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IMMUNOLOGICAL RESPONSE CHARACTERISTICS IN INDIVIDUALS WITH OVERLAPPING BRONCHIAL ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Abstract
This study addresses the immunological characteristics of patients with asthma, COPD, and their overlap (ACO). A correlation analysis involving ten clinical and immunological indicators was performed, and based on the relationship between IL-8 and IFN-γ, a prognostic index was developed to assess the likely course of bronchial asthma and COPD overlap. This index enables prediction of disease progression and supports the selection of appropriate therapeutic strategies.

Keywords: BA, COPD, ACO, cytokines, IgE, correlation analysis.

Introduction

In our country, as in many regions worldwide, the prevalence of bronchopulmonary disorders such as bronchial asthma and chronic obstructive pulmonary disease (COPD) continues to increase. The coexistence of these two conditions substantially elevates the likelihood of complications arising both from the primary disease and from comorbid states, which places this issue among the most clinically significant challenges in modern pulmonology [2, 3, 8, 15].

A key question in contemporary clinical practice concerns the mechanisms linking the development of overlapping chronic respiratory diseases—particularly asthma and COPD—with structural and functional alterations in the bronchopulmonary system and immune dysregulation. Numerous authors emphasize that the overlap or mutual layering of bronchial asthma and COPD is often driven by various immune disturbances that diminish host resistance to microbial pathogens [1, 9, 14].

Other researchers argue that the asthma–COPD overlap (ACO) represents a heterogeneous state characterized by different combinations of immune

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abnormalities stemming from two distinct pathophysiological processes. Some patients with ACO exhibit features typical of Th2-mediated atopy, including airway inflammation, eosinophilia, increased IgE levels, and involvement of cytokines such as IL-4, IL-5 and IL-9. In contrast, another subset displays immunological patterns more characteristic of COPD, such as neutrophilic inflammation and disequilibrium of cytokines including IL-6, IL-8 and tumor necrosis factor [4, 7, 20, 25].

Extensive cytokine research underscores their pivotal and multifaceted roles in orchestrating immune, allergic, and inflammatory responses in respiratory pathologies. Emerging evidence on the activity and regulatory functions of these mediators increasingly refines current concepts of pulmonary disease pathogenesis. As understanding of cytokine interactions advances, new opportunities arise for targeted modulation of inflammation and other pathophysiological processes underlying lung injury [5, 6, 11, 16].

Given these considerations, the objective of our study was to evaluate the distinct features of the immune profile in patients presenting with overlapping bronchial asthma and COPD.

Materials and methods:

We examined the immunological parameters in a cohort of 159 individuals diagnosed with various bronchopulmonary disorders. This sample included 62 patients with bronchial asthma (BA), 67 patients with chronic obstructive pulmonary disease (COPD), and 30 individuals with asthma–COPD overlap (ACO). A control group was represented by 20 practically healthy volunteers.

Participants were eligible for inclusion if they had a confirmed diagnosis of asthma and/or COPD and were between 18 and 75 years of age.

Exclusion criteria included:

acute cardiac pathology (e.g., recent myocardial infarction);

cerebrovascular disorders such as stroke or transient ischemic attacks;

malignant tumors of any localization;

advanced renal or hepatic insufficiency;

pregnancy or lactation in women;

severe endocrine diseases;

pronounced autoimmune disorders.

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Quantitative determination of IL-4, IL-8, TNF-α and IFN-γ levels was performed using commercial ELISA kits (LLC "Cytokin", St. Petersburg), following the standard enzyme immunoassay protocol.

Statistical analysis of the collected data was carried out using methods of variation statistics, employing the Fisher–Student criteria as well as Pearson's χ^2 test.

Research Results:

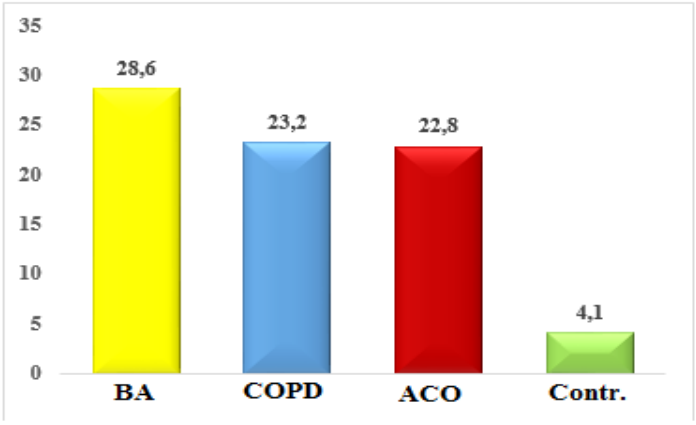
In the present study, we performed a comparative assessment of pro-inflammatory and anti-inflammatory cytokine levels (IL-4, IL-8, TNF-α, IFN-γ) across the examined patient groups (Table 1).

