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SEVERE COURSE OF BRONCHIAL ASTHMA PROGNOSING

Ключові слова: *бронхіальна астма, фенотип, фактори ризику, прогнозування.*

Bronchial asthma (BA) is one of the most important medical and social problem around the world. The prevalence of asthma in different countries ranges from 1 % to 16 % [1–3].

But asthma is often diagnosed untimely, especially in severe cases, mimicking other conditions such as chronic obstructive pulmonary disease, chronic bronchitis, upper respiratory pathologies, gastroesophageal reflux disease. Therefore, particular attention should be paid to the severity of asthma due to the high risk of severe, life-threatening exacerbations requiring significant economic costs [9]. In connection with this, there was a need for a review of existing views about the diagnosis and management of this disease, which has also drawn attention in international documents of the American Thoracic Society and the European Respiratory Society (ATS/ERS, 2014–2017 yy.), where it is emphasized that it is clinically advisable to isolate certain asthma phenotypes [13, 15].

Asthma is a heterogeneous disease, with various underlying disease processes [10, 15]. Famous clusters of demographic, clinical and/or pathophysiological characteristics are often referred to "asthma phenotypes" [11, 12]. For patients with severe asthma, specific treatment regimens based on the phenotype are proposed [10, 15]. However, to date, there has been no study of the links between specific pathophysiological features and specific clinical patterns or the response to treatment.

Literary sources do not adequately cover issues related to the severity of asthma, phenotype-related clinical outcomes or the consequences of severe asthma, which are a fundamental category of clinical epidemiology and are associated with clinically important patient experiences. It is such clinical phenomena as death, the presence of disease, discomfort, disability, dissatisfaction with the quality of life [4].

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For the patient with asthma, the most important is the ability to influence the severity of clinical symptoms, namely, to gain control over them, increase tolerance to physical activity, and improve quality of life. For clinicians, it is important to eliminate future risks, including exacerbations of the disease and severe functional disorders (the development of lung hyperinflation).

Therefore, the purpose of this study was to predict the impact of risk factors on the uncontrolled course of BA, reduced tolerance to physical activity, deterioration of quality of life, the development of lung hyperinflation, the emergence of severe asthma exacerbations.

Methods. 160 patients with severe asthma were examined, in which at the specialized medical care level the final phenotypes of the disease were established: allergic asthma — 60,0% of patients (allergic rhinitis — 34,4 %, polyposis — 3,8 %, atopic dermatitis — 0,6 %) and non-allergic asthma — 40,0 %. Among these patients, other phenotypes of severe BA were distinguished: BA with a late onset — 40,6 %, BA with obesity — 33,1 % and BA with fixed bronchial obstruction — 14,4 % of patients. Asthma associated with chronic obstructive pulmonary disease (COPD) was detected in 20,6 % of patients, BA with concomitant diseases — cardiovascular diseases — 58,8 %, sleep obstructive apnea-hypopnea syndrome (SOAHS) — 12,5 %, gastroesophageal reflux disease (GERD) — 10,0 %.

Data collection and their mathematical processing were carried out with the help of licensed software products included in the package Microsoft Office Professional 2003, license Russian Academic OPEN No Level № 17016297. Statistical analysis was carried out with the help of mathematical and statistical capabilities of MS Excel [6].

In order to assess the risk of the presence of certain features among the observation groups, the odds ratio and its 95% confidence interval were calculated (CI) [5, 7, 8].

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To assess the generalized probability of development of individual events under the influence of several risk factors, the Cochran-Mantel-Hensel criterion was used with the help of software Review Manager (RevMan 5.3) [14].

The work was performed at the costs of the state budget of Ukraine.

Results. After establishing the final diagnosis in patients, the prediction of the influence of risk factors on the uncontrolled course of asthma, reduction of tolerance to physical activity, deterioration of the quality of life, the development of lung hyperinflation, the emergence of severe asthma exacerbations was determined taking into account the phenotype of the disease. Additional criteria for diagnosis (risk factors) and prediction of severe BA course taking into account the phenotypes of the disease have been developed.

During process of analysis of the obtained data it was established that the severity of the asthma course is influenced by: the phenotype of the disease, the pulmonary function violation, the type of inflammation in the tracheobronchial tree, severe exacerbations, allergic and related pathologies. Risk factors for uncontrolled asthma are presented in Table 1.

