

## ORIGINAL ARTICLE

# THE MAIN EPIDEMIOLOGICAL AND DIAGNOSTICAL FEATURES OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN SERVICEMEN OF THE ARMED FORCES OF UKRAINE IN THE CONDITIONS OF JOINT FORCES OPERATION

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## ABSTRACT

**The aim:** The aim of the work was to determine the leading epidemiological, diagnostical features, disturbance of spirometric indices, changes in the immune system in servicemen with COPD, who take part in Joint Forces Operation (JFO).

**Materials and methods:** 89 male patients were examined, who sought medical help for COPD, group B. They were divided into two groups. 1 group (42 patients) – with COPD, who took part in the JFO not more than 6 month, the 2 group consisted of 47 patients with COPD, who took part in the JFO during the period more than 6 month.

**Results:** The patients in the group 2 had veraciously more points of cough and sputum expectoration in daily amount of 30 and more ml. The type of sputum in 53.2% patients was predominantly mucus-pus. There were also more percentage of patients with feeling short of breath and the high point, achieved at CAT. There were significant differences in systolic and diastolic blood pressure levels, LV mass index between two groups.

**Conclusions:** It was found that servicemen who took part in JFO for more than 6 months had a more severe course of COPD with a higher score in the CAT and probably lower obstructive ventilatory indices, in a probably higher percentage of cases there were detected such a concomitant pathology as AH stage II and GERD. They had Th17 immune response predomination with significant elevation of IL-17, TGF- $\beta$ , IL-6 concentrations in serum and high concentration of soluble adhesion molecules.

**KEY WORDS:** Obstructive ventilatory defects, immune, external respiration function, fuel combustion products

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## INTRODUCTION

Chronic obstructive pulmonary disease (COPD), according to the WHO expert evaluation, is one of the most common human diseases. It is characterized by a progressive increase of irreversible obstruction as a result of chronic inflammation, which is based on the morphological changes of all structures of the lung tissue with the overlay of cardiovascular system and respiratory muscles into the pathological process [1, 2]. The pathological process begins in bronchial mucosa: in response to the external pathogens the secretory apparatus functions are violated (mucus hypersecretion, bronchial secretions qualitative changes), infection joins, the cascade of reactions develops, leading to the bronchi, bronchioles and surrounding alveoli affect [3].

Clinical observations of the last years confirm a great variety in the disease course of COPD and its heterogeneity in clinical, functional, radiological, and pathomorphological findings that reveal different pathogenetic mechanisms of obstructive syndrome [2]. Inflammation has a key role in the pathogenesis of COPD. It has been confirmed by numerous studies that COPD patients develop significant

elevation of systemic inflammatory markers – interleukin-6 (IL-6), C-reactive protein (CRP), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), fibrinogen and total leukocyte count in the peripheral blood. Studies also show that persistent systemic inflammation predicts poorer prognosis for COPD patients [4, 5].

Over the last decade, the problem of diagnosis and treatment of COPD has become especially relevant for servicemen of the Armed Forces of Ukraine. This is due to the widespread use of smoking on the background of significantly increased psycho-emotional overload, constant work in stress, everyday contact with different dusts, fuel combustion products and, also, the location of certain categories of military, where access to specific instrumental research may be limited.

## THE AIM

The aim of the work was to determine the leading epidemiological, diagnostical features, disturbance of spirometric indices, changes in the immune system in servicemen with COPD, who take part in Joint Forces Operation (JFO).

