Clinical Case Reports International

Research Article
Published: 24 Oct, 2022

Pathological Immunity Changes in Comorbid Patients with Exacerbation of Bronchial Asthma

*Feshchenko Y[1], Illyinskaya I[2] and Kuryk L[3]**

[1]Department of Tuberculosis and Pulmonology, F.G. Yanovsky National Academy of Medical Sciences of Ukraine, Ukraine

[2]Departmentof Immunology, F.G. Yanovsky National Academy of Medical Sciences of Ukraine, Ukraine

[3]Department of Pulmonology, F.G. Yanovsky National Academy of Medical Sciences of Ukraine, Ukraine

Abstract

Aim: To investigate immunological changes in patients with exacerbation of bronchial asthma with different severity and controllability depending on the presence of comorbid pathology.

Materials and Methods: The work is based on the analysis of data from a comprehensive clinical and laboratory examination of 190 patients with exacerbation of asthma. The relative content of T-lymphocytes and their main subpopulations was determined on a flow cytofluorimeter FACS Calibur (Canada) by phenotyping lymphocytes with monoclonal antibodies (BECKMAN COULTER, USA) to surface membrane differentiation antigens (CD): CD3+19- (pan T-cells), CD4+-8+- (T–helpers/inducers), CD4-8+ (cytotoxic T lymphocytes), CD3-16+ (natural killers). To identify the imbalance of immunoregulatory subpopulations of T cells, the immunoregulatory index was calculated - the ratio of the number of CD4+8- Lf and CD4-8+ Lf. To calculate the absolute content in the peripheral blood of individual populations of Lf, leukogram indicators determined on the hematological analyzer ABH-miscros60, France were used. The proliferative activity of lymphocytes was evaluated in cultures of whole blood in the reaction of blast transformation of these cells with morphological accounting of the results. Statistical processing of the obtained data was carried out using licensed software products included in the Microsoft Office Professional 2007 package, license Russian Academic OPEN No Level No. 43437596 in Excel.

Conclusion: In moderate asthma, the frequency of pathological changes in the T-system of immunity did not depend on the presence of comorbid pathology, as a rule. In severe asthma, an increase in the content of pan-T cells occurred 1.2 times more often than in moderate asthma, but this was not observed in people with concomitant pathology. In this group, the frequency of increasing the content of T-helpers and decreasing the content of cytotoxic T-cells in patients with severe asthma without concomitant diseases was 1.3 times more frequent than in patients with comorbid pathology. No pathological changes in the T-system were detected in patients with controlled asthma. In partially controlled asthma, these changes were registered 1.5 times more often than in controlled asthma, and in its uncontrolled course, the prevalence of pathological changes in the T-system of immunity was much higher than in the two previous groups. In patients with concomitant diseases, these changes, as a rule, had a higher frequency than in patients without comorbid pathology.

Keywords:Comorbid pathology; Immunity; Exacerbation of asthma

OPEN ACCESS

Correspondence:
Kuryk Lesya, Department of Pulmonology, F.G. Yanovsky National Academy of Medical Sciences of Ukraine, Ukraine, E-mail: lkurik@gmail.com

Received Date: *05 Sep 2022*
Accepted Date: *19 Oct 2022*
Published Date: *24 Oct 2022*

Citation:
Feshchenko Y, Illyinskaya I, Kuryk L. Pathological Immunity Changes in Comorbid Patients with Exacerbation of Bronchial Asthma. Clin Case Rep Int. 2022; 6: 1410.

Introduction

In the last two decades, researchers have paid considerable attention to the problem of comorbidity in bronchial asthma BA [1-4]. Comorbidity is a combination of several chronic diseases in one patient, which mutually affect each other. It has been proven that the interaction of diseases, their pathomorphosis and age significantly changes the course of the main disease, the nature and severity of complications, worsens the patient's quality of life, limits or complicates the treatment and diagnostic process. It is known that patients with comorbid pathology, including the gastrointestinal tract, which is very common among this category of patients, have an increased risk of developing asthma exacerbations and a greater severity of their course. Comorbidity negatively affects the prognosis of the disease and significantly increases the probability of a fatal outcome. The presence of comorbid diseases leads to an increase in the length of hospitalization, causes disability,

and prevents the implementation of rehabilitation measures [5-12]. Discrepancies in the data of different authors regarding the prevalence of comorbid pathology in patients with asthma, in particular the digestive organs, and its influence on the course of asthma and the features of immunological changes determined the purpose of the work - to investigate immunological changes in patients with exacerbation of bronchial asthma with different severity and controllability depending on the presence comorbid pathology.

