showing that 40–90% of patients with asthma have symptoms of allergic rhinitis [20]. Conversely, in the group of patients with nonallergic phenotype of T2-endotype asthma, a significant number of patients (40.7%) had chronic sinusitis with nasal polyps, often combined with hypersensitivity to nonsteroidal anti-inflammatory drugs. This observation is consistent with that

of previous studies, according to which 45–76% of patients with chronic sinusitis with nasal polyps have symptoms of asthma, and in 14% of cases, chronic sinusitis with nasal polyps is linked to hypersensitivity to nonsteroidal anti-inflammatory drugs [21–23]. However, Hakansson et al. [24], upon comparing individual parameters characterizing various asthma phenotypes in patients with chronic sinusitis with nasal polyps, have shown no relationship between atopy and chronic sinusitis with nasal polyps. Some studies have revealed that nonallergic phenotype of T2-endotype asthma was most often associated with central obesity [13, 25]. Our analysis also revealed a high body mass index in patients with nonallergic phenotype of asthma.

A subsequent univariate analysis showed that patients with nonallergic phenotype of T2-endotype asthma have a higher chance of developing severe asthma. This group included a higher number of patients with severe asthma and lower FEV_1 numbers compared to patients with allergic phenotype of asthma. An increase in the frequency of daytime and nighttime asthma symptoms was higher in patients with nonallergic phenotype of asthma, whereas the number of exacerbations requiring systemic CSs and hospitalizations were comparable in both groups. We found that an increase in FEV_1 was associated with a decrease in the chances of a more severe course of asthma (p=0.004), regardless of asthma phenotype. In general, similar data were obtained by other researchers who noted a more severe course of nonallergic phenotype of T2-endotype asthma and a more significant decrease in pulmonary function indicators in this category of patients [13, 26, 27]. Suruki et al. [28] have shown that patients with severe asthma have a higher risk of developing exacerbations. In addition, some studies have determined a relationship between the severity of nonallergic phenotype of T2-endotype asthma and chronic sinusitis with nasal polyps and hypersensitivity to nonsteroidal anti-inflammatory drugs [23, 29]. However, we were unable to identify such a relationship.

As we previously noted, in the group of patients with allergic phenotype of asthma, the proportion of patients with severe asthma was smaller compared to patients in group 2, where the proportion of patients with asthma of moderate severity was greater. Further, concomitant diseases (allergic rhinitis and allergic conjunctivitis) were not associated with an increased chance of developing a severe course of asthma, which is generally consistent with the data of Toppila Salmi et al. [9]. Moreover, this concomitant pathology in our study increased the chances of developing a mild course of asthma.

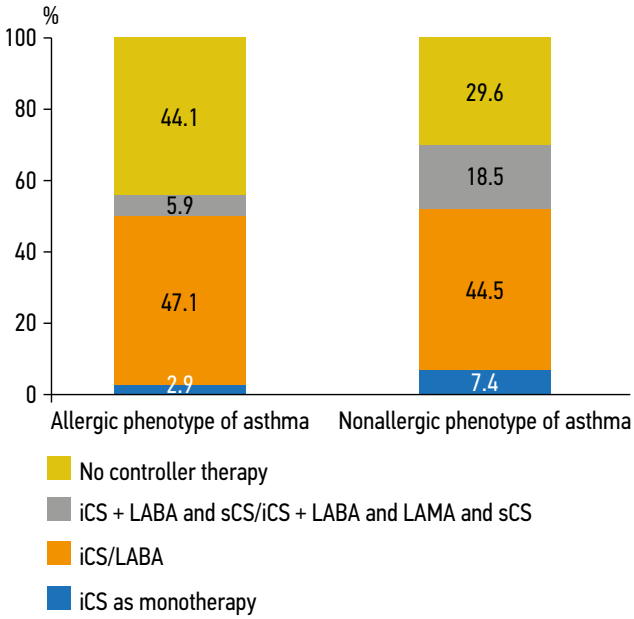

Fig. 3. Controller medication characteristics; iCS: inhaled corticosteroids; LABA: long-acting β2 agonists; sCS: systemic corticosteroids; LAMA: long-acting muscarinic antagonists.