Table 1 The concentration of cytokines in the group of subjects

	BA (n=62)	COPD (n=67)	ACO (n=30)	Counter.
IL-4	28.6±1.7*	23.2±1.5	22.8±1.2	8.7±0.3
IL-8	18.7±1.4	27.8±1.3	39.6±1.1*	11.6±0.4
TNF-α	35.3±2.5	39.7±2.2	46.2±1.7*	21.4±0.1
IFN-γ	11.7±0.6	14.3±1.5*	12.4±0.2	19.1±0.9

Note: *Values are significant in relation to the control group (P<0.05-0.001)

According to numerous studies, Th2-type cytokine-producing cells predominate in the airways affected by asthma. $CD8^+$ lymphocytes, eosinophils, and mast cells are the main sources of IL-4, which may contribute to hyperreactivity of the bronchial tree [10, 13, 19, 24]. Our results demonstrated that IL-4 levels were highest in the BA group (28.6 ± 1.7 pg/ml), exceeding those in the COPD group by approximately 3.97-fold and in the ACO group by 1.25-fold (P < 0.01) (Pic. 1.)



Pic. 1. The level of IL-4 in the groups of subjects

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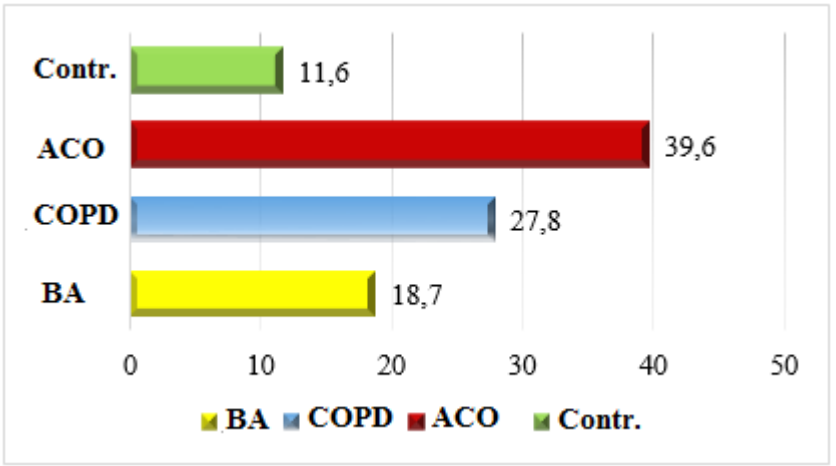
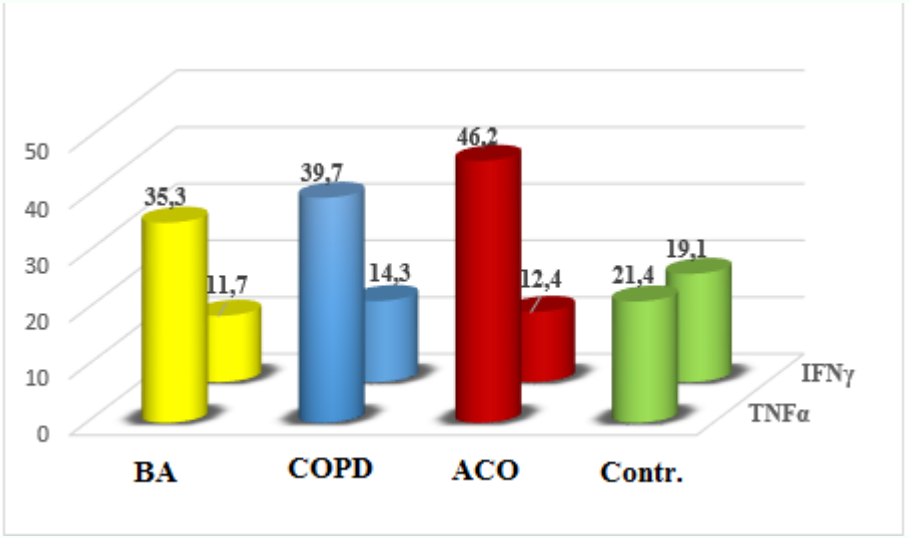
In patients with COPD and asthma–COPD overlap (ACO), elevated IL-8 levels in sputum have been reported, reflecting neutrophil-mediated inflammation [12]. In our cohort, IL-8 concentrations were highest in the ACO group (39.6 ± 1.1 pg/ml), representing a 2.1-fold increase relative to the BA group and 1.42-fold increase compared to the COPD group ($P < 0.01$) (Pic.2)



