Research Article
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Evaluation of Cytokine Dynamics in Patients with Multiple and Concomitant Closed Chest Injuries

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AIM OF THE STUDY An actual problem of the modern approach to the management of patients in the post-traumatic period with the aim of predicting, preventing and treating complications of post-traumatic pneumonia is the assessment of the dynamics of the cytokine profile in this period.

MATERIAL AND METHODS Investigations were carried out at the time of hospitalization prior medical interventions. During the research the following methods were used: clinical, physical, instrumental, follow-up, radiation (MRI, CT, X-Ray), endoscopic, laboratory.

Blood was taken from the peripheral vein on the first, third, fifth, seventh and ninth day of hospitalization to determine the interlikin profile. The definition of Pro-inflammatory cytokines: IL-1, IL-6 and IL-10 in the blood serum performed by ELISA on the immunofermental analyzer Abbott AXSYM using standard kits ProCon ("Protein contour", St. Petersburg, Russia). Data were processed statistically using Student's t-test.

RESULTS Analysis of the results of determination of IL-1 in the serum of patients DK showed that in all stages of the disease, in addition to IV, the contents of this cytokine exceeded the control values in varying degrees of severity.

While the levels of IL-1 in the serum of patients with the 1ststage of the disease was 4.0 times; stage 2–3.4 times; the third stage is 1.5 times higher than normal. And only in patients with very severe stage of pneumonia contents IL-1 did not differ from the norm.

A similar picture was observed when determining the serum content of patients with a very severe stage of pneumonia, and only in contrast to the level of IL-1 in patients with a very severe stage of pneumonia, the IL-6 content remained significantly higher than normal. So, the content of IL-10 in patients with a very severe stage of pneumonia of stage I, II, III and IV of the disease averaged 330.7±24.5, respectively; 210.5±17.3; 123.4±15.3 and 98.5±12.7 pg/ml (in all cases $p<0.05$).

CONCLUSION The results obtained in a comparative study of contents of proinflammatory cytokines (IL-1, IL-6 and TNF-a) in the blood serum showed that the determination of the spectrum of cytokines in peripheral blood, in our opinion, is the most perspective and can be a key marker for early detection of inflammation.

Key words: post-traumatic pneumonii, interlikin profile, peripheral blood serum

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ALV – artificial lung ventilation

CT – computed tomography

ELISA – enzyme linked immunosorbent assay

IL – interleukin

MRI – magnetic resonance imaging

TBI – traumatic brain injury

INTRODUCTION

Injury to the chest is an extensive and rather diverse group, including both a closed chest injury with multiple bilateral rib fractures and severe deformity of the chest, and an injury to vital organs (lungs and heart) with bilateral open or tension pneumothorax, large hemothorax.

In the general structure of trauma among the population, the proportion of combined chest trauma is 8–10%. Closed injury predominates, with multiple and associated injuries most often characterized by a severe course, and in some cases are one of the main causes of a large number of deaths [1]. The combined trauma of the chest and the musculoskeletal system often leads to severe pulmonary complications, for example, the development of pneumonia, which is largely facilitated by massive blood loss, especially with extensive fractures of the long bones of the limbs and pelvic bones, leading to the development of anemia, hypoxia, and impaired blood coagulation. An aggravating circumstance is the forced prolonged stay of the victims in a motionless state, weakness [2, 3].

Multiple and combined trauma of the chest is accompanied by respiratory and hemodynamic abnormalities, including significant reduction of oxigenic lung function and, consequently, deterioration of blood oxygen [4, 5]. Mortality from nosocomial pneumonia, which is the second most frequently detected among infectious complications, is almost 50% [6, 7], and therefore the treatment and prevention of pneumonia in patients with polytrauma is of particular importance [5, 8–15].

With the formation of complications during a traumatic illness in patients with concomitant trauma, *T*-suppressors are activated and the production of immunoglobulins decreases. In addition, cytotoxic reactions, suppression of proliferative activity, and a decrease in the quantity and quality of cytokines accompany different variants of post-traumatic syndrome. An imbalance in cytokine regulation, rather than proinflammatory cytokinemia, is of primary importance in the development of impaired immunoreactivity [10, 16].

Pneumonia is an acute infectious inflammation of the lung tissue with a predominant lesion of the alveoli with the presence of previously absent clinical and radiological signs of local lesions that are not associated with other known causes [17]. This definition emphasizes the infectious nature of the inflammatory process, excluding pulmonary inflammations of another origin (immune, toxic, allergic, eosinophilic, etc.), for which, in order to avoid terminological confusion, it is advisable to use the term "pneumonitis", traditionally denoting only infectious lesions with "pneumonia" [17]. Infectious pneumonia develops on the 3rd day, and the clinic manifests itself more clearly on the 5th day in connection with the attachment of a variety of pathogenic microflora and at the same time increasing pronounced immunosuppression.

Aim of study: to study and evaluate the dynamics of cytokine indices in the post-traumatic period in patients with multiple and concomitant closed chest trauma to predict and prevent complications.

MATERIAL AND RESEARCH METHODS

The study included patients who gave their consent to participate in it and were inpatient treatment in the Departments of General Surgical Intensive Care, Traumatology, General Surgery and Neurosurgery of Bakhrushins City Clinical Hospital in the period from 2010 to 2019.

The study included 147 victims (56 female and 81 male) with combined and multisystem chest trauma, complicated and not complicated by pneumonia; age-from 16 to 82 years (on average, for women-55.1 ± 6.5, for men-48.2 ± 3.4 years).

In this study victims who underwent tracheotomy or other operations on the respiratory tract were not included, and the use of the apparatus of artificial ventilation (mechanical ventilation) was short that did not result in an additional pathogenetic changes in the development of pneumonia.