Gender and age of patients are found to be predictors of severe asthma [9, 30]. We have shown that elderly patients have an increased risk of developing severe asthma. However, our univariate analysis did not show a significant effect of the patient's gender on the risk of developing severe asthma, although in the literature there is evidence of a more severe course of asthma in women, which is associated with the influence of ovarian hormones (estrogen and progesterone) on T2 inflammation [31].

Finally, high levels of peripheral blood eosinophils are also a predictor of severe asthma [32, 33]. Studies by Casciano [34] and Oppenheimer [35] have shown that the severity of asthma can be associated with a high level of peripheral blood eosinophils. In our study, patients in both groups had increased levels of peripheral blood eosinophils.

Table 2. Main predictors of asthma severity

Predictor	OR [95% CI]	*p*	VIF
Age at the time of examination, years	1.08 [1.02; 1.14]	0.006	1.17
Absolute number of eosinophils in peripheral blood	1.07 [0.84; 1.37]	0.567	2.89
Number of exacerbations requiring hospitalization	2.98 [0.38; 23.62]	0.301	2.15
Total number of nighttime symptoms per week	1.42 [1.01; 2.00]	0.041	1.31
FEV_1 (% from project value)	0.96 [0.92; 0.99]	0.03	1.13
Exacerbations requiring the use of corticosteroids	1.19 [0.3; 4.62]	0.807	3.08

Note: FEV_1: forced expiratory volume in 1 s; CS: corticosteroids; OR: odds ratio; CI: confidence interval; VIF: variance inflation factor.

However, univariate analysis revealed that an absolute number of eosinophils do not increase the risk of developing severe asthma.

At the final stage of the study, we conducted a multivariate analysis of predictors of severe asthma. The following parameters were studied as independent variables by selection with exclusion based on the Akaike information criterion: age of patients at the time of examination, absolute number of eosinophils, number of hospitalizations for exacerbations, number of exacerbations requiring the use of systemic CS, total number of night symptoms per week, and FEV_1 (percent of project values). Analysis showed that the absolute number of peripheral blood eosinophils, the number of hospitalizations for exacerbations, and exacerbations requiring the use of systemic CS did not increase the risk of severe asthma. In turn, the patient's age at the time of examination, an increase in the number of nighttime symptoms, and a low FEV_1 are reliable criteria for the increased risk of severe asthma.

Study limitations

The study was limited by the small sample size.

CONCLUSION

Allergic and nonallergic phenotypes of T2-endotype asthma have clinical differences, which can be determined during analysis of clinical and anamnestic data. Patients with nonallergic phenotype of T2-endotype asthma are characterized by the late onset of the disease, absence of clinically significant sensitization, and concomitant pathology in the form of rhinosinusitis with nasal polyps, combined with hypersensitivity to nonsteroidal anti-inflammatory drugs. In addition, patients with this asthma phenotype are more likely to experience a severe course of the disease. In contrast, patients with allergic asthma are characterized by an early onset and milder course of the disease, concomitant allergic rhinitis, and other allergic diseases in a significant number of cases and clinically significant sensitization.

Our data showed that parameters, such as the number of nighttime symptoms per week, low FEV_1, and patient age, should be considered as significant predictors of severe asthma. Awareness of primary care physicians and specialists (allergists, pulmonologists, otorhinolaryngologists) regarding risk factors of severe asthma will help with earlier identification of patients with severe asthma and the prescription or timely correction of controller anti-inflammatory therapy to prevent severe exacerbations.

ADDITIONAL INFORMATION

Funding source. This work was supported by Russian Foundation for Basic Research, project N 19-05-50094.

Competing interests. The authors declare that they have no competing interests.

Authors' contribution. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work. M.R. Khakimova — formed a group of asthma patients and performed clinical examination of asthma patients, analyzed data, reviewed the literature, wrote the manuscript; A.R. Valeeva, N.Sh. Kurmaeva — selected patients with asthma; O.V. Skorokhodkina — shaped the conceptual framework, directed the project, analyzed data, wrote the manuscript.

