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CONTENTS

ORIGINAL ARTICLES

- Influence of acute blood loss on the dynamics of pro-inflammatory cytokine content in the context of traumatic brain injury, blunt abdominal trauma, and skeletal trauma**
Nataliia V. Izhytska, Rostyslav D. Levchuk, Arsen A. Hudyma, Iryna V. Antonyshyn 713
- Effects of hypoxic training cycle on peripheral hemodynamics of wrestlers**
Georgiy A. Demchenko, Serik Abdreshov, Laura Koibasova, Oksana Cherednichenko, Ulbossin Kozhaniyazova, Makpal Yessenova, Anar Yeshmukhanbet, Kadyrzhan Altynbek 721
- The histological image of the muscular component of the diaphragm in experimental animals following the creation of carboxyperitoneum by means of standard pressure of different duration**
Myroslav Kritsak, Tetiana Gargula, Oleh Yasinovskiy, Olena Levchyk, Oksana Balitska, Victor Shatskyi 727
- Aberrant expression of CD markers in patients with acute leukemia**
Aymen Radhi Habeeb, Hamid AL-Tameemi, Dina A.A. Abdullah, Rand Muhammed Abdul-Hussein Al-Hussein, Ali Khudhair Ahmed 734
- Peculiarities of psychological trauma in police officers-combatants with different combat experience and their psychological rehabilitation**
Olena O. Yevdokimova, Ivan M. Okhrimenko, Volodymyr M. Filonenko, Ihor V. Klymenko, Kateryna R. Mannapova, Olena Yu. Sashurina, Oleksandr Yu. Shlomin 742
- Evaluating the impact of domestic violence on Postpartum Post-Traumatic Stress Disorder (PTSD): A prospective study of perinatal mental health outcomes in high-risk populations**
Eirini Orovou, Antigoni Sarantaki, Maria Tzitiroidou-Chatzopoulou, Nikolaos Rigas, Evangelia Antoniou 749
- Detection of IgM and IgG antibodies of measles in aborted women**
Mohammed Jasim Mohammed Shallal, Hayder Raad Abbas, Nadia Saddam Fahad 755
- Assessment of the mineral composition of teeth in children of the mountain zone of Transcarpathia region**
Oksana Klitynska, Gennadii Tkach, Orest Bun, Liudmyla Horzov, Stepan Bozhyk, Volodymyr Shetelya, Natalia Layosh 761
- Role of sclerostin in the bone and thyroid metabolism in patients with ovarian polycystic syndrome**
Zainab Tawfeeq Al-Joubouri, Shaymaa Galeel Shamran, Maha Luay Aziz, Ali A. Al-Fahham 768
- The impact of extreme conditions of service activities on the functional and psycho-emotional state of law enforcement officers**
Ivan M. Okhrimenko, Olha M. Pasko, Liudmyla M. Prudka, Tetyana V. Matienko, Olga M. Smirnova, Inha A. Serednytska, Nataliia V. Lebedieva 775

REVIEW ARTICLES

- Legal status of ayurveda in the healthcare system**
Vitalii M. Pashkov, Oleksii S. Soloviov, Yevhen Gnedik 782
- Adverse Childhood Experiences and the psychopathogenesis of chronic pain: A narrative review**
Lidiia V. Butska, Natalia M. Falko 789
- Modern view on the epidemiology, risk factors, prevention and screening of pseudoexfoliation syndrome in the context of glaucoma prophylaxis**
Volodymyr O. Melnyk, Borys I. Palamar 797
- Cost-benefit analysis of mobile dental clinics in remote areas of Ukraine**
Inessa I. Yakubova, Maksym V. Makarenko, Nataliya M. Krupnyk, Anna-Sofiya A. Krupnyk 803

CLINICAL CASES

Common signs, uncommon condition: A case report of a 41-year-old woman with a large left-sided esophageal hiatus hernia and a benign esophageal leiomyoma

Aleksandra Cader, Piotr Ostrowski, Michał Ptak, Katarzyna Kotrych, Joanna Stępniewska

809

Autoimmune encephalitis with LGI1 antibodies: A report of two cases

Aleksander Gawda, Mateusz Roszak, Alicja Sierakowska, Maciej Piotrowiak, Aleksandra Szczerbaniewicz, Iwona Gawda, Beata Łabuz-Roszak

816

VARIA

Language-dependent performance of large language models in medical diagnostics: A comparative study of ChatGPT-4o and Claude 3.5 Sonnet

El Habib El Mahdaoui, Yaroslav O. Mykhalko

821

Application of the medicine GPT model in diagnosing rare diseases in the emergency department

Esmail Haj Obeid, Jakub Ulrych, Jan Krupa, Maciej Malinowski, Michał Krasowski, Alicja Kalinowska, Wiktoria Pietras, Adrian Kozieł, Zofia Kurek, Aleksander Jentkiewicz

826

Artificial intelligence in the value system of future doctors

Olga M. Khrystenko, Anatoliy V. Vykhreshch, Oksana I. Novitska, Larysa Ya. Fedoniuk, Ihor D. Drach, Marta I. Rudenko

831

Functionality and protection of personal data when using Ukrainian-language mHealth apps

Vadym I. Pishta, Sandra O. Boldizhar, Tereziia P. Popovych, Nazar T. Holovatskiy, Anatoliy M. Potapchuk, Mykhailo M. Hechko

838

Influence of acute blood loss on the dynamics of pro-inflammatory cytokine content in the context of traumatic brain injury, blunt abdominal trauma, and skeletal trauma

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ABSTRACT

Aim: To determine the dynamics of the content of pro-inflammatory cytokines, Tumor Necrosis Factor- α (TNF- α) and Interleukin-1 β (IL-1 β), in blood serum under conditions of traumatic brain injury (TBI), blunt abdominal trauma (BAT), and skeletal trauma (ST), complicated by acute blood loss, after 3, 7, 14, 21, and 28 days of the post-traumatic period.

Materials and Methods: Under thiopental sodium anesthesia, male Wistar line rats were subjected to modeled TBI, BAT, and ST. In separate groups, acute blood loss of the amount 1,5% of body weight was additionally modeled. The content of TNF- α and IL-1 β in blood serum was determined after 3, 7, 14, 21, and 28 days of the post-traumatic period.

Results: Experimental traumas of various localizations were accompanied by a pronounced systemic pro-inflammatory reaction, manifested by a significant increase in serum levels of pro-inflammatory cytokines TNF- α and IL-1 β . The maximum of disturbances was observed in the early post-traumatic period, followed by a decrease, which only reached the control level in the case of TBI and ST. In conditions of BAT, the indicators were significantly higher compared to other localized traumas. When the modeled mechanical traumas of various localizations were complicated by acute blood loss of the amount 1,5% of body weight, the disturbances in the content of TNF- α and IL-1 β in the blood serum became greater. The TNF- α content in all experimental groups increased up to the 7-th day, remained at the same level up to day 14, and then decreased. The IL-1 β content in blood serum reached its maximum as early as 1 day of the post-traumatic period and then decreased, but both indicators did not reach the control level by the 28-th day. In conditions of BAT, the indicator was significantly higher after 3–21 days of the post-traumatic period compared to other experimental groups.

Conclusions: Mechanical traumas of various localizations significantly differ in the nature of the manifestations of the systemic inflammatory reaction and react differently when complicated by acute blood loss. The greatest increase in the serum content of TNF- α and IL-1 β is noted in conditions of blunt abdominal trauma.

KEY WORDS: trauma, blood loss, inflammation, cytokines

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INTRODUCTION

A characteristic feature of modern traumatism is the increasing frequency of high-energy mechanical injuries of various localizations, complicated by massive blood loss [1]. The vast majority of fatal cases occur in the acute period of trauma (up to 2 days), the pathogenesis of which is dominated by traumatic shock [2]. However, it has been proven that bringing the injured person out of shock does not guarantee their further survival. The injured and victims have every chance of dying in a much later post-traumatic period due to the development of multiple organ failure [3] and infectious complications [4]. Their main causes are secondary damage to internal organs caused by the systemic post-traumatic reaction to inflammation [5]. The patterns of its development, and its dependence on the nature and location of the trauma, remain far from a definitive solution and attract increasing attention from the scientific community.

Cytokines play a key role in the body's inflammatory response [6]. The balance of pro-inflammatory and anti-inflammatory cytokines plays an important protective

role in traumatized patients. However, in severe trauma, cytokines are also capable of enhancing damage to the body [7] and determining the prognosis of the injured [8, 9].

Acute blood loss is often a severe consequence of traumatic injury and causes numerous traumatic deaths. The combination of acute blood loss and trauma can provoke a cascade of post-traumatic inflammatory and immune reactions that may lead to multi-organ damage or even death [10]. In particular, acute blood loss was observed in over 26% of civilian casualties and about 80% of wounded military personnel with traumatic brain injury (TBI) [11]. Complication of trauma with acute blood loss increases the mortality rate, which can reach up to 50% [12]. High concentrations of circulating interleukins (IL) 6, 10, 8, and 12 were observed during traumatic hemorrhagic shock within 7 days of the post-traumatic period [13].

However, the patterns of the pro-inflammatory cytokine reaction in response to mechanical trauma complicated by acute blood loss, depending on the trauma's location, have been insufficiently studied.

AIM

To determine the dynamics of the content of pro-inflammatory cytokines Tumor Necrosis Factor- α (TNF- α) and IL-1 β in blood serum under conditions of traumatic brain injury (TBI), blunt abdominal trauma (BAT), and skeletal trauma (ST), complicated by acute blood loss, after 3, 7, 14, 21, and 28 days of the post-traumatic period.

MATERIALS AND METHODS

Experiments were conducted on 316 mature white male Wistar line rats weighing 200–220 g. Under thiopental sodium anesthesia at a dose of 40 mg kg⁻¹, TBI, BAT, and ST, standardized by lethality, were modeled [14]. In experimental group 1, TBI was modeled by applying a single-dose impact to the skull with an energy of 0,375 J [15]. In experimental group 2, BAT was modeled by a single-dose impact to the epigastric region with an energy of 0,177 J cm⁻² [16]. In experimental group 3, ST was induced by a dosed mechanical impact to each femur with an energy of 0,637 J [16]. In experimental groups 4, 5, and 6, rats with TBI, BAT, and ST, respectively, were additionally modeled acute blood loss of the amount 1,5% of body weight by transecting the femoral vein. The volume of blood loss was controlled by the gravimetric method. Hemostasis was ensured by applying a ligature.

Rats from the experimental groups under anesthesia were taken out of the experiment after 3, 7, 14, 21, and 28 days of the post-traumatic period by total bleeding from the heart. Cytokines were determined in the blood serum by the enzyme-linked immunosorbent assay (ELISA) using standard reagents adapted for white rats („Elabscience Biotechnology Inc”) on an RT-2100C ELISA analyzer (Ratyo, China). The concentration of the studied cytokines was determined by the calibration graph provided in the instruction and expressed in pg/ml. Rats in the control group were only anesthetized and euthanized after 14 days of the post-traumatic period.

All experiments were performed in compliance with the „General ethical principles of animal experiments,” approved by the First National Congress on Bioethics (Kyiv, 2001) and consistent with the provisions of the „European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes” (Strasbourg, 1986), as well as the conclusion of the Bioethics Commission of I. Horbachevsky Ternopil National Medical University of the Ministry of Health of Ukraine № 82 of September 3, 2025.

Statistical analysis of numerical results was performed using the STATISTICA 10.0 software package („StatSoft Inc.”, USA), disc serial number BXXR303F737429FA-8. The median (Me), lower (LQ), and upper (UQ) quartiles, which are presented in the tables, were calculated. The significance of differences was assessed using the non-parametric Mann-Whitney criterion.

FRAMEWORK

The article was written within the framework of a complex research topic of the Educational and Scientific Institute of Modelling and Analysis of Pathological Processes of the I. Horbachevsky Ternopil National Medical University

of the Ministry of Health of Ukraine “Research into the pathogenetic patterns of post-traumatic and inflammatory-degenerative damage to organs and systems and their correction” (State Registration No. 0124U000154).

RESULTS

The studies showed (Table 1) that, compared to the control, the serum content of TNF- α following TBI increased and reached a maximum after 7 days of the post-traumatic period, which was statistically significant compared to the control group (by 28,9%, $p < 0,05$) and the result after 3 days (by 13,7%, $p < 0,05$). Subsequently, the indicator gradually decreased and, starting from the 21st day of the post-traumatic period, reached the control level ($p > 0,05$). After 28 days, the indicator was also significantly lower compared to the results after 3 and 7 days (by 8,0 and 21,4%, respectively, $p < 0,05$).

Under conditions of modeled BAT, the serum content of TNF- α increased compared to the control and statistically significantly exceeded the control level at all time points of the post-traumatic period: after 3 days – by 31,1%, after 7 days – by 41,1%, at 14 days – by 38,2%, at 21 days – by 23,9%, after 28 days – by 15,9% ($p < 0,05$). In dynamics, the indicator reached its maximum as early as day 3 and remained at the same level until the 14-th day of the post-traumatic period ($p > 0,05$). By the 28-th day, the indicator decreased and became significantly lower compared to the results at 3, 7, and 14 days of the experiment (by 11,5, 17,8, and 16,1%, respectively, $p < 0,05$), but remained 15,9% higher than in the control ($p < 0,05$).

Modeling ST also caused an increase in the serum content of TNF- α compared to the control. The result increased during 3 and 7 days of the post-traumatic period and exceeded the control level by 16,7 and 21,0% ($p < 0,05$). Subsequently, the indicator changed cyclically. After 14 days, the indicator decreased (by 17,0% compared to the result at 3 days, $p < 0,05$, and by 20,0% compared to the result at 7 days, $p < 0,05$). However, after 21 days of the post-traumatic period, the indicator increased again – by 19,0% compared to the result at 14 days ($p < 0,05$) and exceeded the control group by 15,0% ($p < 0,05$). By the 28-th day, a decrease in the indicator was noted, which reached the control level ($p > 0,05$).

Comparison of the experimental groups of rats with mechanical trauma of various localizations showed that after 3 days of the post-traumatic period, the serum content of TNF- α was statistically significantly higher in rats with modeled BAT: after 3, 21, and 28 days – compared to rats with TBI (by 15,6, 14,7, and 14,4%, respectively, $p_{1-2} < 0,05$); at 7 days – compared to rats with ST (by 16,6%, $p_{2-3} < 0,05$); after 14 days – compared to the groups of rats with TBI and ST (by 21,5%, $p_{1-2} < 0,05$, and by 42,8%, $p_{2-3} < 0,05$, respectively). It should be noted that the serum content of TNF- α in the dynamics of the post-traumatic period in rats with TBI and ST did not differ significantly ($p_{1-3} > 0,05$). The exception was day 14. At this time, the indicator in rats with TBI was statistically significantly higher than in rats with ST (by 17,5%, $p_{1-3} < 0,05$).

Table 1. Influence of acute blood loss on the serum TNF- α content (pg l⁻¹) after modeling traumatic brain injury, blunt abdominal trauma, and skeletal trauma ((Me (LQ;UQ)) – median (lower and upper quartiles)

Group of rats	Examination period				
	3 day	7 day	14 day	21 day	28 day
Control	44.73 (42.97; 47.71)				
Group 1 TBI	50.70* (49.30; 54.13)	57.67 ³ (55.42; 60.55)	50.89* (48.28; 52.83)	48.28 (43.68; 49.58)	45.33 ^{3,7} (42.10; 48.61)
Group 2 BAT	58.63* (55.09; 62.46)	63.09* (60.44; 65.31)	61.82* (58.31; 64.36)	55.42 ^{7,14} (50.24; 57.03)	51.86 ^{3,7,14} (50.24; 53.48)
Group 3 ST	52.18* (50.24; 55.42)	54.13* (51.21; 57.35)	43.30 ^{3,7} (40.37; 44.00)	51.54 ¹⁴ (48.27; 52.75)	44.67 (43.02; 51.86)
Group 4 TBI + blood loss	58.31* (53.56; 60.86)	64.83 ^{*#3} (61.26; 65.94)	62.93 [#] (56.30; 65.07)	55.74 ^{*#7,14} (53.15; 57.03)	52.34 ^{*#7,14} (49.26; 54.85)
Group 5 BAT + blood loss	60.86* (59.03; 64.36)	69.09 ^{*#3} (67.44; 70.94)	68.46 ^{*#3} (65.62; 69.87)	60.23 ^{*#7,14} (57.35; 62.61)	53.48 ^{*3,7,14,21} (50.88; 56.06)
Group 6 ST + blood loss	55.42* (52.51; 57.99)	58.95* (54.44; 61.50)	58.63 ^{*#} (56.22; 61.18)	53.48* (51.82; 55.90)	49.58 ^{*3,7,14,21} (44.01; 51.05)
p ₁₋₂	<0.05	>0.05	<0.05	<0.05	<0.05
p ₁₋₃	>0.05	>0.05	<0.05	>0.05	>0.05
p ₂₋₃	>0.05	<0.05	<0.05	>0.05	>0.05
p ₄₋₅	>0.05	<0.05	<0.05	<0.05	>0.05
p ₄₋₆	>0.05	>0.05	>0.05	>0.05	>0.05
p ₅₋₆	<0.05	<0.05	<0.05	<0.05	>0.05

Notes. Here in table 2:

1. * – differences compared to the control group are statistically significant ($p < 0,05$);
2. # – differences in relation to injured rats without acute blood loss are statistically significant ($p < 0,05$);
3. p₁₋₂ – significance of differences between experimental groups 1 i 2;
4. p₁₋₃ – significance of differences between experimental groups 1 i 3;
5. p₂₋₃ – significance of differences between experimental groups 2 i 3.
6. p₄₋₅ – significance of differences between experimental groups 4 i 5;
7. p₄₋₆ – significance of differences between experimental groups 4 i 6;
8. p₅₋₆ – significance of differences between experimental groups 5 i 6;
9. ^{3,7,14,21} – the differences regarding the results at 3, 7, 14, and 21 days are statistically significant. ($p < 0,05$).

Source: compiled by the authors of this study

Additional blood loss was accompanied by a deepening of the observed disturbances (Table 2). The serum content of TNF- α in all experimental groups was statistically significantly higher than in the control group at all time points of the post-traumatic period. In conditions of TBI, the indicator increased up to day 7, exceeded the result after 3 days of observation by 11,2% ($p < 0,05$), and became 44,9% higher compared to the control ($p < 0,05$). Subsequently, the indicator remained at the same level until day 14 of the post-traumatic period ($p > 0,05$), and then gradually decreased. After 28 days, it was 19,3 and 16,8% lower compared to the results at 7 and 14 days of the experiment ($p < 0,05$), but exceeded the control level by 17,0% ($p < 0,05$).

In rats with BAT and acute blood loss, the serum content of TNF- α also gradually increased up to day 7 of the post-traumatic period, becoming 13,5% higher compared to

the result after 3 days ($p < 0,05$) and exceeding the control level by 54,5% ($p < 0,05$). The indicator remained at the same level until day 14 of the post-traumatic period ($p > 0,05$), and then decreased. After 28 days, it became significantly lower compared to all previous observation times ($p < 0,05$), but continued to be 19,6% higher than in the control ($p < 0,05$).

In conditions of ST, the serum content of TNF- α reached its maximum as early as 3 days of the post-traumatic period and became 23,9% higher than in the control ($p < 0,05$). Up to day 21, the indicator continued to remain at the same level ($p > 0,05$), and then decreased and became statistically significantly lower compared to all previous observation times ($p < 0,05$), but remained 10,9% higher than in the control ($p < 0,05$).

Comparison of the experimental groups of rats with mechanical trauma of various localizations complicated

Table 2. Influence of acute blood loss on the serum IL 1 β content (pg l⁻¹) after modeling traumatic brain injury, blunt abdominal trauma, and skeletal trauma ((Me (LQ;UQ)) – median (lower and upper quartiles)

Group of rats	Examination period			
	3 day	3 day	3 day	3 day
Control	37.52 (35.18; 38.46)			
Group 1 TBI	51.78* (49.32; 54.24)	45.61 ³ (44.37; 48.70)	41.27 ³ (39.40; 48.08)	39.40 ³ (33.77; 40.64)
Group 2 BAT	59.12* (57.90; 60.94)	57.90* (54.23; 60.94)	53.01* (49.93; 57.29)	42.51 ^{3,7,14,21} (39.40; 44.31)
Group 3 ST	49.91* (45.61; 53.01)	39.40 ³ (36.27; 43.13)	42.51* (40.33; 45.92)	38.15 ^{3,7,14} (36.27; 41.20)
Group 4 TBI + blood loss	54.84* (52.08; 56.07)	48.08* (45.15; 52.08)	44.06 ³ (38.15; 47.31)	41.89 ^{3,7,14} (39.40; 44.68)
Group 5 BAT + blood loss	66.20* [#] (64.79; 67.98)	65.54* ^{#7} (63.37; 67.98)	60.03* ^{#3,7} (58.20; 63.67)	51.78* ^{#3,14,21} (50.09; 53.92)
Group 6 ST + blood loss	51.78* (47.15; 53.31)	45.61* (42.51; 47.46)	44.38* (40.02; 47.46)	44.37 ³ (41.14; 46.23)
p ₁₋₂	<0.05	<0.05	<0.05	>0.05
p ₁₋₃	>0.05	<0.05	>0.05	>0.05
p ₂₋₃	<0.05	<0.05	<0.05	>0.05
p ₄₋₅	<0.05	<0.05	<0.05	<0.05
p ₄₋₆	>0.05	>0.05	>0.05	>0.05
p ₅₋₆	<0.05	<0.05	<0.05	<0.05

Notes. See Table 1.

Source: compiled by the authors of this study

by acute blood loss showed that after 7, 14, and 21 days of the post-traumatic period, the serum content of TNF- α was statistically significantly higher in rats with BAT, compared to rats with TBI ($p_{4-5}<0.05$); after 3, 7, 14, and 21 days of the post-traumatic period – compared to rats with ST ($p_{5-6}<0.05$).

It is important to compare the TNF- α content in blood serum in rats with mechanical trauma of various localizations and the analogous groups in which acute blood loss of the amount 1,5% of body weight was additionally modeled. Studies showed that in conditions of TBI, additional blood loss contributed to an increase in the indicator after 7, 14, 21, and 28 days of the post-traumatic period (by 12,4, 23,6, 15,4, and 15,6 %, respectively, $p<0.05$). In conditions of BAT, additional blood loss caused an increase in the indicator after 7, 14, and 21 days of the post-traumatic period (by 9,5, 10,7, and 8,7%, respectively, $p<0.05$). In conditions of ST, additional blood loss caused a statistically significant increase in the blood indicator only after 14 days of the experiment – by 35,4% ($p<0.05$).

In turn, the serum content of IL-1 β under the influence of mechanical trauma of various localizations increased compared to the control as early as 3 days of the post-

traumatic period (Table 1). At this time, after modeling TBI, the indicator exceeded the control by 38,0% ($p<0.05$), and then – after 7 days – decreased (by 16,7% compared to the result at 3 days, $p<0.05$) and remained at the same level after 14 and 21 days of the experiment ($p>0.05$). During these periods, the indicator continued to be statistically significantly higher than the control by 15,0, 21,6, and 10,0%, respectively ($p<0.05$). After 28 days, the indicator decreased again and reached the control level ($p>0.05$).