It is known that the severity of traumatic brain injury and the nature of comorbid pathology very often determine the ongoing immune changes and determine the outcome of treatment [7, 18–21]. Therefore, the study groups included victims only with concussion, which objectively did not affect the development

of pneumonia. Exclusion criteria: the presence of the affected diseases affecting the immune status-endocrine, autoimmune, infectious, infectious-allergic pathology, diseases of the liver, nervous system and kidneys. The state of the cardiovascular system at all on-suffering was satisfactory, did not affect the nature of the study and the results obtained, the victims had no fundamental differences in the clinical signs, making it possible to obtain objective data at the time of the study. The ratio of multiple and concomitant chest trauma, as well as the compatibility of similar injuries in men and women in percentage terms, were almost the same (Table 1). Multiple and concomitant chest trauma included multiple fractures of the ribs (two or more), collarbone, as well as damage to the pleura, lung and diaphragm. In case of combined injuries, the presence of damage to the chest with fractures of the bones of the extremities, pelvis, spine without compression of the spinal cord, concussion and damage to the abdominal organs was considered.

Table 1

Distribution of patients with chest trauma

The nature of the injury	Women	Men
	n (%)	*n* (%)
Multiple chest injury	22 (39.3)	34 (42.0)
Concomitant injury:	34 (60.7)	47 (58.0)
-chest and bone fractures of the limbs	3 (5.4)	5 (6.2)
-chest and pelvic bone damage	2 (3.6)	2 (2.5)
-chest, spine and abdominal injury	2 (3.6)	2 (2.5)
-chest and minor traumatic brain injury (concussion)	14 (25)	19 (23.5)
-chest, bone fractures of the limbs and mild traumatic brain injury (concussion)	10 (17.9)	15 (18.5)
-chest, spinal injury and mild traumatic brain injury (concussion)	3 (5.4)	4 (4.9)

The severity of the condition in those admitted to the hospital in the first 24 hours after the injury was assessed using the *ISS* scales-combined injury, where the minimum score was 15, and according to the *AIS* scale-multiple trauma – score 3.

As you can see from the Table 2, most of the victims were taken to the admission department of the hospital in the first 6 hours from the moment of injury. Upon admission to a hospital (department of general intensive care, general surgery, traumatology and neurosurgery), after a clinical examination, they were treated in the required amount. Resuscitation measures were carried out according to indications, including the use of artificial lung ventilation (ALV) using a PB-740 apparatus in *CMV* mode (mainly during the first 24 hours) or assisted ventilation, anticoagulant and hormonal therapy, infusion of crystalloid and colloid solutions. For antibiotic therapy, III generation cephalosporins were used. The medical complex also included funds aimed at improving microcirculation, vitamins, systemic medications, symptomatic therapy.

Table 2

Time of admission of victims to the emergency room of the hospital from the moment of injury

Time watch	Women (*n* = 56)		Men (*n* = 81)		*R*
	n	%	*n*	%	
until 6	42	75.0	61	75.3	> 0.05
6-11	12	21.4	17	21.0	> 0.05
12-23	1	1.8	2	2.5	> 0.05
24 and more	1	1.8	1	1,2	> 0.05

The most typical but important methods were used to examine the victims. In addition to follow-up and clinical studies, instrumental studies were carried out. According to the indications, the patients underwent radiography, MRI and CT, fibrobronchoscopy. We carefully studied the clinical and biochemical blood tests.

For the analysis of cytokine profiles, 32 patients with practically the same clinical symptoms, nature and extent of injury were selected, some of whom later developed post-traumatic pneumonia, but there were no other complications. It was from them that blood was taken from a peripheral vein in an amount of 20 ml and centrifuged for 5 minutes at a speed of 1500 / min to separate the plasma. Then the plasma in cryocontainers manufactured by *Nunc* (Denmark) with a block of 1.8 ml containers was frozen at a temperature of-196° C immediately after separation.

In the blood serum enzyme immunoassay analyzer *Abbott "AXSYM ™"* detected proinflammatory and anti-inflammatory cytokines: *IL*-1, *IL*-6 and *IL*-10. To do this, on the 1st, 3rd, 5th, 7th and 9th days after the injury (the days most likely for the development of the first radiological and clinical signs of pneumonia), special test kits were used, separately for each patient.

Statistical analysis of the data obtained was carried out using *Microsoft Excel XP* and *Statistika* 6. Statistical processing of the study data included the creation of tables and diagrams, as well as the analysis of the most important indicators: mean value, standard deviation, standard deviation of the mean, confidence interval and relative error. The statistical significance of the differences between the signs in individual groups was compared using the Student's test (t); the differences were considered statistically significant at a 5% significance level according to the Student's table, p <0.05. There was no statistical significance of differences at p > 0.05.

Analysis of the literature data on the cytokines *IL*-1, *IL*-6, and *IL*-10 [18, 22-28] made it possible to formulate the grounds for the selection of specific cytokines with the properties required for the study.

Rapid response and induction of the synthesis of interleukins *IL*-1, *IL*-6 and *IL*-10 causes the following reactions.

I. Strengthening the expression of interleukins for the formation of a rapid acute phase response.

II. Early response mediators cause the body to react quickly.

For the compilation and analysis of cytokinograms, 4 groups were formed. The criteria for inclusion in a particular group: a) the presence or absence of signs of pneumonia; b) the severity of pneumonia.

I-there are no clinical signs of pneumonia;

II-pneumonia of mild or moderate severity;

III-severe pneumonia;

IV-extremely severe pneumonia.

As you can see from the Table 3, the content of *IL*-1, *IL*-6, *IL*-10 in the studied victims in the first 24 hours of hospital stay practically did not depend on the characteristics and nature of the injuries.