Materials and Methods

The work is based on the analysis of the anamnesis data and comprehensive clinical examination of 337 patients with exacerbation of BA and 255 patients who underwent immunological research in the laboratory of clinical immunology. The distribution of patients with exacerbation of BA with different severity and controllability by gender and age is presented in the (Table 1). The analysis of these data showed that in all groups the majority of patients were women, which corresponds to the gender characteristics of this disease. Most of the examined patients with moderate and severe asthma were of working age (86.3% and 87.2%, respectively), while with mild BA - only 46.7% ($p<0.05$).

There was no statistical difference between the fates of patients of different age categories with controlled and partially controlled asthma; however, in the group of patients with an uncontrolled course of the disease, there was a 2.4-fold decrease in the percentage of young and middle-aged patients and a 1.3-fold increase in the number of people elderly ($p<0.05$), which corresponds to the well-known features of BA. Concomitant diseases were recorded in 252 of 337 (74.8%) people, 144 (42.7%) of them had pathology of the digestive organs, and the absence of comorbidity was observed in 85 (25.2%) patients. Among this group, there were 15.4% more men than among the group of patients with concomitant diseases (40.0% and 24.6%, respectively; $p<0.05$). There was no difference in the age composition between the groups (Table 2).

To assess the severity and controllability of asthma, we used criteria based on international recommendations (GINA, 2014) and given in the unified clinical protocol of primary, secondary (specialized) medical care "Bronchial asthma and adapted clinical guidelines for bronchial asthma [13-15].Average severity of asthma exacerbation was determined in 125 (65.8%) patients, severe - in 65 (34.2%). 18 (9.5%) patients had a controlled course of the disease, 131 (68.9%) partially controlled, uncontrolled 41 (21.6%) patients. Comorbid pathology of digestive organs was recorded in 83 (43.7%) patients with exacerbation of BA. The most common diagnosis was cholecysto-cholangitis, which was present in 63 (75.9 %) patients, gastritis, duodenitis and reflux esophagitis were noted in 31 (37.3 %), pancreatitis in 12 (14.5 %), hepatitis in 6 (7.2%), gastric or duodenal ulcer - in 4 cases (4.8%), intestinal candidacies was established in 2 cases. It should be noted that almost a third of these.

Patients had a combined pathology of the digestive organs. The remaining 107 (56.3%) persons with exacerbation of asthma had no comorbid diseases. They were included in the comparison group.The relative content of T-lymphocytes and their main subpopulations was determined on a flow cytofluorimeter FACSCalibur(Canada) by phenotyping lymphocytes with monoclonal antibodies (BECKMAN COULTER, USA) to surface membrane differentiation antigens (CD): CD3+19- (pan T-cells), CD4+8- (T–helpers/inducers), CD4-8+ (cytotoxic T lymphocytes), CD3-16+ (natural killers). To identify the imbalance of immunoregulatory subpopulations of T cells, the Immunoregulatory Index (IRI) was calculated - the ratio of the number of CD4+8- Lf and CD4-8+ Lf. To calculate the absolute content in the Peripheral blood (PC) of individual populations of Lf, leukogram indicators determined on the hematological analyzer ABH-micros 60, France were used. The proliferative activity of lymphocytes was evaluated in cultures of whole blood in the Reaction of Blast Transformation (RBTL) of these cells with morphological accounting of the results [16].

Statistical processing of the obtained data was carried out using licensed software products that were included in the Microsoft Office Professional 2007 package, license OPEN No Level No. 43437596. To confirm the reliability of the difference in the obtained frequency indicators, the method of alternative variation was used with the determination of the student's two-tailed *t*-test. The level of probability was taken as the value of the Probability indicator (p) between groups, which was equal to or less than 0.05 [17,18].

Results and Discussion

WithBA of moderate severity, an increase in the content of pan-T cells was found in 37.7% of patients, and its frequency did not depend on the presence of concomitant diseases. An increase in the content of T-helpers occurred in 22.9% of patients without comorbid pathology, and in its presence, an insignificant increase in the frequency of high

Table 1: Gender and age distribution of patients with bronchial asthma with different severity and controllability.