Modeling BAT after 3 days of the post-traumatic period also caused a significant increase in the serum content of IL-1 β compared to the control (by 57,6%, $p<0.05$). After 7 days of the experiment, the indicator decreased (by 8,3% compared to the result of the 3-rd day, $p<0.05$) and remained at the same level until 21 days ($p>0.05$). Despite the decrease, the indicator after 7, 14, and 21 days was significantly higher than in the control (by 44,5, 54,9, and 41,3%, respectively, $p<0.05$). By the 28-th day, the indicator decreased again (by 19,8% compared to the result of the 21-th day, $p<0.05$) and remained 13,3% higher than in the control ($p<0.05$).

Following ST, the dynamics of the serum IL-1 β content were similar. The indicator reached a maximal increase at

3 days of the post-traumatic period (by 33,1%, $p < 0,05$). Subsequently, after 7 days, the indicator decreased – by 11,1% compared to the result of the 3-rd day ($p < 0,05$), reached a minimum value at 14 days, and reached the control level ($p > 0,05$). After 21 days, the indicator increased again (by 13,3% compared to the control, $p < 0,05$) and then decreased again, reaching the control value ($p < 0,05$).

Comparison of the experimental groups with mechanical traumas of various localizations showed that from 3 to 21 days of the post-traumatic period, the serum content of IL-1 β was statistically significantly higher in the group of rats with BAT compared to other experimental groups ($p_{1-2} < 0,05$, $p_{2-3} < 0,05$). After 3, 7, and 21 days of the post-traumatic period, the differences between the groups of rats with TBI and ST were not significant ($p_{1-3} > 0,05$). Similarly, no significant differences were found between all experimental groups after 28 days of the post-traumatic period ($p_{1-2} > 0,05$, $p_{1-3} > 0,05$, $p_{2-3} > 0,05$).

Modeling additional blood loss compared to the control also caused a statistically significant increase in the serum content of IL-1 β after 3 days of the post-traumatic period (Table 2). At this time, in rats with TBI and acute blood loss, the indicator reached its maximum value and was 46,2% higher than in the control. Subsequently, up to 21 days of the post-traumatic period, the indicator gradually decreased, but did not statistically significantly differ from the result at 3 days ($p > 0,05$) and was significantly higher than in the control: at 7 days – by 31,4% ($p < 0,05$), at 14 days – by 28,1% ($p < 0,05$), at 21 days – by 17,4% ($p > 0,05$). After 28 days of the post-traumatic period, the indicator continued to decrease, becoming 23,6% lower compared to the result at 3 days ($p < 0,05$) and reached the control level ($p > 0,05$).

Against the background of BAT and acute blood loss, the serum content of IL-1 β changed cyclically compared to the control: with periods of increase – after 3 and 14 days of the post-traumatic period (by 66,5 and 74,2%, respectively, $p < 0,05$) and decrease – after 7 and 28 days. During these periods, the indicator exceeded the control by 49,4 and 38,0%, respectively ($p < 0,05$). Comparison of the experimental groups showed that at all time points of the post-traumatic period, the IL-1 β content in the blood serum of rats with BAT and acute blood loss was statistically significantly higher than in the analogous groups of rats with TBI and ST ($p_{4-5} < 0,05$, $p_{5-6} < 0,05$). In these groups, the differences in the studied indicator were not significant ($p_{4-6} > 0,05$).

Comparison with groups of traumatized rats without blood loss showed that on the background of TBI and blood loss, the serum IL-1 β content was statistically significantly higher only after 7 days of the post-traumatic period (by 14,3%, $p < 0,05$). After modeling BAT and acute blood loss, the indicator significantly prevailed after 3, 14, 21, and 28 days of the post-traumatic period (by 76,4, 74,2, 60,0, and 38,0%, respectively, $p < 0,05$). After modeling ST, acute blood loss did not cause significant deviations in the serum IL-1 β content ($p > 0,05$).

DISCUSSION

Thus, the modeled traumas are accompanied by a pronounced systemic pro-inflammatory reaction, which reaches its maximum in the early post-traumatic period. The basis for the excessive release of cytokines is the massive release of Damage-Associated Molecular Patterns (DAMPs), related to injury. DAMPs, interacting with Toll-like receptors, stimulate innate immune system cells and activate the complement cascade, which triggers the production and release of cytokines. In case of significant trauma, an excessive amount of cytokines released locally enters the systemic circulation and can cause Systemic Inflammatory Response Syndrome (SIRS), which, with inadequate treatment, can be complicated by secondary damage to tissues and organs, leading to the formation of Multiple Organ Dysfunction Syndrome (MODS). Under these conditions, another „vicious“ pathological circle is closed, where secondary tissue damage causes additional release of DAMPs and cytokines, continuing immune activation [17].

One of the first and most potent cytokines in the inflammatory response to trauma is TNF- α , the concentration of which increases in the early post-traumatic period and is produced by damaged tissues, and then primarily by monocytes and macrophages that migrate to the injury zone [18]. Important properties of TNF- α include stimulating the formation of other pro-inflammatory mediators, activating and aggregating neutrophils at the early stage of inflammation, enhancing the functional activity of monocytes and macrophages, promoting the removal of damaged and necrotic tissues [19], and inducing apoptosis [20]. With increasing severity of trauma, especially combined trauma, an increase in the blood concentration of TNF- α is noted [21], which is associated with increased mortality and poor long-term recovery.

The IL-1 family includes IL-1 α and IL-1 β , which are produced by macrophages and neutrophils. The IL-1 β isoform is the most common in traumatic injuries and is produced at the early stage of trauma. Its function is similar to DAMPs and involves stimulating immune cells to produce cytokines and other inflammatory mediators. All this can lead to uncontrolled inflammatory reactions and cause damage to tissues and organs [22]. It has also been proven that IL-1 β participates in enhancing apoptosis, leukocyte adhesion to endothelial cells, disrupting the blood-brain barrier, and forming edema [23].

Thus, the increased concentration of the studied pro-inflammatory cytokines in the blood serum in conditions of TBI, BAT, and ST in the early post-traumatic period indicates the formation of SIRS, which can stimulate a cascade of reactions capable of causing secondary damage to internal organs with the development of multiple organ dysfunction. Starting from the 7-th day of the post-traumatic period, the content of TNF- α and IL-1 β gradually decreases and, in conditions of TBI and ST, normalizes, which indicates the development of an adequate compensatory anti-inflammatory response and the activation of restoration processes. However, after modeling BAT, the content of the studied cytokines remains elevated until the 14-th day,

followed by a decrease that does not reach the control level. Therefore, mechanical impact to the abdominal cavity causes damage accompanied by prolonged generation of pro-inflammatory cytokines and an inadequate compensatory anti-inflammatory response. The basis of the observed reaction is, on the one hand, the mechanical injury of a larger volume of tissues, and on the other hand, the formation of secondary damage to the gastrointestinal tract organs already in the acute post-traumatic period, which is associated with the activation of the sympathoadrenal system, vasoconstriction of abdominal arteries, and reduced intestinal perfusion. All this causes damage to enterocytes and the intestinal barrier function. Our previous studies indicate that against the background of experimental TBI, ST, and especially their combination, the absorptive and barrier function of the intestines is impaired, lipid peroxidation processes are activated in the intestinal wall, and microbial translocation occurs [24, 25]. These disturbances significantly deepen the systemic inflammatory reaction in the post-traumatic period and indicate the important role of the intestines in the progression of inflammation, which is also mentioned in the works of other authors [26].

The pathogenesis of these disturbances is based on the release of alarmins and other damage-associated molecular structures by damaged enterocytes, the generation of reactive oxygen species by hypoxic intestinal epithelium caused by mitochondrial dysfunction and activation of cellular oxidases. All these factors activate the intestinal immune system with increased production of pro-inflammatory cytokines and chemokines [27]. That is why the release of pro-inflammatory mediators in conditions of BAT is more prolonged over time and is characterized by a greater amplitude of disturbances compared to TBI and ST.

In conditions of modeled mechanical traumas of various localizations complicated by acute blood loss, the disturbances in the content of TNF- α and IL-1 β in the blood serum are greater. The content of TNF- α in all experimental groups increases up to the 7-th day, remains at the same level until day 14, and then decreases, but does not reach the control level. In conditions of BAT, the indicator is significantly higher after 3–21 days of the post-traumatic period compared to other experimental groups.

In turn, the serum content of IL-1 β after modeling TBI, BAT, and ST reaches its maximum as early as 1 day of the post-traumatic period and then decreases, but does not reach the control level by the 28-th day. It should be noted that on the background of BAT, the increase in the studied indicator is biphasic, with the first increase at 1 day and the second at 14 days of the post-traumatic period. Despite this, in this experimental group, the indicator is statistically significantly higher compared to other experimental groups at all time points of the post-traumatic period.

In conditions of complication of the modeled traumas with acute blood loss, the amplitude of the increase in the content of the studied cytokines increases. On the background of TBI and acute blood loss compared to traumatized rats without blood loss, the TNF- α content is significantly higher after 7 and 14 days of the post-traumatic period, and IL-1 β

after 7 days. In conditions of BAT and acute blood loss, the TNF- α content is higher after 7, 14, and 21 days, and the IL-1 β content at 3, 14, 21, and 28 days of the post-traumatic period, respectively. In conditions of ST and acute blood loss, the TNF- α content is higher after 14 days, and the IL-1 β content does not differ significantly.

Thus, additional acute blood loss against the background of modeled mechanical traumas of various localizations significantly deepens the systemic inflammatory reaction, manifested by an increase in the amplitude of disturbances in the serum content of TNF- α and IL-1 β , which is significantly higher than the control at all time points of the post-traumatic period. Again, in conditions of BAT and acute blood loss, the indicators are significantly higher compared to other experimental groups at practically all time points of the post-traumatic period. Attention is drawn to the fact that in traumatized rats against the background of additional blood loss, the content of the studied indicators was significantly higher than in traumatized rats without blood loss. The intensity of cytokine reaction modulation under the influence of blood loss in rats with mechanical traumas can be represented as follows:

ST $\leftarrow$ TBI $\leftarrow$ BAT

Our data confirm the results of studies by other authors who state that acute traumatic blood loss significantly deepens the systemic reaction to inflammation. Under conditions of reduced perfusion, hypoxia, and impaired metabolic heat production, resident immune cells secrete TNF- α , IL-1 α , and neutrophil chemokines (CXCL1/2) [28]. Due to these mechanisms, neuroinflammation is deepened, which was observed in a mouse model of TBI and acute blood loss [29], and systemic inflammation is enhanced with higher expression of TNF- α and an increase in the number of CD8+ lymphocytes in a mouse model of combined closed TBI, femoral fracture, and hemorrhagic shock [30]. Especially pronounced vascular vasoconstriction during traumatic hemorrhagic shock is noted in the gastrointestinal tract, which impairs intestinal perfusion, leading to damage to enterocytes and intestinal barrier dysfunction. These disturbances contribute to bacterial translocation and the release of DAMP mediators and reactive oxygen species, enhancing systemic inflammation. The deepening of microcirculation disturbances against the background of trauma with additional blood loss is considered a key mechanism for deepening the systemic reaction to inflammation. That is why the greatest disturbances in the concentrations of TNF- α and IL-1 β in blood serum in our studies are noted precisely on the background of BAT.

Thus, mechanical traumas of various localizations significantly differ in the nature of the manifestations of the systemic inflammatory reaction and react differently when complicated by acute blood loss, which is important for developing strategies for systemic correction.

CONCLUSIONS

1. Experimental TBI, BAT, and ST are accompanied by a pronounced systemic pro-inflammatory reaction,

manifested by a significant increase in the serum content of pro-inflammatory cytokines TNF- α and IL-1 β , with a maximum of disturbances in the early post-traumatic period and a subsequent decrease, which only reaches the control level in the case of TBI and ST. In conditions of BAT, the indicators are significantly higher compared to other localized traumas.

- When the modeled mechanical traumas of various localizations are complicated by acute blood loss of the amount 1,5% of body weight, the disturbances

in the serum content of TNF- α and IL-1 β become greater. The content of TNF- α in all experimental groups increases up to the 7-th day, remains at the same level until day 14, and then decreases. The serum content of IL-1 β reaches its maximum as early as 1 day of the post-traumatic period and then decreases, but both indicators do not reach the control level by the 28-th day. In conditions of BAT, the indicator is significantly higher after 3–21 days of the post-traumatic period compared to other experimental groups.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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Effects of hypoxic training cycle on peripheral hemodynamics of wrestlers

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ABSTRACT

Aim: To monitor peripheral hemodynamics in the upper and lower extremities of wrestlers practicing different wrestling styles to control adaptive changes in the body after a cycle of interval hypoxic training with intense physical activity.

Materials and Methods: The athletes trained intensively in a hypoxic chamber for 21 days, 2 hours a day. We monitored their ECG, heart rate, and central and peripheral hemodynamic parameters. The results obtained were processed using traditional methods of variation statistics in the Microsoft program Excel (Microsoft Corporation, Redmond, Washington, DC, USA). The arithmetic means, and the deviations ($M + SE$) were calculated as %. The significance of the difference in means was assessed using the Fisher and Student t-test.

Results: Hypoxic training with varied loads using simulators and sparring resulted in the positive physiological adaptation of athletes. Interval hypoxic training for 120 minutes with an intense load and normoxic breaks at an O_2 concentration of 14.2% to 12% effectively improved the hemodynamics of wrestlers. The changes affected all studied parameters of the cardiovascular system. Vascular reactions during muscular work were aimed at hydrodynamic optimization of the circulatory system. Complex changes in blood flow and elastic-viscous properties of blood vessels worked to optimize heart function during physical exercise. Higher elastic resistance of large arteries provided the necessary increase in blood flow rate in large, medium, and small arteries and veins.

Conclusions: These results justify using interval hypoxic training with physical activity to increase the functionality of the cardiovascular system, peripheral hemodynamics, and microvasculature in the body of athletes. Based on the above, we could recommend an intense hypoxic training cycle with physical activity in 24 120-minute workouts with a protein and vitamin food supplement to increase the wrestlers' cardiovascular system functional capacity.

KEY WORDS: hypoxia, physical activity, cardiovascular system, hemodynamics, physiological adaptation, rheography

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INTRODUCTION

Modern sports activities place high demands on the state of the cardiovascular system (CVS) of athletes. Intense muscle activity leads to a lack of oxygen, which results in hypoxia. CVS compensates for tissue hypoxia, delivering O_2 to organs and tissues [1]. It is necessary to assess the functional state of athletes during training and monitor their CVS adaptation to various physical activities.

Regular hypoxic training helps adapt the body to constant stimuli, increasing its functional and physical fitness [2]. Physical training can occur in different environmental conditions (atmospheric pressure level and air temperature, water, gravity, etc.). Adaptation of the peripheral circulatory system of athletes with varied muscle activity to environmental conditions requires attention. Analyzing training results from the point of view of the impact of the volume and intensity of training on the athlete's body is still challenging.

Rheography allows for identifying the specifics of peripheral blood circulation in athletes with different training directions [3]. A rheographic curve is highly informative regarding various aspects of regional circulation in a target organ [4]. The rheogram shape and amplitude depend mainly

on the patency and tone of the vascular bed and the heart propulsion ability. A rheogram allows for assessing the patency of large (main) arteries, volumetric pulse blood filling of the target organ, the tone and elasticity of arteries of different calibers, and the state of venous outflow [5]. Today, rheography is a promising method widely used in clinical diagnostics and physiological research [4].

Many papers study central hemodynamic parameters in athletes of different sports and under different training conditions [6]. However, the functioning of the peripheral CVS in people involved in sports is understudied. Still, there is a need for constant monitoring of peripheral blood circulation in athletes during training. Therefore, we studied the specifics of peripheral hemodynamics in practicing wrestlers after interval hypoxic training with intense physical activity.

AIM

The study aimed to monitor peripheral hemodynamics in the upper and lower extremities of wrestlers practicing different wrestling styles to control adaptive changes in the body after a cycle of interval hypoxic training with intense physical activity.

MATERIALS AND METHODS

STUDY DESIGN AND POPULATION

The studies were conducted at the Institute of Genetics and Physiology of the Kyiv National Science Ministry of Education and Science of the Republic of Kazakhstan using the "Reo-spectrum" rheographic complex (Neurosoft LLC, Ivanovo, Russia). The study included 40 athletes aged 17 to 22 years. All subjects were previously familiarized with the content of the study, and their informed consent was obtained. Interval hypoxic training (IHT) took place in 2 hypoxic chambers - the first chamber with a useful area of 15 m² DP -30 (PRC, 2018) and in a large hypoxic chamber with an area of 40 m² - DP -50 (PRC, 2023), in which athletes' lifting heights were simulated at 3000 m, 3500 m, 4000 m, 4500 m and 5000 m above sea level (asl), under normal atmospheric pressure. The cycle of IHT classes was 21 days.

The athletes first trained in a small hypoxic chamber for 60 minutes, imitating an altitude of 3,000 m asl at the beginning (with an O₂ content of 14.2%) and ending at an altitude of 5,000 m asl (O₂ content – 12%). In the hypoxic chamber, the athletes did 20 minutes of leg stretching on an exercise bike and 20 minutes on a treadmill, then loaded the arms for 20 minutes with a kettlebell and a barbell or on a rowing simulator. When changing the simulator, they left the chamber for 3-4'. Then, after 10 minutes of rest, they sparred for 60 minutes in a large chamber under the supervision of a coach. While in the large chamber, they also took normoxic breaks for 3-4 minutes after 20 minutes of intense training to control saturation and blood pressure. In each chamber, training began at the oxygen concentration relevant for 3,000 m asl; the altitude increased by 500 m every 10 minutes to reach 5,000 m asl after 20 minutes. This oxygen concentration remained till the end of the training session. The athletes were constantly monitored while in the chamber. Their pulse was to be below 130 bpm and saturation above 65%. If not, the athletes reduced the load. Then, the athletes were followed up within 24 hours after the last training session.

On the training day, the athletes also received 120 g of a protein-vitamin food supplement (reg. no. KZ7500361.24.01.03089).

DEFINITION

The arterial inflow indicators included basic resistance, rheographic index (conventional unit), reflecting the state of volumetric blood flow of the main arteries of the lower extremities, the relation between amplitude and frequency (AFI, conventional unit), characterizing the intensity of arterial blood flow in the segment under study depending on the heart rate, and average and maximum vascular refilling rate (V_{REF} Ohm-sec). The vascular tone and elasticity indicators included the dirotic index (%) and diastolic index (%). The venous outflow (%) was measured from the body segment under study.

DATA COLLECTION

Rheovasograms were recorded in 2 symmetrical segments of the limbs - "thigh - lower leg" and "shoulder - forearm"

in the initial lying position before the start of the training cycle and after 21 training sessions in the hypoxic chamber. ECG in the second standard lead, blood pressure, and heart rate were simultaneously recorded. The rheogram was recorded according to the standardized approach and processed automatically in real time [7]. The processing of the results considered the sections of the peripheral part of the circulatory system.

ETHICS

The study was approved by the Ethics Commission of the Institute of Genetics and Physiology, Almaty, Kazakhstan (Conclusion N5 as of 07/25/2022).

STATISTICAL ANALYSIS

The results obtained were processed using traditional methods of variation statistics in the Microsoft program Excel (Microsoft Corporation, Redmond, Washington, DC, USA). The arithmetic means, and the deviations ($M + SE$) were calculated as %. The significance of the difference in means was assessed using the Fisher and Student t-test.

FRAMEWORK

The study was conducted under a scientific project no. 15-PTF-23-24 of the Ministry of Science and Higher Education of the Republic of Kazakhstan.

RESULTS

During the background recording of the rheovasogram, the "shoulder-forearm" and "thigh-shin" indicators in the studied athletes were within average normative values (Fig. 1, Fig. 2).

At rest, systolic blood pressure in the thigh, leg, and arm in all areas was at the same level, in the range of 116 ± 3.4 to 67 ± 3.1 mmHg. After hypoxic training in the shoulder-forearm area, the heart rate was 8.1% lower than the control values. The heart rate indicators of the studied athletes in the thigh-shin area were 8.2% less than before training. In all groups, a low heart rate was noted in a state of muscle rest compared to physiological norms. After the hypoxic training cycle, the heart rate decreased even more. ECG showed a corresponding lengthening of the cardiac cycle and an increase in wave R, resulting from a high fitness level of athletes involved in the study and the economization of heart activity.

Changes in rheovasographic indicators after hypoxic training are shown in Table 1, Table 2. Thus, the rheographic index showed that the pulse blood filling of the arteries after hypoxic training increased by 223.4% in the arm and 337.2% in the leg. A sharp increase in the rheographic index indicated more intense blood flow in those body segments. This vascular reaction was associated with the blood vessel adaptation to increased loads when inhaling a gas mixture with a low O₂ content and a resulting dilatation of arterial vessels. Due to increased blood flow, basic resistance increased in all studied segments of the athletes' limbs, including 11% in the arm and 231% in the leg. The AFI in athletes after hypoxic training decreased by 34% in the lower extremities (leg) and by 29% in the upper extremities (arm) compared to the control.

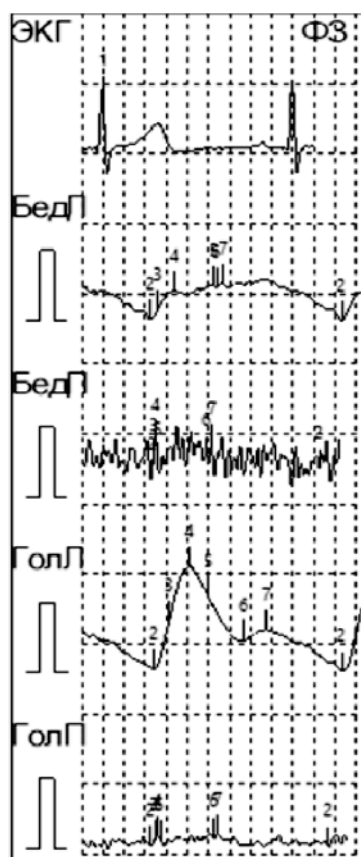


Fig. 1. Fragments of electrocardiograms and rheovasograms of the lower extremities before the start of training

Notes: Patient: Berdekhanov Kudainazar; Age: 21 years; ЭКГ – ECG; БедЛ – left thigh; БедП – right thigh; ГолЛ – left lower leg; ГолП – right lower leg

Picture taken by the authors

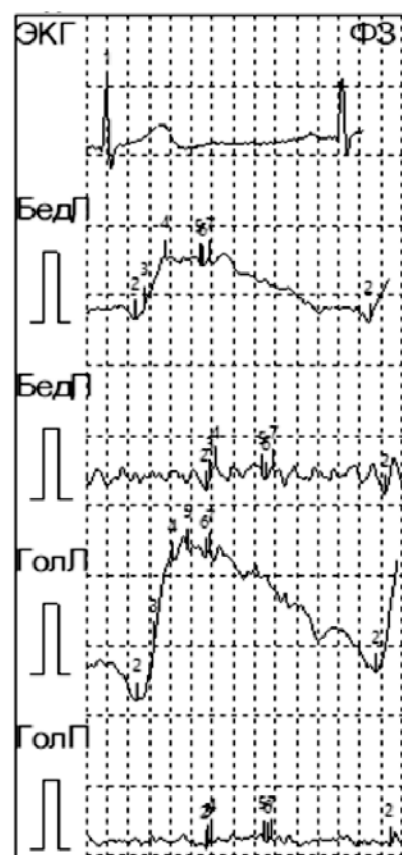


Fig. 2. Fragments of electrocardiograms and rheovasograms of the lower extremities after a cycle of 21 training sessions in the hypoxic chamber.

