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Post-traumatic stress disorder: Clinical and laboratory changes and potential for immune disorders

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Background. The spread of post-traumatic stress disorder (PTSD) and overcoming its consequences, including immune-related disorders, is one of the critical issues requiring extensive study and resolution in practical medicine, particularly under present conditions in Ukraine.

Materials and methods. The study group consisted of 79 (27.5%) patients with verified PTSD: 46 (58.2%) female and 33 (41.8%) male, with an average age of 38.7±7.2 years; a control group of 20 apparently healthy people was used. The National Institute of Mental Health (NIMH) American National Center for PTSD (2013) questionnaire was used to verify PTSD. In addition, history taking, clinical examination, general and biochemical laboratory tests, and statistical analysis were performed.

Results. All patients with PTSD experienced clinical disorders and changes in laboratory indicators, with a probable increase in absolute and relative values of neutrophils and mononuclear cells, an increase in the levels of acute phase proteins, and activation of transaminases. In addition, these patients were characterized as immunocompromised patients with the potential to study immunological disorders.

Conclusions. The results of the review of the scientific literature and the clinical and paraclinical manifestations that we found in patients with PTSD indicate the role of immune mechanisms in the development of this syndrome and necessitate expanding diagnostic measures among such patients with the different pathogenetic approach of their management.

Keywords: Post-Traumatic Stress Disorder, COVID-19, Post-Infectious Disorders, Immunocompromised Patients.

Introduction

The 21st century was called the "century of trauma" by the famous psychologist Robert Emmons [6]. The COVID-19 pandemic has become a traumatic psychophysical factor on a global scale. It has led to mass deaths, the manifestation of post-COVID complications, disability, and loss of mental health with the formation of post-traumatic stress disorder (PTSD) [30]. Post-traumatic stress disorder is a severe mental condition resulting from a traumatic event [4]. PTSD occurs as a delayed or prolonged reaction to a stressful event or situation (short-term or long-term), which has the subjective nature of a threat or disaster and can cause general distress in almost every person. The term "post-traumatic stress disorder" was first introduced in the USA (1960–1970) [17]. In the setting of the COVID-19 pandemic, a full-fledged war has become another threatening challenge for Ukraine. Since the active phase of the war in Ukraine has continued since February 2022, the number of physically and psychologically injured patients is increasing. Leading Ukrainian experts in psychology and psychotherapy noted the formation of "collective trauma" in Ukrainians [6].

In general, stressful events of varying intensity accompany a person throughout life, but not everyone develops a pathology. According to various sources, prevalence rates of PTSD among survivors of extreme situations range from 10% (among witnesses) to 90% (among severely injured persons). In most cases, the symptoms of PTSD disappear within a few weeks after the experienced event. In almost 50% of patients, symptoms disappear within a year without treatment, and a chronic continuous course of PTSD develops in 10–20% of cases [17]. Patients with acute stress disorders predominated at the beginning of the full-fledged war in Ukraine. Currently (a year after the start of the conflict escalation), people with PTSD dominate, which is a consequence of experienced traumatic events.

Thus, under present conditions in Ukraine, the problem of PTSD spreading and overcoming its consequences, including immune-dependent disorders, is one of the topical issues requiring extensive study and resolution in practical medicine.

The objective of our study was to analyze data from the questionnaire, clinical and paraclinical manifestations in PTSD patients, and to single out a group of immunocompromised patients with the potential of studying immunological disorders and different pathogenetic approaches to their management.

Materials and Methods

The study was conducted following the 7th revision of the Declaration of Helsinki Human Rights (2013) principles, the Council of Europe Convention on Human Rights and Biomedicine, and the relevant laws of Ukraine. Approval was obtained from the Ethics Committee of Danylo Halytsky Lviv National Medical University (protocol No. 1/22 dated Feb 27, 2022).