Thus, the fall in FEV1 below 60 % of the predicted values significantly increases the risk of loss of control by 18,69 times, reducing the inspiratory capacity below 80 % of the predicted values — by 16,19 times. Lung hyperinflation (determined according to the bodyplethysmography data) increases the probability of uncontrolled course by 4,13–7,8 times, depending on the bodyplethysmography index.

There are also risk factors that significantly increase the probability of uncontrolled asthma: AR (3,94 times), obesity (6,07 times), eosinophilic (14,88 times) and neutrophilic (5,76 times) inflammation. Table 1 shows that the most

Table 1. Risk factors for uncontrolled asthma (ACQ > 1,5 points) in patients with severe asthma (odds ratio and 95 % confidence interval)

Risk factors	Odds ratio	95 % confidence interval	Factor proportion, %
FEV_1 less than 60 %	18,69	7,61–45,90	2,3
IC less than 80 %	16,19	5,38–48,70	1,9
ITGV more than 120 %	4,78	2,39–9,53	6,8
ITGV/TLC more than 55 %	5,39	2,63–11,05	6,0
RV more than 120 %	4,13	2,11–8,08	7,6
RV/TLC more than 30 %	7,8	3,51–17,34	4,2
AR	3,94	1,96–7,91	7,3
GERD	11,15	1,38–90,22	0,8
Eosinophilic inflammation	14,88	4,29–51,64	1,7
Non-compliance with the treatment regimen	2,61	1,37–4,96	10,4
Irreversible bronchial obstruction	7,58	3,72–15,46	5,0
Neutrophilic inflammation	5,76	1,84–18,02	2,7
Small airways obstruction	2,20	1,16–4,15	11,7
Pathology of CVS	2,42	1,26–4,63	10,7
Late onset asthma	2,61	1,38–4,95	10,6
SOAHS	11,15	1,38–90,22	0,8
Severe exacerbations	4,77	1,91–11,92	4,2
BMI more than 30 kg/m^2	6,07	2,89–12,76	5,3
Total:	4,86	4,05–5,83	100

Note. The odds ratios for all risk factors are statistically significant, $p < 0,05$

Table 2. Risk factors for the lung hyperinflation development (RV ≥ 120, RV/TLC ≥ 30, ITGV ≥ 120, ITGV/TLC ≥ 55) in patients with severe asthma (odds ratio and 95 % confidence interval)

Risk factors	Odds ratio	95 % confidence interval	Factor proportion, %
FEV_1 less than 60 %	14,12	5,55–35,93*	5,5
Inflammation (eosinophilic or neutrophilic)	3,42	1,71–6,84*	16,0
Irreversible bronchial obstruction	11,48	5,43–24,30*	7,5
Small airways obstruction	6,86	3,28–14,33*	10,7
Pathology of CVS	2,47	1,27–4,83*	21,0
Late onset asthma	5,72	2,86–11,42*	12,4
Severe exacerbations	8,71	3,75–20,21*	7,2
BMI more than 30 kg/m^2	0,86	0,35–,10	19,7
Total:	4,94	3,82–6,40*	100

Note. * — the odds ratio for risk factors is statistically significant , $p < 0,05$

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Table 3. Risk factors for reducing exercise tolerance (6-minute walk test < 300 meters) in patients with severe asthma (odds ratio and 95 % confidence interval)

Risk factors	Odds ratio	95 % confidence interval	Factor proportion, %
FEV_1 less than 60 %	7,54	2,77–20,48	5,2
IC less than 80 %	18,45	7,65–44,49	2,9
ITGV more than 120 %	8,0	3,65–17,55	6,2
ITGV/TLC more than 55 %	3,15	1,53–6,47	11,4
RV more than 120 %	4,3	2,06–8,98	9,6
RV/TLC more than 30 %	2,87	1,38–5,95	11,5
Inflammation (eosinophilic or neutrophilic)	3,44	1,66–7,13	10,5
Irreversible bronchial obstruction	5,30	2,48–11,31	8,3
Small airways obstruction	20,80	6,08–71,14	2,5
Pathology of CVS	11,48	3,86–34,17	3,8
Late onset asthma	2,20	1,08–4,44	14,6
SOAHS	8,56	3,03–24,16	3,2
Severe exacerbations	12,58	5,45–29,07	3,9
BMI more than 30 kg/m^2	7,41	3,44–15,98	4,6
Total:	5,85	4,72–7,24	100

Note. The odds ratios for all risk factors are statistically significant, p < 0,05.

important factors in controlling the symptoms of asthma are small airways obstruction, cardiovascular pathology and late onset of asthma — 11,7 %, 10,7 % and 10,6 % respectively.