Notes: Patient: Berdekhanov Kudainazar; Age: 21 years; ЭКГ – ECG; БедЛ – left thigh; БедП – right thigh; ГолЛ – left lower leg; ГолП – right lower leg

Picture taken by the authors

Table 1. Rheovasographic indicators in the shoulder-forearm area in athletes after a cycle of hypoxic training

Indicators	Before hypoxic training (control)	After hypoxic training	P value (reliability) <
Heart rate, beats/min	62.1±1.8	57.1±1.7	-
Basic resistance, ohm	784 ±20	706 ±19	0.05
Rheographic index, c.u.	0.16 ±0.06	0.32 ±0.05	0.01
AFI, c.u.	1.139 ±0.34	3.33 ±0.31	0.001
VREF max, ohm-sec	0.621±0.17	0.72±0.14	-
VREF avg, ohm-sec	0.465±0.14	0.522±0.023	0.05
Dicrotic index, %	64±5	47±6	0.05
Diastolic index, %	52±3	63±4	0.05
Air defense, %	45.5 ± 2.4	59.5 ± 3.3	0.001

Source: compiled by the authors of this study

The vascular tone and elasticity indicators have changed in both groups after training in the hypoxic chamber. The dicrotic index, indicating peripheral vascular resistance in pre- and postcapillaries, decreased by 26.6% in the arm and 19.6% in the leg. The diastolic index increased by 21.1% in the arm and 15.5% in the leg, evidencing increased arterial blood outflow. A decrease in the dicrotic index indicated

a decrease in the arterial and venous tone after training.

The V_{REF} average values indicated increased blood filling of small and medium-sized arteries. After hypoxic training, V_{REF} max increased by 15.9% in the arm and 94.3% in the leg. V_{REF} avr also increased after training by 12.3% in the arm and 5% in the leg. Thus, the analysis of the slow (V_{REF} avr) and quick (V_{REF} max) vascular refilling rate, specified by the

Table 2. Rheovasographic indicators in the thigh-tibia area in athletes after a cycle of hypoxic training

Indicators	Before hypoxic training (control)	After hypoxic training	P value (reliability) <
Heart rate, beats/min	61±1.7	58 ±1.3	
Basic resistance, ohm	795 ±18	646 ±216	0.05
Rheographic index, c.u.	1.128 ±0.08	9.93 ±0.09	0.01
AFI, c.u.	1.170 ±0.07	1.465 ±0.09	0.01
VREF max, ohm-sec	0.610 ±0.012	1.185 ±0.09	0.01
VREF avg, ohm-sec	0.615 ±0.03	0.646 ±0.04	
Dicrotic index, %	46±4	37±3	0.05
Diastolic index,%	58±5	67±4	
Venous outflow, %	53.8±2.7	78.2 ± 3.1	0.05

Source: compiled by the authors of this study

tone of medium and small vessels after hypoxic training, increased in all segments (arm and leg), also evidencing a decrease in venous tone.

Venous outflow in athletes was significantly reduced after the hypoxic training cycle – by 19% in the arm and 15% in the leg. In the control group, it amounted to 112.5% in the arm and 53% in the leg.

DISCUSSION

Hypoxic chamber training imitates a high-altitude hypoxic environment using hypoxic tools, providing appropriate hypoxic stimulation to trainees to improve their aerobic metabolism and hypoxia tolerance [8]. Additional protein and vitamin nutrition during intense physical activity with hypoxia improves the body's physiological state and adaptation [9].

Dosed physical activity is accompanied by one of the most natural adaptive reactions for the body, which requires good interaction with all parts of the circulatory system. Skeletal muscles comprise most body mass and require intense blood flow during exercise [10, 11]. Blood flow in skeletal muscles is controlled by the same local mechanisms that regulate vascular resistance depending on the metabolic needs of muscle tissue [12]. During heavy physical activity, blood flow in athletes increases 15-25 times and amounts to 50-80 ml/min per 100 g of tissue, relative to blood flow at rest in untrained individuals and amounts to 3-4 ml/min per 100 g of tissue [13]. Physical activity has a training effect involving the body's adaptation mechanisms.

Peripheral circulation is the final link in the activity of the CVS, supplying the muscular system with oxygen and nutrients during its work during training.

After hypoxic training with normoxia, we identified a characteristic change in the speed of blood flow in large vessels and also in small and medium-sized vessels. An increase in these indicators is considered characteristic of a decrease in the distensibility of large and medium-sized arteries, for example, due to increased tone, and medium-sized vessels react to a greater extent. Several

authors have suggested that periodic changes in blood flow during muscle loads can directionally change the diameter of the involved arterial vessels [14].

Heart rate decreases after training and prolonged stay at altitudes (acclimatization) [15]. In this study, physical activity under hypoxic conditions supported the heart rate decrease in all segments studied.

With an increase in hypoxic load (a decrease in the oxygen content in the inhaled air from 20.4 to 12%), the RI has doubled in the arm and increased by 8.8 times in the leg, causing dilatation (relaxation) of the arterial vessels. Dilated arterioles and venules supplied more blood due to increased arterial inflow and venous outflow. Therefore, RI and blood flow volumetry showed more intense arterial blood flow in the arms and legs of the athletes. The tone and elasticity of arm and leg arterial vessels and peripheral vascular resistance of pre- and postcapillaries were reduced after a cycle of hypoxic training. As is known, the reaction of small arteries and large arterioles is predominantly controlled by the nervous system [16].

Various factors, mainly muscle contraction during physical activity, ensure upward blood flow. Repeated prolonged static loads and periodic and prolonged tension of lower extremities muscles after hypoxic training increase venous outflow.

Analysis of the dynamics of rheovasographic indicators showed that the nature of changes in hemocirculation in athletes includes changes in both the arterial and venous parts of the vascular bed. The most pronounced changes in peripheral blood circulation were detected in the areas (thigh – lower leg) affected by the sport the athletes were practicing. Our studies involved athletes who put stress on their legs and arms. The capacity of the vascular bed of the lower extremities is much larger than the vascular bed of the arms, so the changes in the lower extremities are more significant.

Thus, changes at the level of the peripheral link of the CVS in athletes' training speed and endurance are aimed at creating conditions for maximum extraction of oxygen

from the blood into the tissues, which is manifested in a decrease in the tone of arterial vessels and vessels at the level of the metabolic link. Adaptation to hypoxia activates all physiological systems, which compensate for hypoxia. This substantiates the high effectiveness of hypoxic training and improves the state of external respiratory organs. The key role of effects in developing microcirculatory changes is played by the opening of reserve capillaries and arteriovenous shunts, accompanied by a decrease in peripheral resistance.

During hypoxic training, a positive course of the adaptation process is observed, accompanied by optimal changes in the conditioned reflex activity of the athlete [17]. After hypoxic training, athletes experience changes in the function of all parts of the complex circulatory system - the heart, great vessels of the body and limbs, blood vessels, skeletal muscles, and the microcirculatory system. A significant restructuring of hemodynamics during muscular work is accompanied by several vascular reactions aimed at hydrodynamic optimization of the circulatory system. Changing the elastic-viscous properties of blood vessels under load is important for optimizing heart function. By increasing the elastic resistance of large arteries, the necessary increase in the speed of blood flow in the vascular system is achieved, and complex shifts in blood flow occur in other organs and tissues.

CONCLUSIONS

Rheovasograms of athletes before and after the training cycle showed a significantly increased arterial inflow and a decreased tone of medium and small vessels and the skeletal muscle microvascular bed. We observed how the peripheral circulatory system adapted to intensive activity under hypoxia. A cycle of 120 minutes of hypoxic training at an O₂ concentration from 14.2% to 12% with an intense training load and normoxic breaks effectively improved the physical performance of wrestlers by improving the hemodynamic function of their mid-level vessels and microvasculature. The results justify using cycles of 21 training sessions of hypoxic training with normoxia and intense physical activity for 120 minutes to increase the functionality of the peripheral part of CVS in wrestlers. Thus, the hemodynamic parameters of athletes of various specializations may be associated with the specifics of their sport and the prevalence of certain types of physical activity. Exposure to physical activity can lead to morphological and functional changes in the vascular system of professional athletes.

Based on the above, we could recommend an intense hypoxic training cycle with physical activity in 24 120-minute workouts with a protein and vitamin food supplement to increase the wrestlers' CVS functional capacity.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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A – Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article

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The histological image of the muscular component of the diaphragm in experimental animals following the creation of carboxyperitoneum by means of standard pressure of different duration

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ABSTRACT

Aim: To investigate the morphology of the rat diaphragmatic pedicles in the normal state and to evaluate the changes that occur under modelled carboxyperitoneum of different durations.

Materials and Methods: The study was conducted on sexually mature rats of the reproductive period, housed in an accredited vivarium. The animals were divided into six groups: intact, control, and four main groups. In the main groups, carboxyperitoneum at standard pressure was modelled for one, three, and five hours.

Results: The study of microdissections revealed the destruction of the basal membranes of muscle fibres, which, upon histological examination, appeared as a continuous, heterogeneous, structureless mass. The mass also contained single or grouped preserved pyknotic nuclei and macrophages. The muscle fibres were deformed and fragmented in large areas, and transverse striations were absent. The myofibrils were uncoiled and partially lysed or coagulated, acquiring an intense homogeneous eosinophilic colour. The nuclei in the areas of fibre lysis were absent. The capillaries present in the endomysium were full-blooded, while the arterioles in the perimysium contained plasma or a small number of erythrocytes.

Conclusions: The assessment of the intensity of the noted changes in the experimental groups with varying durations of carboxyperitoneum revealed a direct correlation between the observed histological changes and the duration of pneumoperitoneum, with notable implications for the morphology of the right and left crus of diaphragm.

KEY WORDS: crus of the diaphragm, rat, pneumoperitoneum, intra-abdominal pressure, morphology

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INTRODUCTION

Nowadays, both doctors and patients are increasingly favouring laparoscopic techniques over open surgery. This preference is driven by the minimally invasive nature of laparoscopy, which reduces the risk of adverse outcomes such as infection and bleeding. Additionally, the shorter healing time and postoperative period associated with laparoscopy are attractive benefits. The traditional approach to laparoscopic surgery involves creating a pneumoperitoneum through the insufflation of carbon dioxide, also known as carboxyperitoneum (CP). This allows for the separation of organs and their parts, facilitating their identification and dissection. However, there is evidence that the presence of this gas in the abdominal cavity can lead to cardiopulmonary failure, particularly in cases where there is long-term high abdominal pressure. This highlights the need for further investigation into this potentially life-threatening cause. [1].

Laparoscopic techniques are undergoing continuous improvement, both in terms of the design and functionality of surgical devices and the experience of surgeons. This evolution is further enhancing the use of laparoscopy for both minor and complex abdominal surgery. There are reports in the literature indicating that carbon dioxide

itself leads to a disturbance of the internal environment of the abdominal cavity, which in turn causes changes in haemodynamics, namely an increase in central venous pressure and mean arterial pressure. Furthermore, some data indicate cases of life-threatening conditions associated with carboxyperitoneum, including renal dysfunction [2], pulmonary oedema and gas embolism [2, 3]. The technology of laparoscopic surgery has undergone significant advancements over the past three decades, with ongoing developments. However, there has been comparatively less focus on how modifying the laparoscopic surgery environment can enhance clinical outcomes [1, 4].

There is a debate among the medical community regarding the type of gas used for pneumoperitoneum. The objective is to determine the optimal pressure level for creating the optimal space in the abdominal cavity for surgery. It is widely accepted that different durations and levels of carboxyperitoneum (CP) have varying effects on the abdominal organs. These effects contribute to the development of metabolic processes and even thrombosis. [5-7].

The injection of carbon dioxide into the abdominal cavity exerts uniform pressure in all directions. Of particular

importance is the pressure exerted on the posterior wall of the abdomen, where the inferior vena cava and aorta are located, as well as the pressure in the cranial direction on the diaphragm, which leads to compression of the thoracic cavity [3, 8, 9].

It is recognised that the residual quantity of carbon dioxide situated between the dome of the diaphragm and the liver has the potential to cause postoperative discomfort in the shoulder blade region [10]. CP increases intrathoracic pressure by raising the diaphragm and restricting lung excursion [9]. As CP levels rise, cardiac output declines and systemic vascular resistance rises. This prompts the body to initiate compensatory tachycardia, a general reaction to increased intra-abdominal pressure. The objective is to compensate for the reduced stroke volume and normalise cardiac output [5, 11].

The majority of literature indicates that laparoscopic cholecystectomy, the most common laparoscopic surgery, can be successfully performed at a lower CP than the standard abdominal pressure level in approximately 90% of patients undergoing laparoscopic cholecystectomy [6]. The standard pressure of gas for inflating the abdomen is typically between 14 and 16 mmHg. However, this can result in changes to circulation and may pose certain risks. To address this, alternative lower pressures have been proposed as an option to the standard pressure [5, 6].

AIM

To investigate the morphology of the rat diaphragmatic crus in the normal state and to assess its changes during simulated carboxyperitoneum of different durations at an intra-abdominal pressure of 10 mmHg.

MATERIALS AND METHODS

The research on laboratory animals was conducted in accordance with the provisions of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes of 18 March 1986, Council of Europe Directive 2010/63/EU, and the Law of Ukraine, On

Protection of Animals from Cruelty'. The experimental study was conducted on sexually mature rats of the reproductive period (5 months), weighing (215.0±20.0) grams. The rats were sourced from an accredited vivarium at the I. Horbachevsky Ternopil National Medical University (Table 1). The experiments were conducted in the morning indoors at a temperature of 18-20°C, relative humidity of 60-80% and illumination of 200 lux. The animals were euthanised by an overdose of thiopental sodium at a rate of 75 mg/kg of body weight intraperitoneally.

All animals, with the exception of the intact group, were anaesthetised with a combination of Ketamine Solutions (90 mg/kg) and Xylazine (10 mg/kg) via intramuscular injection throughout the course of the experiment. In the control group, the abdominal wall was punctured with a Veress Needle for a period of five hours in order to ascertain whether anaesthesia and laparocentesis have an impact on the morphology of the diaphragm. In the main groups, carboxyperitoneum was created, according to the copyright certificate for the work No. 126409 of 16 May 2024 [12], with the KARL STORZ electronic laparoflator 264300 20 insufflator at the level of 10 mmHg and the carbon dioxide supply rate at the level of 0.1 l/min, for 1, 3 and 5 hours (Fig. 1). According to studies, this level of pressure in rats corresponds to a pressure of 15 mmHg in an adult [13, 14]. During the experiment, the animal was observed to breathe independently and did not require external lung ventilation.

After the experiment, the rat diaphragm was sampled in accordance with the copyright certificate for the work No. 126059 dated 29 April 2024 [15]. The sampled diaphragm is shown in Fig. 2.

The crura of the diaphragm were isolated from the macro preparations and fixed in a 10% solution of neutral formalin. The material was then dehydrated in ethyl alcohols of increasing concentration and embedded in paraffin. Histological sections 5-7 µm thick were made from each paraffin block on a microtome and stained with hematoxylin and eosin after deparaffinisation.

Table 1. Distribution and characteristics of animals in the groups

Group of animals	Characteristics of the group
Intact group (n = 10)	Diaphragm sampling for morphological assessment as a norm
Control group (n = 10)	Diaphragm sampling after laparocentesis with the Veress Needle without creating carboxyperitoneum
I the main group (n = 10)	Diaphragm sampling after creating carboxyperitoneum at 10 mmHg for 1 hour
II the main group (n = 10)	Diaphragm sampling after creating carboxyperitoneum at 10 mmHg for 3 hour
III the main group (n = 10)	Diaphragm sampling after creating carboxyperitoneum at 10 mmHg for 5 hours
IV the main group (n = 10)	Diaphragm sampling on day 7 after carboxyperitoneum creation at 10 mmHg for 5 hours
Total animals – 60	

Source: compiled by the authors of this study



Fig. 1. The creation of carboxyperitoneum in a rat using an insufflator

Picture taken by the authors

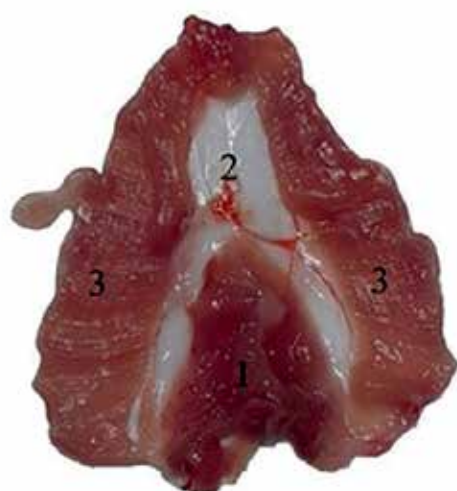


Fig. 2. The taken macrosection of the diaphragm: 1 – crus of the diaphragm; 2 – tendon part; 3 – rib part

Picture taken by the authors

RESULTS

The study of the preparations yielded a morphological picture of the normal crus of the diaphragm obtained from the intact group. This was represented by transversely striated muscle fibres forming a dense layer. There was a pronounced heterogeneity of muscle fibres, myofibrils and the presence of adipose tissue in the perimysium. There was slight variation in muscle fibre thickness and the sarcoplasm displayed a light eosinophilic colour. However, the tinctorial properties were heterogeneous and often the sarcoplasm acquired a deep structure. The elongated-oval nuclei were located under the sarcolemma and were not always evenly spaced and oriented parallel to the fibre. Transverse striation in the form of straight or arcuate stripes is also distinguishable on longitudinal sections. However, the visualisation of transverse striations was not always clear. The stroma is notably thin, comprising primarily of blood-filled capillaries and a limited number of fibrocytes (Fig. 3). The morphological characteristics of the specimens obtained from the control group of rats were found to be consistent with those of the intact group of animals. It can be reasonably concluded that the

application of anaesthesia and laparocentesis with a Veress needle, without the creation of carboxyperitoneum, does not result in significant morphological alterations within the crus of the diaphragm.

The application of intra-abdominal pressure at 10 mmHg resulted in the emergence of pathological alterations in the isolated diaphragmatic region. Consequently, following the introduction of carboxyperitoneum for an hour, the muscle layer exhibited partial loss of compactness due to the accumulation of fluid in the perimysium and endomysium, accompanied by the presence of cellular infiltrates and adipose tissue. The nuclei lost their monomorphism and appeared outside their usual localisation. The sarcoplasm is extremely heterogeneous, with foci of its compaction replaced by liquefaction, disintegration and, on occasion, cytolysis. This was combined with a change in the orientation of the fibres themselves. However, alongside these changes, there were compact muscle groups with minimal alterations and well-visualised transverse striations that remained preserved. The venous part of the vascular bed was covered in unevenly expressed haemorrhage. The arterioles and small arteries were usually poorly haemorrhaged and exhibited

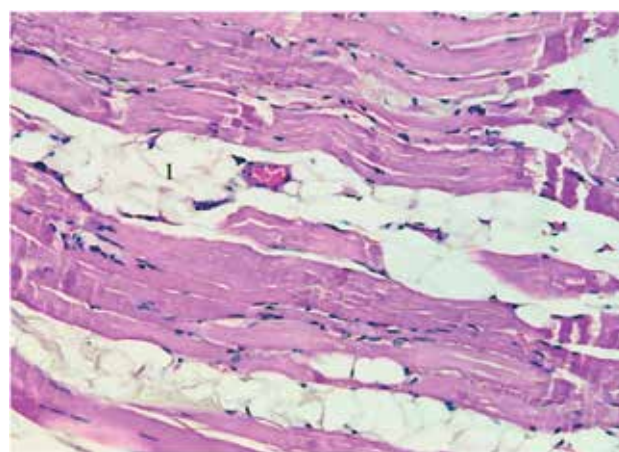


Fig. 3. Histological structure of the crus of the diaphragm of a control group of rat. Fatty tissue in the perimysium(1). Haematoxylin and eosin staining. $\times 200$

Picture taken by the authors

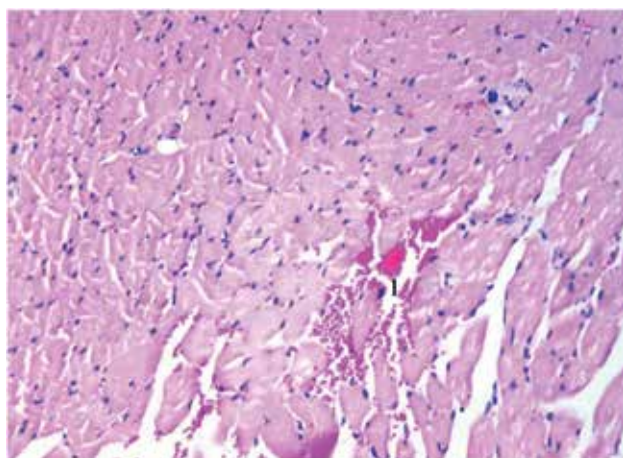


Fig. 4. Hemorrhage in the muscle of the crus of the diaphragm in a rat after 1 hour. Hematoxylin and eosin staining. $\times 100$

Picture taken by the authors

endothelial damage in the form of endothelial swelling, luminal breakdown and peeling. A distinctive feature was small focal and scattered haemorrhages (Fig. 4).

Following a three-hour examination, degenerative changes in the sarcoplasm were observed, along with the destruction of the basal membranes of muscle fibres. This resulted in the formation of a continuous heterogeneous, structureless mass, which was found to contain single or grouped preserved pyknotic nuclei and macrophages. Additionally, muscle fibres were deformed and fragmented in large areas. Transverse striations are usually absent. The myofibrils are uncoiled and partially lysed or coagulated, acquiring an intense homogeneous eosinophilic colour. Nuclei are absent in areas of fibre lysis. Capillaries in the endomysium are full-blooded, while arterioles in the perimysium contain plasma or a small number of erythrocytes. Oedema is uneven, with some areas exhibiting sharp expression. Additionally, adipose infiltration and proliferation of collagen fibres around vessels were observed (Fig. 5).

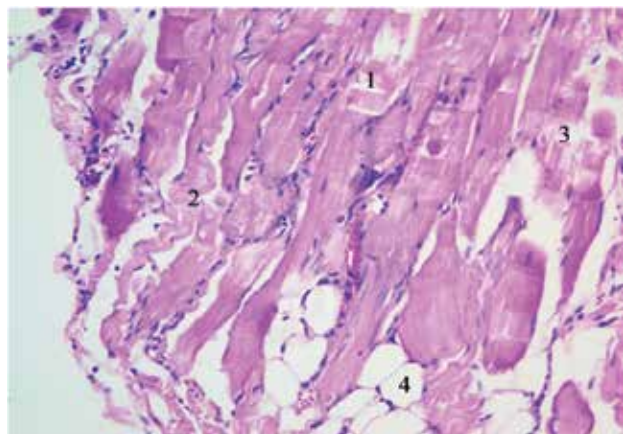


Fig. 5. The histological structure of the muscle of the crus of the diaphragm in a rat after 3 hour. Fragmentation of muscle fibres (1), their deformation (2) and lysis (3). Adipose infiltration of connective tissue (4). Hematoxylin and eosin staining $\times 200$

Picture taken by the authors

Following a five-hour period, there was a notable increase in the involvement of the structural components of the crus of the diaphragm in the pathological process. Histological analysis revealed that the full range of structural changes initially observed had reached a point of maximum severity. The deformation of muscle fibres, their fragmentation and lysis were particularly pronounced in comparison to observations made at the one- and three-hour time points. There was an increase in fibre heterogeneity, as observed on transverse sections. This was evidenced by the rounded appearance of muscle fibres and a reduction in diameter, which indicated partial atrophy of the diaphragmatic muscle. In response to the injury, cellular inflammatory infiltrates occurred. A distinctive feature was the presence of haemorrhagic infiltration, haemorrhages were more common and intense. Erythrocytes infiltrated the endomysium. Another characteristic feature was haemorrhagic seepage of necrotic fibres (Fig. 6).