Table 3

The content of IL-1, IL-6, IL-10 (pg / ml) in blood plasma, depending on the severity of the general condition of the victim, taking into account the classification of K.G. Nikulin, L.I. Dvoretsky [19]

Group, severity of pneumonia	*n*	*IL*-1	*IL*-6	*IL*-10	Points *(SOFA)*
Group I, no pneumonia	10	106.5 [3] (99.5; 111.8)	165.2 [2, 3] (160.5; 171.7)	110.2 [2, 3] (107.5; 115.7)	0 [1, 2, 3] (0; 1.0)
Group II, mild to moderate pneumonia	14	105.8 [3] (98.4; 110.4)	167.6 [2, 3] (160.4; 171.3)	110.6 [2, 3] (102.5; 115.5)	2.0 [2, 3] (1.0; 3.0)
Group III, severe pneumonia	5	97.8 [3] (96.9; 103.8)	177.8 (177.3; 183.7)	84.2 (79.8; 84.6)	4.0 (3.0; 5.0)
Group IV, very severe pneumonia	3	91.7 (90.9; 94.9)	187.3 (182.8; 193.7)	79.7 (77.7; 84.1)	5.0 (4.0; 5.0)

Notes: [1] *pu*≤ 0.05 compared to the same indicator in group II; [2] pu≤0.05 compared to the same indicator in group III; [3] pu≤0.05 compared to the same indicator in group IV

In order to assess the results obtained using correlation analysis, the dependence of the interleukin content on the general condition of the victims was determined. The following data were obtained:

-the content of *IL*-1 in blood plasma did not affect the general condition and did not determine its severity; the correlation coefficient *(r)* between them was observed at a fairly low level and amounted to only-0.19;

-the number of *IL*-6 and the general condition of patients were in direct relationship; *r* was +0.57;

-the ratio of the *IL*-10 content and the nature of the general condition of the victims looked different and had an inverse relationship, with *r* being-0.67.

RESEARCH RESULTS

The content of *IL*-1 in the studied patients by groups. In the I group as a first observed at day 9-sedate gradual decrease of its level, while at the affected groups II-IV to 7th days marked "splash" the

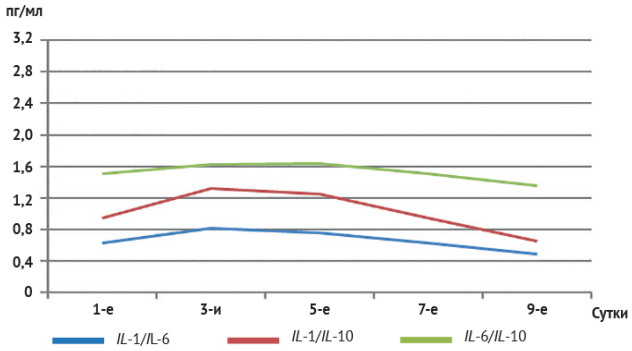
content of this indicator. Later, after 2 days, the picture changed somewhat. In groups II and III, a decrease in the level of *IL*-1 was observed, while in group IV, the trend towards an increase in the level of *IL*-1 continued.

The content of *IL*-6 in the studied patients by groups. The first 7 days of the levels of this cytokine substantially similar indices correspond to *IL*-1 in all four groups. Further, the level of *IL*-6 in the patients of group IV increased sharply, while *IL*-1 remained approximately at the same values.

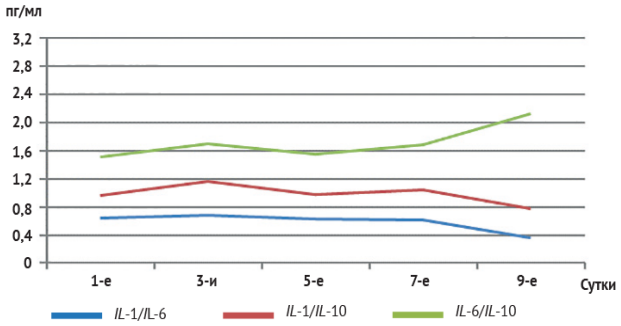
The content of *IL*-10 in the studied patients by groups. Changes in the level of this indicator were similar to those obtained when evaluating *IL*-1 and *IL*-6. The patients of group I showed a gradual decrease in its content in the blood plasma from the moment of admission to the hospital and up to the 9th day. In the affected groups II – III, an increase in the content of *IL*-10 was revealed by the 7th day, and on the next 2 days, on the contrary, a decrease. In the patients of the most severe group (IV), all the first 9 days, there was a tendency for an increase in the content of *IL*-10.

Thus, in the patients of group I, all 9 days, starting from admission, there was a gradual decrease in the content of both *IL*-1 and *IL*-6, and *IL*-10. The dynamics of the studied parameters in the affected groups II – IV showed a significant increase in them on the 7th day, followed by a decrease within two days (except for the IV group, in which the process of increase continued).