Risk factors for the development of lung hyperinflation in patients with severe asthma are presented in Table 2.

TThe risk factors that significantly increase the lung hyperinflation development (RV ≥ 120, RV / TLC ≥ 30, ITGV ≥ 120, ITGV / TLC ≥ 55) are: FEV_1 below 60 %, eosinophilic or neutrophilic inflammation, irreversible bronchial obstruction, small bronchial obstruction, pathology of the cardiovascular system, late onset of asthma, severe exacerbations, obesity. The most important factors in the lung hyperinflation development include: eosinophilic or neutrophilic inflammation (16,0 %), small airways obstruction (10,7 %), concomitant cardiovascular disease (21,0 %), late onset of asthma (12, 4 %), obesity (19,7 %).

Risk factors that significantly reduce exercise tolerance are presented in Table 3.

The most important factors in reducing exercise tolerance are: late onset asthma (14,6 %), eosinophilic or neutrophilic inflammation (10,5 %), impaired pulmonary function — ITGV/TLC greater than 55 % (11,4 %), RV/TLC over 30 % (11,5 %).

Risk factors that reliably contribute to asthma exacerbation are presented in Table 4.

The most important factors of asthma exacerbations are the following disorders of the pulmonary function: FEV_1 below 60 % (9,9 %), ITGV/TLC over 55 % (9,7 %),

Table 4. Risk factors for asthma exacerbations (according to medical history) in patients with severe asthma (odds ratio and 95% confidence interval)

Risk factors	Odds ratio	95 % confidence interval	Factor proportion, %
FEV_1 less than 60 %	2,29	1,03 — 5,11	9,9
IC less than 80 %	21,00	8,52 — 51,74	2,1
ITGV more than 120 %	6,15	2,80 — 13,50	5,8
ITGV/TLC more than 55 %	2,68	1,29 — 5,60	9,7
RV more than 120 %	2,89	1,38 — 6,04	9,5
RV/TLC more than 30 %	2,71	1,29 — 5,72	9,2
AR	4,31	2,03 — 9,15	7,2
GERD	5,12	1,36 — 19,19	2,0
Eosinophilic inflammation	5,05	2,17 — 11,73	4,9
Irreversible bronchial obstruction	5,69	2,57 — 12,58	6,1
Neutrophilic inflammation	3,30	1,28 — 8,51	4,8
Small airways obstruction	3,32	1,49 — 7,38	8,3
Pathology of CVS	7,24	2,65 — 19,73	4,3
Late onset asthma	4,50	2,07 — 9,75	7,1
SOAHS	4,68	1,77 — 12,35	3,8
BMI more than 30 kg/m^2	6,40	2,94 — 13,93	5,5
Total:	4,40	2,94 — 13,93	100

Note. The odds ratios for all risk factors are statistically significant, p < 0,05.

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Table 5. Risk factors for quality of life impairment (according to the questionnaire SGRQ > 25 points) in patients with severe asthma (odds ratio and 95 % confidence interval)

Risk factors	Odds ratio	95 % confidence interval	Factor proportion, %
FEV_1 less than 60 %	9,68	3,67 — 25,58*	4,4
ITGV more than 120 %	3,78	1,36 — 10,50*	7,1
ITGV/TLC more than 55 %	3,23	1,16 — 8,98*	7,6
RV more than 120 %	2,65	1,06 — 6,60*	9,7
RV/TLC more than 30 %	3,44	1,13 — 10,47*	6,6
AR	1,56	0,64 — 3,77	12,8
Irreversible bronchial obstruction	1,17	0,52 — 2,63	16,9
Small airways obstruction	2,91	1,26 — 6,70*	10,2
Pathology of CVS	8,38	3,19 — 22,05*	4,9
Late onset asthma	3,32	1,27 — 8,67*	8,2
Severe exacerbations	5,78	1,31 — 25,49*	3,6
BMI more than 30 kg/m^2	2,93	1,05 — 8,15*	7,9
Total:	3,24	2,46 — 4,26*	100

Note. * — the odds ratio of risk factors is statistically significant, $p < 0,05$.