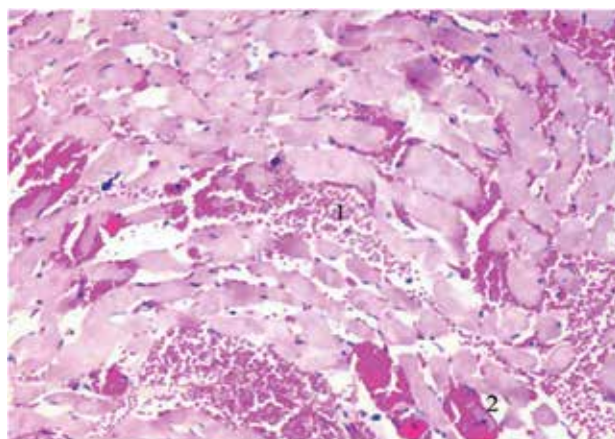


Fig. 6. Histological structure of the muscle of the crus of the diaphragm in a rat after 5 hours. Diffuse haemorrhages (1) and haemorrhagic soaking of necrotic fibres (2). Hematoxylin and eosin staining. $\times 200$

Picture taken by the authors

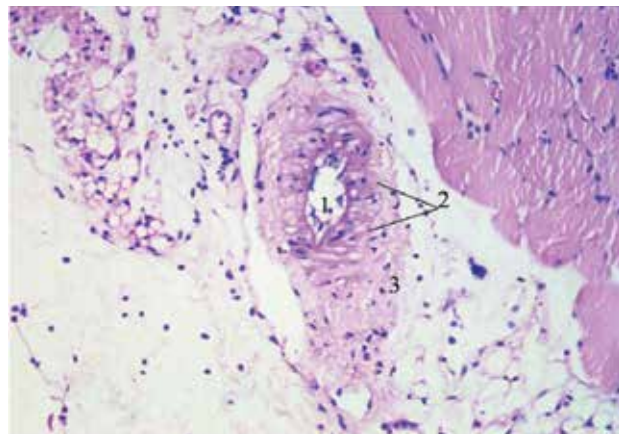


Fig. 7. Histological structure of the muscle of the crus of the diaphragm in a rat after 7 days. Endothelial desquamation (1), vessel wall (2), oedema, proliferation of collagen fibres in the perivascular space (3). Hematoxylin and eosin staining. $\times 200$

Picture taken by the authors

The micrograph taken on the seventh day after carboxyperitoneum creation revealed significant changes in the arterial vessels. The endothelium was exfoliated and located freely in bloodless lumens. The wall thickened, the boundaries of its layers were erased, and the myocytes had a vacuolated appearance. Additionally, oedema, polymorphic cell infiltrates, and connective tissue proliferation were observed around the vessels (Fig. 7).

DISCUSSION

Over the past decade, the range of surgical interventions has expanded from conventional laparoscopic cholecystectomy to interventions on the stomach and intestines, as well as on extrahepatic bile ducts and retroperitoneal organs. As the number of operations has grown, so too has the duration of interventions in acute care settings. There has been an increase in the number of surgical procedures performed on elderly and senile patients with serious concomitant diseases of the cardiovascular and pulmonary systems, for whom additional aggression in the form of CP becomes clinically significant [5, 6, 9]. It is inevitable that gas insufflation into the abdominal cavity will result in an increase in intra-abdominal pressure [2, 9, 16]. The use of laparoscopic technologies has led to the emergence of new complications specific to such interventions, including gas insufflation into the abdominal cavity [17].

The analysis of the literature revealed sufficient data on the effect of carboxyperitoneum on the diaphragm, the respiratory system as a whole and other abdominal organs. However, there is a notable gap in the available data, specifically regarding the histological structure of parts of the diaphragm after carboxyperitoneum of different durations. During the course of the experiment, we created intra-abdominal pressure for different periods of time by compressing a blood pressure monitor cuff. We then studied the histological structure of the muscular part of the diaphragm. We observed changes that are characterised by the development of haemodynamic disorders, disorganisation of fibrous structures of connective tissue, dystrophic changes in muscle tissue, and the occurrence of an inflammatory reaction. By assessing the intensity of these changes in experimental groups with different durations of intra-abdominal pressure, it is possible to establish a direct correlation between the severity of structural changes and the duration of exposure to the experimental factor in the bodies of the experimental animals [18].

The initial step in laparoscopic surgery is the creation of a pneumoperitoneum, which is achieved by introducing carbon dioxide through a Veress needle or a port in the abdominal wall. The standard pressure used is approximately 15 mmHg, as referenced in various literature sources. [3, 5, 6, 7]. This pneumoperitoneum allows for optimal visualization and manipulation of surgical instruments within the abdominal cavity. Increased intra-abdominal pressure due to pneumoperitoneum causes a number of cardiopulmonary changes. It is important

to note that increased intra-abdominal pressure leads to an increase in carbon dioxide uptake, which can result in hypercapnia and acidosis. To avoid these complications, it is essential to perform hyperventilation [2, 3]. Additionally, this pressure shift the diaphragm upwards, reducing lung compliance and decreasing pleural cavity volume while increasing maximum airway pressure [19, 20]. This results in a reduction in the diaphragm's functional capacity, as evidenced by our study. Our findings revealed structural alterations in muscle fibres, with deformation, fragmentation and lysis reaching their peak after five hours of carboxyperitoneum. This indicates a notable decline in the contractile capacity of the diaphragm. This was also observed after 1 and 3 hours, but to a lesser extent, which confirms that these changes depend on the duration of the pressure created in the abdominal cavity by carbon dioxide.

There is evidence to suggest that helium insufflation could be an alternative to CO₂ insufflation. It has been reported that helium has little or no effect on lung function in pigs. However, concerns about helium's blood solubility and the risk of gas embolism have meant that it has not been used routinely in humans [1, 2].

Studies of the last decade have been conducted using carboxyperitoneum with a lower pressure of 7-8 mmHg. A comparative analysis of indicators indicates that pain syndrome (frenicus symptom) was observed 36.7% more frequently in patients in the laparoscopy group with standard pressure than when using lower pressure. Additionally, the incidence of postoperative complications was lower when a lower pressure was used [6-8]. The majority of surgeons categorise them into three groups [5]. The first group of complications is related to the specifics of anaesthesia, which often has to be performed in the forced position of the patient during gas insufflation into the abdominal cavity. This is in fact the method used to create a model of the 'increased intra-abdominal pressure' syndrome. The second group of complications is caused by the pharmacological effect of the gas. The third group is caused by the peculiarities of performing manipulations in the confined space of the abdominal cavity filled with gas.

The objective of the experiment, conducted on rabbits, was to simulate chronic elevated intra-abdominal pressure and observe the changes in the diaphragm. Following an intense contraction of the respiratory muscle, an adaptation was observed which resulted in functional efficiency improvements in relation to the workload. However, this also made the muscle vulnerable to oxidative stress [19, 20].

CONCLUSIONS

The results of the histological examination demonstrate that general anaesthesia with pneumoperitoneum at standard pressure, created by carbon dioxide, affects the condition of the crus of the diaphragm. The morphological changes are characterised by the development of muscle fibre deformation, fragmentation and lysis, with the presence of haemorrhagic infiltration. In transverse sections, muscle

fibres became rounded and reduced in diameter, which is a sign of atrophy. The intensity of these changes was assessed in the experimental groups with different durations of carbon dioxide pneumoperitoneum. It was found that there is a direct correlation between the histological changes and the duration of pneumoperitoneum exposure on the morphology of the right and left crus of diaphragm.

PROSPECTS FOR FURTHER RESEARCH

The next stage of our research will focus on studying other areas of the muscular part of the diaphragm. In addition, we will examine how this organ responds to pneumoperitoneum, created by carbon dioxide at a lower pressure level (5 mmHg), and compare the results obtained at a pressure of 10 mmHg.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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Aberrant expression of CD markers in patients with acute leukemia

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ABSTRACT

Aim: The current study designed to evaluate the abnormal expression prevalence of Cluster of Differentiation (CD) markers in Iraqi patients diagnosed with AL at the Medical City Hospitals.

Materials and Methods: A total of 175 newly diagnosed leukemia patients (110 males and 65 females) aged between 1 and 85 years were included. Bone marrow aspiration and flow cytometry were used to analyze CD marker expression. Data on hematological parameters, immunophenotypic profiles, and demographic characteristics were recorded and statistically analyzed.

Results: The present study identified aberrant expression of CD markers, including CD13, CD19, CD33, CD34, CD117, CD56, CD5, TdT, HLA-DR, and CD79a, across different leukemia subtypes. Acute myeloid leukemia (AML) was the most prevalent subtype (46.2%), followed by B-acute lymphoblastic leukemia (B-ALL) (26.2%) and T-acute lymphoblastic leukemia (T-ALL) (8.5%). CD34 was highly expressed in AML, B-ALL, and T-ALL cases, while CD13 and CD33 were predominantly expressed in AML. CD56 and CD117 were associated with multiple myeloma (MM).

Conclusions: The study demonstrated a high ratio of abnormal CD marker expression in AL cases, aligning previous data from various area around the world. Identifying aberrant antigen expression patterns through immunophenotyping aids in diagnosing leukemia and distinguishing neoplastic cells from normal hematopoietic precursors.

KEY WORDS: acute leukemia, flow cytometry, CD markers, immunophenotyping, aberrant expression

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INTRODUCTION

Cancer is abnormal growth which the Cells divide autonomously in pathological states. Among the cancers, Acute leukemia which is a clonal hematopoietic condition that causes immature cells (blasts) to be produced in bone marrow and peripheral blood. Acute leukemia is categorized into two distinct types—acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) - based on the morphology of immature cells, immunological and cytogenetic characteristics, clinical presentation, and molecular abnormalities, with myeloblasts and lymphoblasts being predominant [1, 2]. Acute leukemia is a heterogeneous group of malignant tumors that differ in clinical, morphologic, immunologic, and molecular characteristics. They also demonstrate distinctive surface antigen expression patterns (Cluster of Differentiation (CD) antigens) [3]. In acute leukemia, blast cells or precursor cells from various lineages exhibit distinct subsets of surface molecules, known as cluster of differentiation (CD) antigens. Each leukemia subtype is characterized by specific CD markers, which play a vital role in the classification and diagnosis of hematological

malignancies [4]. Monoclonal antibodies (MAbs) detect the presence or absence of antigens on or within cell populations, producing distinct immunostaining patterns that identify specific cell lineages and aid in the diagnosis of acute leukemia. Immunophenotyping of leukemia cells is crucial for identifying malignant leukemia cells, determining their maturation stage, and detecting potential aberrant antigen expression. This allows physicians to monitor individual treatment and detect residual disease [5]. Flow cytometry can determine CD marker expression on leukocytes. However, CD markers are associated with some cases of AL. The flow cytometry technique analyzes several phenotypic and functional characteristics within individual cells or entire cell populations [6]. The potential to measure various characteristics of individual cells in suspension helps study leukemic cells. It utilizes monoclonal antibodies to identify cell markers exactly. Flow cytometry immunophenotyping can distinguish neoplastic cells from normal hematopoietic precursors due to distinctive abnormal phenotypes that enable exact identification and differentiation from normal cells, even when occurring at extremely low frequencies [7].

AIM

The current study conducted to evaluate the frequency of abnormal CD marker expression in AL cases among Iraqi patients at the Hematology Center, Medical City Hospital.

MATERIALS AND METHODS

STUDY DESIGN AND PATIENT SELECTION

The present retrospective study was carried out at the Iraqi Center for Hematology, a specialized clinical facility within the Medical City at Baghdad Teaching Hospital, Iraq. It included 175 newly diagnosed leukemia patients who underwent bone marrow aspiration. The patients' ages ranged from 1 to 85 years, comprising 110 males and 65 females, during the period from July 2024 to July 2025. Patient data, including demographic characteristics, hematological parameters, and immunophenotypic profiles, were studied. The study protocol adhered to ethical guidelines and was approved by the Scientific committee in University of Bilal Alrafedain, College of Medical and Health Technologies.

INCLUSION AND EXCLUSION CRITERIA

Patients diagnosed with leukemia based on clinical, hematological, and immunophenotypic criteria were included. While the cases with incomplete medical records, patients with metastasis or those undergoing treatment prior to data collection were excluded.

DATA COLLECTION

Demographic data, including age and gender, were recorded. Patients were stratified into age groups: younger than 10 years, 11-20 years, 21-30 years, 31-40 years, 41-50 years, 51-60 years, 61-70 years, 71-80 years, and above 80 years. Gender distribution was also analyzed.

LABORATORY TESTS

Complete blood count (CBC) parameters, including hemoglobin (Hb), white blood cell (WBC) count, platelet count, and peripheral blast percentage, were assessment.

SAMPLE COLLECTION

The sample preferred for the study was bone marrow aspirate; peripheral blood was used when the bone marrow aspirate was not possible. Approximately 2-2.5ml of bone marrow aspirate was collected from all patients. A Bone marrow aspiration procedure was done from the posterior superior iliac spine was accessed under strict aseptic conditions and necessary precautions. Simultaneously, a 5 mL blood sample was drawn from each patient into an ethylenediaminetetraacetic acid (EDTA) tube and promptly sent for a complete blood count (CBC) analysis using an automated blood counter (Sysmex KX-21N). The EDTA blood samples were also tested for ESR and blood cell morphology.

Bone marrow aspirates and peripheral blood smears were made from the blood sample and spread onto the slides. These slides were air-dried and stained with Wright-Giemsa stain. Myeloperoxidase staining used as special stains were routinely used in all cases when required based on the morphological details of the leukemic blasts.

FLOW CYTOMETRY

Blast cell immunophenotyping in bone marrow aspirate and peripheral blood samples was conducted using the BD FACSCalibur Flow Cytometer [8].

The diagnosis of acute leukemia was determined based on the presence of $\geq 20\%$ blast cells in the bone marrow smear, in accordance with WHO criteria, with immunophenotyping findings corroborating the diagnosis. The antibodies used to CD markers detection included CD5, CD13, CD19, CD22, CD31, CD33, CD34, CD56, CD58, CD64, CD79alpha, CD117, cMPO, HDL-AR and TdT which conducted for each leukemia subtype.

LEUKEMIA CLASSIFICATION AND IMMUNOPHENOTYPING

Acute Leukemia cases which included in the current study were classified into Acute Myeloid Leukemia (AML), B-Acute Lymphoblastic Leukemia (B-ALL), T-Acute Lymphoblastic Leukemia (T-ALL), Multiple Myeloma (MM), Small Lymphocytic Lymphoma (SLL), and finally Pro-Acute Lymphoblastic Leukemia (Pro-ALL)

IMMUNOPHENOTYPING FLOW CYTOMETRY PROCEDURE:

Flow cytometric immunophenotyping is a valuable tool for determining lineage in acute leukemia by detecting the expression of lineage-specific Cluster of Differentiation (CD) markers. The flow cytometry Instrument and software used in the current study was BD FACS Canto II/BD FACS DIVA.

1. Carefully add surface markers monoclonal Ab cocktail to the bottom of the tube, making sure nothing adheres to the side wall of the tube
2. Dispense 100 μ l of sample to the bottom of the tube and avoid leaving any trace of the sample on the side wall of the tube
3. Vortex gently for 3-5 seconds and incubate in the dark for 20 minutes
4. If you have tubes that require cytoplasmic staining, start staining surface markers along with other tubes after 20 minutes of incubation. Add 100 μ l treasure reagent A only to the tube requiring cytoplasmic staining and incubate for 5 minutes in the dark
5. Dispense 20 μ l of lyse to tube, mix by capping tubes and inverting them several times, and incubate for 10 minutes in the dark
6. Centrifuge at 700-800 ref (1500 rpm) for 5 minutes, carefully remove supernatant
7. For tubes intended for cytoplasmic staining, add 50 μ l treasure reagents B, add monoclonal for cytoplasmic staining and gentle vortex (3-5 seconds), and incubate for a minimum of 20 minutes in the dark
8. Wash tubes for surface markers staining 3 μ l wash buffer suspended in 0.5 ml buffer and acquired cells on the FACS control (Shwani et al., 2023).

STATISTICAL ANALYSIS

Data analysis was performed using the Statistical Package for Social Sciences (SPSS) version 26. Descriptive statistics were applied to summarize the data, with numerical variables presented as mean and standard deviation (SD) and categorical variables reported as frequency and percentage

RESULTS

A total of 175 diagnosed acute leukemia cases extracted from Medical City Hospital were retrospectively analyzed in this study. A high prevalence was in the age group younger than 10 years ($n=52$) (29.7 %), followed by the 11-20 Years ($n=27$) (15.4 %) group, and the least was seen in the 80 above ($n=6$) (3.4 %) group. The median age of the patients was 33 years. The age group-wise number and percentage shown in Table 1.

Regarding gender, males represent 110 (62.8%) cases, while females represent 65 (37.1%). Acute leukemia expressed a higher prevalence in males compared to females, as shown in Figure 1 and Table 2.

According the data in Table 3, the level of Hb was between 4.5 and 12.7 gm/dl with a mean of 8.3 gm/dl;

most patients had leukocytosis increased WBC count ($>50 \times 10^9$), Thrombocytopenia ($<100 \times 10^9$) were and An elevated peripheral blast cell count greater than 20%, with an average of 57%, was observed.

The classification as numbers and percentages of acute leukemia types were expressed in Table 4 According to this Table, the distribution of types of leukemia shown AML was the more prevalent type among the studied group, and Based on immunophenotypic analysis of leukemic cells, among these 175 patients, there were 81 cases of AML (46.2%), 46 cases of B-ALL (26.2%), 15 cases of T-ALL (8.5%), 10 cases of MM (5.2 %), 13 cases of SLL (7.4 %) and 10 cases of Pro-ALL (5.2 %).

The current study and through the immunophenotyping of acute leukemia patterns revealed that most AML showed

Table 1. Age distribution among 175 cases of acute leukemia

Age group	Number of cases	Percentage [%]
≤ 10 YEARS	52	29.7
11-20 YEARS	27	15.4
21-30 YEARS	8	5.5
31-40 YEARS	7	4.0
41-50 YEARS	16	9.1
51-60 YEARS	21	12
61-70 YEARS	20	11.4
71-80 YEARS	18	10.2
80 above	6	3.4
Total	175	100

Source: Own materials

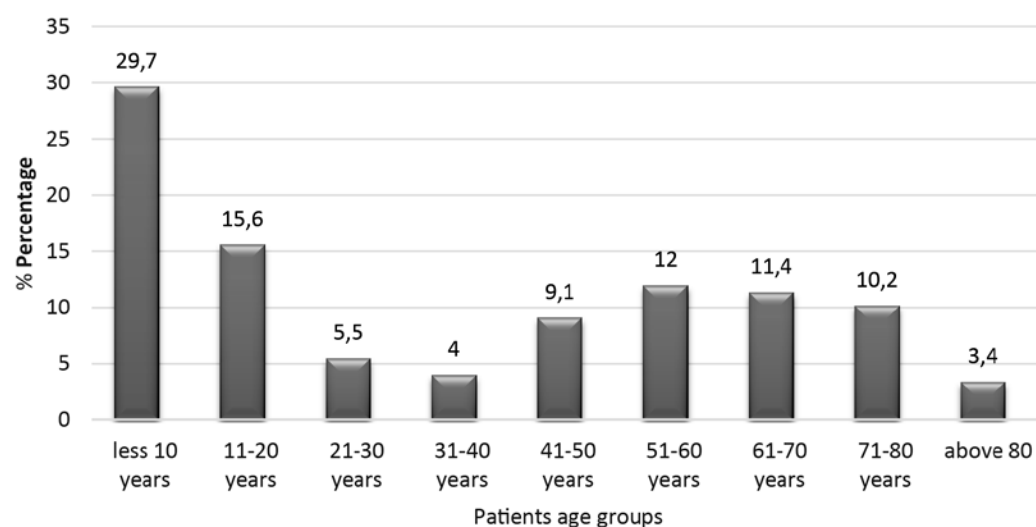


Fig. 1. The distribution of the patients among age groups

Source: Own materials

Table 2. Gender distribution of 175 cases of leukemia

Gender	Frequency (n)	Percentage [%]
Male	110	62.8
Female	65	37.1
Total	175	100

Source: Own materials

Table 3. Mean hematological values of 175 cases of leukemia

Hematological Parameter	Mean $\pm$ SD	Minimum	Maximum
Hb (gm/dl)	8.3 $\pm$ 2.06 gm/dl	4.5	12.7
WBC count	51.9 $\pm$ 107.27 $\times 10^9$	0.8 $\times 10^9$	122 $\times 10^9$
Platelet count	96.3 $\pm$ 100.18 $\times 10^9$	17 $\times 10^9$	340 $\times 10^9$
Blast cells count(BM-PB)	56.8 $\pm$ 23.3%	4%	88%

Source: Own materials

Table 4. Flow cytometry immunophenotyping diagnoses of the cases

Leukemia type	Flow cytometry Diagnosis	Number of Cases	Percentage [%]
Acute leukemia	Acute Myeloid Leukemia (AML)	81	46.2
	B-Acute Lymphoblastic Leukemia (B-ALL)	46	26.2
	T-Acute Lymphoblastic Leukemia (T-ALL)	15	8.5
	Multiple Myeloma (MM)	10	5.2
	Small Lymphocytic Lymphoma (SLL)	13	7.4
	Pro-Acute Lymphoblastic leukemia(Pro-ALL)	10	5.2
	Total	175	100

Source: Own materials

Table 5. The expression frequency and percentage of each CD marker across cases of AML, B-ALL, and T-ALL cases

T-ALL n(%)	B-ALL n(%)	AML n(%)	Immunophenotyping marker
-----	2(4.3)	-----	CD5
1(6.6)	9(19.5)	40(49.3)	CD13
1(6.6)	3(6.5)	-----	CD19
-----	25(54.3)	-----	CD22
-----	2(4.3)	-----	CD31
-----	4(8.6)	41(50.6)	CD33
2(13.3)	20(43.4)	42(51.8)	CD34
-----	-----	8(9.8)	CD56
-----	22(47.8)	-----	CD58
-----	-----	15(15.8)	CD64
3(20)	27(58.6)	5(6.1)	CD79 alpha
1(6.6)	-----	43(53.08)	CD117
1(6.6)	1(2.1)	25(30.8)	MP0
-----	-----	35(43.2)	HDL-AR
2(13.3)	19(41.3)	4(4.9)	TdT

Source: Own materials

Table 6. The expression frequency and percentage of each CD marker across cases of multiple myeloma (MM), small lymphocytic lymphoma (SLL), and pro-B acute lymphoblastic leukemia (Pro-ALL)

Pro-ALL n(%)	SLL n(%)	MM n(%)	Immunophenotyping markers
-----	4(30.7)	-----	CD5
8(72.7)	-----	-----	CD13
-----	3(23.07)	-----	CD19
-----	-----	-----	CD22
-----	3(23.07)	-----	CD31
8(72.7)	-----	-----	CD33
5(45.4)	-----	-----	CD34
1(9.09)	-----	2(20)	CD56
-----	-----	-----	CD58
8(72.7)	-----	-----	CD64
-----	-----	-----	CD79 alpha
8(72.7)	-----	1(10)	CD117
8(72.7)	-----	-----	MPO
-----	-----	-----	HDL-AR
-----	-----	-----	TdT

Source: Own materials

positive for CD13, CD33, C34, CD117, and HLA-DR, followed by other markers. Most cases of B-ALL showed Positive for CD22 and CD34, CD58, and CD 79 alpha markers, followed by other markers. At the same time, most T-ALL exhibited Positive for CD34, CD79 alpha, and TdT markers, which are included in Table 5.