Course of asthma	Gender				Age								Total	
	men		woman		up to 30 years		31-50 years		51-70 years		older than 70 years			
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Severity of bronchial asthma:														
- medium	61	55.8	159	74.2*	25	70,0	81	86.8	89	45.2	6	3.0	220	61.1
- heavy	35	28.9	82	71.1*	11	9.4*	43	36.8	59	50.4*	4	3.4	117	34.7*
Control of bronchial asthma:														
- controlled	18	36.7	31	63.3*	8	14.6	19	39.0	22	46.3	0	0,0	49	14.5
- partially controlled	53	27.9	137	72.1*	28	14.7	74	37.9	64	43.2	8	4.2	190	56.4#
-uncontrollable	25	25.5	73	74.5*#	5	6.1#•	34	29.6#•	59	60.2#•	3	4.1	98	29.1#•
Total	96	28.5	241	71.5*	41	12.2	127	37.7	145	43.0	11	3.3	337	

Notes:*: Gender differences are statically proven ($p<0.05$); •: the difference of the indicator in comparison with the indicator of the group of patients with BA with its average severity was statically confirmed ($p<0.05$); #: the difference of the indicator in comparison with the indicator of the group of patients with controlled BA was statically confirmed ($p<0.05$);•: the difference of the indicator in comparison with the indicator of the group of patients with controlled BA was statically confirmed ($p<0.05$)

Table 2: Gender and age composition of patients with bronchial asthma with comorbid pathology.

Age and gender	Patients with bronchial asthma							
	Total (n=337)		Without comorbidity (n=85)		With comorbidity (n=252)		Including with concomitant pathology of digestive organs (n=144)	
	n[1]	%	n[1]	%	n[1]	%	n[1]	%
Gender composition								
-men	96	28.5	34	40.0	62	24.6[#]	22	15.3[#]
- women	241	71.5[*]	51	60.0[*]	190	75.4[*#]	122	84.7[*#°]
Age structure								
- up to 30 years	34	10.1	9	10.6	25	9.9	11	7.6
- 30 - 50 years	133	39.5	30	35.3	103	40.9	61	42.4
- 51 - 69 years	156	46.3	42	49.4	114	45.2	64	44.4
- 70 years and more	14	4,2	4	4,7	10	4,0	8	5.6
- average age	48.9±0.7		49.0 ± 1.5		48.9 ± 0.9		50.0 ± 1.5	

Notes:[*]: Gender differences are statically proven (p<0.05); [#]: The difference of the indicator in comparison with the indicator of the group of BA patients without accompanying pathology is statically proven (p<0.05); [°]: The difference of the indicator in comparison with the indicator of the group of patients with BA with accompanying pathology is static

Table 3: Pathological changes of the T-system of immunity in patients with exacerbation of bronchial asthma with different severity of the disease depending on the presence of comorbid pathology.

Indexes	Groups of examinees											
	Total			Without accompanying pathology			With comorbid diseases			With pathology of digestive organs		
	n	n[1]	%	n	n[1]	%	n	n[1]	%	n	n[1]	%
1	2	3	4	5	6	7	8	9	01	11	12	13
Bronchial asthma												
↑pan-T cells	230	84	36.5	105	38	36.2	125	46	36.8	64	24	37.5
↑T-helpers	165	39	23.6	93	21	22.6	72	18	25	40	9	22.5
↓cytotoxic T-lymphocytes		45	27.3		27	29		18	25.0[°]		10	25.0[°]
↑immunoregulatory index		25	15.2		14	15.1		11	15.3		6	15
↑RBTL with FGA	224	25	11.2	102	12	11.8	122	13	10.7	64	8	12.5
Moderate bronchial asthma												
↑pan-T cells	162	61	37.7	86	31	36	84	31	36.9	38	14	36.8
↑T-helpers	143	35	24.5	83	19	22.9	68	18	26.5[°]	32	8	25
↓R of cytotoxic T-lymphocytes		37	25.9		23	27.7		16	23.5[°]		8	25
↑immunoregulatory index		20	14		12	14.5		10	14.7		5	15.6
↑RBTL with FGA	158	16	10.1	83	9	10.8	80	7	8.8	38	4	10,5
Severe bronchial asthma												
↑pan-T cells	74	28	37.8	29	12	41.4[#]	45	16	35.6[°]	25	10	40.0[·]
↑T-helpers	32	5	15.6[#]	20	3	15.0[#]	12	2	16.7[#]	8	1	12.5[·]
↓R of cytotoxic T-lymphocytes		11	34.4[#]		7	35.0[#]		4	33.3[#]		2	25.0[°·]
↑immunoregulatory index		13	17.8		4	20.0[#]		3	25.0[#°]		1	12.5[°·]
↑RBTL with FGA	73	13	17.8	29	7	24.1[#]	44	6	13.6[#°]	25	4	16.0[°]

Notes:[#]: The difference of the indicator in comparison with the indicator of the group of patients with moderate BA was statistically proven (p<0.05); °: The difference of the indicator in comparison with the indicator of the group of BA patients without concomitant diseases was proven statistically (p<0.05); [°]: The difference of the indicator in comparison with the indicator of the general group of patients with BA with concomitant diseases was proven statistically (p<0.05).

content of T-helpers was observed (Table 3).