REFERENCES

1. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2023. Available from: www. ginasthma.org. Accessed: 18.07.2023.

2. Clinical recommendations. Bronchial asthma. 2021. (In Russ). Available from: https://raaci.ru/dat/pdf/BA.pdf. Accessed: 23.05.2023.

3. Sergeeva GR, Emelyanov AV, Leshenkova EV, Znakhurenko AA. Biomarkers of airways inflammation in patients with severe asthma in a real clinical practice. *Pulmonology*. 2020;30(4):437–445. (In Russ). doi: 10.18093/0869-0189-2020-30-4-437-445

4. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*. 2014;43(2):343–373. doi: 10.1183/09031936.00202013

5. Nenasheva NM. T2-high and T2-low bronchial asthma, endotype characteristics and biomarkers. *Pulmonology*. 2019;29(2):216–228. (In Russ). doi: 10.18093/0869-0189-2019-29-2-216-228

6. Nagase H, Adachi M, Matsunaga K, et al. Prevalence, disease burden, and treatment reality of patients with severe, uncontrolled asthma in Japan. *Allergol Int*. 2020;69(1):53–60. doi: 10.1016/j.alit.2019.06.003

7. López-Tiro J, Contreras-Contreras A, Rodríguez-Arellano ME, Costa-Urrutia P. Economic burden of severe asthma treatment: A real-life study. *World Allergy Organ J*. 2022;15(7):100662. doi: 10.1016/j.waojou.2022.100662

8. Round table resolution. Lung diseases issue in Russia. In: X All-Russian Congress of Patients "Interaction of the authorities and the patient community as a basis for building patient-oriented healthcare in the Russian Federation". Moscow, November 29, 2019. (In Russ). Available from: https://vspru.ru/media/853321/4.pdf. Accessed: 12.07.2023.

9. Toppila-Salmi S, Lemmetyinen R, Chanoine S, et al. Risk factors for severe adult-onset asthma: A multi-factor approach. *BMC Pulm Med*. 2021;21(1):214 doi: 10.1186/s12890-021-01578-4

10. Battaglia S, Benfante A, Spatafora M, Scichilone N. Asthma in the elderly: A different disease? *Breathe (Sheff)*. 2016;12(1):18–28. doi: 10.1183/20734735.002816

11. Pavlidis S, Takahashi K, Kwong F, et al. "T2-high" in severe asthma related to blood eosinophil, exhaled nitric oxide and serum periostin. *Eur Respir J*. 2019;53(1):1800938. doi: 10.1183/13993003.00938-2018

12. Kozlova OA, Sekicki-Pavlenko OO. Theoretical framework for the socio-economic research on age and ageing in the context of contemporary demographic trends. *Alter Economics*. 2022;19(3): 442–463. (In Russ). doi 10.31063/AlterEconomics/2022.19-3.3