Immunophenotyping study of acute leukemia types elucidated that most multiple myeloma (MM) cases showed Positive for CD56 and CD117, while Small Lymphocytic Lymphoma (SLL) showed positive for CD5, CD19, and CD31; in addition, most cases of Pro-Acute Lymphoblastic leukemia (Pro-ALL) showed Positive expression for CD13, C33, CD64, and CD117, followed by other markers as shown in Table 6.

DISCUSSION

The present study analyzed the immunophenotypes of blasts from 175 patients with acute leukemia to assess the prevalence of aberrant markers within the current patient cohort. The patients were categorized into six distinct groups: AML, B-ALL, T-ALL, MM, SLL, and Pro-ALL. According to ages, the higher prevalence of cases were documented in patients with age younger than ≤ 10 years, then 11-20 years group, and only one case was in age group higher than 80 years, and these results in line with the findings expressed by Balasubramanian et al., [9] which found the higher number of cases were diagnosed in the age group of 1-6 y then 6-12 years age group. The mean age of patients in the current study was 33 years, and in the study achieved by Balasubramanian et al., [9] was 9.2 y. This difference may belong to the differences in sample size which included in both studies.

Another study found the majority of patients were children aged less than 10 y, accounting for 38% (n=152), while 15.5% (n=70) belonged to the 11–20 y age group. Additionally, 15% (n=60) of patients fell within the 21–30-year age range, with the remaining cases primarily consisting of adults [10].

According to numbers of cases for each type of Acute leukemia in current study, the most cases were AML. And these results agrees with Rathee et al., [11] which found that acute myeloid leukemia was more prevalent than other types of leukemia.

Male patients showed a greater prevalence of leukemia than female patients, and these results agree with the previous study showed a higher incidence of males than females on a global scale [12]. Also, the current study is completely consistent with the previous study which found the leukemia was observed more frequently in male patients, accounting for 64.5% (n=258) of cases, compared to 35.5% (n=142) in females, resulting in a male-to-female ratio of 1.8:1. The majority of affected individuals were under 20 years of age [10].

According to the types of Acute leukemia, the current study shows the majority of cases were AML, then B-ALL, T-ALL, MM, SLL and the lower cases were Pro-ALL. These results are consistent with several previous studies found among a total of 650 leukemia cases were analyzed during the period 2008–2012, 33.8% of patients were diagnosed with AML, while 17.2% were affected by other forms [11].

The first test performed on individuals suspected of having leukemia is a complete blood count (CBC), which shown the alterations in bone marrow can induced by leukemic cells. In patients with acute leukemia, the decline

in hemoglobin levels in the bloodstream primarily results from the replacement of healthy bone marrow cells with cancerous ones, which deplete the essential nutrients required for hemoglobin production, consistent with previous studies [13]. The present study showed decreased platelet counts. Thrombocytopenia is a well-recognized hallmark of acute leukemia, with a well-established association between declining platelet counts and an increased risk of bleeding. Abuhelwa et al. [14] who report that bleeding in leukemia is directly linked to low platelet levels. Another defining characteristic of acute leukemia is leukocytosis, a marked elevation of white blood cells in circulation. This condition arises from the excessive production of immature white blood cells (blast cells) in the bone marrow. According to a study by the American Society of Hematology (2013), leukocytosis in leukemia results from the aberrant activation of signaling pathways that govern the proliferation and differentiation of hematopoietic stem cells [15].

Our study thoroughly analyzed the prevalence of CD marker expression in AML patients CD34 was the predominant marker across all phases, with CD33 and CD13 closely following, these findings aligning with previous study achieved by Aisha et al. [16]. In B-ALL and T-ALL cases, abnormal expression of CD79 α , CD22, and CD58 was observed, consistent with Najim et al. [17].

T-ALL cases in present study expressed CD34, CD79 α , and TdT, markers indicative of immature T-cells. TdT, commonly used to identify immature lymphoid cells, was reported in 39.5% to 93.8% of T-ALL cases in previous studies (18-20), and consistent with our findings. CD34, a marker of immaturity, has expression in 34.2% of T-ALL cases in one study and is crucial for minimal residual disease detection. Our results documented CD34 expression in 13.3% of T-ALL cases. CD79 α , typically associated with B-cell lineage, was expressed aberrantly in 20% of T-ALL cases, while 58.6% of B-ALL cases showed its presence, in agreement with Gupta et al. [20].

Flow cytometry revealed AML was characterized by CD13, CD33, CD34, CD117, and HLA-DR, consistent with prior studies. (21-23) CD13 and CD33 were commonly expressed in AML blasts, aiding differentiation from normal myeloid cells. CD34 is significantly overexpressed in AML, useful for detecting minimal residual disease and monitoring therapy [21, 23, 24] Similarly, CD117 is overexpressed and serves as a diagnostic marker linked to specific AML subtypes and prognosis [25, 26] HLA-DR, expressed in most AML cases, is associated with specific subtypes and cytogenetic profiles [25, 26] Overall, CD13, CD33, CD34, CD117, and HLA-DR play essential roles in diagnosing and prognosticating AML, aiding in differentiation from other hematologic conditions and guiding clinical decision-making.

According to markers expression in B-ALL, CD22 is a universal B-cell marker found on the surface of B lymphocytes at various stages. It is considered a potential alternative for B-cell identification, especially in cases where CD19 is not viable due to antigen loss post-CD19 CAR-T therapy. However, CD22 expression can be partial or dim in some patients, which may limit its effectiveness as a sole gating marker [27].

Another marker is CD34 which is typically associated with hematopoietic progenitor cells and is expressed in certain B-cell progenitors. Its presence in CD34+CD19–CD22+ cells suggest a role in the recurrence of B-ALL, indicating that these progenitors might contribute to relapse after CD19-targeted treatments [28].

CD58 is another marker used in the immunophenotyping of B-ALL. While the specific role of CD58 in the context of B-ALL was not detailed in the provided abstracts, it is generally used in combination with other markers for comprehensive analysis. CD79 alpha is a marker used for intracellular staining and is a reliable alternative to CD19 for exact gating B-cells in flow cytometric investigate, especially post-CD19 CAR-T therapy. It is expressed normally in all B-ALL cases studied, making it a consistent marker for B-cell identification [27].

In B-ALL, the markers CD22, CD34, CD58, and CD79 alpha play crucial roles in diagnosis and monitoring. CD22 and CD79 alpha are particularly important for identifying B-cells post CD19 CAR-T therapy, although CD22's effectiveness can be limited by partial or dim expression. CD34+CD19–CD22+ progenitors may contribute to relapse, highlighting the need for comprehensive marker analysis in treatment strategies.

However, the current study found some cases with multiple myeloma (MM) showed Positive for CD56 and CD117, which are markers used in the diagnosis and prognosis of these hematologic malignancies. And these results consistent with many previous studies found CD56 is present in around 70% of multiple myeloma (MM) cases and is linked to worse clinical outcomes. It enhances MM cell proliferation and survival by activating the RSK2/CREB1 signaling pathway. (29) However, the absence of CD56 is a defining characteristic of plasma cell leukemia and a specific subset of multiple myeloma with less aggressive features [30]. Another study found CD117 expression is less common compared to CD56 in MM, with studies showing expression in about one-third of cases [31].

In overall, CD56 is more commonly associated with MM and has significant implications for disease progression and treatment strategies. CD117, while less frequently expressed in MM, remains a valuable marker in the context of myeloid leukemias. However, understanding the pattern of expression for these markers can aid in the management and therapeutic targeting of these diseases.

CONCLUSIONS

The current study shown the prevalence of aberrant CD marker expression in Iraqi patients with AL, and referring to the significance of flow cytometry in diagnosis and classification. AML was the most common subtype, followed by B-ALL and T-ALL. Key markers such as CD13, CD33, and CD34 were frequently expressed in AML, while CD22, CD34, and CD79a were predominant in B-ALL. Aberrant expression of CD markers provides critical insights into leukemic cell lineage and disease progression. These findings consistent with international data, and may aid in give insight to completely understanding the mechanism of acute leukemia development then good protocol management development which may be aid in increase the life quality of patients with acute leukemia.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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Peculiarities of psychological trauma in police officers-combatants with different combat experience and their psychological rehabilitation

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ABSTRACT

Aim: The aim is to investigate the peculiarities of psychological trauma manifestation in police officers-combatants with different combat experience and to substantiate recommendations for their psychological rehabilitation based on the Gestalt approach

Materials and Methods: The research, conducted in 2023-2024, involved 69 male police officers-combatants with different combat experience: up to 1 year (Group A, n = 33) and more than 1 year (Group B, n = 36). Research methods: analysis and generalization, psycho-diagnostic, mathematical statistics.

Results: It has been found that armed conflict participants with more combat experience had more pronounced symptoms of PTSD; the difference between the indicators of Groups A and B is significant ($p \leq 0.05$). It has been found that the dominant type of response to a traumatic event in both groups of combatants is the protective mechanism of physiological arousal (63.6 % in Group A and 66.7 % in Group B). Practical recommendations for the psychological rehabilitation of combatants who suffered psychological trauma using Gestalt therapy have been proposed.

Conclusions: It has been found that the Gestalt approach allows solving the following tasks of working with psychological trauma: to help combatants realize and respond to traumatic experiences, to overcome existing traumas, to increase the adequacy of self-perception and self-esteem, to reduce anxiety, tension, emotional instability, and self-doubt in difficult life situations.

KEY WORDS: PTSD, war, psychological trauma, psychological rehabilitation, Gestalt approach, police officers-combatants

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INTRODUCTION

Today, one of the most pressing issues in the work of psychologists is the problem of restoring the mental health of combatants who have experienced the traumatic events of war. The psycho-traumatic situations of war can cause post-traumatic stress disorders (PTSD), depression, suicidal tendencies, difficulties in social adaptation, etc. [1, 2]. In Ukraine, the problem of finding the most effective psychotherapeutic and psycho-correctional approaches to psychological assistance to people who have suffered psychological trauma is relevant due to the widespread occurrence of stressful events and various psychological traumas. Participation in hostilities is a stressful factor of the highest intensity, which is highly likely to lead to combat stress and psychological trauma [3, 4]. Combat psychological trauma leads to mental disorders, full or partial loss of combat capability, dramatically changing the behavior, moral, and psychological state of combatants [5], which necessitates substantiation of the areas of psychological assistance.

According to scientists [6-9], there are many approaches to understanding the nature of psychological trauma and,

accordingly, psychological methods of dealing with it. Usually, the source of trauma is the affective experiences of a person caused by external stimuli and the inability of the psyche (defense mechanisms) to cope with a significant shock. The Gestalt approach plays an important role in this process as a result of interrupting the process of experiencing a traumatic event.

According to experts [10], Gestalt therapy is a popular, effective, and, at the same time, the least researched method of psychological rehabilitation of combatants with signs of trauma. Scientists [11] note that the Gestalt approach is a fairly effective method of therapy in dealing with anxiety, phobia, depression, psychosomatic disorders, sleep disorders (nightmares), suicidal tendencies, intrapersonal and interpersonal conflicts, maladaptive personality traits (anxiety, aggressiveness, irritability), etc., which makes it possible to use this approach in work with psychological trauma and PTSD in combatants.

An incomplete action/situation occurs due to the constant interruption of the contact cycle between the body and the environment by defense mechanisms. The essence of the "incomplete action" effect is that after a traumatic event, it

is impossible to complete it; it is impossible to relax due to excess energy (tension) that has no conditions for realization; the event is remembered, emotions continue to press, various tensions arise in the bodily and emotional sphere that are not related to the current situation, which greatly disorients a person and causes various projections [12, 13]. Incomplete actions can be in the form of unfulfilled needs, unfulfilled feelings, and emotions that seek completion. Therefore, the study of the peculiarities of the manifestation of psychological trauma in police officers-combatants and the substantiation of recommendations for their psychological rehabilitation based on the Gestalt approach is timely and relevant.

AIM

The aim is to investigate the peculiarities of psychological trauma manifestation in police officers-combatants with different combat experience and to substantiate recommendations for their psychological rehabilitation based on the Gestalt approach.

MATERIALS AND METHODS

The research, conducted in 2023-2024, involved 69 male police officers-combatants with different combat experience: up to 1 year (Group A, $n = 33$) and more than 1 year (Group B, $n = 36$). All study participants took part in combat operations to repel the aggressor in 2022-2024 in the Kharkiv oblast and, at the time of the study, were undergoing inpatient treatment in medical and rehabilitation facilities with signs of psychological trauma. The main criteria for inclusion of participants in the study were: 1) male gender of the police officers; 2) participation of police officers in combat operations since the beginning of the Russian full-scale invasion (from February 2022); 3) duration of participation of police officers in combat operations (up to 1 year or more than 1 year); 4) presence of signs of psychotrauma (PTSD) in the participants; 5) stay in inpatient treatment in medical and rehabilitation facilities. Moreover, all participants were informed that their involvement in the study was solely for scientific purposes, and they provided informed consent for voluntary participation. The exclusion criterion was the personal desire of the research participant to withdraw from the study. The study participants' age, education, marital status, and income level were not considered. The research was

organized, and the results were processed at the Department of Sociology and Psychology of Kharkiv National University of Internal Affairs (KhNUiA, Kharkiv, Ukraine)

Research methods: theoretical (analysis and generalization of ideas about the problem under study); empirical (psycho-diagnostic methods); methods of mathematical statistics (quantitative and qualitative analysis of the research results – finding averages and percentages). Psycho-diagnostic methods included [14]: 1) PTSD Checklist (PCL-5) – to identify the main symptoms of PTSD to diagnose PTSD; 2) Impact of Event Scale (IES-R) – to identify the three main symptoms of PTSD (intrusion, avoidance, and increased excitability) and assess their severity; 3) Mississippi scale for combat-related posttraumatic stress disorder – to measure the signs of PTSD.

The methods of mathematical statistics were used to process the data obtained. The compliance of the sample data distribution with the Gauss' law was assessed using the Shapiro-Wilk W test. It was found that the data distributions of Group A and Group B are normal, which allowed us to assess the reliability of the difference between the indicators using the Student's t -test. The results are presented as $M \pm m$, where M is the arithmetic mean, and m is the standard error of the mean. The reliability of the difference was set at $p \leq 0.05$. All statistical analyses were performed using STATISTICA 6.1 software (No. AGAR909E415822FA), adapted for medical and biological research.

The procedure for organizing the study and the topic of the article were previously agreed with the committee on compliance with Academic Integrity and Ethics of the KhNUiA. Also this study followed the regulations of the World Medical Association Declaration of Helsinki. Informed consent was received from all participants who took part in this study.

RESULTS

The results of the study of psychological trauma manifestation in police officers-combatants with different combat experiences using three psycho-diagnostic methods are presented in Table 1.

The PTSD Checklist (PCL-5) is a questionnaire with a standardized PTSD self-assessment scale containing 20 questions, each of which corresponds to key symptoms of PTSD (obsessions, avoidance, negative changes in cognition and mood, changes in arousal and reactivity). The result is

Table 1. The peculiarities of psychological trauma manifestation in police officers-combatants ($n=69$) with different combat experiences according to different psycho-diagnostic methods, Mean $\pm$ m, in points

Psycho-diagnostic methods	Group A ($n=33$)	Group B ($n=36$)	The difference	Reliability of the difference, t ; p
PTSD Checklist, PCL-5	32.2 $\pm$ 1.02	35.9 $\pm$ 1.13	3.7	2.43; ≤ 0.05
Impact of Event Scale, IES-R	44.6 $\pm$ 1.65	51.3 $\pm$ 1.76	5.7	2.36; ≤ 0.05
Mississippi scale for combat-related PTSD	109.3 $\pm$ 2.19	117.8 $\pm$ 2.32	8.5	2.66; ≤ 0.05

Legend: n – number of police officers; t – Student's t -test value; p – confidence interval.

Source: compiled by the authors of this study

expressed in points: the higher the total score, the more severe the manifestation of PTSD. The study showed that in combatants with less combat experience (Group A), PTSD symptoms are less pronounced compared to Group B; the difference is 3.7 points and is significant ($p \leq 0.05$). The following ratio of PTSD levels in combatants of the study groups was also found: absence of PTSD – 30.3 % in Group A and 13.9 % in Group B; marginal PTSD – 45.5 % in Group A and 44.4 % in Group B; the presence of PTSD – 24.2 % in Group A and 41.7 % in Group B. In general, the following features of PTSD are characteristic of combatants: unmotivated vigilance, negative attitudes toward oneself and others, alienation from others, blaming oneself and others for what happened, sleep disturbances, anxiety, nervousness, and spontaneous memories.

The Impact of Event Scale (IES-R) contains 22 questions that are divided into three subscales: “intrusion,” “avoidance,” and “excitability.” Each question is scored on a 5-point scale. The reaction to the traumatic event (level of PTSD) was determined in points. The higher the score, the more pronounced the response to the traumatic event. It was found that the reaction was more pronounced in Group B combatants than in Group A by 5.7 points ($p \leq 0.05$). In addition, 12.1 % of combatants in Group A and 5.6 % in Group B had a low reaction to the traumatic event; 66.7 % in Group A and 52.7 % in Group B had a moderate response; 21.2 % of the combatants in Group A and 41.7 % in Group B had a pronounced reaction. The study’s results also showed that the dominant type of response to a traumatic event in combatants of both groups is the protective mechanism of physiological arousal (63.6 % in Group A and 66.7 % in Group B). Symptoms of this type of response to a traumatic event were manifested by difficulty falling asleep, insomnia, increased irritability, outbursts of anger, decreased attention, tension, and somatic disorders. The intrusion was observed in 21.2 % of combatants in Group A and 16.7 % in Group B, accompanied by intrusive thoughts and nightmares; 15.2 % of Group A combatants and 16.7 % of Group B combatants were characterized by avoidance as a type of response to the traumatic event, which was manifested by an attempt not to think, and by displacing the event from memory.

The Mississippi scale for combat-related PTSD consists of 35 statements, each of which is rated on a 5-point scale. If the total score exceeds 97 points, this indicates a pronounced impact of the trauma and suspected PTSD. It was found that combatants with more combat experience (Group B) have a significantly higher level of PTSD symptoms than those in Group A by 8.5 points ($p \leq 0.05$). It was also found that 24.2 % of combatants in Group A and 44.4 % in Group B have a high level of stress response (suspected PTSD); an average level (adaptation disorders) – 60.6 % of combatants in Group A and 47.3 % in Group B; a minimum level (well-adapted) – 15.2 % of combatants in Group A and 8.3 % in Group B. The empirical study shows that combatants with more combat experience have more pronounced PTSD symptoms, which necessitates professional assistance in dealing with trauma.

One of the most popular methods in dealing with psychological trauma is the Gestalt approach (Gestalt therapy),

which allows for a more holistic and complete processing of the psychological traumatic experience of combatants. Psychological work with psychological trauma in the Gestalt approach is aimed at the psychological rehabilitation of combatants and accelerating their adaptation to the outside world, acquiring the ability to consciously choose their behavior and consciously respond to psychologically traumatic experiences. The information needed to work with trauma is obtained from the behavior of combatants “here and now.” The Gestalt approach, through expanding self-awareness, encourages a combatant to accept themselves as they are, with their negative experiences and socially unacceptable qualities, with their psychological traumas and repressed conflicts; it is not assumed that combatants need to free themselves from anything, as in this case completely, they will lose their uniqueness and individuality. This approach does not seek to immediately change the combatant’s behavior and quickly eliminate traumatic symptoms; this approach offers a different view of the individual – the emphasis is not on understanding (interpreting) the situation and the combatant’s behavior, nor on teaching automatic behavioral patterns, but on awareness, experience, and freedom of choice. Work with psychological trauma is aimed at restoring the interrupted integral cycle of contact (cycle of needs fulfillment), completing the unfinished situation of the past that affects behavior in the present, and overcoming the mechanisms of its interruption (defense mechanisms), which relieves traumatic symptoms, transforms traumatic maladaptive reactions into adaptive protective responses. The most effective mechanisms (methods) for interrupting the natural course of the contact cycle (the process of experiencing, the process of self-regulation) are confluence (merging), introjection, projection, retroreflection, and deflection.

Combatants are characterized by confluence with their comrades-in-arms – the use of “we” when referring to their experiences and the inability to distinguish their experiences from those of their comrades-in-arms. The work should be aimed at separating the combatant from the environment. In PTSD, combatants are characterized by the symptom of avoidance (deflection), which manifests itself in avoidance of discussing traumatic events. In the work, the therapist should interrupt the client’s action when they avoid contact or use a technique to enhance their emotions, gestures, or posture at the psychologist’s request. In this way, the combatants can understand their condition and realize their hidden emotions. PTSD is also characterized by pronounced aggression, which can be projected. In the work, it is necessary to interrupt the projection of the combatant, offering them the opportunity to redirect the statement, which helps them realize their true feelings. Introjection is characteristic of the combatant – responsibility for their condition is assigned to the state and the army, misunderstanding of others, and actions to improve their condition are minimized. The work is aimed at activating the adaptation mechanism.

This approach widely uses a variety of verbal and non-verbal techniques and methods, many of which are borrowed from

other areas of psychotherapy (art therapy, psychodrama, transactional analysis): awakening sensory perception, working with breathing, body or voice, expressing emotions, working with dreams and imagination, psychodrama, drawing, modeling, music, dance, etc. The main goal of the interaction between a psychologist and a combatant is to activate the combatant's internal personal reserves, which leads to personal growth. Attention is paid to what the combatant says and how it is expressed, to breathing, voice changes, emotional tones, repetition, postures, and bodily tension, which helps to reveal the combatant's feelings more fully.

Based on the above and the results of our research, we have developed practical recommendations for the psychological rehabilitation of combatants based on the Gestalt approach.

1) The first stage of psychological rehabilitation should be a comprehensive diagnosis that will identify psychological trauma, assess symptoms and concomitant disorders (sleep disorders, aggression, depression, anxiety disorders, etc.), adaptation disorders, and PTSD. Effective correctional work can only be built based on a thorough psychological examination. The first step in diagnosing PTSD is to establish the fact of experiencing a traumatic event. Comprehensive diagnostic work should be applied to all categories of police officers-combatants, as this allows us to understand the essence of the problem, regardless of their combat experience.

2) The rehabilitation process should be individualized depending on the diagnosis results, taking into account personality traits, maladaptive behaviors, different typologies of the individual, social situations, and health status. The choice of psychotherapeutic methods is determined by the combatant's personality characteristics. A longer stay in a combat zone usually provokes personal changes; taking this into account determines the construction of the rehabilitation work and the choice of specific tools.

3) Depending on the specifics of the situation, the current state of the combatant, etc., the following methods of work should be used: counseling (individual, family, group), psychological support, training sessions, and various forms of psychotherapy (group, family, individual). Combat experience can change the format of the rehabilitation process: with greater combat experience (more than 1 year, in particular), there is a transition from group to individual (family) methods of work. A similar situation applies to the intensity of measures: with more pronounced symptoms of psychotrauma (PTSD), the duration of psychocorrectional and psychotherapeutic work can increase from 1 month to 3 months.

4) Psychological counseling is conducted to resolve a problem situation, promote personal development, and correct interpersonal relationships. Individual and family counseling is important for correcting interpersonal relationships and eliminating emotional disorders in combatant families.