**Table I.** Basic clinical and diagnostic parameters of servicemen with COPD (M±m)

Parameter	Group 1 (n=42)	Group 2 (n=47)	Probability value (p)
Average age, years	47.3±2.1	48.4±2.2	p>0.05
Duration of participation in JFO, month	4.6±1.4	9.6±1.5	p<0.05
Body mass index, kg/m <sup>2</sup>	27.5±1.5	28.3±1.8	p>0.05
Smocking, n (%)	31 (73.8%)	42 (89.4%)	p>0.05
Smocking index, pack/years	15.4±2.5	29.8±2.9	p<0.05
Contact with fuel combustion products, month	2.3±0.6	4.8±0.5	p<0.05
Cough, points	2.1±0.1	2.8±0.2	p<0.05
Sputum, points	2.8±0.1	3.3±0.1	p<0.05
Sputum's nature:			
mucus, n (%)	26 (61.9%)	22 (46.8%)	p<0.05
mucus-pus, n (%)	16 (38.1%)	25 (53.2%)	p<0.05
Feeling short of breath, n (%)	12 (28.6%)	21 (44.7%)	p<0.05
Dyspnea according to mMRC, points	2.1±0.01	2.3±0.01	p>0.05
CAT, points	15.8±0.4	24.5±0.6	p<0.05
Scattered dry rales, n,%	11 (26.2%)	31 (65.6%)	p<0.05
Voice hoarseness, n (%)	12 (28.6%)	27 (57.4%)	p<0.05
Harsh respiration, n,%	9 (21.4%)	15 (31.9%)	p<0.05
Sa O <sub>2</sub> , %	98.6±0.9	97.6±0.4	p>0.05
Combined pathology:			
GERD, n, %	14 (33.3%)	21 (44.7%)	p<0.05
AH, stage I, n,%	9 (21.4%)	13 (27.7%)	p>0.05
AH, stage II, n,%	2 (4.8%)	11 (23.4%)	p<0.05
Bronchial asthma, n,%	5 (11.9%)	8 (17.1%)	p>0.05

Note: n – number of patients.

**Table II.** Basic functional parameters in patients with COPD (M±m)

Parameter	Group 1 (n=42)	Group 2 (n=47)	Probability value (p)
VC (% out of due)	89.4±2.9	81.8±2.7	p>0.05
FEV1 (% out of due)	72.6±1.7	66.1±1.6	p<0.05
FEV1/FVC (%)	65.6±1.9	64.7±2.2	p>0.05
FVC ((% out of due)	73.5±1.8	64.9±2.1	p<0.05
FEV1 gain, %	3.6±0.8	4.7±1.1	p>0.05
LV mass index, g/m <sup>2</sup>	126.6±3.6	134.4±3.7	p<0.05
Systolic BP, mm Hg	147.3±2.1	163.5±2.7	p<0.05
Diastolic BP, mm Hg	92.6±2.3	98.3±2.1	p<0.05

Note: n – number of patients.

## MATERIALS AND METHODS

In order to solve the presented aim 89 male patients were examined, who sought medical help for COPD, group B. They were divided into two groups. 1 group (42 patients) – with COPD, who took part in the Joint Forces Operation not more than 6 month, the 2 group consisted of 47 patients with COPD, who took part in the Joint Forces Operation during the period more than 6 month. Average age of the patients constituted (47.6±3.4) years; all patients were on examination and hospitalised in the clinics of National Military-Medical Clinical Centre.

Diagnosis of COPD was established according to the Order No. 555 of the Ministry of Health of Ukraine based

on the anamnesis, physical examination, spirometry and post bronchodilator test, results of mMRC and CAT, roentgenography [3]. Written informed consent was obtained from all patients before they had started in the study in accordance with the provisions of the Helsinki Declaration; the study protocol had been agreed with the Bioethics Commission of National Military-Medical Clinical Centre and Bogomolets National Medical University. The research of the external respiration function (ERF) with a characteristic of the main bronchial obstruction indicators (forced vital capacity of lungs (FVCL), pulmonary forced expiratory volume in 1 minute (FEV1) was conducted