13. Pakkasela J, Ilmarinen P, Honkamäki J, et al. Age-specific incidence of allergic and non-allergic asthma. *BMC Pulm Med*. 2020;20(1):9. doi: 10.1186/s12890-019-1040-2
14. Litonjua AA, Carey VJ, Burge HA, et al. Parental history and the risk for childhood asthma. Does mother confer more risk than father? *Am J Respir Crit Care Med*. 1998;158(1):176–181. doi: 10.1164/ajrccm.158.1.9710014
15. Akdis CA, Agache I, editors. EAACI Global atlas of asthma. 2nd ed. Zurich: European Academy of Allergy and Clinical Immunology; 2021.
16. Rönmark EP, Ekerljung L, Mincheva R, et al. Different risk factor patterns for adult asthma, rhinitis and eczema: Results from West Sweden Asthma Study. *Clin Transl Allergy*. 2016;(6):28. doi: 10.1186/s13601-016-0112-0
17. Burte E, Bousquet J, Siroux V, et al. The sensitization pattern differs according to rhinitis and asthma multimorbidity in adults: The EGEA study. *Clin Exp Allergy*. 2017;47(4):520–529. doi: 10.1111/cea.12897
18. Agache I, Rocha C, Beltran J, et al. Efficacy and safety of treatment with biologicals (benralizumab, dupilumab and omalizumab) for severe allergic asthma: A systematic review for the EAACI Guidelines: Recommendations on the use of biologicals in severe asthma. *Allergy*. 2020;75(5):1043–1057. doi: 10.1111/all.14235
19. Matucci A, Vultaggio A, Maggi E, Kasujee I. Is IgE or eosinophils the key player in allergic asthma pathogenesis? Are we asking the right question? *Respir Res*. 2018;19(1):113. doi: 10.1186/s12931-018-0813-0
20. Vujnovic SD, Domuz A. Epidemiological aspects of rhinitis and asthma: Comorbidity or united airway disease [Internet]. Asthma diagnosis and management: Approach based on phenotype and endotype. InTech; 2018. Available from: http://dx.doi.org/10.5772/intechopen.76773. Accessed: 07.07.2023.
21. Chichikova NV. Bronchial asthma and diseases of the nasal cavity and paranasal sinuses: The unity of the pathological processes in the respiratory system. *Russ Med J*. 2015;(18):1132–1136. (In Russ).
22. Kowalski ML, Agache I, Bavbek S, et al. Diagnosis and management of NSAID-Exacerbated Respiratory Disease (N-ERD): A EAACI position paper. *Allergy*. 2019;74(1):28–39. doi: 10.1111/all.13599
23. Rajan JP, Wineinger NE, Stevenson DD, White AA. Prevalence of aspirin-exacerbated respiratory disease among asthmatic patients: A meta-analysis of the literature. *J Allergy Clin Immunol*. 2015; 135(3):676–681.e1. doi: 10.1016/j.jaci.2014.08.020
24. Hakansson K, Thomsen SF, Konge L, et al. A comparative and descriptive study of asthma in chronic rhinosinusitis with nasal polyps. *Am J Rhinol Allergy*. 2014;28(5):383–387. doi: 10.2500/ajra.2014.28.4076
25. Appleton SL, Adams RJ, Wilson DH, et al.; North West Adelaide Health Study Team. Central obesity is associated with nonatopic but not atopic asthma in a representative population sample. *J Allergy Clin Immunol*. 2006;118(6):1284–1291. doi: 10.1016/j.jaci.2006.08.011
26. Romanet-Manent S, Charpin D, Magnan A, et al.; EGEA Cooperative Group. Allergic vs nonallergic asthma: What makes the difference? *Allergy*. 2002;57(7):607–613. doi: 10.1034/j.1398-9995.2002.23504.x
27. De Nijs SB, Venekamp LN, Bel EH. Adult-onset asthma: Is it really different? *Eur Respir Rev*. 2013;22(127):44–52. doi: 10.1183/09059180.00007112
28. Suruki RY, Daugherty JB, Boudiaf N, Albers FC. The frequency of asthma exacerbations and healthcare utilization in patients with asthma from the UK and USA. *BMC Pulm Med*. 2017;17(1):74. doi: 10.1186/s12890-017-0409-3
29. Dyneva ME, Kurbacheva OM, Savlevich EL. Bronchial asthma in combination with chronic rhinosinusitis with nasal polyps: Epidemiology, prevalence and peculiarities of their relationship. *Russ J Allergy*. 2018;15(1):16–25. (In Russ). doi: 10.36691/RJA185
30. Hirano T, Matsunaga K. Late-onset asthma: Current perspectives. *J Asthma Allergy*. 2018;(11):19–27. doi: 10.2147/JAA.S125948
31. Fuseini H, Newcomb DC. Mechanisms driving gender differences in asthma. *Curr Allergy Asthma Rep*. 2017;17(3):19. doi: 10.1007/s11882-017-0686-1
32. Solomon Y, Malkamu B, Berhan A, et al. Peripheral blood eosinophilia in adult asthmatic patients and its association with the severity of asthma. *BMC Pulm Med*. 2023;23(1):96. doi: 10.1186/s12890-023-02383-x
33. Boonpiyathad T, Sözener ZC, Satitsuksanoa P, Akdis CA. Immunologic mechanisms in asthma. *Semin Immunol*. 2019; (46):101333. doi: 10.1016/j.smim.2019.101333
34. Casciano J, Krishnan JA, Small MB, et al. Value of peripheral blood eosinophil markers to predict severity of asthma. *BMC Pulm Med*. 2016;16(1):109. doi: 10.1186/s12890-016-0271-8
35. Oppenheimer J, Hoyte FC, Phipatanakul W, et al. Allergic and eosinophilic asthma in the era of biomarkers and biologics: Similarities, differences and misconceptions. *Ann Allergy Asthma Immunol*. 2022;129(2):169–180. doi: 10.1016/j.anai.2022.02.021