A decrease in the content of cytotoxic T-lymphocytes was observed in 27.7% of patients with BA of moderate severity without concomitant pathology and 23.5% of patients with concomitant diseases (p<0.05), including one in four patients with diseases of the digestive organs.A high immunoregulatory index was recorded in (14.5 ± 15.6)% of patients with BA of moderate severity, and dependence on the presence of comorbid pathology was not detected.

Every tenth patient with moderate asthma had an increased proliferative response of T cells to mitogen, regardless of the presence of concomitant diseases.In severe asthma, an increase in the content of pan-T cells occurred in 41.4% of patients without concomitant diseases, i.e., 1.2 times more often than in moderate asthma, in 35.6% of patients with comorbid pathology - (p<0.05) and in 40.0% of people with diseases of the digestive organs.

In patients with severe asthma, a decrease in the content of T-helpers was recorded only in 15.0% of cases in the absence of

Table 4: Pathological changes in the T-system of immunity in patients with exacerbation of bronchial asthma with different controllability of the disease depending on the presence of comorbid pathology.

Indexes	Groups of examinees											
	Total			No concomitant pathology			With comorbid diseases			With pathology of digestive organs		
	n	n[1]	%	n	n[1]	%	n	n[1]	%	n	n[1]	%
1	2	3	4	5	6	7	8	9	10	11	12	13
Bronchial asthma												
↑pan-T cells	230	84	36.5	105	38	36.2	125	46	36.8	64	24	37.5
↑T-helpers	165	39	23.6	93	21	22.6	72	18	25	40	9	22.5
↓cytotoxic T-lymphocytes		45	27.3		27	29		18	25		10	25
↑immunoregulatory index		25	15.2		14	15.1		11	15.3		6	15
↑RBTL with FGA	224	25	11.2	102	12	11.8	122	13	10.7	64	8	12.5
Controlled bronchial asthma												
↑pan-T cells	26	9	34.6	5	1	20	21	8	38.1°	8	3	37.5°
↑T-helpers	3	0	0	1	0	0	2	0	0	2	0	0
↓R of cytotoxic T-lymphocytes		1	33.3		0	0		1	50.0°		1	50.0°
↑immunoregulatory index		0	0		0	0		1	50.0°		0	0.0$^{\cdot}$
↑RBTL with FGA	26	3	11.5	6	1	16.7	20	2	10.0°	8	1	12.5
Partially controlled bronchial asthma												
↑pan-T cells	157	48	30.6	77	23	29.9$^{\#}$	80	25	31.3$^{\#}$	45	15	33.3$^{\#}$
↑T-helpers	116	29	25.0$^{\#}$	69	17	24.6$^{\#}$	47	12	25.5	27	7	25.9$^{\#}$
↓R of cytotoxic T-lymphocytes		32	27.6		20	29.0$^{\#}$		12	25.5$^{\#\circ}$		8	29.6$^{\#\cdot}$
↑immunoregulatory index		17	14.7$^{\#}$		11	15.9$^{\#}$		6	12.8$^{\#\circ}$		4	14.8$^{\#}$
↑RBTL with FGA	154	13	8.4	74	6	8.1$^{\#}$	80	7	8.8	46	5	10.9
Uncontrolled bronchial asthma												
↑pan-T cells	37	22	59.5$^{\bullet}$	13	9	69.2$^{\#\bullet}$	24	13	54.2$^{\#\circ}$	11	6	54.5$^{\#\circ}$
↑T-helpers	36	9	25		3	23.1$^{\#}$	23	6	26.1$^{\#}$		2	18.2$^{\#\bullet\cdot}$
↓R of cytotoxic T-lymphocytes		9	25		4	30.8$^{\#}$		5	21.7$^{\#\circ}$		1	9.1$^{\#\bullet\cdot}$
↑immunoregulatory index		6	16.7		1	7.7$^{\#\bullet}$		5	21.7$^{\#\bullet\circ}$		2	18.2$^{\#\circ}$
↑RBTL with FGA	34	5	14.7$^{\bullet}$	12	1	8.3$^{\#}$	22	4	18.2$^{\#\bullet\circ}$	10	2	20.0$^{\bullet\bullet\circ}$