The study was conducted from September 2022 to January 2023 based on the Department of Clinical Immunology and Allergology of Danylo Halytsky Lviv National Medical University. The NIMH American National Center for PTSD (2013) questionnaire was used to verify PTSD. Inclusion criteria were adults of both sexes aged 18 to 65 with a history of severe COVID-19 and stress due to war or other catastrophic events, as well as the presence of post-traumatic stress symptoms lasting more than one month. The questionnaire consisted of 4 blocks of questions: 1 – symptoms of a repeated traumatic event experience (min. one symptom); 2 – symptoms of avoidance (min. one symptom); 3 – symptoms of agitation and reactivity (min. two symptoms); 4 – symptoms of impaired cognitive functions and mood (min. two symptoms). Each block contained 8–10 symptoms; the questionnaire included a question about the duration of the corresponding manifestations at the end (the questionnaire is attached). Each positive answer (Yes) was evaluated as the presence of a symptom: symptoms of a repeated experience (min. one positive answer); avoidance symptoms (min. one positive response); symptoms of agitation and reactivity (min. two positive answers); symptoms of cognitive functions and mood (min. two positive answers). The total (minimum) number of positive answers for diagnosing PTSD is six.

Exclusion criteria: persons who experienced stressful events for up to one month, children, pregnant women, patients with AIDS, and patients with autoimmune, oncological, acute infectious, and chronic cardiovascular, pulmonary, neurological, and other concomitant decompensated diseases, as well as patients who abuse alcohol, narcotic substances or have been exposed to toxic or chemical substances.

The control group consisted of 20 apparently healthy people of the appropriate age and sex, who scored 0 to 5 points according to the questionnaire.

A general examination of patients and basic paraclinical laboratory tests were carried out: complete blood count (CBC), urinalysis, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, and C-reactive protein (CRP) levels. All examination and test data of patients were entered into the author's "Questionnaire of Clinical and laboratory data of PTSD," developed by us.

A descriptive statistical method was used to process empirical data of patients from the study group, their systematization and quantitative description, and visual representation in the form of charts. In the case of normal data distribution or Gaussian distribution, the Shapiro-Wilk test was used; in the case of non-normal data distribution, the non-parametric Mann-Whitney U-test was used. In addition, the following methods were used to compare data between the study and control groups: analysis of variation series – calculation of the arithmetic mean and its mean error (M±m), p – the significance of the difference in the results obtained in the groups (probability of error when rejecting the null hypothesis according to the results of the Student's t-test).

Results

Two hundred eighty-seven patients were referred for consultation; the study group included 79 (27.5%) subjects who were verified with PTSD according to the questionnaire, of which 46 (58.2%) were female, and 33 (41.8%) were male patients, the average age was 38.7±7.2 years, and body mass index (BMI) was 22.0 to 29.0. Patients of the study group included employees – 29 (36.7%), workers (including agricultural workers) – 26 (32.9%), homemakers – 9 (11.4%), military – 8 (10.1 %), and doctors – 7 (8.90 %). In addition, 19 of them had the status of temporarily displaced persons.

Based on the results of anamnestic data analysis, patients considered themselves practically healthy before COVID-19 and/or experienced stress due to military hostilities (which met the inclusion criteria). Therefore, the regular intake of medicinal drugs was denied; only when needed, painkillers (non-steroidal anti-inflammatory drugs), vitamins, herbal sedatives, local antiseptics, and disinfectants were taken occasionally.

The analysis of the questionnaire data is presented in Figure 1. As it is shown, the symptoms that lasted more than one month were as follows:

1. Symptoms of the repeated traumatic event experience – recurring memories or dreams related to the event – 42 (53.2%) patients, palpitations – 40 (50.6%), sweating – 49 (62.0%), anxiety – 65 (82.3%) patients. Note that 24 (30.4%) people stated elevated blood pressure (BP) for the first time after experiencing a traumatic event.

2. Symptoms of avoidance – avoidance of places, events, or objects that remind of the experience – 56 (70.9%) patients.

3. Symptoms of agitation and reactivity – easily frightened – 42 (53.2%) people, feeling of tension, increased "alertness" – 56 (70.9%), difficulty concentrating – 67 (84.8%), difficulty falling asleep – 57 (72.1%), feelings of irritability, outbursts of anger – 53 (67.1%) patients.

4. Symptoms of impaired cognitive functions and mood – problems with remembering critical features of the traumatic event – 19 (24.1%), negative thoughts about themselves or the world – 47 (59.5%), constant negative emotions – 54 (68.4%), loss of interest in previous activities – 48 (60.6%), feeling alienated from friends/family – 26 (32.9%), feeling of social isolation – 25 (31.6%), difficulties with feeling positive emotions – 68 (86.1%) patients.