СПИСОК ЛИТЕРАТУРЫ

1. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2023. Режим доступа: www.ginasthma.org. Дата обращения: 18.07.2023.
2. Клинические рекомендации. Бронхиальная астма. 2021. Режим доступа: https://raaci.ru/dat/pdf/BA.pdf. Дата обращения: 23.05.2023.
3. Сергеева Г.Р., Емельянов А.В., Лешенкова Е.В., Знахуренко А.А. Биомаркеры воспаления дыхательных путей у пациентов с тяжелой бронхиальной астмой в реальной клинической практике // Пульмонология. 2020. Т. 30, N 4. С. 437–445. doi: 10.18093/0869-0189-2020-30-4-437-445
4. Chung K.F., Wenzel S.E., Brozek J.L., et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma // Eur Respir J. 2014. Vol. 43, N 2. P. 343–373. doi: 10.1183/09031936.00202013
5. Ненашева Н.М. Т2-бронхиальная астма: характеристика эндотипа и биомаркеры // Пульмонология. 2019. Т. 29, № 2. С. 216–228. doi: 10.18093/0869-0189-2019-29-2-216-228
6. Nagase H., Adachi M., Matsunaga K., et al. Prevalence, disease burden, and treatment reality of patients with severe, uncontrolled asthma in Japan // Allergol Int. 2020. Vol. 69, N 1. P. 53–60. doi: .1016/j.alit.2019.06.003
7. López-Tiro J., Contreras-Contreras A., Rodríguez-Arellano M.E., Costa-Urrutia P. Economic burden of severe asthma treatment: A real-life study // World Allergy Organ J. 2022. Vol. 15, N 7. P. 100662. doi: 10.1016/j.waojou.2022.100662
8. Резолюция Круглого стола «Проблема легочных заболеваний в России» // X Всероссийский конгресс пациентов «Взаимодействие власти и пациентского сообщества как основа построения пациент-ориентированного здравоохранения в Российской Федерации», Москва, 29 ноября 2019 года. Режим доступа: https://vspru.ru/media/853321/4.pdf. Дата обращения: 12.07.2023.