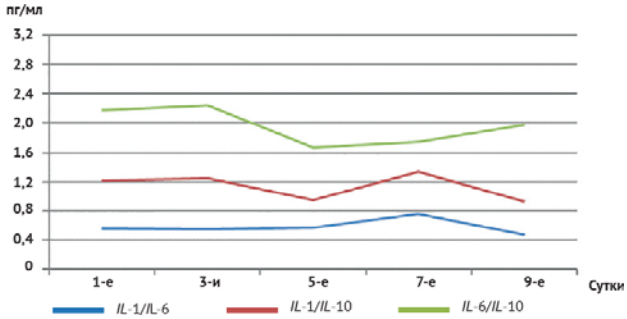
When processing and analyzing the information received, we came to the following conclusion: in the affected groups, the level of interleukins differs not only in absolute quantity, but also in the relationship between them. We would like to draw your attention to the fact that after the admission of patients to the emergency department and during the first 24 hours in groups I and II, the ratio of the content in blood plasma *IL*-I / *IL*-10, *IL*-6 / *IL*-10 and *IL*-1 / *IL*-10 turned out to be less than 1.5 and 1.0, respectively, that is, it was at a lower level than in groups III – IV, in which this ratio was higher than the reference values. The data obtained indicate that with the progression of pathological processes and the aggravation of the general condition of the victims, the values of the *IL*-1 / *IL*-10, *IL*-6 / *IL*-10 indicators become higher. This fact is explained by an objective increase in the content of *IL*-1 and *IL*-6 and is shown on cytokinograms 1-4. Interleukins activate macrophages, fibroblasts and endothelial cells, forming homeostasis. During injury *IL*-1 promotes occurrence fibroblast and platelet growth factor, *IL*-6 and tumor necrosis factor alpha (TNF-α) [7, 20, 29]. The latter, together with the transforming factor of the rostrum, promote an increase in the local content and, accordingly, the proliferation of endothelial cells and fibroblasts in the damaged area [30]. Interleukin, in turn, is involved in the synthesis and appearance of other representatives of the cytokine series. Thus, a series of interdependent biochemical responses to a traumatic state is observed in the body, with an increase in the number of other cytokines and cells [31].



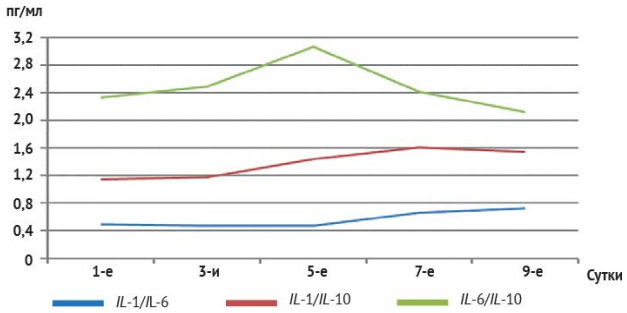
Cytokine panel 1. Patients without pneumonia



Cytokine panel 2. Patients with mild and moderate pneumonia



Cytokine panel 3. Patients with severe pneumonia



Cytokine panel 4. Patients with extremely severe form of pneumonia

Table 4

The content of IL-1 (pg / ml) in the observed victims at different time periods after admission to the hospital [Me (25%; 75%)] with mean values of 30.0 pg / ml as normal

Severity of pneumonia	Type of injury	24 hours from the moment of injury				
		1st	3rd	5th	7th	9th
No pneumonia	Combined, *n* = 5	111.8 * (108.3; 112.0)	104.6 (103.5; 107.7)	81.8 (78.2; 87.5)	67.5 (66.2; 69.4)	58.7 (58.0; 60.2)
	Plural, *n* = 5	99.5 (97.3; 105.7)	100.2 (98.2; 102.8)	84.1 (82.7; 84.3)	72.1 (71.1; 72.4)	61.4 (59.7; 65.9)
Mild to moderate pneumonia	Combined, *n* = 8	109.6 * (105.8; 112.6)	102.6 (99.8; 108.8)	82.7 (75.4; 88.7)	148.5 (140.4; 151.9)	69.2 (65.2; 73.4)
	Plural, *n* = 6	100.5 (96.7; 103.7)	100.6 (99.2; 107.1)	82.8 (78.6; 89.1)	146.0 (137.9; 157.7)	71.4 (69.9; 77.7)
Severe pneumonia	Combined, *n* = 3	103.8 (96.6; 108.9)	98.5 (92.8; 105.7)	99.8 (90.7; 100.1)	140.7 (139.4; 143.4)	87.6 (80.9; 91.5)
	Plural, *n* = 2	96.8 (95.8; 97.8)	94.2 (90.7; 97.8)	93.7 (92.6; 94.6)	144.4 (137.5; 151.2)	80.7 (79.7; 81.7)
Very heavy degree of pneumonia	Combined, *n* = 2	92.9 (90.9; 94.9)	88.2 (81.1; 95.2)	91.1 (83.9; 138.0)	138.0 (134.5; 141.5)	153.1 (150.7; 155.5)
	Plural, *n* = 1	91.7	86.9	90.7	130.3	151.2

Notes: *-pu≤0.05 compared with the indicator in the same follow-up period in patients with multiple trauma

Table 5

The content of IL-6 (pg / ml) in the observed victims at different time periods after admission to the hospital [Me (25%; 75%)] with mean values of 50.0 pg / ml as normal

Severity of pneumonia	Type of injury	24 hours from the moment of injury				
		1st	3rd	5th	7th	9th
No pneumonia	Combined, *n* = 5	171.7 (166.8; 174.1)	165.6 (158.8; 67.6)	150.9 (147.1; 153.7)	138.8 (136.7; 139)	124.5 (112.8; 125.0)
	Plural, *n* = 5	162.5 (160.5; 163.5)	158.3 (157.8; 159,)	145.5 (142.0; 147.7)	133.5 (132.5; 138.1)	117.5 (114.7; 126.1)
Mild to moderate pneumonia	Combined, *n* = 8	168.6 (157.4; 171.5)	161.4 (148.6; 167.3)	147.8 (141.2; 156.2)	188.6 (180.8; 190.2)	176.0 (166.9; 181.0)
	Plural, *n* = 6	166.1 (161.2; 171.3)	160.5 (152.5; 166.8)	152.9 (149.1; 154.3)	182.0 (180.8; 190.5)	170.3 (168.2; 173.4)
Severe pneumonia	Combined, *n* = 3	177.3 (172.6; 183.7)	174.2 (148.6; 178.5)	167.7 (160.7; 172.1)	184.8 (179.3; 191.7)	179.7 (171.9; 185.7)
	Plural, *n* = 2	183.4 (177.8; 189.0)	177.5 (172.4; 182.6)	199.1 (165.1; 174.3)	187.3 (185.7; 188.9)	181.2 (177.7; 184.7)
Very severe pneumonia	Combined, *n* = 2	185.0 (182.8; 187.3)	183.4 (181.2; 185.6)	191.6 (189.4; 193.8)	204.9 (204.7; 205.1)	208.0 (207.5; 208.6)
	Plural, *n* = 1	193.7	192.6	199.1	201.7	210.2