Pic. 2. The level of IL-8 in the groups of subjects

Analysis of TNF-α levels revealed no significant differences between the BA and COPD groups; however, in the ACO group, TNF-α was elevated by approximately 1.3 times (46.2 ± 1.7 pg/ml, $P < 0.01$), likely reflecting a more intense inflammatory process in these patients.



Pic. 3. The level of TNFα and IFNγ in the groups of subjects

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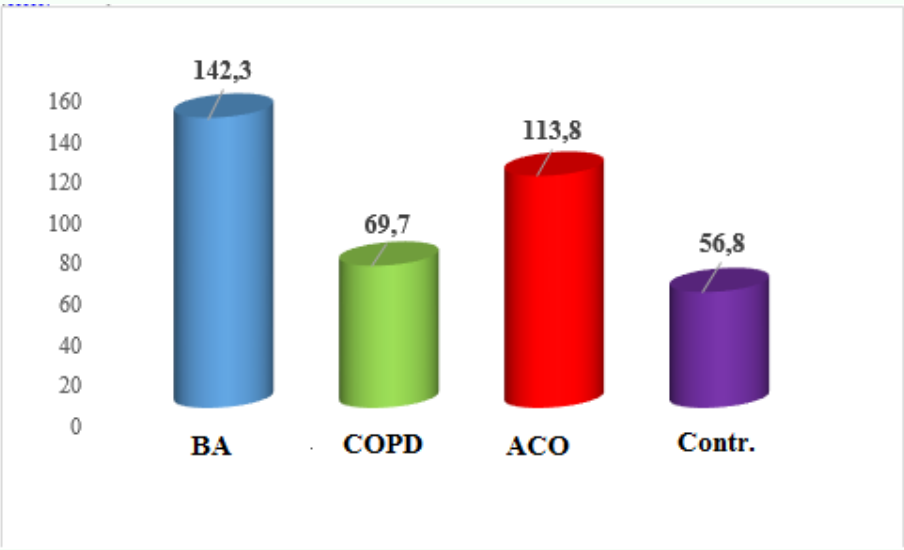
Interferon-gamma (IFN-γ), a marker of Th1-mediated immune responses typically associated with non-allergic inflammation, was reduced across all groups, with the lowest levels observed in the BA group (11.7 ± 0.6 pg/ml, $P < 0.01$).(Pic.3)

A comparative evaluation of pro- and anti-inflammatory cytokines during exacerbations demonstrated that IL-4 synthesis was highest in the BA group, exceeding levels in the COPD group by 3.97-fold and the ACO group by 1.25-fold ($P \leq 0.01$). IL-8 concentrations were elevated in the ACO group, whereas TNF-α showed a notable increase only in the ACO group. IFN-γ was decreased in all groups, most prominently in BA patients. These findings reflect both the type and intensity of airway inflammation, highlighting the contribution of these cytokines to bronchial remodeling and the irreversible nature of obstruction in these diseases. Chronic eosinophilic and neutrophilic inflammation likely underpins these changes, underscoring the pivotal role of cytokines in the pathogenesis of BA, COPD, and ACO, as well as their potential as markers of disease severity.

The main biological role is the unique ability to bind to the surface of human mast cells and basophils [17, 21, 23].

Immunoglobulin E (IgE), synthesized predominantly by mucosal plasma cells, plays a key role in immediate hypersensitivity reactions by sensitizing tissues. Our data indicated a marked elevation of IgE in BA patients (142.3 ± 0.9 ng/ml vs. 56.8 ± 0.6 ng/ml in controls, $P < 0.01$). In COPD and ACO patients, IgE levels were increased by 1.2-fold and 2-fold, respectively (69.7 ± 1.3 ng/ml and 113.8 ± 1.6 ng/ml, $P < 0.01$).