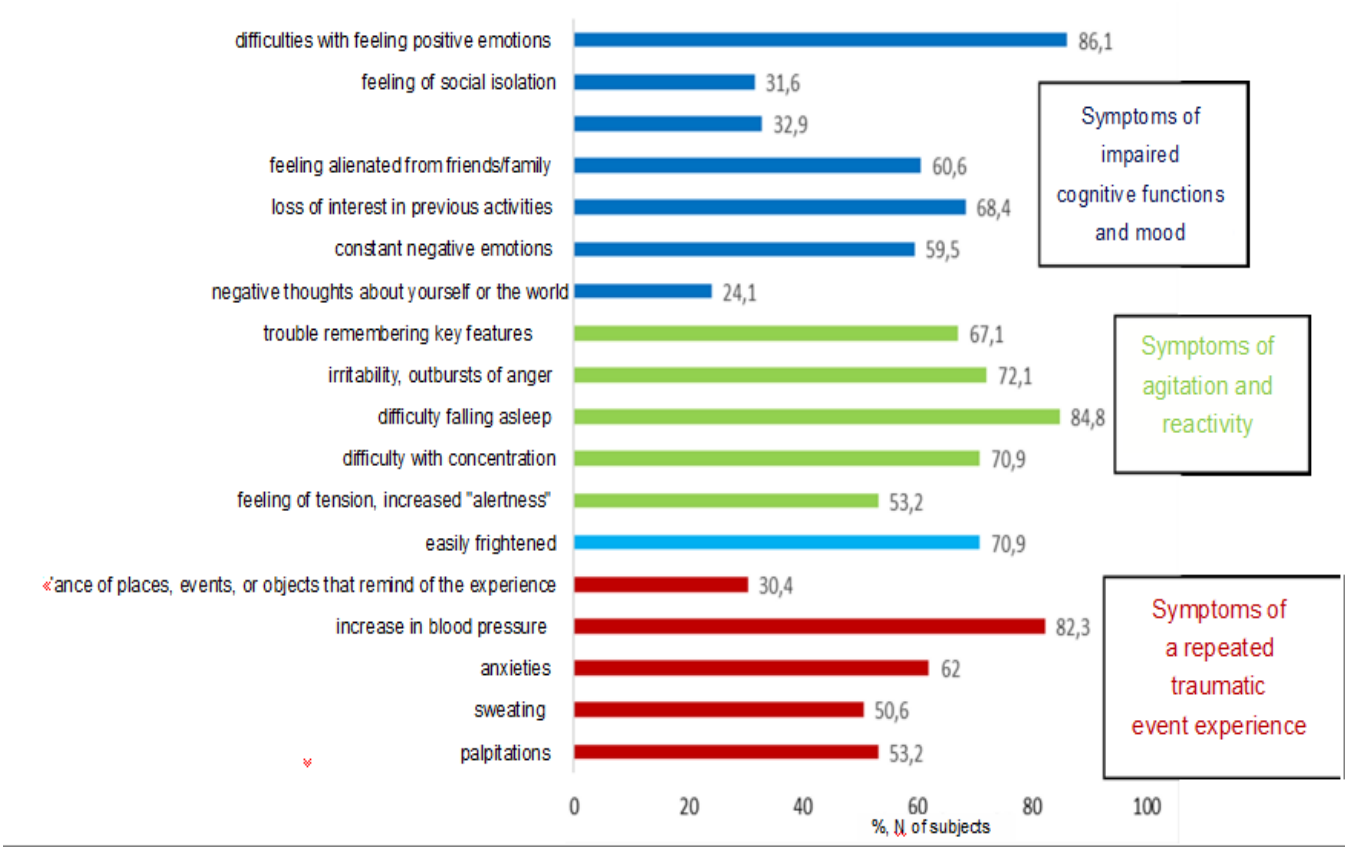

Figure 1. Analysis of data from the patient questionnaire of the study group, n=79 (%)

The analysis of anamnestic data showed that among patients with PTSD, 67 (84.8%) subjects were infected with COVID-19 in 2020–2022, of which 11 (16.4%) had an asymptomatic form, confirmed by serological data, 36 (53.8%) patients had a mild form, 12 (17.9%) people have a moderate form with treatment in outpatient conditions, and eight (11.9%) people had a severe form with the need for oxygen support in intensive care units. In total, symptoms related to stress disorders (specified in the questionnaire) first appeared in the settings of SARS-CoV2 infection in 18 (22.8%) patients with COVID-19 and persisted for more than six months.