**Table III.** Immune and cytokine status of patients with COPD (M±m)

Immunological parameters	Group 1 (n=42)	Group 2 (n=47)	Probability value (p)
CD54 <sup>+</sup> lymphocytes, %	13.1±0.5	18.6±1.1	p<0.05
CD11b <sup>+</sup> lymphocytes, %	19.4±0.9	32.9±1.8	p<0.05
CD62L <sup>+</sup> lymphocytes, %	25.3±1.6	37.2±1.3	p<0.05
TNF-α, pg/mL	118.6±5.7	122.5±6.9	p>0.05
IL-6, pg/mL	27.9±1.3	40.1±2.4	p<0.05
IFN-γ, pg/mL	128.6±3.9	133.9±2.8	p>0.05
IL-4, pg/mL	10.7±0.9	18.1±1.1	p<0.05
TGF-β, pg/mL	89.3±5.4	125.8±8.3	p<0.05
IL-17A, pg/mL	27.3±1.1	58.1±2.6	p<0.05
sVCAM, pg/mL	35.3±1.6	56.1±2.9	p>0.05
sICAM-1, ng/mL	278.3±12.4	345.4±12.7	p<0.05

Note: \* - probability value (p<0,05)

using computer spirometry with the help of the «Spirosift SP-5000» (Fukuda Denshi, Japan). The post-bronchodilator test of bronchial obstruction reversibility was made using 400 mkg of salbutamol. All patients underwent echocardiography with estimation of the left ventricular mass index (LV mass index) to verify hypertension stage.

Levels of pro- and anti-inflammatory cytokines, interleukin-17A (IL-17A), interferon-γ (IFN-γ), content of soluble adhesion molecules sICAM-1, sVCAM-1 were measured by sets certificated in Ukraine for ELISA testing under the methods of «Pro Con» (Russia), «Dialone (France)», transforming growth factor-β (TGF-β) by «Genzyme diagnostics». Lymphocyte subpopulation with phenotypes CD54<sup>+</sup>, CD11b<sup>+</sup>, CD62L<sup>+</sup> were identified using indirect immunofluorescence technique with monoclonal antibodies.

Statistic processing of data was performed using a software package Microsoft XP «Excel» and standard version of Statistical Package for the Social Sciences (SPSS) 17.0. Statistically significant was p-value of p<0.05.

## RESULTS

All the patients had been confirmed to have the main diagnostic criterions for COPD – were older than 40 years, had a long smoking history and clinical and functional signs of the disease (cough with sputum, shortness of breath during exercise; according to spirometry - decrease in FEV1/FVC <70%, irreversible bronchial obstruction, increase in FEV1 <12%.

Table I showed basic clinical, demographic characteristics and the main complaints of the patients. Two groups of patients were randomized according to the age, but such indicators as duration of participation in JFO, smoking index, contact with fuel combustion products were significantly different. More longer term in JFO was accompanied with the great psycho-emotional stress and bad habits – smoking and veraciously higher smoking index.

It should be noted, that the patients in the group 2, who took part in the JFO for the time more than 6 month, had veraciously more points of cough and sputum expectoration

in daily amount of 30 and more ml, which usually excreted in the morning with intense cough. The type of sputum in 53.2% patients was predominantly mucus-pus. There were also more percentage of patients with feeling short of breath and the high point, achieved at CAT. Simultaneously, interviewing showed short breath of 2 scores in both groups using mMRC scale and short breath more than 10 points in both groups using CAT. Herewith all patients were classed to the group B in accordance with the Order No. 555. Frequency of exacerbations in both groups of patients is 0,5 – 1 times per year. The combined pathology in this group of patients was increasingly presented by the gastroesophageal reflux disease at 44.7% cases and arterial hypertension stage II – at 17.1% cases.

Analysis of pulmonary function, patients' complaints, life history and physical examination revealed that all the research participants had the stage 2 of airflow limitation according to GOLD spirometric classification (table II). It also should be noted that in the group 1 obstructive ventilatory defects were less pronounced than in the 2 group. Spirometry showed that obstruction was evaluated as irreversible during the bronchodilation test (gain of FEV1 was less 12%) in all patients.