5) Psychological support should be provided to increase the individual's existing internal resources and create

additional ones. Insufficient internal resources can lead to PTSD. Training to increase internal resources should aim at developing adaptive interpersonal interaction, self-help, and self-support. Apply self-regulation training, raising awareness of the "here and now." Gestalt therapy techniques should be used for such training: self-regulation can be increased by influencing oneself with words, mental images, breathing control, and body awareness. The tools used should vary depending on the combat experience and the symptoms of psychotrauma (PTSD). In the presence of more pronounced personality changes, verbal and game methods may be inferior to experimental techniques (nonverbal, bodily, etc.).

6) As components of psychotherapy, we consider it appropriate to use dialogue techniques, techniques of working with feelings and body, and an experiment to complete the experience of trauma at different levels. The following techniques are also becoming relevant: "Concentration on Feelings" with the methods: "Sharpening the Body Sensation", "Experience of the Continuity of Emotions"; "Integration of Polarities" technique; "Work with Dreams" technique; "Overcoming Resistance" technique with methods: "Turning Emergence into Contact", "Working with Projection. Identification of Projections", "Working with Projections. Assimilating Projections", "Working with Retroreflection. Study of Misdirected Behavior", "Working with Retroreflection. Returning the Action to the Outside World", "Working with Retroreflection. Muscle Mobilization", "Working with Introjection. Introjection and Food", "Working with Introjection. Expulsion and Digestion of Introjections"; methods "Empty Chair", "Two Chairs", "Exaggeration", interruptions with redirection of the statement. It is important to be attentive to the problems and goals of therapy and the manifestations of the "here and now." The above techniques are rational for all categories of police officers-combatants with signs of psychological trauma. However, their combination should be based on the personal characteristics of the combatants and take into account the typological indicators of the individual, the adaptive capabilities of the combatants, and the situation of support for police officers by their immediate social (professional) environment.

7) Group psychotherapy should be conducted separately with combatants and their family members. If Gestalt therapy is used in work with PTSD, an individual form of work is more effective. Contraindications to family psychotherapy with families of combatants are psychopathy or temporary psychotic states in a family member. When working with psychological trauma in police officers-combatants, the following position should be taken into account: the more complex the problem, the more individualized it becomes.

8) It is necessary to organize psychological education for combatants and their families to understand the nature of psychological trauma and familiarize them with possible reactions to traumatic events, forms of first aid and self-help, and ways to respond in conflict situations. Increasing awareness and social comfort should be linked to the need to increase combatants' self-esteem. First of all, the

importance of maintaining positive self-perception and self-confidence in atypical social life situations, combined with measures to develop psycho-emotional well-being, is indicated.

DISCUSSION

According to experts [5], about 15 million Ukrainians will need psychological support because of the war; in war-affected areas, one in five people lives with some form of mental disorder. Ukrainians who have suffered from the war since 2014 most often have PTSD, depression, anxiety, etc. [15].

Many scientists [1] have worked on the problem of psychological trauma and investigated its various aspects, studied its essence and structure, psycho-traumatizing factors, consequences of psychological trauma, factors influencing the formation of combat trauma, the specifics of assisting combatants with psychological trauma, prevention of development and diagnosis of PTSD. However, the problem has not been studied sufficiently. For example, the psychological consequences of combatants' participation in hostilities are explained in different ways; there are no reliable methods for the prevention and correction of psychological trauma [16].

In a broad sense, psychological trauma is a deeply individualized negative reaction of a person to a traumatic event without serious mental disorders and with the possibility of successful adaptation to the environment [17]. Scientists [6] emphasize that a psychologically traumatic event is an extremely significant event for a person that threatens life or health, causes intense fear and a sense of helplessness, and causes substantial emotional stress and further negative experiences. It can be hostilities, serious bodily injury, death or injury of a loved one, amputation of a limb, etc. [7].

A review of the scientific literature [18] shows that psychological reactions to a stressful event occur in all combatants but may differ in severity and consequences. It is noted [19] that the level of influence of a psycho-traumatic event on a person depends on the strength of the effect and personal reactions to a stressful situation. A psycho-traumatic event (stressor), having violated the integrity of the psyche, causes traumatic stress, which then turns into psychological trauma, the extreme manifestation of which is PTSD, which occurs as a prolonged or delayed reaction to traumatic stress [2]. A prerequisite for an event to be traumatic for a person, leading to psychological trauma, is significant emotional stress, blocking of basic needs, and personal reaction to the situation (the necessary efforts to integrate the situation exceed the adaptive capacity of the person) [5].

According to experts [20], psychological trauma is usually manifested by physical, psychological, and social consequences (symptoms). Psychological symptoms include anger, irritability, mood swings, difficulty concentrating, anxiety, fear, etc.; physical symptoms include insomnia or nightmares, fright for no reason, strong heartbeat, pain, fatigue, nervousness, muscle tension, etc.; social

symptoms include feelings of guilt, shame, self-blame, separation from others, proneness to conflict, etc. According to scientists [9], PTSD is manifested by three main characteristic symptoms: intrusion, avoidance, and hyperarousal. Intrusion is the repeated experience of an event in the form of flashbacks, during which a person acts or feels as if the event is repeating itself; nightmares, etc.; avoidance is the avoidance of memories of circumstances and people similar to traumatic events; excessive arousal is hypervigilance against threats, fearfulness, irritability, difficulty concentrating, sleep problems, sleep disturbances (nightmares), negative attitude towards oneself, etc. PTSD can develop in 25-30 % of combatants of all ages, regardless of their service [11].

Scientists [9] believe that psychotherapy is the most effective method of psychological assistance to combatants who have suffered psychological trauma. However, there is a problem of choosing the most optimal approach in dealing with psychological trauma. We have substantiated the use of the Gestalt approach in dealing with psychological trauma in police officers–combatants in a full-scale war in Ukraine. In the Gestalt approach, work with trauma is aimed at restoring the interrupted cycle of contact (realization of needs) and transforming traumatic maladaptive reactions into adaptive protective reactions [10]. This approach widely uses the method of unfinished actions, dialogue techniques, and various ways of working with feelings and bodies.

Gestalt therapy targets traumatic memories. The work is based on the nature of psychological trauma – it aims to restore the interrupted integral cycle of contact on the principle of “here and now” – to identify the mechanisms of interruption. Stopping contact depends on the person's characteristic traits. Emphasis is placed on awareness of the mechanisms of interruption “here and now,” their transformation into adaptive protective reactions, readiness to make choices (self-regulation), acceptance of responsibility, increased attention to feelings, self-knowledge, and acceptance of oneself as one is. Various techniques and methods are used to realize reactions, feelings, needs, and body, accept responsibility, identify mechanisms of contact interruption, etc. The main goal of working with psychological trauma is to change the victim's attitude to the fact of the presence of a psycho-traumatic event in their life.

The practical significance of the findings is that the results of the research can help psychologists in working with combatants to address the problem of psychological trauma, as well as become the basis for a more in-depth study of the chosen topic.

CONCLUSIONS

1. The peculiarities of the manifestation of psychological trauma in police officers–combatants have been studied, and it has been found that in the case of police officers with more combat experience, the symptoms of PTSD, which were analyzed by three psycho-diagnostic methods, were more pronounced. The difference between Groups A and B scores

is significant ($p \leq 0.05$). The research results have also shown that the dominant type of response to a traumatic event in both groups of combatants is the protective mechanism of physiological arousal (63.6 % in Group A and 66.7 % in Group B). Symptoms of this type of response to a traumatic event were manifested by difficulty falling asleep, insomnia, increased irritability, outbursts of anger, decreased attention, tension, and somatic disorders. The intrusion was observed in 21.2 % of combatants of Group A and 16.7 % of Group B, manifested by intrusive thoughts and nightmares; 15.2 % of combatants of Group A and 16.7 % of Group B were characterized by avoidance as a type of response to the traumatic event, manifested by an attempt not to think, and by displacing the event from memory.

2. Practical recommendations based on the data obtained for the psychological rehabilitation of combatants who suffered psychological trauma during hostilities using Gestalt therapy have been proposed. An important condition for using Gestalt therapy is tolerance to severe anxiety, readiness to re-experience trauma, and the absence of life crises. The work should be aimed at accepting oneself as a holistic

person with positive and negative traits, the ability to experience all negative emotions (fear, anger, pain, aggression, despair, etc.), activating internal resources for self-help and self-support, changing attitudes towards the fact of a traumatic event in one's life, and transforming traumatic maladaptive reactions into adaptive protective responses. Training in resilience, self-regulation, awareness of the "here and now," acceptance of responsibility, and increased attention to feelings is mandatory – full knowledge of oneself and the outside world, gaining the ability to consciously choose one's behavior, awareness, and emotional response to psycho-traumatic experience. It is advisable to use various Gestalt therapy techniques: work with breathing, body or voice, expression of emotions and feelings, work with dreams and imagination, psychodrama, drawing, modeling, music, dance, etc., to reduce anxiety, tension, emotional instability, and self-doubt in difficult life situations.

PROSPECTS FOR FURTHER RESEARCH

The next step is to study the manifestations of PTSD depending on the individual psychological characteristics of police officers who participated in combat operations.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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Evaluating the impact of domestic violence on Postpartum Post-Traumatic Stress Disorder (PTSD): A prospective study of perinatal mental health outcomes in high-risk populations

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ABSTRACT

Aim: To investigate the connection between a woman's history of DV, encompassing the perinatal period, and the development of postpartum PTSD within high-risk populations: EMCS and Assisted Vaginal Deliveries (AVD).

Materials and Methods: A sample of 125 mothers who gave birth with emergency cesarean section and elective assisted vaginal delivery in two Greek hospitals have consented to participate in the two phases of the survey, in the 2nd day postpartum and a follow-up in the 6th week postpartum. Socio-demographic data and PCL-5 for DSM-5 were used to diagnose PTSD and PTSD Profile. Of the 125 mothers who consented to participate in the study, 113 replied to the follow-up in the sixth week after birth.

Results: The results show that, from the total sample, 73.5% (n=83) delivered by emergency cesarean section, while 26.5% (n=30) delivered through assisted vaginal delivery. Also, a statistically significant dependence was found between the presence of Domestic Violence during pregnancy and postpartum PTSD ($\chi^2=22.014$, $p<0.001$) and between the presence of Domestic Violence during pregnancy and postpartum profile PTSD ($\chi^2=26.635$, $p<0.001$).

Conclusions: This survey shows a high prevalence rate of PTSD in victims of domestic violence after a traumatic birth experience. The findings also emphasize the critical need for psychological support for women with a history of domestic violence, particularly during childbirth, to minimize the likelihood of mental health traumas.

KEY WORDS: perinatal mental health, domestic violence, emergency cesarean section, postpartum PTSD, PTSD profile, assisted vaginal delivery

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INTRODUCTION

Domestic violence (DV) is a devastating experience that impacts over 10 million individuals in the United States annually. This pervasive issue often occurs in private settings, making it easy to ignore or rationalize [1]. However, DV can occur in various relationships beyond just intimate partners. It can also manifest as violence between parents and children, adult children and elderly parents, or even among siblings [2]. Abuse manifests in various ways, such as physical and emotional violence, sexual assault, financial manipulation, and psychological coercion or intimidation aimed at harming or controlling an intimate partner. It can occur at any stage of life and affects individuals across different sexual orientations, ethnicities, religions, genders, and socioeconomic statuses [3]. While DV can occur in any intimate relationship, statistics show that the majority of these incidents involve men as perpetrators and women as victims. This pattern of male-perpetrated violence against women contributes significantly to the prevalence and severity of the issue, making it a substantial public health concern. The prevalence of DV, especially against women, is staggering. Some estimates suggest that up to one-third of all women experience DV at some point in their lives [4]. Pregnancy is considered a high-risk period for the onset

and intensification of intimate partner violence. Shockingly, it is identified as a leading cause of maternal mortality in countries like the UK, USA, and Australia [5, 6]. In Greece, within a sample of 546 pregnant women, the prevalence of violence was 6%, while 3.4% had experienced abuse since the beginning of their pregnancy, primarily from their spouse or partner. This statistic highlights that the issue of intimate partner violence during pregnancy is not just a concern in English-speaking countries but is also a serious issue in other cultural contexts, including Greece [7, 8]. Victims of abuse may exhibit a wide array of physical and mental health symptoms stemming from the trauma of DV. These symptoms can include depression, suicidal thoughts, panic attacks, substance abuse disorders, and sexual and reproductive health challenges [9]. However, one of the less recognized but severe consequences of DV is the development of Post-Traumatic Stress Disorder (PTSD). PTSD is a psychiatric disorder that can occur in individuals who have experienced or witnessed a traumatic event (Criterion A). While commonly associated with veterans or victims of major disasters, PTSD can also arise from ongoing personal trauma (Complex PTSD), such as that experienced in cases of DV [10]. Victims of DV often endure repeated traumatic events which can lead to the

classic symptoms of PTSD, including: a) re-experiencing, b) avoidance, c) arousal and d) cognition and mood symptoms [11]. PTSD arising from DV remains under-recognized, partly because the private nature of the abuse complicates its identification and treatment. Moreover, the stigma surrounding DV can prevent victims from seeking help or openly discussing their experiences, thereby delaying diagnosis and intervention. Statistics on DV demonstrate the significant prevalence of PTSD and Complex PTSD among survivors of DV. Research indicates that PTSD is experienced by a substantial percentage of women who are victims of intimate partner violence, ranging from 51% to 75%, and this is notably higher than the average prevalence of PTSD in the general population, which is around 10.4% among women [12].

On the other hand, postpartum PTSD can stem from perceived or actual traumatic experiences during childbirth or the postpartum period. Approximately, 3% of women who give birth may develop PTSD following childbirth. However, the incidence of postpartum PTSD can be significantly higher, reaching up to 15% to 25% in populations who experienced birth traumas [13, 14]. These traumas may include scenarios like a prolapsed cord, emergency cesarean sections (EMCS), the use of vacuum extractors or forceps during delivery, the infant requiring neonatal intensive care unit (NICU) admission, feelings of powerlessness or inadequate support during delivery, or severe physical complications or injuries related to pregnancy or childbirth [15]. Researchers have shown that for some women, the stress of childbirth is further exacerbated by the presence of DV. This can aggravate the mental health challenges faced by postpartum women, potentially leading to increased levels of trauma, anxiety, and depression. It is a fact that the coexistence of childbirth-related stress and DV presents a complex situation that can significantly impact the psychological well-being of new mothers. The heightened emotional and physical demands of childbirth, combined with the stressors of abusive relationships, can intensify feelings of vulnerability and helplessness, which may contribute to or worsen postpartum mental health issues [16]. In addition, research has demonstrated that a mother's history of childhood abuse can expose her to a risk of developing PTSD during the perinatal period, that is 12 times higher than average. This increased risk is linked to the re-victimization of the mother [17] and the reactivation of past traumas during a traumatic childbirth [18]. The available research suggests that postpartum PTSD is a serious condition that can heighten the risk of negative maternal and neonatal health outcomes [19, 20] even at subclinical levels of PTSD [15]. The subclinical level of PTSD, sometimes referred to as „PTSD profile,” describes a situation where individuals exhibit the most significant symptoms of the PTSD but do not meet all diagnostic criteria. This partial presentation of PTSD is associated with various negative outcomes, including increased rates of alcoholism, suicidal thoughts, excessive use of health services, and higher rates of absenteeism in the workplace [21].

AIM

Recognizing the relationship between DV and the increased risk of postpartum PTSD is essential for supporting mothers who have recently given birth and addressing their mental health needs effectively. Therefore, the aim of this prospective study is to investigate the connection between a woman's history of DV, encompassing the perinatal period, and the development of postpartum PTSD within high-risk populations: EMCS and Assisted Vaginal Deliveries (AVD).

MATERIALS AND METHODS

This prospective study took place from March to July 2023, at the obstetrics clinics of the General Hospitals of Athens „Elena Velizelou” and „Alexandra” in Greece. The study was approved by the Hospitals Ethics Commissions. Study participants were all the women who gave birth with EMCSs and AVD, since EMCS and AVD were considered serious risk factors for birth trauma and postpartum PTSD as well [22]. Demographic and medical data for all women were obtained from their medical surveillance dossiers. Women who had difficulties understanding the Greek language, had cognitive challenges that would impede comprehension of the questions or measurement tools, were underage mothers, used psychotropic substances or drugs, or gave birth at other hospitals in the region were excluded from the research.

DATA AND MEASURES

Data were collected in two stages:

a) The first stage was the 2nd day after EMCS or AVD. At this stage, social-demographic and medical data were collected from 125 mothers who met the above criteria, as well as responses to the Domestic Violence Questionnaires, and criteria specifically adapted for women with EMCS and for those undergoing AVD (Criteria A).

b) During the second stage (6th week postpartum), through a telephone interview, the mothers responded to questions on the PTSD scale. This specific time period was chosen in order to meet the criterion of symptom duration of over 4 weeks. More specifically, an assessment for PTSD was carried out in mothers who had a traumatic birth experience (Criterion A), in order to diagnose whether the PTSD arises from chronic exposure to DV or not.

SOCIO-DEMOGRAPHIC QUESTIONNAIRE

The Socio-demographic Questionnaire designed for the research project covers various aspects such as demographic details, social background, medical history (including obstetric and neonatal information), and mental health characteristics of the participants.

DOMESTIC VIOLENCE

The presence of DV was assessed using the AAS (Abuse Assessment Screen) questionnaire [23] and the DV questionnaire developed by Antoniou in 2019 [8], including questions investigating DV throughout the woman's life by anyone, also covering the period of pregnancy.

POSTTRAUMATIC STRESS CHECKLIST (PCL-5) FOR DSM-V

The PCL-5, authored by the National Center of PTSD Staff according to DSM-V [24], and was translated and weighted into the Greek language by the investigator midwife [25]. The PCL-5 is a self-report measure designed to assess and evaluate PTSD and its symptom profile. In this investigation, women answered 20 questions via telephone, corresponding to the symptoms of Criteria B (re-experiencing), C (avoidance), D (negative thoughts and feelings), and E (arousal and reactivity). Responses were scored on a 5-point scale, ranging from 0 to 4. A score of one or more in Criteria B and C, and two or more in Criteria D and E, are considered indicative of clinical findings. If all four criteria are met in conjunction with the Criterion A, a diagnosis of postpartum PTSD is deemed possible. Based on the symptoms, women were categorized into (a) provisional PTSD diagnosis (by fulfilling all the criteria) and (b) PTSD Profile (fulfilling only criteria B, C, D). The PCL-5 demonstrates excellent psychometric properties for diagnosing PTSD across postpartum population groups [25].

STATISTICAL ANALYSIS

To investigate the existence of a significant relationship between domestic violence, type of delivery, postpartum PTSD and PTSD profile, the χ^2 independence test was used and Odds Ratio (OR) and 95% Confidence Interval were calculated. The analysis was performed in SPSS software setting a significance level of 5%.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This specific prospective study was conducted from March to July 2023 at the Obstetrics Clinics of the "Elena Venizelou" General Hospital and the "Alexandra" General Hospital in Athens. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Hospitals a) Elena Venizelou: protocol code 003 and approval date 22/03/2023 and b) Alexandra: protocol code 562 and approval date 23/09/2022.

RESULTS

The analysis was conducted on data from 113 women, of the 125 who consented to participate in the study and received the questionnaires, with an average age of 31.2 (SD = 5.5) years. The results show that, from the total sample, 73.5% ($n = 83$) delivered by EMCS, while 26.5% ($n = 30$) delivered through AVD. Table 1, provides a summary of the total sample characteristics.

In Table 2, the relationship between experiences of DV, the type of delivery, PTSD and profile PTSD is presented. From the χ^2 test, a statistically significant dependence was found between the presence of DV during pregnancy and postpartum PTSD ($\chi^2 = 22.014$, $p < 0.001$) and between the presence of DV during pregnancy and postpartum profile PTSD ($\chi^2 = 26.635$, $p < 0.001$). On the contrary, there is no statistically significant dependence was found between the presence of DV during pregnancy and type of delivery ($\chi^2 = 2.345$, $p = 0.126$). More specifically, among women who had never experienced DV in their lives, 5.7% developed postpartum PTSD. In contrast, among women who

experienced DV in their lives 42.3% developed postpartum PTSD. Results indicate that women who had experienced DV in their lives have a 12.0 (95% CI = [3.7, 39.6]) times greater risk of developing postpartum PTSD.

Furthermore, results show that among women who had never experienced DV in their lives, 14.9% developed postpartum profile PTSD. In contrast, among women who experienced DV in their lives 69.2% developed postpartum profile PTSD. Results indicate that women who had experienced DV in their lives have a 12.8 (95% CI = [4.6, 35.5]) times greater risk of developing postpartum profile PTSD.

DISCUSSION

This investigation aimed to examine the relationship between a woman's history of DV and the development of postpartum PTSD and PTSD profile within high-risk populations, specifically those who underwent EMCS and AVD. However, a significant association was identified between DV and postpartum PTSD and PTSD profile. Specifically, women who were victims of DV were independently associated with the development of postpartum PTSD and PTSD profile.

Several studies have indicated that perinatal complications can result from DV [26, 27]. For instance, Shahmir's study [26] demonstrates that DV during pregnancy is associated with adverse maternal outcomes, such as anemia and preterm birth. Abujilban et al [27] also identified an increased risk of pre-eclampsia, CS, and greater analgesic use during birth and postpartum. Furthermore, Lockington et al., in a study on intimate partner violence and perinatal outcomes, revealed that victims had a higher risk of preterm birth, pre-labor rupture of membranes, and lower birth weight.

However, the paper published by Vahdani et al. asserts that there was a significant association between DV and placental abruption.

The results of this study indicate that victims of DV, exhibited an increased incidence of postpartum PTSD. Few studies have examined the impact of DV on postpartum PTSD [19, 28, 29] and other psychological outcomes, and our findings are consistent with these previous researches. One hypothesis posits that exposure to chronic trauma, such as DV, is a contributing factor to the development of PTSD, as the victim's life is continuously at risk.

Although research on the subtype of PTSD and DV is limited [30], this prospective study is the first to investigate the development of PTSD profiles in women exposed and not exposed to DV with traumatic birth experiences. Nevertheless, the findings suggest that women with a history of DV, demonstrated independent associations with the development of postpartum PTSD profiles. It is imperative to acknowledge that CS rates in Greece exceed 50% of all births [14].

STRENGTHS AND LIMITATIONS

This study presents critical insights into the intersection of DV and the development of postpartum PTSD among a high-risk population in Greece, where CS rates significantly exceed the European average [1]. Our findings provide crucial localized insights and pave the way for targeted intervention. Considering the strengths of our results,

Table 1. Total Sample Medical and Socio-demographic Characteristics

		n	%
Nationality	Greek	94	83.2%
	Other	19	16.8%
Family Status	Married	101	89.4%
	In relationship	9	8.0%
	Divorced	2	1.8%
	Single/Not in a relationship	1	0.9%
Education	Technical school	5	4.4%
	High Schol	34	30.1%
	University/College	60	53.1%
	Master	12	10.6%
	PhD	2	1.8%
Occupation	Unemployed	35	31.0%
	Employee	78	69.0%
Previous deliveries	None	55	48.7%
	Vaginal delivery	24	21.2%
	Cesarean section	21	18.6%
	2 or more vaginal deliveries	6	5.3%
	2 or more cesarean sections	6	5.3%
	Cesarean and vaginal delivery	1	0.9%
Miscarriages/ Abortions	No	86	76.1%
	Miscarriages	20	17.7%
	Abotions	6	5.3%
	Both	1	0.9%
Pathological history	No	95	84.1%
	Yes	18	15.9%
Gynecological history	No	97	85.8%
	Yes	16	14.2%
Mental health history	No	100	88.5%
	Yes	13	11.5%

Source: compiled by the authors of this study

we can state that they display contextual relevance. This study addresses a gap in maternal health research by focusing on the effects of DV and personality traits on postpartum PTSD, particularly in the context of traumatic birth experiences, such as EMCS or AVD. This is especially relevant for Greece, where a high CS rate poses unique challenges and opportunities for maternal healthcare improvements [2].