According to the anamnestic data, we also learned that 28 (35.4%) patients of the study group attended consultations with psychologists and psychotherapists, 25 (31.6%) took antidepressants, 11 (13.9%) subjects refused to take antidepressants for various reasons, 36 (45.6%) took sleeping pills, and 47 (59.5%) patients regularly took various sedatives, which they selected independently.

Analysis of the laboratory test results showed that changes in general and biochemical indicators were found among all patients with PTSD, namely: lymphopenia was found in 15 (18.9%) people; lymphocytosis – 26 (32.9%), monocytosis – 31 (39.2%), neutropenia – 18 (22.8%), and an increase in the neutrophil count – 27 (34.1%) patients. ESR was slightly elevated in 19 (24.1%) patients, and elevated CRP was found in 24 (30.4%) individuals. Nine (11.4%) people had slightly increased ALT and AST liver enzyme levels. On the other hand, all subjects' creatinine was within physiological values. We conducted a comparative analysis of laboratory parameters in patients with PTSD and the control group, presented in Table 1.

Table 1

Comparative assessment of laboratory indicators in patients with PTSD and the control group, M±m

Indicators		Control, n=20	Patients, n=79	p
WBC	g/L	6.21±0.61	6.71±0.59	0.557
Total neutrophils	%	61.72±7.91	43.00±5.71	0.058
	g/L	3.82±0.22	2.88±0.11*	0.001
Lymphocytes	%	27.91±5.31	45.81±7.10*	0.046
	g/L	1.73±0.12	3.07±0.51*	0.010
Monocytes	%	5.51±0.42	7.20±0.70*	0.038
	g/L	0.34±0.02	0.48±0.04*	0.002
Eosinophils	%	3.62±0.71	2.60±0.32	0.192
	g/L	0.22±0.04	0.17±0.02	0.266
ESR	mm/h	8.32±1.22	10.50±2.01	0.352
CRP	mg/L	5.51±1.01	8.11 ±2.13	0.283
ALT	units/L	22.71±1.01	27.41±3.09	0.152
AST	units/L	22.91±1.38	26.53±2.05	0.148
Creatinine	μmol/L	73.42±8.06	70.41±7.19	0.782

Note: p is the probability of a difference between study groups

Total and relative values of CBC indicators were analyzed. As can be seen from Table, the total neutrophil count (p=0.001), mononuclear cells (lymphocytes (p=0.010), and monocytes (p=0.002)) in patients with PTSD were significantly higher compared to the control group. As for relative indicators, their values in mononuclear lymphocytes were also considerably higher compared to the control group: lymphocytes (p=0.0461) and monocytes (p=0.038).

As described above, we did not obtain a statistically significant difference compared with the control group. However, there were individuals with slightly increased indicators of acute phase proteins and liver transaminases among patients with PTSD.

Discussion

In the process of studying the nature of PTSD, for many years, scientists have studied the neurophysiological mechanisms of a traumatic event and the effect of such factors as age, gender, the presence of concomitant somatic pathology, genetic features of the response to stress, etc. on them [10]. In particular, it was determined that risk factors for developing PTSD are male gender, younger age, and fewer years of formal education [11]. In our study, PTSD was found, to a greater extent, among women and mostly young people. However, these data were predictable since most people who applied for consultation were women. Furthermore, from the anamnesis, we learned that the symptoms appeared during/after COVID-19 in 22.8% of patients and persisted for more than six months. This allows us to assume the presence of post-COVID disorders (or the development of long COVID-19) in these patients, which are associated with PTSD in this case [29,30].

Based on many data, it has been determined that the neuroendocrine stress response is realized through the interaction of two leading systems – the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis, which transmit signals to peripheral organs and the immune system [15]. Under acute stress, the hypothalamus secretes corticotropin-releasing hormone (CRH), which activates the HPA axis. Corticotropin-releasing hormone, through interaction with the corresponding receptors of the pituitary gland, causes the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary into the bloodstream. In turn, ACTH stimulates the synthesis of glucocorticoids (cortisol) in the adrenal cortex [9]. At the same time, the sympathetic nervous system (SNS) is activated, and catecholamines (adrenaline, noradrenaline) are synthesized. Physiologically the effect of these hormones is known to cause increased heart rate and elevated blood pressure [22]. Manifestations of tachycardia and increased blood pressure, recorded in the questionnaire and revealed during an objective examination, confirmed the

data on the involvement of SNS in the process of PTSD development. Moreover, these symptoms appeared in patients for the first time after a stressful event.