Notes:$^{\#}$: The difference of the indicator in comparison with the indicator of the group of patients with controlled asthma was proven statistically (p<0.05);$^{\#}$: The difference of the indicator in comparison with the indicator of the group of patients with partially controlled asthma was proven statistically (p<0.05); $^{\circ}$: The difference of the indicator in comparison with the indicator of the group of BA patients without concomitant diseases was proven statistically (p<0.05); $^{\cdot}$:The difference of the indicator in comparison with the indicator of the general group of patients with BA with concomitant diseases was proven statistically (p<0.05).

concomitant diseases (p<0.05), in almost the same number of patients with comorbid pathology and in 12.5% - of people with concomitant diseases digestive organs (p<0.05).A decrease in the number of cytotoxic T cells in severe BA was more frequent than in patients with a moderate-severe course of the disease - 1.3 times in people without concomitant diseases(p<0.05) and 1.4 times in its presence (p<0.05). There was no difference in the frequency of reduction in the content of cytotoxic T-lymphocytes in groups of patients with BA with different severity in the presence of concomitant pathology of the digestive organs, but it was significantly lower than in the other two groups of patients with severe (Table 3).

The frequency of pathological changes in the T-system of immunity in patients with exacerbation of BA with different controllability depending on the presence of comorbid pathology is presented in the (Table 4).

No patient with controlled BA showed an increase in the content of T-helpers. A decrease in the content of cytotoxic T-lymphocytes in this group was determined in one patient out of two in the presence of concomitant diseases, and in none - in their absence. An increase in the reaction of ballast transformation in patients with controlled asthma was recorded in 1 of six patients without comorbid pathology (16.7%), in 2 of 20 patients with its presence (10.0%; p<0.05), in including in one out of 6 patients with concomitant diseases of the digestive organs.

In patients with partially controlled BA, a high content of T-cells, was recorded 1.5 times more often in patients without accompanying pathology than in the case of a controlled course of the disease (in 29.9%; p<0.05), and in patients with its presence, - 1.2 times less (p<0.05). In 33.3% of patients with partially controlled BA, in the presence of diseases of the digestive organs, there was an increase in the content of pan-T lymphocytes, which was significantly lower than in controlled BA. In this group, high levels of T-helper cells were determined in every fourth patient, and dependence on the presence of concomitant diseases was not observed.

A decrease in the content of cytotoxic T cells was observed in one third of patients without concomitant diseases and with pathology of digestive organs (p<0.05) and in 25.5% of patients with concomitant diseases (p<0.05). The increased immunoregulatory index occurred

in 15.9% of people without concomitant diseases and 24% more often than in patients with comorbid pathology ($p<0.05$), and the difference in the frequency of this indicator increase in patients with diseases of the digestive organs in comparison with the frequency in the group of patients with controlled asthma without comorbidities, none were identified. An increase in the proliferative response of lymphocytes to FHA was registered in (8.1±10.9) % of patients with partially controlled asthma, and its dependence on the presence of concomitant diseases was not determined.

In patients with uncontrolled BA, the frequency of pathological changes of the T-immune system was much higher than in controlled and partially controlled disease, with maximum indicators in patients without concomitant diseases, while in patients with comorbid pathology, it was, as a rule, significantly lower. However, the frequency of growth of the immunoregulatory index in patients with uncontrolled BA was low and amounted to 7.7%, but in patients with concomitant diseases it was 2.8 times higher, including 2.4 times higher in the presence of diseases of the digestive organs. It was established that in patients with concomitant diseases, high rates of RBTL with FGA were (2.2 and 2.4) times higher than in patients without concomitant pathology.

Conclusion

In moderate BA, the frequency of pathological changes in the T-system of immunity did not depend on the presence of comorbid pathology, as a rule. In severe BA, an increase in the content of pan-T cells occurred 1.2 times more often than in moderate AD, but this was not observed in people with concomitant pathology. In this group, the frequency of increasing the content of T-helpers and decreasing the content of cytotoxic T cells in patients with severe BA without concomitant diseases was 1.3 times more frequent than in patients with comorbid pathology. No pathological changes in the T-system were detected in patients with controlled BA. In partially controlled BA, these changes were registered 1.5 times more often than in controlled BA, and in its uncontrolled course, the prevalence of pathological changes in the T immune system was much higher than in the two previous groups. In patients with concomitant diseases, these changes, as a rule, had a higher frequency than in patients without comorbid pathology.