Table 6

The content of IL-10 (pg / ml) in the observed patients at different time periods after admission to the hospital [Me (25%; 75%)] with mean values of 18.0 pg / ml as normal

Severity of pneumonia	Type of injury	24 hours from the moment of injury				
		1st	3rd	5th	7th	9th
No pneumonia	Combined, *n* = 5	112.8 (110.7; 115.7)	98.8 (96.7; 100.7)	92.8 (88.7; 94.6)	88.3 (80.9; 88.9)	80.2 (75.7; 82.9)
	Plural, *n* = 5	107.7 (107.5; 109.7)	101.5 (91.7; 102.2)	94.7 (87.7; 95.6)	86.7 (82.3; 87.1)	81.1 (79.5; 81.8)
Mild to moderate pneumonia	Combined, *n* = 8	112.6 (109.3; 117.8)	98.4 (95.0; 105.4)	90.1 (89.2; 108.1)	107.9 (98.0; 113.1)	89.8 (87.2; 94.5)
	Plural, *n* = 6	105.7 (99.6; 110.1)	95.3 (89.7; 99.7)	89.6 (84.5; 93.8)	103.4 (98.7; 112.8)	90.2 (85.9; 92.7)
Severe pneumonia	Combined, *n* = 3	84.6 (79.8; 87.0)	80.8 (71.2; 81.4)	104.6 (93.4; 108.1)	105.5 (98.0; 109.8)	88.7 (87.6; 97.7)
	Plural, *n* = 2	81.7 (79.2; 84.2)	78.8 (78.7; 78.8)	100.1 (99.7; 100.5)	109.4 (108.2; 110.7)	90.4 (90.2; 90.6)
Very heavy degree of pneumonia	Combined, *n* = 2	80.9 (77.7; 84.1)	74.2 (71.4; 76.9)	65.7 (63.7; 67.7)	83.6 (81.4; 85.7)	98.4 (95.9; 100.9)
	Plural, *n* = 1	79.7	76.8	59.0	86.5	98.7

DISCUSSION

Pathological conditions are manifested, among other things, by an inflammatory response, in which an excess of the production of future neurotoxic mediators, a hyper-amount of *IL*-1 and other pro-inflammatory cytokines is detected. The latter are directly involved in systemic and local changes. During this process, a decrease in the number of anti-inflammatory cytokines (*IL*-10, etc.) and neurotrophic factors responsible for the nature and manifestation of inflammation, a decrease in the production of pro-inflammatory cytokines are also formed. In this way, the severity of tissue damage is controlled. One of the main qualities of *IL*-1 is the ability to positively influence the growth of antigen-sensitive *T*-lymphocytes. At the same time, *IL*-1 is not considered a growth factor for *T*-lymphocytes. It induces the synthesis of *IL*-2 and *IL*-4, which are growth factors secreted by *T-helper (Th)* [25-28, 32, 33].

At the same time, *IL*-1 increases the contrast of receptors for *IL*-2 and *IL*-4, forming the prerequisites for autocrine correction of the proliferation of *T-helper*. The latter, secreting *IL*-4, maximally dynamically activate the production of *IL*-1.

IL-1, in addition to belonging to a special immune response, is also one of the main factors that is responsible for the formation of two nonspecific defense models-local inflammation and acute phase reaction of the body as a whole when it is affected by an infection [23-28, 33-37]...

IL-6 is one of the most potent cytokines that shape and mediate the inflammatory process and immune response. This is due to the fact that it has a greater number of biotechnological targets and cellular sources of production.

The latter can be several types of cells: keratinocytes, fibroblasts, monocytes-macrophages, *T-helper* lymphocytes and endothelial cells [23, 38].

Various factors, viruses, bacteria, influencing cells, create conditions for the rapid synthesis of *IL*-6. The active and characteristic response to all these internal and external agents suggests that *IL*-6 is a member of the group of early mediators. This feature plays an important role in the active response of the body as a whole to the appearance of pathological agents or after tissue damage.

The set of medico-biological effects of *IL*-6 is quite diverse and manifests itself not in the excessive proliferation of cells for the intended purposes, but in the possibility of their differentiation at the last stages of development. As such a factor, *IL*-6 is involved in the transformation of antisuppressors of antigen-specific cytotoxic leukocytes into complete effectors of cell lysis. The differentiating capabilities of *IL*-6 have something to do with *B* cells. At the same time, the absence of stimulating properties for growth does not prevent it from actively participating in the preparation for the synthesis and transformation of cell antibodies into their energetic producers [22, 24–30, 35, 39].

The characteristic features of *IL*-6 allow this cytokine to be included in the category of the main internal controllers of inflammatory responses and immune responses in the body.

IL-10 carries vivid anti-inflammatory characteristics, including in the fight against fever, it is reproduced by *T*-cells and is practically a direct antagonist of pro-inflammatory cytokines (in our study, *IL*-1 and *IL*-6). It destroys their derivatives, there is a reactive proliferation of *T*-cells for antigens. Also, one of its main properties is the ability to suppress the release of *TNF*-(leukocyte interferon) and *IL*-1 *b* and *IL*-6 by activated monocytes. Moreover, at the same time, *IL*-10 has the ability to improve the synthesis of immunoglobulin *IgE*. In total, all these possibilities stimulate the formation of an immune response according to the humoral type [22, 40].