Synthesized biologically active substances affect immunocompetent cells (ICC). According to modern studies, increased levels of peripheral blood monocytes, CD4+ lymphocytes, CD8+ lymphocytes, natural killer (NK) and B-cells, and pro-inflammatory cytokines (interleukin 17 (IL-17), IL-12) were observed in patients with PTSD [2, 28]. Furthermore, according to the data of 20 studies (meta-analysis of 2015), an increase in the levels of pro-inflammatory cytokines was also determined in patients diagnosed with PTSD: IL-6, IL-1, IL-1ß, interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α), acute phase proteins (CRP) in the settings of decreased levels of anti-inflammatory markers (IL-10, etc.).

ICC is known to be mobilized from the bone marrow to the periphery, where they come into contact with molecular structures associated with danger–alarmins – DAMP (Damage associated molecular patterns). Alarmins (for example, mitochondrial reactive oxygen species) are etiological and stimulating factors of local or systemic inflammatory reactions without the influence of pathogens or tissue destruction [7]. DAMPs bind PRR (Pattern recognition receptors) and RAGE (Receptor for advanced glycation end products), activate TLRs (Toll-like receptors) on cells of innate immunity and stimulate the activity of nuclear factor kappa-B (NF-kB) for the production of pro-inflammatory cytokines [8]. There is a case of "vicious cycle" development – the influence of pro-inflammatory cytokines (IL-6, IL-1β, and TNF-α) on the synthesis of acute phase proteins and, accordingly, excessive activation of the complement system and maintenance of inflammation [10]. The ICC role in PTSD pathogenesis was confirmed in the studies of Wohleb ES et al., in particular, the initiation of the pro-inflammatory cytokine synthesis by monocytes through the activity of NF-kB was revealed [26].

Furthermore, the studies of Tan KS and Elkhatib proved the norepinephrine effect on lymphocytes, in particular, their activation of the pro-inflammatory cytokine synthesis through the stimulation of the NF-kB, B-Raf-ERK1/2, and p38 pathways [5, 25]. The studies of Kuan PF and O'Donovan A found the increased peripheral activity of NF-kB and transcriptional changes in monocytes, which maintained the inflammatory process in patients with PTSD [12, 18]. Increased pro-inflammatory cytokines led to hyperreactivity of the HPA axis [15]. Physiologically, the interaction of cortisol with the corresponding receptor inhibits inflammation by stimulating the transcription of anti-inflammatory genes in the nucleus or inhibiting the expression of pro-inflammatory proteins in the cytosol [10]. Michopoulos V et al.'s work showed that under chronic stress conditions, cortisol could not inhibit the NF-kB-mediated release of pro-inflammatory cytokines and, thus, makes the inflammatory process chronic [15].

Scientists from Emory University (USA) proved that neuroinflammatory changes could explain clinical symptoms of PTSD. Scientists identified the mechanisms of neuroinflammation due to increased peripheral inflammation: 1) transport of IL-1α, IL-1β, IL-6, and TNF-α by cytokine-specific transporters through the blood-brain barrier; 2) activated cytokine receptors on afferent nerve fibers (for example, the vagus nerve) transmit cytokine signals to the corresponding areas of the brain; 3) microglial cells activated by cytokines synthesize monocyte chemoattractant protein (MCP-1), which stimulates the chemotaxis of activated monocytes, macrophages, and lymphocytes to the brain. Furthermore, the ability of pro-inflammatory cytokines to change the functions (synthesis, reuptake, release) of neurotransmitters to influence the synthesis of serotonin through the kynurenine pathway has been proven [3,19]. Serotonin is known to belong to the regulatory hormones and increase the synthesis of anti-inflammatory cytokines. However, pro-inflammatory cytokines increase the activity of IDO (Indoleamine-pyrrole 2,3-dioxygenase), which converts tryptophan (the main amino acid of serotonin) to kynurenine. As evidence, it was determined in the experiment that interferon therapy (IFN-α) in patients with PTSD increased the increase of kynurenine and decreased tryptophan levels, which contributed to the development of depression, anxiety, impaired cognition, memory disorders, etc. Therefore, pro-inflammatory cytokines can reduce the concentration of serotonin, affecting the kynurenine pathway, which leads to the cognitive and somatic manifestations of PTSD. In addition, activated microglia and astrocytes produce cytokines contributing to neuroinflammation [10]. Such mechanism of the development of the inflammatory process was confirmed in the studies on animal models, highlighted in the works of Deslauriers J and Levkovitz Y. It has been emphasized that inflammation can affect the nervous system cells, the neurotransmitter synthesis and their signal transmission related to fear, anxiety, and regulation of emotions [4, 14].