Pic.4. IgE level in examined patients (ng/ml) with BA, COPD, ACO

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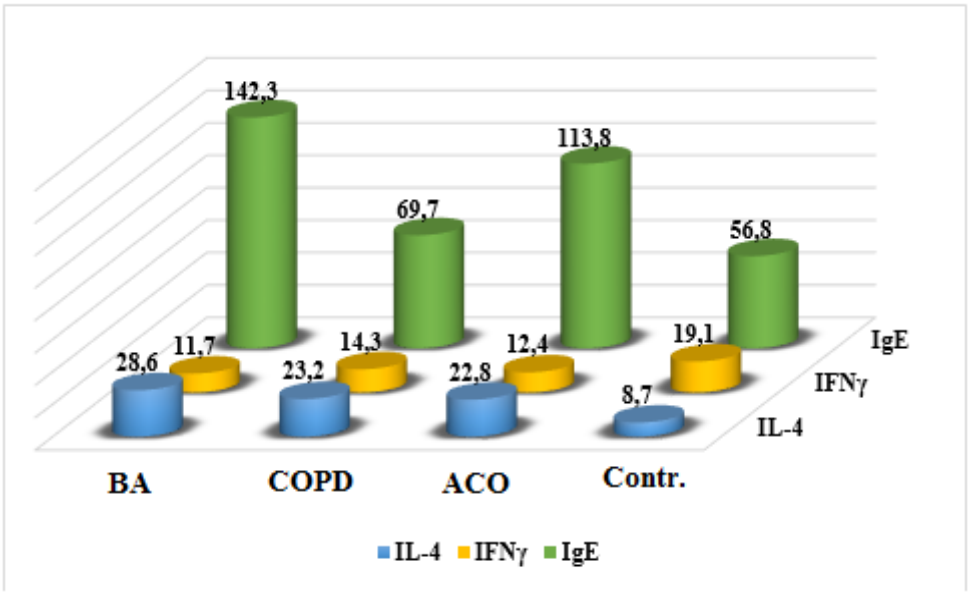
Previous analyses demonstrated a clear correlation between IL-4 and IFN-γ levels and IgE synthesis, especially in BA patients, suggesting a leading role of BA in ACO development. (Pic. 4.).



Pic.5. Level of IL-4, INFγ and IgE in examined patients (ng/ml)with BA, COPD, ACO

IL-4 is crucial for the induction of $CD4^+$-mediated immune responses, defining a distinct inflammatory pattern. While IL-4 primarily contributes to airway inflammation in BA, it also participates in COPD pathogenesis, promoting eosinophilic inflammation and facilitating airway remodeling through growth factor activation [18, 22]. Dysregulation of these immune mechanisms contributes to chronicity and exacerbation of bronchial pathology.

This once again proves that the violation of the mechanisms of immunological reactivity leads to the development of chronicity and aggravation of pathological processes in the bronchial tree.

Next, we carried outcorrelation analysis (Table 1) of clinical and immunological parameters in those examined in the BA group. 16 connections were revealed, of which 10 (r=0-0.3) are positive and 6 are negative. (Table 2.)

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Table 2 Correlation indicators of patients with bronchial asthma

	IL-4	IL-8	TNF-α	IFN-γ	IgE	CRP	LN	Vit D	fibrin	Eoz
IL-4	1									
IL-8	0.04	1								
TNF-α	0.031	0.184	1							
IFN-γ	-0.038	-0.31	-0.0406	1						
IgE	0.11	0.004	0.1151	-0.039	1					
CRP	0.09	0.074	0.2012	-0.041	0.18	1				
LN	-0.27	-0.127	-0.0505	0.111	-0.01	-0.01	1			
Vit D	0.05	0.179	0.1352	-0.029	0.18	0.06	-0.011	1		
fibrin	0.066	0.17	0.1419	-0.051	0.01	0.02	-0.113	0.046	1	
Eoz	0.274	0.143	0.0465	-0.091	-0	0.14	-0.102	0.075	0.1779	1

Correlation analysis of clinical and immunological parameters revealed multiple relationships within each group. In the BA group, 16 correlations were identified, including 10 positive (r = 0–0.3) and 6 negative. IL-4 showed a direct correlation with eosinophils (r = 0.27) and an inverse relationship with lactoferrin (r = –0.27). IL-8 was directly associated with TNF-α (r = 0.18) and vitamin D (r = 0.17), and inversely with IFN-γ (r = –0.31) and lactoferrin (r = –0.12). TNF-α correlated positively with IgE, CRP, vitamin D, and fibrinogen (r = 0.11–0.2), while IFN-γ had a direct relationship with lactoferrin. IgE levels were positively correlated with CRP and vitamin D, and CRP also correlated with eosinophils. Lactoferrin demonstrated three negative correlations with vitamin D, fibrinogen, and eosinophils, which in turn correlated positively with each other.