9. Toppila-Salmi S., Lemmetyinen R., Chanoine S., et al. Risk factors for severe adult-onset asthma: A multi-factor approach // BMC Pulm Med. 2021. Vol. 21, N 1. P. 214. doi: 10.1186/s12890-021-01578-4
10. Battaglia S., Benfante A., Spatafora M., Scichilone N. Asthma in the elderly: A different disease? // Breathe (Sheff). 2016. Vol. 12, N 1. P. 18–28. doi: 10.1183/20734735.002816
11. Pavlidis S., Takahashi K., Kwong F., et al. "T2-high" in severe asthma related to blood eosinophil, exhaled nitric oxide and serum periostin // Eur Respir J. 2019. Vol. 53, N 1. P. 180093. doi: 10.1183/13993003.00938-2018
12. Козлова О.А., Секицки-Павленко О.О. Теоретические основания определения возрастных границ и возрастной структуры населения в контексте демографического старения // Alter Economics. 2022. Т. 19, № 3. С. 442–463. doi 10.31063/AlterEconomics/2022.19-3.3
13. Pakkasela J., Ilmarinen P., Honkamäki J., et al. Age-specific incidence of allergic and non-allergic asthma // BMC Pulm Med. 2020. Vol. 20, N 1. P. 9. doi: 10.1186/s12890-019-1040-2
14. Litonjua A.A., Carey V.J., Burge H.A., et al. Parental history and the risk for childhood asthma. Does mother confer more risk than father? // Am J Respir Crit Care Med. 1998. Vol. 158, N 1. P. 176–181. doi: 10.1164/ajrccm.158.1.9710014
15. Akdis C.A., Agache I., editors. EAACI Global atlas of asthma. 2nd ed. Zurich: European Academy of Allergy and Clinical Immunology, 2021.
16. Rönmark E.P., Ekerljung L., Mincheva R., et al. Different risk factor patterns for adult asthma, rhinitis and eczema: Results from West Sweden Asthma Study // Clin Transl Allergy. 2016, N 6. P. 28. doi: 10.1186/s13601-016-0112-0
17. Burte E., Bousquet J., Siroux V., et al. The sensitization pattern differs according to rhinitis and asthma multimorbidity in adults: The EGEA study // Clin Exp Allergy. 2017. Vol. 47, N 4. P. 520–529. doi: 10.1111/cea.12897
18. Agache I., Rocha C., Beltran J., et al. Efficacy and safety of treatment with biologicals (benralizumab, dupilumab and omalizumab) for severe allergic asthma: A systematic review for the EAACI Guidelines: Recommendations on the use of biologicals in severe asthma // Allergy. 2021. Vol. 75, N 5. P. 1043–1057. doi: 10.1111/all.14235
19. Matucci A., Vultaggio A., Maggi E., Kasujee I. Is IgE or eosinophils the key player in allergic asthma pathogenesis? Are we asking the right question? // Respir Res. 2018. Vol. 19, N 1. P. 13. doi: 10.1186/s12931-018-0813-0
20. Vujnovic S.D., Domuz A. Epidemiological aspects of rhinitis and asthma: Comorbidity or united airway disease [интернет]. Asthma diagnosis and management: Approach based on phenotype and endotype. InTech, 2018. Режим доступа: http://dx.doi.org/10.5772/intechopen.76773. Дата обращения: 07.07.2023.
21. Чичкова Н.В. Бронхиальная астма и заболевания полости носа и околоносовых пазух: единство патологических процессов в дыхательной системе // Русский медицинский журнал. 2015. N 18. С. 1132–1136.
22. Kowalski M.L., Agache I., Bavbek S., et al. Diagnosis and management of NSAID-Exacerbated Respiratory Disease (N-ERD): A EAACI position paper // Allergy. 2019. Vol. 74, N 1. P. 28–39. doi: 10.1111/all.13599
23. Rajan J.P., Wineinger N.E., Stevenson D.D., White A.A. Prevalence of aspirin-exacerbated respiratory disease among asthmatic patients: A meta-analysis of the literature // J Allergy Clin Immunol. 2015. Vol. 135, N 3. P. 676–681.e1. doi: 10.1016/j.jaci.2014.08.020
24. Hakansson K., Thomsen S.F., Konge L., et al. A comparative and descriptive study of asthma in chronic rhinosinusitis with nasal polyps // Am J Rhinol Allergy. 2014. Vol. 28, N 5. P. 383–387. doi: 10.2500/ajra.2014.28.4076
25. Appleton S.L., Adams R.J., Wilson D.H., et al. North West Adelaide Health Study Team. Central obesity is associated with nonatopic but not atopic asthma in a representative population sample // J Allergy Clin Immunol. 2006. Vol. 118, N 6. P. 1284–1291. doi: 10.1016/j.jaci.2006.08.011
26. Romanet-Manent S., Charpin D., Magnan A., et al.; EGEA Cooperative Group. Allergic vs nonallergic asthma: What makes the difference? // Allergy. 2002. Vol. 57, N 7. P. 607–613. doi: 10.1034/j.1398-9995.2002.23504.x
27. De Nijs S.B., Venekamp L.N., Bel E.H. Adult-onset asthma: Is it really different? // Eur Respir Rev. 2013. Vol. 22, N 127. P. 44–52. doi: 10.1183/09059180.00007112
28. Suruki R.Y., Daugherty J.B., Boudiaf N., Albers F.C. The frequency of asthma exacerbations and healthcare utilization in patients with asthma from the UK and USA // BMC Pulm Med. 2017. Vol. 17, N 1. P. 74. doi: 10.1186/s12890-017-0409-3
29. Дынева М.Е., Курбачева О.М., Савлевич Е.Л. Бронхиальная астма в сочетании с хроническим полипозным риносинуситом: эпидемиология, распространенность и особенности их взаимоотношения // Российский аллергологический журнал. 2018. Т. 15, № 1. С. 16–25. doi: 10.36691/RJA185
30. Hirano T., Matsunaga K. Late-onset asthma: Current perspectives // J Asthma Allergy. 2018. N 11. P. 19–27. doi: 10.2147/JAA.S125948
31. Fuseini H., Newcomb D.C. Mechanisms driving gender differences in asthma // Curr Allergy Asthma Rep. 2017. Vol. 17, N 3. P. 19. doi: 10.1007/s11882-017-0686-1
32. Solomon Y., Malkamu B., Berhan A., et al. Peripheral blood eosinophilia in adult asthmatic patients and its association with the severity of asthma // BMC Pulm Med. 2023. Vol. 23, N 1. P. 96. doi: 10.1186/s12890-023-02383-x
33. Boonpiyathad T., Sözener Z.C., Satitsuksanoa P., Akdis C.A. Immunologic mechanisms in asthma // Semin Immunol. 2019. N 46. P. 101333. doi: 10.1016/j.smim.2019.101333
34. Casciano J., Krishnan J.A., Small M.B., et al. Value of peripheral blood eosinophil markers to predict severity of asthma // BMC Pulm Med. 2016. Vol. 16, N 109. P. 1. doi: 10.1186/s12890-016-0271-8
35. Oppenheimer J., Hoyte F.C., Phipatanakul W., et al. Allergic and eosinophilic asthma in the era of biomarkers and biologics: Similarities, differences and misconceptions // Ann Allergy Asthma Immunol. 2022. Vol. 129, N 2. P. 169–180. doi: 10.1016/j.anai.2022.02.021