When analyzing the data obtained, we came to the conclusion that the content of *IL*-6 and *IL*-10 depends on the severity of the disease in the victims and has an important diagnostic value, while the content of *IL*-1 has very insignificant variability and practically does not differ from constants. This confirms the relevance of a comparative enzyme-linked immunosorbent assay according to various other sources [7, 15-17, 20-31, 33, 35-37, 41-44], which undoubtedly shows interest in the search for new approaches to predicting complications, the possibility of prevention and timely adequate therapy (immunocorrection) of post-traumatic complications and confirms the semantic load of interleukins for clinical research.

CONCLUSION

The study and assessment of the body's immune capabilities in combination with the implementation of previously adopted and positively recommended clinical, laboratory and instrumental research methods in patients with multiple and concomitant trauma suggest that the appearance of the first signs of pneumonia coincides with a change in the content of interleukins in the blood (see cytokinograms) by 3-and-5th day, which is comparable to the shock state of the victim and is accompanied by the formation of a cytokine cascade, and this, despite the relatively small number of observations, can still contribute to the diagnosis of pneumonia in the early stages and the appropriate therapy.

The body's immune response begins in the first hours after injury. However, changes in interleukin parameters appear by the 3-5th day.

With a positive dynamics of traumatic illness on the first day, the levels of *IL*-1 and *IL*-10 significantly increase in the victims, while the *IL*-6 indicators increase more slowly. The following relationships were identified: *IL*-1 / *IL*-10 <1.0; *IL*-6 / *IL*-10 <1.5. When the negative dynamics of pathological changes in the same time period there was an inverse pattern: enough marked increase in the level of *IL*-6 and minor-*IL*-1 and *IL*-10. The ratios were as follows: *IL*-1 / *IL*-10> 1.0; *IL*-6 / *IL*-10> 1.5.

Thus, the results obtained in a comparative study, the content of pro-and anti-inflammatory cytokines (*IL*-1, *I* L-6 and *IL*-10) in blood serum showed that the determination of the spectrum of cytokines in the peripheral blood, in our opinion, is promising and may be a key marker for early detection of inflammation; it is necessary and highly informative for the immunoassay monitoring of the post-traumatic period at different time intervals. We would also like to note that the timely compilation and analysis of cytokinograms makes it possible to improve the diagnosis and prediction of the development of post-traumatic pneumonia in patients with multiple and concomitant chest injuries, to optimize and carry out adequate therapeutic measures. The data obtained make it possible to develop in more detail a program of immunocorrection in this category of patients for the prevention of post-traumatic complications.

CONCLUSION

1. In the early post-traumatic period in patients with chest trauma, there is a dramatic increase in the production of pro-and anti-inflammatory cytokines, which is a nonspecific response of the body to injury.

2. Production of pro-and anti-inflammatory cytokines in the uncomplicated course of the post-traumatic period by the 9th day tends to normalize. When pneumonia occurs, the content of all cytokines increases again by 5-7 days and tends to normalize after 9 days in all patients, except for patients with extremely severe pneumonia. In patients with extremely severe pneumonia, the content of all cytokines continues to increase.

3. The production of pro-and anti-inflammatory cytokines in the first day of the post-traumatic period predetermines the severity of subsequent purulent-septic complications. As the subsequent pneumonia aggravated, the production of the anti-inflammatory cytokine *IL*-10 becomes statistically significantly lower, accounting for 72.3% (p <0.05) of the *IL*-10 level in patients without further development of pneumonia. The production of pro-inflammatory interleukin *IL*-1 is 86.1% (p <0.05, statistically significant), and the production of pro-inflammatory interleukin *IL*-6 increases, amounting to 113.4% (p <0.05) on the 1st day.