This study has several limitations, particularly regarding sample size and generalizability. The sample, while strategically selected to address specific research questions, was relatively small and may not fully represent the broader population of women at risk of postpartum PTSD. Considering that these rates involve EMCS and AVD (rare for Greece), our sample, although numerically limited, is deemed satisfactory, and the researchers exerted considerable effort to collect it. If the researchers had chosen the general population of

postpartum women, criterion A for PTSD, which involves exposure to trauma, would not have been met.

PRACTICAL VALUE

Future research should aim to include a more extensive and diverse participant pool to enhance the generalizability of these findings. Although our statistical approach identifies associations, it fails to explore complex causal relationships. Subsequent studies could benefit from incorporating multifactorial analysis techniques, such as multivariate regression or structural equation modeling, to delve deeper into the dynamics between domestic violence, personality traits, and PTSD. The exclusion criteria, while necessary for the study's focus, may have limited the inclusiveness of the findings.

Future investigations should consider strategies to include those with language barriers or cognitive impairments to ensure a comprehensive understanding of this issue across

Table 2. Domestic Violence, Type of Delivery, PTSD and Profile PTSD

		Domestic Violence				χ^2	p	OR	95% CI
		No		Yes					
		n	%	n	%				
Type of Delivery	AVD	26	29.9%	4	15.4%	2.345	0.126	2.34	0.74-7.48
	EMCS	61	70.1%	22	84.6%				
PTSD	No	82	94.3%	15	57.7%	22.014	<0.001	12.0	3.7-39.6
	Yes	5	5.7%	11	42.3%				
Profile PTSD	No	74	85.1%	8	30.8%	26.635	<0.001	12.8	4.6-35.5
	Yes	13	14.9%	18	69.2%				
OR= Odds Ratio, 95% CI = 95% Confidence Interval for OR									

OR= Odds Ratio, 95% CI = 95% Confidence Interval for OR

Source: compiled by the authors of this study

all vulnerable groups. Addressing the representativeness of female violence victims in this study is crucial.

CONCLUSIONS

This study presented the relationship between DV throughout a woman's life and the development of postpartum PTSD and PTSD profile following a triggering factor, such as a traumatic birth experience. The study's results showed that for the majority of DV victims, the emergency delivery process led to the re-experiencing of the violence, activating the mechanism for the development

of a new trauma. This highlights the connection between previous traumatic experiences, such as psychological or physical violence, and the vulnerability of women during childbirth. The sense of loss of control, intense pressure, and the power dynamics they may experience with healthcare professionals seem to trigger the reappearance of symptoms and amplify emotional distress. This finding emphasizes the critical need for psychological support for women with a history of DV, particularly during childbirth, to minimize the likelihood of developing new trauma and therefore PTSD or PTSD profile.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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Detection of IgM and IgG antibodies of measles in aborted women

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ABSTRACT

Aim: To detect anti-measles viruses IgG and IgM antibodies using rapid test Cassette and enzyme-linked immunosorbent assay (ELISA).

Materials and Methods: From October 2024 to December 2024, 352 blood samples obtained from female individuals, including 176 women who had abortions and 176 women with normal pregnancies. IgG and IgM samples were detected using the Cassette and ELISA methods.

Results: Recent measles virus infections, as indicated by rapid IgM test results, showed no significant difference between the abortion group and the control group $p=0.248$. Additionally, past infections, confirmed by rapid IgG tests, were not significantly different between the patient group and the control group $p=0.135$. Overall, there was no significant difference in measles virus IgM and IgG levels between the abortion and control groups $p>0.05$.

Conclusions: The level of education showed significant impact on abortion. Age, residency, and occupation do not affect the risk of abortion, while a low level of education is a significant risk factor for abortion. MV, there was no significant difference in the levels of IgM and IgG between the abortion group and the control group.

KEY WORDS: measles virus, immunoglobulin, enzyme-linked immunosorbent assay, abortions

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INTRODUCTION

Infection with measles virus (MV) results in highly contagious and severe febrile illness, this respiratory virus causes fever and one of the three „Cs”: cough, coryza, or conjunctivitis [1]. MV is primarily transmitted through respiratory droplets over short distances, while small-particle aerosols, which can remain airborne for extended periods, transmit it less frequently [2]. MV loses 60% of its infectivity within 3–5 days at room temperature, with a half-life of 2 hours at 37°C and 30 minutes at 56°C [3]. During pregnancy, measles infection is linked to an increased risk of early labour, spontaneous abortion, and low birth weight in new-borns [4]. If measles occurs late in pregnancy, it can result in congenital infection, potentially leading to severe encephalitis in new-borns. Pregnant individuals are also at a higher risk for complications such as pneumonia compared to non-pregnant women [4–5]. Immune responses to MV are crucial for viral elimination and the development of protective immunity [6]. MV-specific IFN- γ -producing T cells and IgM antibodies appear in the blood as the rash fades, and the infectious virus is cleared within a week [1, 6]. IgM antibodies typically disappear within 6 to 8 weeks. IgG titers develop rapidly, peak within 3 to 4 weeks, and then gradually decline, usually persisting for life [7]. The adaptive immune response involves the production of specific MV antibodies. The nucleoprotein (N) induces the most abundant and rapidly produced antibodies. Antibodies targeting the hemagglutinin (H) and fusion (F) proteins neutralize the virus and provide protection [8]. During the recovery phase, high levels of interleukin 4, interleukin 10, and interleukin 13 indicate a

Th2 response that aids in producing protective antibodies against MV [1, 6–7]. The primary humoral response involves the production of IgM antibodies, which appear with the rash and can be detected for 6–8 weeks, confirming an MV diagnosis. This is followed by the sustained production of MV-specific IgG [6, 9].

AIM

The aim of this study is to detect anti-measles viruses IgG and IgM antibodies using rapid test Cassette and enzyme-linked immunosorbent assay (ELISA).

MATERIALS AND METHODS

PARTICIPANTS AND STUDY DESIGN

The study was conducted from October 2024 until the end of December 2024. Samples were collected from the Gynecology and Pediatrics Teaching Hospital and Al-Rumaita General Hospital in Al-Muthanna Governorate. The study encompassed a total of 352 individuals, including 176 females who had previously undergone abortions, and another 176 females with normal pregnancies and healthy parents who served as a control group. The age range of all participants ranged from 18 years to 45 years.

INCLUDING CRITERIA

Categorized patients based on specific criteria. All patients participating in this study using specific data pertaining to their needs. The following patients were enrolled in the study and had their information gathered, as detailed in the questionnaire: A medical history from the family. Date

of birth, place of residence, and profession were all pieces of demographic data.

EXCLUDING CRITERIA

The study established specific inclusion criteria for patients based on age groups, and patients 46 years old or older were excluded. Also, patients with autoimmune diseases or chronic diseases were excluded.

SAMPLES COLLECTION

In total 4 ml of control and patient whole blood samples were obtained from the patients and the control group. The samples were centrifuged for 5 minutes at 4000 rpm. The rapid test and the enzyme-linked immunosorbent assay (ELISA) were used to detect IgG and IgM antibodies against measles virus).

MEASLES VIRUS IGG AND IGM INVESTIGATION

Measles virus IgG and IgM were measured and detected according to ELISA kit instructions (SunLong Biotech Co., LTD). The Rapid Cassette test was conducted using a kit from (Hangzhou New link Biotech CO., Ltd.).

STATISTICAL ANALYSIS

Data were collected, summarized, analysed, and presented using SPSS version 23 and Microsoft Excel 2010.

Categorical variables (qualitative) were expressed as counts and percentages. The normality of numeric variables was assessed using the Kolmogorov-Smirnov test. Normally distributed numeric variables were reported as mean and standard deviation, while non-normally distributed numeric variables were reported as median and interquartile range.

ETHICAL CONSIDERATIONS

Participation in the study was subject to informed consent. All participants had beta-thalassemia major. This protocol was approved by the Board of the Research Ethics Committee of the Health Office in Al-Muthanna Governorate, according to the ethical number (No. 866 on 1/8/2022). Informed consent was obtained from all patients and members of the control group. All samples taken from those patients were within the direct supervision of specialist physicians in hospitals.

RESULTS

The Sociodemographic characteristics of the abortion and control groups are presented in Table (1). The comparison of mean ages between the two groups showed no significant difference $p=0.327$, as illustrated in Figure 1.

The mean age of the abortion group was 26.25 ± 5.81 years, ranging from 18 to 44 years, while the control group's mean age was not specified but ranged from 18 to 40

Table 1. Sociodemographic characteristic compared between abortion group and control group

Characteristic	Abortion group n = 176	Control group n = 176	p
Age (years)			
Mean± SD	26.25 ±5.81	26.84 ±6.12	0.327 I NS
Range	18 -44	18 -40	
18-19 years	9 (5.1 %)	23 (13.1 %)	0.009 C **
20-24 years	51 (29.0 %)	67 (38.1 %)	0.071 C NS
25-29 years	55 (31.3 %)	39 (22.2 %)	0.054 C NS
30-34 years	36 (20.5 %)	24 (13.6 %)	0.089 C NS
35-39 years	18 (10.2 %)	16 (9.1 %)	0.718 C NS
40-44 years	7 (4.0 %)	7 (4.0 %)	1.000 C NS
Residency			
Urban	43 (24.4 %)	45 (25.6 %)	0.806 C NS
Rural	133 (75.6 %)	131 (74.4 %)	
Occupation			
Not employed	159 (90.3 %)	154 (87.5 %)	0.396 C NS
Employee	17 (9.7 %)	22 (12.5 %)	
Education Level			
Illiterate	94 (53.4 %)	59 (33.5 %)	0.001 C ***
Primary	44 (25.0 %)	73 (41.5 %)	
Secondary	19 (10.8 %)	26 (14.8 %)	
Tertiary	19 (10.8 %)	18 (10.2 %)	

n: number of cases; SD: standard deviation; I: independent samples t-test; C: chi-square test; NS: not significant; ***: significant at $p \leq 0.001$

Source: Own materials

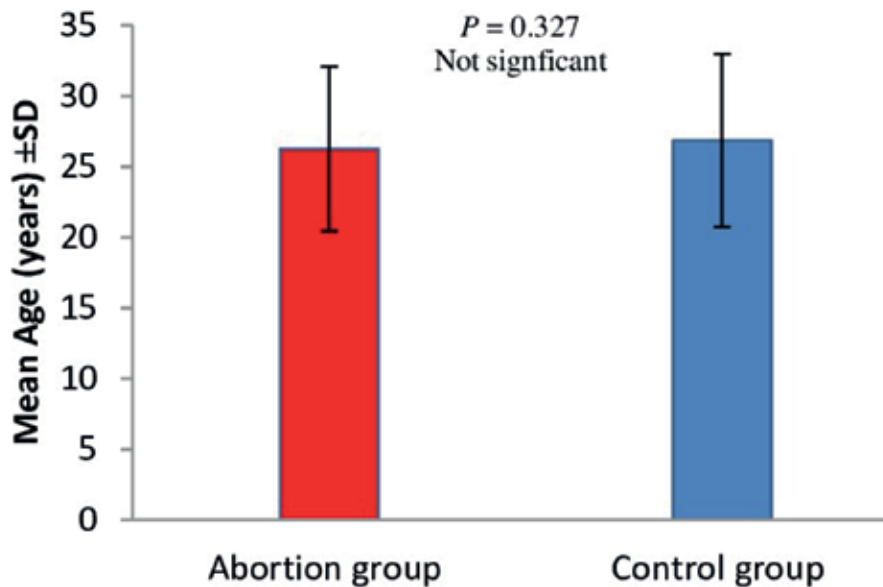


Fig. 1. Comparison of mean age between abortion group and control group. There was no significant difference between individuals in relation to age groups included in these two groups

Source: Own materials

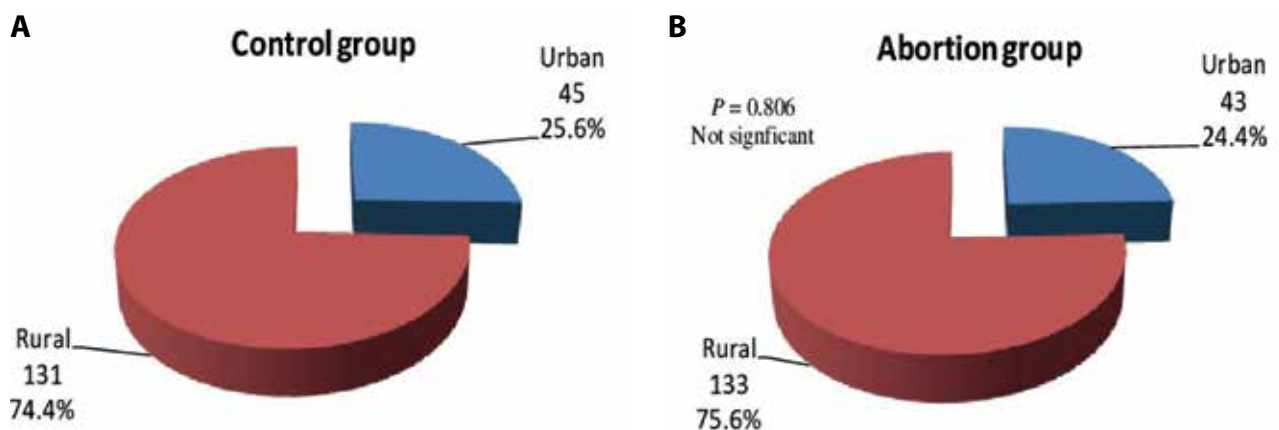


Fig. 2. Comparison of patients' residency between control group (A) and abortion group (B)

Source: Own materials

years. There was no significant difference in residency proportions between the abortion and control groups $p=0.806$, as shown in Figures 2A, 2B.

The abortion group had a higher proportion of women from rural areas 133 women, 75.6% compared to urban areas 43 women, 24.4%. Similarly, the control group had more women from rural areas 45 women, 25.6% than urban areas 131 women, 74.4%. Occupation did not significantly affect the risk of abortion $p=0.396$. In the abortion group, the majority of women were unemployed 159 women, 90.3%, similar to the control group 154 women, 87.5%. Education level had a significant impact on abortion $p=0.001$. In the abortion group, 94 (53.4%) women were illiterate, 44 (25.0%) women had primary education, and 19 (10.8%) women had secondary education. In the control group, 59 (33.5%) women were illiterate, 73 (41.5%) women had primary education, and 26 (14.8%) women had secondary

education, as shown in Figure 3. When categorized into educated and uneducated groups, the difference was also significant $p<0.001$, with a higher proportion of uneducated women in the abortion group 53.4% compared to the control group 33.5%, as depicted in Figure 4.

Table 2 presents the results of rapid tests for the measles virus among women in the abortion and control groups. The rapid IgM test results indicated no significant difference in recent measles virus infections between the abortion and control groups $p=0.248$. Similarly, the rapid IgG test results showed no significant difference in past measles virus infections between the two groups $p=0.135$.

DISCUSSION

The results indicate that maternal age does not appear to be a significant cause or risk factor for abortion among the enrolled women. However, a study [10], found that maternal

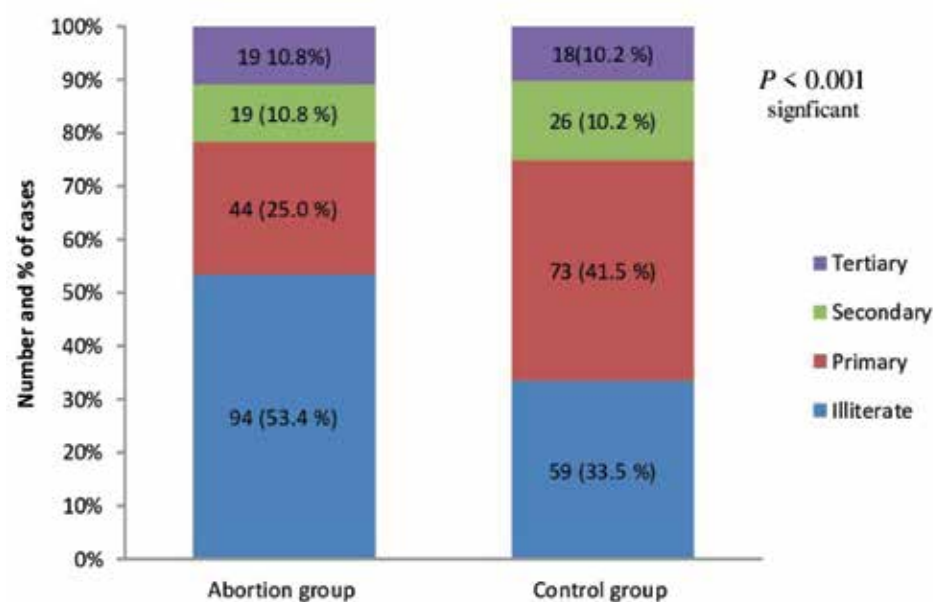


Fig. 3. Comparison of proportions of patients based on level of education between abortion group and control group

Source: Own materials

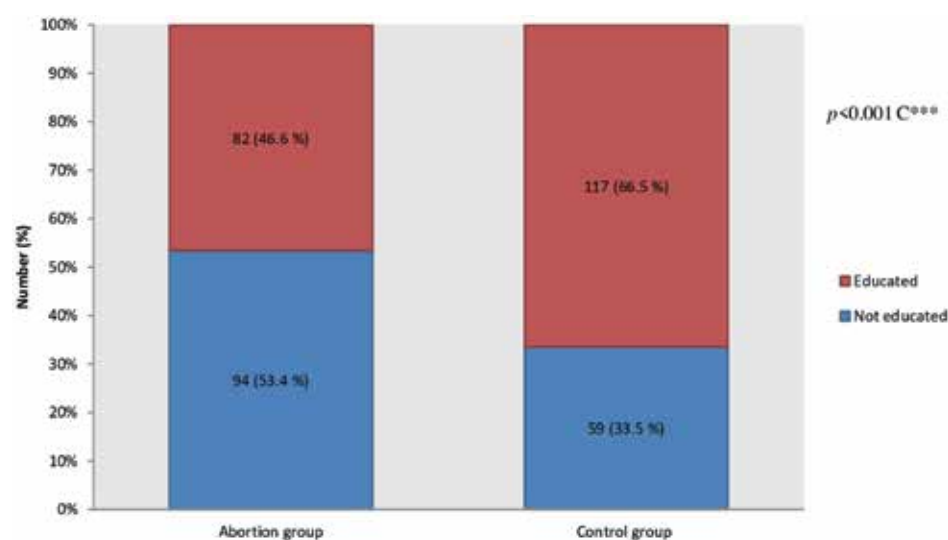


Fig. 4. Comparison of proportions for the educated and not educated groups of the aborted and non-aborted women

Source: Own materials

Table 2. Results of IgG and IgM antibodies detected by rapid test for Measles virus in abortion group and in control group.

Characteristic	Abortion group n = 176	Control group n = 176	p
Rapid IgM MV			
Positive	3 (1.7 %)	0 (0.0 %)	0.248 F NS
Negative	173 (98.3 %)	176 (100.0 %)	
Rapid IgG MV			
Positive	9 (5.1 %)	3 (1.7 %)	0.139 F NS
Negative	167 (94.9 %)	173 (98.3 %)	

n: number of cases; F: Fischer exact test; NS: not significant

Source: Own materials

age of 35 years and older is significantly associated with an increased incidence of abortion. Similarly, a recent report from Duhok city in Iraq by [11]. An increase in maternal age has been identified as a significant risk factor for abortion. Additionally, according to a recent report by [12]. Maternal age is a significant risk factor for recurrent abortion. The probability of miscarriage is contingent upon the established upper threshold of maternal age. The likelihood escalates in a nearly linear fashion post the age of 30, culminating in a rate of 54% by the age of 45 and beyond, concomitant with a pronounced decline in both oocyte quality and quantity, as well as an augmented frequency of mitochondrial DNA mutations and errors in meiosis. Furthermore, the incidence of chromosomal abnormalities in embryos derived from older women is significantly elevated when compared to those from women of optimal reproductive age [12], added to the same reference, concluded to further reasons for recurrent miscarriage in association with advanced maternal age, namely, uterine adhesions and reduced function of ovary. In current study, the lack of significant difference in mean age is due to the type of study design in which it was a case control study and in such type of studies there must be a statistical match in age between study group and control group, thus, the researcher in this study intentional enrolled a control group of pregnant women with comparable age to those of group of women with abortion. In addition, the main objective of the current study was to evaluate the possible role of infection and immune abnormalities as causes of recurrent abortion; therefore, other possible causes should be statistically matched including the age to avoid bias in the results that cannot be attributed to viral infection and or immune dysfunction. The possible reasons for higher proportions of rural residency in both study groups may be due to poverty of women enrolled, thus, they seek governmental health services or due to that the Al-Muthanna governorate, already contains higher proportions of people from rural residency in comparison with urban residency. Current results are in accordance with a recent Iraqi study performed in Adiwanayah Province by [13], in which residency showed no significant association with abortion. In addition [11], concluded no significant association between residency and rate of abortion, a result that is comparable to current

study findings. However, some previous authors have shown significant association between rural residency and higher rate abortion and they attributed such higher rate to lack of proper antenatal care and the possible exposure to some environmental factors such as infection at a higher rate in comparison with urban residency [14]. Nevertheless, the changes in lifestyle in rural areas in Iraqi including the availability of water supply, programs of immunization and advances in health services may justify the lack of significant variation in abortion with respect to residency in current study. In this study, occupation has been shown to play no significant role in abortion and this finding is in line with the observation of [15]. On the contrary to this observation [16], concluded that physically demanding work during pregnancy is associated with an increased risk of adverse pregnancy outcomes; however, heavy work such as weight lifting for women is rarely seen in Iraqi communities in addition, most enrolled women in this study were housewives. So far, from current study observation, low level of education is associated with significantly higher risk of abortion and this is in accordance with a recent Iraqi study [17]. In addition, current study is in agreement with [15], who stated that low level of education is significantly associated with risk of abortion. Moreover, a recent study by [18] has documented that low level of education is associated with increased risk of abortion and this finding is again supportive to present study results. Higher education is typically associated with an elevated economic and social standing. In this context, women possessing a higher socioeconomic status are more likely to exhibit reduced risk factors compared to their counterparts, which encompasses superior lifestyle choices, an understanding of the importance of prenatal care, spatial considerations, and appropriate intervals between pregnancies [18]. So far, in this study, measles appears to be not associated with abortion and this finding is in line with several previous studies [19-20].

CONCLUSIONS

Age, residency, and occupation do not affect the risk of abortion, while a low level of education is a significant risk factor for abortion. MV, there was no significant difference in the levels of IgM and IgG between the abortion group and the control group.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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Assessment of the mineral composition of teeth in children of the mountain zone of Transcarpathia region

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ABSTRACT

Aim: To determine the mineral composition of enamel and dentin of temporary and permanent teeth of children in the mountain zone of the Transcarpathian region and to conduct a comparative analysis of the obtained indicators.

Materials and Methods: 25 temporary and 25 permanent teeth were subjected to research. The conditions of selection were the absence of carious lesions. The study was carried out by the method of raster electron spectrometry.