RV more than 120 % (9,5 %), RV/TLC more than 30 % (9,2 %), small airways obstruction (8,3 %), and associated AR (7,2 %), late onset of asthma (7,1 %).

Risk factors that significantly affect the quality of life in patients with severe asthma are presented in Table 5.

The most important factors of the quality of life impairment in patients with asthma are associated AR (12,8 %), irreversible bronchial obstruction (16,9 %), obstruction of small bronchi (10,2 %).

The conducted researches indicate that the definition of individual phenotypes of asthma, their clinical features, types of inflammation and concomitant diseases by prognosing method allows to determine the risk factors that significantly affect the severity of the course of asthma and is the basis for the appointment of pathogenetically based anti-inflammatory and bronchodilator therapy.

Conclusions:

1. Prognosing of the severe course of bronchial asthma can reveal the most important factors that affect the severe course of asthma and allows to prescribe pathogenetically substantiated treatment.

2. The severity of the asthma course depends on: the phenotype of the disease, pulmonary function violation, type of inflammation in the tracheobronchial tree, late onset asthma, severe exacerbations, allergic and related pathologies. Therefore, timely detection of the phenotype of severe asthma, allergic and concomitant diseases is a topical issue of modern pulmonology.

3. Early detection of the phenotype of asthma, the main significant risk factors for the development of uncontrolled asthma, reduced tolerance to physical activity, deterioration in quality of life, the development of lung hyperinflation, the occurrence of severe exacerbations and the timely appointment of adequate basic therapy is the basis of secondary prevention of severe BA.

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Abstract

Aim of study — to carry out prognosis of the influence of risk factors on uncontrolled course of bronchial asthma (BA), decrease of tolerance to physical activity, deterioration of quality of life, development of lung hyperinflation, occurrence of severe exacerbations of asthma.

Methods. 160 patients with severe BA were examined, in which at the specialized medical care level the final phenotypes of the disease were established: allergic asthma — 60,0 % of patients (allergic rhinitis — 34,4 %, polyposis — 3,8 %, atopic dermatitis — 0,6 %) and non-allergic asthma — 40,0 %. Among these patients, other phenotypes of severe BA were distinguished: BA with a late onset — 40,6 %, BA with obesity — 33,1 % and BA with fixed bronchial obstruction — 14,4 % of patients. Asthma associated with chronic obstructive pulmonary disease (COPD) was detected in 20,6 % of patients, BA with concomitant diseases — cardiovascular diseases 58,8 %, sleep obstructive apnea-hypopnea syndrome (SOAHS) — 12,5 %, gastroesophageal reflux disease (GERD) — 10,0 %.

Data collection and their mathematical processing were carried out with the help of licensed software products included in the package Microsoft Office Professional 2003, license Russian Academic OPEN No Level № 17016297. Statistical analysis was carried out with the help of mathematical and statistical capabilities of MS Excel.

In order to assess the risk of the presence of certain features among the observation groups, the odds ratio and its 95 % confidence interval were calculated (CI).

To assess the generalized probability of development of individual events under the influence of several risk factors, the Cochran-Mantel-Hensel criterion was used with the help of software Review Manager (RevMan 5.3).

Results. As a result of the research, it was found that the prognosis of the severe course of bronchial asthma can reveal the most important factors that affect the severe course of asthma. The severity of the asthma course depends on: the phenotype of the disease, pulmonary function violation, type of inflammation in the tracheobronchial tree, late onset asthma, severe exacerbations, allergic and related pathologies. Therefore timely detection of the phenotype of severe asthma, allergic and concomitant diseases is a topical issue of modern pulmonology.

It was determined that early detection of the phenotype of asthma, the main significant risk factors for the development of uncontrolled asthma, reduced tolerance to physical activity, deterioration of the quality of life, the development of lung hyperinflation, the occurrence of severe exacerbations and the timely prescription of adequate basic therapy is the basis of secondary prevention of severe BA.

Conclusions: conducted studies indicate that the definition of individual phenotypes of asthma, their clinical features, types of inflammation and concomitant diseases by prognosing method allows to determine the risk factors that significantly affect the severity of the course of asthma and is the basis for prescription of pathogenetically based anti-inflammatory and bronchodilator therapy.

Key words: bronchial asthma, phenotype, risk factors, prognosis.

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