Since hypertension was observed in both groups of patients, the level of blood pressure was also evaluated. This observation revealed that there were significant differences in systolic and diastolic blood pressure levels, LV mass index between two groups, because 23.4% patients in the 2 group had AH stage II and the 2 level of increasing the BP, instead there were only 4.8% patients with the same stage of AH in the 1 group.

An immunological examination was conducted for all patients, which included the determination of serum concentration of pro- and anti-inflammatory cytokines, the level of soluble adhesion molecules, as well as the expression of activation adhesive molecules on peripheral blood lymphocytes in the examined patients (Table III).

All patients with COPD have been noticed to activate the T-helper cells type 1 of the immune system with a significant prevalence of IFN-γ in blood serum as opposed to other proinflammatory cytokines. Thus, the high serum level of TNF-α was found in both groups. At the same time, an increase in TGF-β serum concentration was found, also in

both groups, which is an immunological feature of bronchial remodelling and the formation of irreversible bronchial obstruction [6], but the higher serum TGF- $\beta$  level was detected in patients of group 2, who had the lower spirometry parameters. At the same time 2 group of patients had higher concentration of IL-17A, TGF- $\beta$  along with increased level of IFN- $\gamma$  and higher level of IL-4. It demonstrated the predomination of Th-17 immune response in this group. This fact also illustrated the immune switching phenomenon from Th1 to Th17 response, which is associated with the prolonged and more severe course of COPD.

Analysis of the data presented in the Table III revealed that patients with COPD and such combined pathology as AH stage II had significantly higher level of activated lymphocytes with different adhesive molecules expression in comparison to patients without AH stage II. Therefore, CD54<sup>+</sup> lymphocytes with ICAM-1 expression level was 41.9% ( $p < 0.05$ ) higher than that of patients of the group 1; CD11b<sup>+</sup> lymphocytes with integrin  $\alpha$ -chain expression level was 69.6% ( $p < 0.05$ ) higher; CD62L<sup>+</sup> lymphocytes (L-selectin that provides adhesion of lymphocytes to endothelial wall) level was 47.1% ( $p < 0.05$ ) higher. This probably was caused by subclinical atherosclerotic inflammation presented in the patients of the group 2 that was accompanied by cell adhesion and aggregation changes that occur during atherosclerotic plaque formation.

High percentage of lymphocytes with adhesion molecules expression in group 1 was combined with high concentration of soluble adhesion molecules in serum. Adhesion molecules play a key role in the immune response and, indeed, in the development of atherosclerotic inflammation since they are expressed on the immune cell surface and bind to their counterparts causing cell adhesion and local accumulation, eventually leading to stasis and thrombosis. Among the early markers that reflect the inflammation activity, especially on early stages of disease, there are ICAM-1, VCAM-1, E-selectin. ICAM-1 is an adhesion molecule from the immunoglobulin family and is expressed on the surface of activated endothelium [5]. High serum concentration of sVCAM was observed in both COPD phenotypes, but was significantly higher in group 2. At the same time, sICAM-1 concentration was 24.1% ( $p < 0.05$ ) higher in the group 2 than that of group 1 high serum concentration of soluble molecules can be explained by concomitant hypertension. Hence, inflammation of higher activity with higher levels of proinflammatory cytokines leads to more vigorous activation of immunocompetent cells and synthesis of adhesion molecules.

Table III shows that the level of proinflammatory cytokines, such as TNF- $\alpha$ , IL-1 $\beta$  and IL-6 was elevated in both groups and did not depend on the term participation in JFO. Also the level of IL-6 was higher in both groups in comparison to the control group, but patients of the 2 group had its concentration 43.7% higher than that in patients of the 2 group.