AUTHORS' INFO

*** Milyausha R. Khakimova**;
address: 49 Butlerov street, 420012 Kazan, Russia;
ORCID: 0000-0002-3533-2596;
eLibrary SPIN: 1875-3934;
e-mail: mileushe7@gmail.com

Alina R. Valeeva;
ORCID: 0009-0007-6528-6774;
eLibrary SPIN: 1485-5669;
e-mail: aliv05@mail.ru

Naira Sh. Kurmaeva;
ORCID: 0000-0002-5505-4984;
eLibrary SPIN: 6678-2044;
e-mail: nkurmaeva@inbox.ru

Olesya V. Skorokhodkina, MD, Dr. Sci. (Med.), Professor;
ORCID: 0000-0001-5793-5753;
eLibrary SPIN: 8649-6138;
e-mail: olesya-27@rambler.ru

ОБ АВТОРАХ

*** Хакимова Миляуша Рашитовна**;
адрес: Россия, 420012, Казань, ул. Бутлерова, д. 49;
ORCID: 0000-0002-3533-2596;
eLibrary SPIN: 1875-3934;
e-mail: mileushe7@gmail.com

Валеева Алина Рамилевна;
ORCID: 0009-0007-6528-6774;
eLibrary SPIN: 1485-5669;
e-mail: aliv05@mail.ru

Курмаева Найра Шафкатовна;
ORCID: 0000-0002-5505-4984;
eLibrary SPIN: 6678-2044;
e-mail: nkurmaeva@inbox.ru

Скороходкина Олеся Валерьевна, д-р мед. наук, профессор;
ORCID: 0000-0001-5793-5753;
eLibrary SPIN: 8649-6138;
e-mail: olesya-27@rambler.ru

* Corresponding author / Автор, ответственный за переписку