Seyma Katrinli et al. confirmed the role of inflammation in developing PTSD and the feasibility of using an immunomodulatory treatment approach to prevent possible infectious, autoimmune, and allergic complications [13].

Scientists from the Department of Psychology at the University of California investigated the empirical hypothesis of a bidirectional relationship between PTSD and the formation of a chronic inflammatory process. To substantiate this hypothesis, scientists put forward several postulates: 1) affecting the brain, peripheral inflammation increases the likelihood of developing PTSD; 2) peripheral cytokines can overcome the blood-brain barrier and initiate the pro-inflammatory cytokine synthesis in the CNS, affecting cognitive processes; 3) PTSD can activate behavioral changes (e.g., sedentary lifestyle, smoking) and physiological processes that increase inflammation; 4) PTSD (physiologically) develops as a result of dysregulation of the adaptive response to stress (distress), including the SNS hyperreactivity and a decreased activity of glucocorticoids produced by the HPA axis. The conclusion confirmed the role of neuro-immuno-endocrine mechanisms in the development of PTSD. Furthermore, in favor of the hypothesis mentioned above, the results of modern genetic studies evidence the involvement of immune mechanisms in the pathogenesis of PTSD [16, 24]. In particular, many studies have proven an immune-genetic predisposition to developing inflammation in PTSD [13, 21,22,27,28].

Our study also revealed clinical changes and disturbances of general and biochemical blood parameters in patients diagnosed with PTSD, which is the basis for the immune system's involvement in its development. Moreover, our retrospective analysis of outpatient medical records showed associative relationships between the clinical, general laboratory, and immune indicators: increase or decrease in the number of lymphocytes, and neutrophils, increase in the monocyte count, and levels of CRP, ESR, and liver enzymes. Therefore, we characterized these patients as immunocompromised.

The findings of our study are significant because the health impairments associated with stress disorders following COVID-19 or in the context of full-scale war have been understudied. Furthermore, according to the data of several studies, it is suggested that these changes are associated with activating the so-called "sluggish" immunotropic infections, which we also plan to investigate in the second stage of work. In the future, the results of our work will allow us to adjust the treatment strategy of immunocompromised patients with PTSD.

In conclusions**:** The development of PTSD among patients, including the past medical history of COVID-19, is a topical issue of mental and somatic health. It indicates the extreme significance of the case today and the requirement for its early diagnosis, therapy, and prevention. Furthermore, the data analysis from the scientific literature and our research indicates the role of immune mechanisms in developing PTSD. It necessitates expanding diagnostic measures among patients who suffered from the consequences of the previous COVID-19 and hostilities in Ukraine with different pathogenetic approaches to their management.

Study limitations.

This study had some limitations and weaknesses – small sample size and incomplete compliance in terms of background health, as some patients were temporarily displaced patients. Also, when patients filled out questionnaires, we included questions about vaccination against SARS-CoV-2 and the probable presence of post-vaccination events. However, we only plan to analyze these data.

In the future, we also plan to study the cytokine profile, activation, and immunoregulatory markers, indicators of apoptotic and antiapoptotic activity of ICC, and their correlation with clinical and paraclinical changes in PTSD patients.

Institutional Review Board Statement: The study was conducted following the 7th revision of the Declaration of Helsinki Human Rights (2013) principles, the Council of Europe Convention on Human Rights and Biomedicine, and the relevant laws of Ukraine. Approval was obtained from the Ethics Committee of Danylo Halytsky Lviv National Medical University (protocol No. 1/22 dated Feb 27, 2022).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

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