## DISCUSSION

It was identified that the long time participation in JFO (more than 6 month) led to the psycho-emotional exhaustion and the high level of bad habit – smoking. It should be noted, that contact with the products of fuel combustion that are formed in

the war zone also contributes to the progression of COPD. The high index of smoking, especially in servicemen with asthma and contact with other risk factors, the irreversibility of bronchial obstruction occurs in a shorter time and is manifested by a greater level of reduction FEV1 and FVC. It was established that a long stay in the JFO with psycho-emotional and physical exhaustion overload contributes to the development of such comorbidities as GERD and AH. In summary, we had found significant disorders the level of blood pressure, less indices of FVC and FEV1. Positively higher serum levels of TGF- $\beta$ , IL-4, IL-17A and CD11b<sup>+</sup>, CD54<sup>+</sup> and CD62L<sup>+</sup>-cells were found in patients with the longer time participation in JFO.

Elevated concentration of TGF- $\beta$  reflects a key role of this cytokine in progression of pathologic changes in the bronchial tree. TGF- $\beta$ , as fibrogenous cytokine, is known to stimulate pathomorphologic changes of the bronchial wall and its remodeling, that eventually leads to development of partially reversible or irreversible bronchial obstruction, that is a basis of COPD pathogenesis [4, 6]. TGF- $\beta$  in combination with IL-6 are known to induce the differentiation of peripheral blood T-cells into Th17 and enhance the synthesis of IL-17 [4, 5].

## CONCLUSIONS

1. It was found that servicemen who took part in JFO for more than 6 months had a more severe course of COPD with a higher score in the CAT test and probably lower obstructive ventilatory defects.
2. It was determined that in servicemen who have been in the JFO for a long time in a probably higher percentage of cases there were detected such a concomitant pathology as arterial hypertension stage II and gastroesophageal reflux disease.
3. Servicemen with COPD, who took part in JFO for more than 6 months had Th17 response predomination with significant elevation of IL-17, TGF- $\beta$ , IL-6 concentrations in serum and high concentration of soluble adhesion molecules along with high expression of receptors to adhesion molecules on activated lymphocytes of peripheral blood.

## REFERENCES

1. Oppenheimer J.J. Chronic Obstructive Lung Disease (COPD) Guidelines. 2020. <https://emedicine.medscape.com/article/297664-guidelines> [date access 05.04.2020]
2. Feshchenko Yu.I. et al. Khronichne obstruktyvne zakhvoryuvannya lehen: novi vidtinky problemy: monohrafiya. [Chronic obstructive pulmonary disease: new shades of the problem: a monograph.] Ivano-Frankivsk. SIMYK.2016.400p (in Ukrainian).
3. Nakaz №555 MOZ Ukrayiny vid 27.06.2013r. Pro zatverdzhennya ta vprovadzheniya medyko-tehnolohichnykh dokumentiv zi standartyzatsiyi medychnoyi dopomohy pry khronichnomu obstruktyvnomu zakhvoryuvanni lehen [Order No.555 of the Ministry of Health of Ukraine as of June 27, 2013. On Approval and Implementation of Medico-Technological Documents on Standardization of Medical Care for Chronic Obstructive Pulmonary Disease]. [http://www.moz.gov.ua/ua/portal/dn\\_20130627\\_0555.html](http://www.moz.gov.ua/ua/portal/dn_20130627_0555.html) [date access 05.04.2020] (in Ukrainian).

4. Zou Y., Chen X., Liu J. et al. Serum IL-1 $\beta$  and IL-17 levels in patients with COPD: associations with clinical parameters. *Int J Chron Obstruct Pulmon Disv.* 2017;12:242-253.
5. McGrath J.C., Stampfli M.R. The immune system as a victim and aggressor in chronic obstructive pulmonary disease. *J Thorac Dis.* 2018;10(17):2011–2017.
6. Di Stefano M., Sangiorgi C., Ghemmi I. et al. TGF- $\beta$  signaling pathways in different compartments of the lower airways of patients with stable COPD. *CHEST.* 2018;4: 851-862.

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#### **Conflict of interest:**

*The Authors declare no conflict of interest.*

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