References

1. Global initiative for asthma. Global strategy for asthma management and prevention. 2021.
2. Feshchenko YI. Adaptovana klinichna nastanova, zasnovana na dokazakh. Bronkhialna astma (Chastyna III). Astma ta alerhiya. 2021;2:5-20.
3. Feshchenko YI, Ilyinska IF, Arefyeva LV, Kuryk LM, Kanarskyi OA, Turchyna IP. Suputnya patolohiya u khvorykh na bronkhialnu astmu. East Eur Sci J. 2021;9(73):8-17.
4. Feshchenko YI, Ilyinska IF, Arefyeva LV, Kuryk LM. Nekontrolovana bronkhialna astma: Suchas nyy stan problem. Astma ta alerhiya. 2018;2:20-5.
5. Nenasheva NM. Obostreniye bronkhial'noy astmy: lecheniye i profilaktika. 2016.
6. Yermolkevich RF, Lapitskiy DV, Metel'skiy SM. Obostreniye bronkhial'noy astmy: Podkhody k diagnostike i lecheniyu. Voyennaya Meditsina. 2011;1.
7. Velychko VI, Bazhora YI, Danylchuk HO. Poshyrenist komorbidnykh staniv ta modyfikovanykh faktoriv ryzyku u patsiyentiv z bronkhialnoyu astmoyu. Simeyna medytsyna. 2019;1(81):119-22.
8. Galimova YS. Zabolevaniya organov pishchevareniya u bol'nykh bronkhial'noy astmoy. Fundamental'nyye issledovaniya. 2010;1:36-40.
9. Cazzola M, Segreti A, Calzetta L, Rogliani P. Comorbidities of asthma: Current knowledge and future research needs. Curr Opin Pulm Med. 2013;19:36-41.
10. Chumak YY. Sovremennyye napravleniya v lechenii bol'nykh bronkhial'noy astmoy s komorbidnymi sostoyaniyami. Problemy ekologicheskoy i meditsinskoy genetiki i klinicheskoy immunologoii. 2013;19(5)349-57.
11. Feshchenko YI, Ilyinska IF, Arefyeva LV. Suputnya patolohiya u khvorykh na bronkhialnu astmu. East Eur Sci J. 2012;9(73):8-17.
12. Vertkin AL. Komorbidnyy patsiyent: rukovodstvo dlya prakticheskikh vrachey. Moskva. 2015:160c.
13. Pro zatverdzhennya ta vprovadzhennya medyko-tekhnolohichnykh dokumentiv zi standartyzatsiyi medychnoyi dopomohy pry bronkhialniy astmi. 2013.
14. Feshchenko YI. Astma: Adaptovana klinichna nastanova, zasnovana na dokazakh. Nats. in-t ftyziatriyi i pulmonolohiyi im. F.G. Yanovskoho, Nats. med. akad. pislyadyplom. osvity im. P.L. Shupyka, Asots. ftyziatriv i pulmonolohiv Ukrayiny. 2019:113.
15. Feshchenko YI, Ilyinska IF, Arefyeva LV. Dyferentsiyuvannya patolohichnykh ta adaptatsiynykh imunolohichnykh mekhanizmiv pry bronkhialniy astmi ta yikh znachennya v prohnozuvanni yiyi nekontrolovanoho perebihu. Astma ta alerhiya. 2020;4:13-24.
16. Babich PN, Chubenko AV, Lapach SN. Primeneniye sovremennyy statisticheskikh metodov v praktike klinicheskikh issledovaniy. Soobshcheniye tret'ye. Otnosheniye shansov: ponyatiye, vychisleniye, interpretatsiya. Ukraíns'kiy medichniy chasopis. 2005;2(46):113-9.
17. Чумак ІО. Sovremennyye napravleniya v lechenii bol'nykh bronkhial'noy astmoys komorbidnymi sostoyaniyami. Problemy ekologicheskoy i meditsinskoy genetiki i klinicheskoy immunologoii. 2013;9(5):349-57.
18. Lapach SN, Chubenko AV, Babich PN. Statisticheskiye metody v mediko-biologicheskikh issledovaniyakh s ispol'zovaniyem Excel. Kiyev Morion. 2001:32.