REFERENCES

1. Khromov BM. Pervaya pomoshch' pri travmakh i transportirovka postradavshikh. Leningrad: Meditsina. Leningr. otd-nie Publ., 1969. (in Russ.).
2. Bondarenko SE, Filippenko VA, Leontieva FS, Tankut VO, Zhygun AI, Akondjom M. Biochemical and Immunological Markers in Patients with Posttraumatic Avascular Necrosis of the Femoral Head and Extend Fracture-Dislocation of the Hip. Trauma. 2016;17(4):79–85 (in Russ.) https://doi.org/10.22141/1608-1706.4.17.2016.77495
3. Chiu JF, Lan SJ, Yang CY, Wang PW, Yao WJ, Su LH, et al. Long-term vegetarian diet and bone mineral density in postmenopausal Taiwanese women. *Calcif Tissue Int.* 1997 Mar;60(3):245–249. PMID: 9069160 https://doi.org/10.1007/pl00005812.
4. Zou W., Restifo N.P. T(H)17 cells in tumour immunity and immunotherapy. *Nat Rev Immunol*. 2010 Apr;10(4):248–256. PMID: 20336152. https://doi.org/10.1038/nri2742.
5. Kim M-H, Choi M-K, Sung C-J. Bone mineral density of Korean postmenopausal women is similar between vegetarians and nonvegetarians. *Nutr Res*. 2007;27:612–617. https://doi.org/10.1016/j.nutres.2007.07.006
6. Kotel'nikov GP, Mironov SP (eds). Travmatologiya. Moscow: GEOTAR-Media Publ., 2017. (in Russ.).
7. Kaur M. Prevalence and associated risk factors of osteoporosis in post-menopausal women in North India. *Mal J Nutr.* 2013;19(3):285–292.
8. Sokolov VA. Dorozhno-transportnye travmy. Moscow: GEOTAR-Media Publ.; 2009. (in Russ.).
9. Barr SI, Prior JC, Janelle KC, Lentle BC. Spinal bone mineral density in premenopausal vegetarian and nonvegetarian women: cross-sectional and prospective comparisons. *J Am Diet Assoc*. 1998 Jul;98(7):760–765. PMID: 9664916 https://doi.org/10.1016/S0002-8223(98)00172-2.
10. Lau EM, Kwok T, Woo J, Ho SC. Bone mineral density in Chinese elderly female vegetarians, vegans, lacto-vegetarians and omnivores. *Eur J Clin Nutr*. 1998 Jan;52(1):60–64. PMID: 9481534 https://doi.org/10.1038/sj.ejcn.1600516.
11. Outila TA, Kärkkäinen MU, Seppänen RH, Lamberg-Allardt CJ. Dietary intake of vitamin D in premenopausal, healthy vegans was insufficient to maintain concentrations of serum 25-hydroxyvitamin D and intact parathyroid hormone within normal ranges during the winter in Finland. *J Am Diet Assoc*. 2000 Apr;100(4):434–41. PMID: 10767899 https://doi.org/10.1016/S0002-8223(00)00134-6.
12. Siani V, Mohamed EI, Maiolo C, Di Daniele N, Ratiu A, Leonardi A, et al. Body composition analysis for healthy Italian vegetarians. *Comparative Study Acta Diabetol.* 2003 Oct;40 Suppl 1:S297–298. PMID: 14618498. https://doi.org/10.1007/s00592-003-0091-1.
13. Fontana L, Shew JL, Holloszy JO, Villareal DT. Low bone mass in subjects on a long-term raw vegetarian diet. *Arch Intern Med*. 2005 Mar 28;165(6):684–689. PMID: 15795346. https://doi.org/10.1001/archinte.165.6.684.
14. Wang YF, Chiu JS, Chuang MH, Chiu JE, Lin CL. Bone mineral density of vegetarian and non-vegetarian adults in Taiwan. *Asia Pac J Clin Nutr*. 2008;17(1):101–106. PMID: 18364334
15. Ho-Pham LT, Nguyen PLT, Le TTT, Doan TAT, Tran NT, Le TA, et al. Veganism, bone mineral density, and body composition: a study in Buddhist nuns. *Osteoporos Int*. 2009 Dec;20(12):2087–2093. PMID: 19350341 https://doi.org/10.1007/s00198-009-0916-z. Epub 2009 Apr 7.
16. Pobedenniy AL. Content of Cytokine in Serum of the Patients with Traumatic Brain Injury During Postoperative Period. *Journal of Clinical and Experimental Medical Research*. 2013;1(1):97–99 (in Russ.).
17. Ananchenko VG, Vakolyuk RM, Vasilenko VV, Vinogradov DL, Gryaznova NA, Dvoretskiy LI; Dvoretskiy LI. (ed.). *Vnutrennie bolezni: rukovodstvo k prakticheskim zanyatiyam po gospital'noy terapii*. Moscow: GEOTAR-Media Publ.; 2010. (in Russ.).