Table 3 Correlation indicators of patients with COPD

	IL-4	IL-8	TNF-α	IFN-γ	IgE	CRP	LN	Vit D	fibrin	Eoz
IL-4	1									
IL-8	0.078	1								
TNF-α	0.05	0.1	1							
IFN-γ	-0.221	-0.33	-0.0956	1						
IgE	0.073	0.03	0.173	-0.016	1					
CRP	0.03	0.12	0.0079	-0.16	0.02	1				
LN	-0.129	-0.15	-0.052	0.129	-0.01	-0.12	1			
Vit D	0.13	0.16	0.096	-0.008	0.09	0.02	-0.10	1		
fibrin	0.045	0.03	0.0524	-0.199	0.12	0.21	-0.01	0.0494	1	
Eoz	0.073	0.01	0.1524	-0.297	0.13	0.23	-0.15	0.064	0.027	1

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In the COPD group, 22 correlations were observed, 11 positive (r = 0–0.5) and 10 negative (r = –0.11 to –0.33), including direct associations of IL-4 with vitamin D, IL-8 with TNF-α, CRP, and vitamin D, TNF-α with IgE and eosinophils, IFN-γ with lactoferrin, IgE with fibrinogen and eosinophils, and CRP with fibrinogen and eosinophils.

Next, a correlation analysis of clinical and immunological parameters was carried out in the group with ACO.

In the course of studying the correlation values between indicators in the ACO group, 33 relationships were identified, of which 22 were positive and 11 were negative. (Table 4)

Table 4 Correlation parameters of patients with ACO

	IL-4	IL-8	TNF-α	IFN-γ	IgE	CRP	LN	Vit D	fibrin	Eoz
IL-4	1									
IL-8	0.33	1								
TNF-α	0.26	0.01	1							
IFN-γ	-0.13	-0.41	-0.281	1						
IgE	0.24	0.42	0.334	-0.129	1					
CRP	0.24	0.19	0.408	-0.13	0.32	1				
LN	-0.17	-0.21	-0.2026	0.08	-0.02	-0.09	1			
Vit D	0.031	0.16	0.052	-0.08	0.2	0.03	-0.09	1		
fibrin	0.34	0.44	0.1602	-0.19	0.3	0.09	-0.24	0.236	1	
Eoz	0.21	0.19	0.1028	-0.14	0.1	0.21	-0.07	0.22	0.3047	1

The ACO group exhibited 33 correlations, of which 22 were positive and 11 negative. Positive correlations included IL-4 with TNF-α, IgE, CRP, and eosinophils, IL-8 with CRP, vitamin D, and eosinophils, TNF-α with fibrinogen and eosinophils, and IgE with vitamin D, fibrinogen, CRP, and eosinophils. Negative correlations were more frequent in this group, ranging from r = –0.12 to –0.41, particularly between IL-4 and IFN-γ, IL-8 and lactoferrin, TNF-α and IFN-γ, and IFN-γ with IgE, CRP, fibrinogen, and eosinophils.

Overall, 71 weakly significant correlations were identified across BA, COPD, and ACO groups, reflecting complex immunological interactions that likely contribute to more severe bronchopulmonary pathology. IL-8 and IFN-γ were the most variable indicators.

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Based on these findings, we calculated the Index of Prognosis of Course of Disease (IPCD), defined as: IPCD=IL-8/IFN-γ

Originally applied in pediatric cystic fibrosis studies (Fayzullaeva, 2017), the IPCD was <1 in healthy controls (0.6 ± 0.15), increased to 2.96 ± 0.3 in BA patients, 1.61 ± 0.12 in COPD, and 3.19 ± 0.17 in ACO. Higher IPCD values corresponded to more severe clinical manifestations, including prolonged disease course, increased complications, and signs of systemic intoxication. (Table 5)

Table 5 The content of IL-8 and IFNγ in the peripheral blood serum of the examined

Indicators	Examined patients			
	K.gr.	BA	COPD	PBAH
IL-8	11.6	34.7	27.8	39.6
IFNγ	19.1	11.7	14.3	12.4
IPCD	0.60	2.96	1.94	3.19
	(0.45-0.75)	(2.66-3.26)	(1.89-1.99)	(3.02-3.36)

Thus, the IL-8/IFN-γ ratio provides a reliable prognostic and diagnostic marker, offering insights into immune status, guiding therapeutic decision-making, and helping predict disease progression in patients with BA, COPD, and ACO.

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