18. Shiganova AM, Vyzhigina MA, Bunatyan KA, Inviyaeva EV, Vinnitskiy LI, Balayan OV, et al. The Role of Immune Monitoring in Major Liver Resections from the Position of the Operative Trauma and Anaesthesia Protection. *Anesteziologiya i Reanimatologiya*. 2013;2: 30–34. (in Russ.)
19. Dvoretskiy LI. Pnevmonii. RMJ.1996; 4(11):1. (in Russ.).
20. Li Y-M, Liu S-H. Estimation of the 10-year probability of osteoporotic fracture in postmenopausal Taiwanese women with FRAX. *Tzu Chi Med J*. 2010;22(1):29–35. https://doi.org/10.1016/S1016-3190(10)60032-8
21. Knurick JR, Johnston CS, Wherry SJ, Aguayo I. Comparison of correlates of bone mineral density in individuals adhering to lacto-ovo, vegan, or omnivore diets: a cross-sectional investigation. *Nutrients*. 2015 May 11;7(5):3416–3426. PMID: 25970147 https://doi.org/10.3390/nu7053416
22. Dyukarev VV, Yudina SM, Korolev AG. Immunopathology, allergology, infectology 2018; (3):27–32. (in Russ.) https://doi.org/10.14427/jipai.2018.3.27
23. Dash N, Kushwaha A. Stress fractures-a prospective study amongst recruits. *Med J Armed Forces India*. 2012 Apr;68(2):118–122. PMID: 24669048 https://doi.org/10.1016/S0377-1237(12)60021-5. Epub 2012 Apr 21.
24. Lousuebsakul-Matthews V, Thorpe DL, Knutsen R, Beeson WL, Fraser GE, Knutsen SF. Legumes and meat analogues consumption are associated with hip fracture risk independently of meat intake among Caucasian men and women: the Adventist Health Study-2. *Public Health Nutr*. 2014;17(10):2333–2343. PMID: 24103482 https://doi.org/10.1017/S1368980013002693
25. Blake GM, Fogelman I. The role of DXA bone density scans in the diagnosis and treatment of osteoporosis. *Postgrad Med J*. 2007 Aug;83(982):509–517. PMID: 17675543 https://doi.org/10.1136/pgmj.2007.057505.
26. National Heart, Lung, and Blood Institute, National Institutes of Health. *Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies*. 2017. Available at: https://www.nhlbi.nih.gov/health-topics/study-quality-assessmenttools. (Accessed April 5, 2021).
27. Ambroszkiewicz J, Klemarczyk W, Gajewska J, Chełchowska M, Franek E, Laskowska-Klita T. The influence of vegan diet on bone mineral density and biochemical bone turnover markers. *Pediatr Endocrinol Diabetes Metab*. 2010;16(3):201–204. PMID: 21092700
28. Bobić J, Cvijetić S, Barić IC, Satalić Z. Personality traits, motivation and bone health in vegetarians. *Coll Antropol*. 2012 Sep;36(3):795–800. PMID: 23213935
29. Krivosíková Z, Krajcovicová-Kudlácková M, Spustová V, Stefíková K, Valachovicová M, Blazícek P, et al. The association between high plasma homocysteine levels and lower bone mineral density in Slovak women: the impact of vegetarian diet. *Eur J Nutr*. 2010 Apr;49(3):147–153. PMID: 19809862 https://doi.org/10.1007/s00394-009-0059-1. Epub 2009 Oct 7.
30. Shesternya NA, Ivannikov SV, Tarasov DA. Plazmennaya koagulyatsiya v travmatologii i ortopedii. Moscow: Binom. *Laboratoriya znaniy Publ*., 2015. (in Russ.).
31. Kudlay DA, Efremov AV, Nacharov YuV, Samsonova EN. Osobennosti dinamiki soderzhaniya provospalitel'nykh tsitokinov interleykina-1β, interleykina-6 i interferona-γ v syvorotke krovi bol'nykh s sochetannoy i mnozhestvennoy travmoy, soprovozhdayushcheysya rabdomiolizom. *Bulletin of the Russian Military Medical Academy*. 2007;1(17):49–52. (in Russ.).
33. Leung SS, Lee RH, Sung RY, Luo HY, Kam CW, Yuen MP, et al. Growth and nutrition of Chinese vegetarian children in Hong Kong. *J Paediatr Child Health*. 2001 Jun;37(3):247–253. PMID: 11468039 https://doi.org/10.1046/j.1440-1754.2001.00647.x.
35. Thorpe DL, Knutsen SF, Beeson WL, Rajaram S, Fraser GE. Effects of meat consumption and vegetarian diet on risk of wrist fracture over 25 years in a cohort of peri- and postmenopausal women. *Public Health Nutr*. 2008 Jun;11(6):564–572. Epub 2007 Aug 9.PMID: 17686206 https://doi.org/10.1017/S1368980007000808
36. Haroon NN, Marwaha RK, Godbole MM, Gupta SK. Role of B12 and homocysteine status in determining BMD and bone turnover in young Indians. *J Clin Densitom*. Jul–Sep 2012;15(3):366–373. PMID: 22521537 https://doi.org/10.1016/j.jocd.2012.01.006. Epub 2012 Apr 20.
37. Kim SY, Kim HH, Nam CM, Kim HC, Suh I, Kang YB. Association of estrogen receptor-alpha gene polymorphism with pathogenesis of osteoporosis in Korean vegetarian men. *Med Princ Pract*. 2010;19(3):200–205. PMID: 20357503 https://doi.org/10.1159/000285288. Epub 2010 Mar 29.
32. Zharkova IV, Kabirova MF, Gerasimova LP, Kogina EN. Local Cytokine Status of Patients with Chronic Mechanical Trauma of the Oral Mucosa and Type 1 Diabetes Mellitus. *Actual Problems in Dentistry*. 2018;14(1):16–18/ (in Russ.) https://doi.org/10.24411/2077-7566-2018-00003
34. Saxena A., Khosraviani S., Noel S., Mohan D., Donner T., Rahim A., et al. Interleukin-10 paradox: A potent immunoregulatory cytokine that has been difficult to harness for immunotherapy. *Cytokine*. 2015;74(1):27–34. PMID: 25481648. https://doi.org/10.1016/j.cyto.2014.10.031.
38. Zhou L., Ivanov I.I., Spolski R., Min R., Shenderov K., Egawa T., et al. LittmanIL-6 programs T(H)-17 cell differentiation by promoting sequential engagement of the IL-21 and IL-23 pathways. *Nat Immunol*. 2007;8(9):967–974. PMID: 17581537 https://doi.org/10.1038/ni1488.
39. Tanaka T., Narazaki M., Kishimoto T. IL-6 in Inflammation, Immunity, and Disease. *Cold Spring Harb Perspect Biol*. 2014;6(10):a016295. PMID: 25190079. https://doi.org/10.1101/cshperspect. a01629
40. Hangody L, Vásárhelyi G, Hangody LR, Sükösd Z, Tibay G, Bartha L, et al. Autologous osteochondral grafting-technique and long-term results. *Injury*. 2008 Apr;39 Suppl 1:S32–39. PMID: 18313470. https://doi.org/10.1016/j.injury.2008.01.041.
41. Zenewicz L.A., Yancopoulos G.D., Valenzuela D.M., Murphy A.J., Karow M., Flavell R.A. Interleukin-22 but not interleukin-17 provides protection to hepatocytes during acute liver inflammation. *Immunity*. 2007;27(4):647–659. PMID: 17919941. https://doi.org/10.1016/j.immuni.2007.07.023.
42. Hunt IF. Bone mineral content in postmenopausal vegetarians and omnivores. *Adv Nutr Res*. 1994;9:245–255. PMID: 7747669 https://doi.org/10.1007/978-1-4757-9092-4_14.
43. Mangels AR. Bone nutrients for vegetarians. *Am J Clin Nutr*. 2014 Jul;100 Suppl 1:469S-475S. PMID: 24898231 https://doi.org/10.3945/ajcn.113.071423.
44. New SA. Do vegetarians have a normal bone mass? *Osteoporos Int*. 2004 Sep;15(9):679–688. PMID: 15258721 https://doi.org/10.1007/s00198-004-1647-9. Epub 2004 Jul 16.

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