Results: In children who permanently live in the mountainous geographical zone of the Transcarpathian region, the mineral composition of enamel and dentin was determined by spectrometry and the following probable differences were established: the carbon content in the enamel of temporary teeth is probably higher compared to the content in the enamel of permanent teeth and in dentin; the content of oxygen, phosphorus, calcium, sodium, magnesium and chlorine in permanent teeth is probably lower in relation to the content in permanent teeth in enamel and dentin ($p < 0.05$).

Conclusions: The accumulation of chemical elements in the teeth is considered a good indicator of qualitative changes in the diet and water supply of the population. The peculiarities of the mineral composition of the hard tissues of the temporary teeth of children who have lived for a long time in the mountainous zone of the Transcarpathian region, namely the presence of sulfur, confirm the fact that the hard tissues of the teeth, especially the temporary ones, are a detector of the state of the ecological environment.

KEY WORDS: teeth, mineral composition, caries prevention, spectral analysis

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INTRODUCTION

The composition of the hard tissues of the teeth is dominated by inorganic elements, among which there are basic, i.e., organ-forming elements that are found in large quantities, which are carbon, oxygen, hydrogen and nitrogen, as well as those that are found in much smaller quantities, such as sodium, calcium, magnesium, potassium, sulfur, phosphorus, chlorine and fluorine, but they take a significant part in the formation of a full-fledged mineral framework of enamel and dentin of teeth [1].

The mineral composition of tooth enamel and dentine is in dynamic equilibrium throughout the entire period of tooth functioning [2], and largely depends on the nature and composition of the food diet and the composition and quality of drinking water consumed by a person [3-7].

Violation of the mineral composition of hard teeth leads to the destruction of the crystal lattice of enamel hydroxyapatites, makes physiological processes of remineralization impossible and, together with cariogenic factors of the oral cavity, leads to the occurrence and progression of caries [8-10].

A number of studies are devoted to the study of the mineral composition of temporary teeth in children who

have been in environmentally polluted areas for a long time [11].

It has been proven that the appearance of such elements as lead and cadmium in the composition of hard tissues of temporary teeth is a marker of the unfavorable ecological background of the territory, long-term living in such conditions poses a threat to human life [12-17].

The use of spectrometry allows you to quickly, painlessly and non-invasively obtain informative parameters and allows you to evaluate and compare the mineral composition of enamel and dentin of teeth [1,18,19].

The study of the mineral composition of enamel and dentin of temporary teeth and its comparison with the mineral composition of hard tissues of permanent teeth in children who live in the same territory, that is, in one geographical area of one country with a specific mineral composition of drinking water and soils in the mountainous part of the Transcarpathian region, is being conducted for the first time and is of scientific interest.

The purpose of the study. To determine the mineral composition of enamel and dentin of temporary and permanent teeth of children in the mountain zone of

Zakarpattia region and to conduct a comparative analysis of indicators.

Materials and methods. 25 temporary and 25 permanent teeth removed according to orthodontic indications in children living in the mountainous area of the Transcarpathian region were subjected to research. The conditions of selection were the absence of carious lesions. Adult teeth were not studied. Teeth were removed, guided by the method of sequential tooth extraction proposed by Hotz A. (1919). First, temporary canines were removed to provide space and correct the position of the lateral incisors, and then the first premolars to correct the position of the canines, which was called „sequential extraction“. The age distribution was formed according to the chronological age of the patient and the degree of formation of the root and apex of the permanent tooth at the time of the patient's request for orthodontic help [20].

The study of the mineral composition of temporary and permanent teeth in children was carried out by the method of raster electron spectrometry. For this, X-ray radiation induced by a proton beam (PIXE, μ -PIXE methods) was used and evaluated on the AZtecOne microanalytical accelerator complex with the X-MaxN20 detector (manufactured by Oxford Instruments plc) B, (Sumy State University of Sumy, Ukraine).

Methodologically, the study of all teeth was carried out in a unified manner, for each tooth an element distribution diagram and a total spectrum map were created separately in enamel and dentin. Fracture surfaces of teeth were used for the study, since it is on the fractures that the natural microrelief structure of enamel prisms and cracks can be well analyzed without polishing/etching [21].

The mineral composition of primary and permanent teeth in children was studied using scanning electron spectrometry. Ultramicroscopic studies were performed using an SEO-SEM Inspect S50-B electron microscope (Sumy State University, Sumy, Ukraine).

For ultramicroscopic study using scanning electron microscopy, the teeth were fixed on graphite Tables and dried in air. Before viewing in a scanning microscope, the samples were sputtered with carbon in a vacuum universal

post “VUP-5”, placed in a scanning electron microscope with a low vacuum camera “REM 102”, photographed at a magnification of $\times 12$ to $\times 10,000$ and stored on an electronic medium. To determine the elemental composition of the teeth, characteristic X-ray radiation induced by a proton beam (PIXE, μ -PIXE methods) was used. The corresponding studies were carried out on an AZtecOne microanalytical accelerator complex with an X-MaxN20 detector (manufacturer Oxford Instruments plc) B, (Sumy State University, Sumy, Ukraine). [22]

The research was conducted in 2021-2022 at the Center for Collective Use of Scientific Equipment „Laboratory of Materials Science of Solar Energy, Sensor and Nanoelectronic Systems“ of Sumy State University within the framework of bilateral initiative cooperation without a formalized agreement.

All studies were conducted after the prior consent of the patients and their parents or guardians, in compliance with safety rules and their compliance with the principles of the Declaration of Helsinki, adopted by the General Assembly of the World Medical Association (1964-2016), the Council of Europe Convention on Human Rights and Biomedicine dated 04.04.1997, the European Convention for the Protection of Vertebrate Animals Used for Research and Other Scientific Purposes (1986), the relevant provisions of the WHO, the International Council of Medical Scientific Societies, the International Code of Medical Ethics (1983) and the relevant laws of Ukraine.

Statistical analysis was carried out using the „Statistica 13.0“ software, which makes it possible to determine the reliability of the results and the values of average statistical errors [17, 23-26].

Research results. 25 temporary and 25 permanent teeth of children living in the mountainous area of Zakarpattia region were studied. Methodologically, the study of all teeth was carried out in a unified way, for each tooth a diagram of the distribution of elements and the total spectrum of the map was created separately in enamel and dentin.

Tables 1 and 2 show average statistical indicators of the elemental composition of the enamel of children's temporary and permanent teeth (Table 1, Table 2).

Table 1. Average statistical indicators of the elemental composition of the enamel of temporary teeth of children living in the mountainous area.

Element	Line type	Weight, %	Sigma weight, %	Atom., %
C	K-series	51.97 $\pm$ 8.32	0.30 $\pm$ 0.02	61.54 $\pm$ 8.26
O		39.13 $\pm$ 3.95	0.30 $\pm$ 0.02	34.78 $\pm$ 3.24
P		3.57 $\pm$ 1.03	0.05 $\pm$ 0.01	1.64 $\pm$ 0.03
Ca		4.41 $\pm$ 1.43	0.06 $\pm$ 0.01	1.56 $\pm$ 0.04
Na		0.40 $\pm$ 0.02	0.04 $\pm$ 0.01	0.25 $\pm$ 0.02
Cl		0.21 $\pm$ 0.01	0.02 $\pm$ 0.01	0.09 $\pm$ 0.01
Mg		0.08 $\pm$ 0.01	0.03 $\pm$ 0.01	0.05 $\pm$ 0.01
S		0.23 $\pm$ 0.01	0.02 $\pm$ 0.01	0.10 $\pm$ 0.01

Source: compiled by the authors of this study

Table 2. Average statistical indicators of the elemental composition of the enamel of permanent teeth of children living in the mountainous area

Element	Line type	Weight, %	Sigma weight, %	Atom., %
C, carbon	K-series	27.53±2.35	0.50±0.02	36.99±3.05
O, oxygen		52.13±5.27	0.40±0.01	52.78±5.85
P, phosphorus		7.79±1.09	0.10±0.01	5.60±0.10
Ca, calcium		9.96±1.26	0.11±0.02	4.14±0.09
Al, aluminum		0.49±0.01	0.02±0.01	0.31±0.02
Na, sodium		0.53±0.02	0.06±0.01	0.38±0.02
Cl, chlorine		0.28±0.01	0.03±0.01	0.14±0.01
F, fluorine		0.48±0.01	0.02±0.01	0.32±0.02
Mg, magnesium		0.16±0.01	0.03±0.01	0.11±0.02

Source: compiled by the authors of this study

The presence of sulfur (0.23±0.01%) was determined in the enamel of temporary teeth of children living in the mountainous area, which is not normally part of the normal composition of the enamel of temporary teeth (Table 1).

In children from the mountainous area of residence, the differences in the elemental composition of the enamel of primary and permanent teeth were as follows: significantly higher content of carbon in the enamel (51.97±8.32%; 27.53±2.35%; $p<0.05$); significantly lower content of phosphorus (3.57±1.03%; 7.79±1.09%; $p<0.05$), calcium (4.41±1.43%; 9.96±1.26%; $p<0.05$); magnesium (0.08±0.01%; 0.16±0.01%; $p<0.05$) and oxygen (39.13±3.95%; 52.13±5.27%; $p<0.05$); significantly lower chlorine content (0.21±0.01%; 0.28±0.01%; $p<0.05$) and sodium (0.40±0.02%; 0.53±0.02%; $p>0.05$) (Table 2).

Aluminum (0.49±0.01%) and fluorine (0.48±0.01%) were found in the enamel of permanent teeth of children living in the mountainous area.

Table 3 and Table 4 present the average statistical indicators of the elemental composition of the dentin of children's temporary and permanent teeth.

The presence of sulfur (0.11±0.05%) was determined in the dentin of temporary teeth of children living in the

mountainous area, which is not normally included in the normal composition of dentin of temporary teeth (Table 3).

Aluminum (0.64±0.03%) and fluorine (0.17±0.01%) were found in the dentin of permanent teeth of children living in the mountainous area (Table 4).

Table 5 contains general data on the elemental composition of enamel and dentine of temporary and permanent teeth of children in the mountainous area. In children from the mountainous area of residence, the differences in the elemental composition of dentin of primary and permanent teeth were as follows: significantly higher carbon content (56.75±7.23%; 37.00±4.34%; $p<0.05$); significantly lower phosphorus content (0.79±0.09%; 4.13±0.12%; $p<0.05$), calcium (0.63±0.08%; 4.11±0.24%; $p<0.05$); oxygen (41.21±3.95%; 52.42±5.78%; $p<0.05$) and magnesium (0.07±0.01%; 0.12±0.01%; $p>0.05$); significantly lower chlorine content (0.10±0.03%; 0.17±0.01%; $p>0.05$) and sodium (0.36±0.04%; 0.45±0.02%; $p>0.05$) (Tab. 5).

Figures 1 and 2 visualize the indicators of the content of oxygen, carbon, calcium and phosphorus, sodium, magnesium, chlorine, aluminum, sulfur and fluorine in the enamel and dentine of temporary and permanent teeth of children in the mountain zone of Transcarpathia region.

Table 3. Average statistical indicators of the elemental composition of the dentine of temporary teeth of children living in the mountainous area.

Element	Line type	Weight, %	Sigma weight, %	Atom., %
C	K-series	56.75±7.23	0.15±0.03	64.14±8.31
O		41.21±3.95	0.15±0.04	34.97±3.15
P		0.79±0.09	0.01±0.01	0.34±0.09
Ca		0.63±0.08	0.01±0.01	0.21±0.05
Na		0.36±0.04	0.02±0.01	0.21±0.03
Mg		0.07±0.01	0.01±0.01	0.04±0.01
Cl		0.10±0.03	0.01±0.01	0.04±0.01
S		0.11±0.05	0.01±0.01	0.04±0.01

Source: compiled by the authors of this study

Table 4. Average statistical indicators of the elemental composition of dentin of permanent teeth of children living in the mountainous area

Element	Line type	Weight, %	Sigma weight, %	Atom., %
C, carbon	K-series	37.00±4.34	0.20±0.04	47.09±5.31
O, oxygen		52.42±5.78	0.20±0.03	48.94±4.90
P, phosphorus		4.13±0.12	0.04±0.02	2.04±0.07
Ca, calcium		4.11±0.24	0.03±0.01	1.59±0.04
Al, aluminum		0.64±0.03	0.02±0.01	0.38±0.02
Na, sodium		0.45±0.02	0.04±0.02	0.30±0.02
Cl, chlorine		0.17±0.01	0.01±0.01	0.08±0.01
F, fluorine		0.17±0.01	0.02±0.01	0.12±0.01
Mg, magnesium		0.12±0.01	0.02±0.01	0.08±0.01

Source: compiled by the authors of this study

Table 5. Elemental composition of enamel and dentin of temporary and permanent teeth of children in the mountain zone

Elements	Weight,%, enamel, temporary teeth	Weight,%, enamel, permanent teeth	Weight,%, dentin, temporary teeth	Weight,%, dentin, permanent teeth
C	51.97±8.32	27.53±2.35	56.75±7.23	37.00±4.34
O	39.13±3.95	52.13±5.27	41.21±3.95	52.42±5.78
P	3.57±1.03	7.79±1.09	0.79±0.09	4.13±0.12
Ca	4.41±1.43	9.96±1.26	0.63±0.08	4.11±0.24
Na	0.40±0.02	0.53±0.02	0.36±0.04	0.45±0.02
Mg	0.08±0.01	0.16±0.01	0.07±0.01	0.12±0.01
Cl	0.21±0.01	0.28±0.01	0.10±0.03	0.17±0.01
Al	-	0.49±0.01	-	0.64±0.03
S	0.23±0.01	-	0.11±0.05	-
F, fluorine	-	0.48±0.01	-	0.17±0.01
P<0,05				

Source: compiled by the authors of this study

Splitting into two charts is necessary to better visualize the probability of the readings, since the readings for oxygen, carbon, calcium and phosphorus are much larger than for the other elements (Fig. 1, Fig. 2).

DISCUSSION

The role of elements such as calcium and phosphate, which are the main components of hydroxyapatite crystals that form the inorganic part of the teeth, has been studied more thoroughly, although the ratio of the concentration of these elements in the enamel and dentine of temporary and permanent teeth of children who have lived in the same area for a long time with a specific composition of drinking water to was now unexamined.

The mountainous geographical zone of Transcarpathia makes up 60-65% of the entire territory – a specific

heterogeneous territory inhabited by people. Quality indicators of drinking water, as the main source of minerals for human life, directly depend on the composition of underground mineral waters, which are distinguished by their diversity. A general parameter for this territorial zone is characterized by a significant deficiency of fluorine, iodine and a number of micro- and macroelements; the level of fluorine in the soil is 0.02 - 0.03 mg/l, in water - 0.3-0.5 mg/l [27].

The determination of statistical differences in the mineral composition of enamel and dentin of temporary and permanent teeth of children in the mountain zone of Transcarpathia region was carried out for the first time.

Research by Mamaladze M, and Jalabadze N. (2022) established that the distribution of essential trace elements in the hard tissues of the teeth is uneven, and fluoride in the

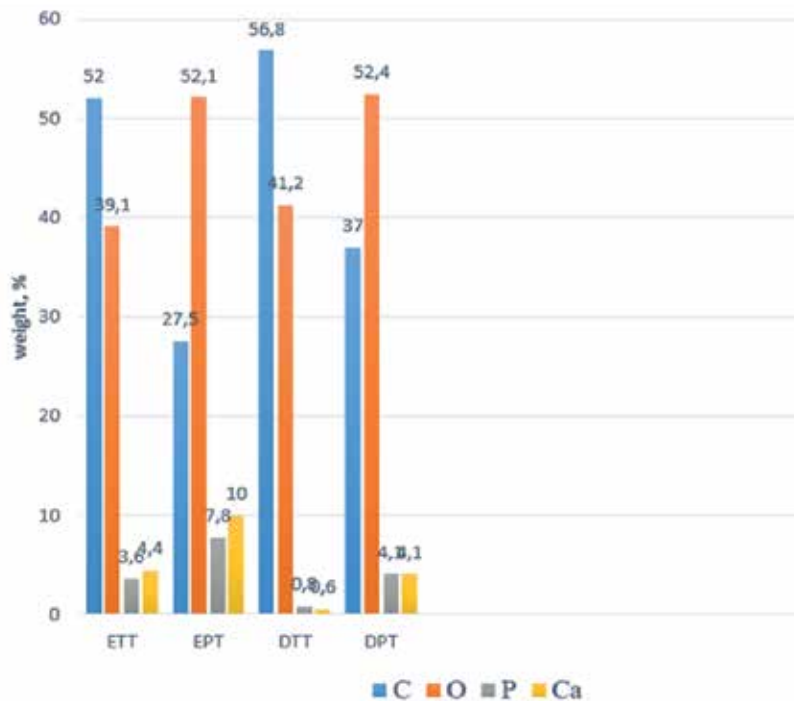


Fig. 1. The content of oxygen, carbon, calcium and phosphorus in the enamel and dentine of temporary and permanent teeth of children in the mountain area (ETT – enamel temporary teeth; EPT – enamel permanent teeth; DTT – dentin temporary teeth; DPT – dentin permanent teeth)

Picture taken by the authors

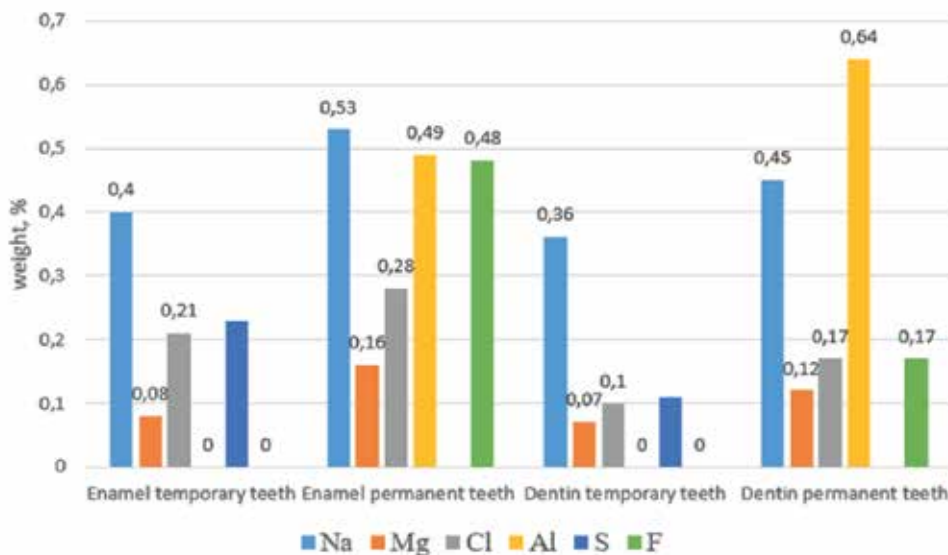


Fig. 2. The content of sodium, magnesium, chlorine, aluminum, sulfur and fluorine in the enamel and dentin of temporary and permanent teeth of children in the mountain area

Picture taken by the authors

hard tissues is contained only in minimal concentrations [18].

Research by Fischer, D et al. In 2013, changes in the concentration of such elements as Mn, Fe, Mg, Cu, K, Cr, Pb, Cd, Ca in the composition of temporary teeth taken from 45 children aged 5-14 years living in the south of Poland, removed with a non-invasive physiological change. The researchers established that the concentration of all metals (Ca, Mg, Cd, Cu, Pb, K, Cr) in the tissues of temporary teeth decreased with age. ($p < 0.05$). The content of Ca was indicated as the value of constant cation balance; the total concentration of all studied metals relative to the

Ca content probably did not change with the age of the children ($p > 0.05$), that is, there is a quantitative balance in the elemental composition of the hard tissues of the teeth [28].

Also, the exact effect of trace elements on the health of the teeth and oral cavity remains unexplored. although, Shaik I and sang. 2021, looked at the presence of trace elements in teeth and their role in dental health and development, their absence can disrupt the healthy development of enamel and dentin and lead to defects in tooth development, as well as caries; at the same time, excessive consumption of

some trace elements can adversely affect the development and health of teeth [1].

Bowen WH found that lead ions replace calcium, as well as calcium and phosphorus in bone mineral crystals, causing hypercalcemia and hyperphosphatemia, ie, lead is considered a caries-promoting element; revealed a direct link between enamel hypoplasia and lead exposure to children [5].

Needleman et al. in their study found an increased incidence of temporary teeth in American suburban children exposed to lead [11]. In addition, a direct relationship between the development of early childhood caries in children and exposure to lead was found [15].

The mineral composition of enamel and dentin was determined by spectrometry in children who live permanently in the mountainous geographical zone of the Transcarpathian region, and the following probable differences were established: the carbon content is probably higher both in the enamel of temporary teeth compared to the content in the enamel of permanent teeth ($51.97 \pm 8.32\%$; $27.53 \pm 2.35\%$; $p < 0.05$) and in dentin ($56.75 \pm 7.23\%$; $37.00 \pm 4.34\%$; $p < 0.05$); the content in temporary teeth is probably lower in relation to the content in permanent teeth: oxygen in enamel ($39.13 \pm 3.95\%$; $52.13 \pm 5.27\%$; $p < 0.05$) and dentin ($41.21 \pm 3.95\%$; $52.42 \pm 5.78\%$; $p < 0.05$); phosphorus in enamel ($3.57 \pm 1.03\%$; $7.79 \pm 1.09\%$; $p < 0.05$) and dentin ($0.79 \pm 0.09\%$; $4.13 \pm 0.12\%$; $p < 0.05$); calcium in enamel ($34.41 \pm 1.43\%$; $9.96 \pm 1.26\%$; $p < 0.05$) and dentin ($0.63 \pm 0.08\%$; $4.11 \pm 0.24\%$; $p < 0.05$); of sodium in enamel

($0.40 \pm 0.02\%$; $0.53 \pm 0.02\%$; $p < 0.05$) and dentin ($0.36 \pm 0.04\%$; $0.45 \pm 0.02\%$; $p < 0.05$); magnesium in enamel ($0.08 \pm 0.01\%$; $0.16 \pm 0.01\%$; $p < 0.05$) and dentin ($0.07 \pm 0.01\%$; $0.12 \pm 0.01\%$; $p < 0.05$); of chlorine in enamel ($0.21 \pm 0.01\%$; $0.28 \pm 0.01\%$; $p < 0.05$) and dentine ($0.10 \pm 0.03\%$; $0.17 \pm 0.01\%$; $p < 0.05$).

Aluminum was determined exclusively in enamel ($0.49 \pm 0.01\%$) and dentin ($0.64 \pm 0.03\%$) of permanent teeth; fluorine was also determined in the enamel ($0.48 \pm 0.01\%$) and dentin ($0.17 \pm 0.01\%$) of permanent teeth. Such an element as sulfur is noted exclusively in enamel ($0.23 \pm 0.01\%$) and dentin ($0.11 \pm 0.05\%$) of temporary teeth.

The accumulation of chemical elements in the teeth is considered a good indicator of qualitative changes in the diet and water supply of the population.

CONCLUSIONS

The use of spectroscopy is a fast, non-invasive and informative method of diagnosis, its use allows to evaluate and compare the mineral composition of enamel and dentin of temporary teeth in children who live in different geographical zones of the same country with a different mineral composition of drinking water and soils.

In our opinion, the presence of sulfur in the enamel and dentin of the temporary teeth of children in the mountain zone is related to the presence of sulfur in the drinking water of this geographical zone, which confirms the fact that the hard tissues of the teeth, especially the temporary ones, are a detector of the state of the individual's ecological environment.

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Role of sclerostin in the bone and thyroid metabolism in patients with ovarian polycystic syndrome

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ABSTRACT

Aim: to evaluate potential role of sclerostin in pathophysiology of Polycystic Ovary Syndrome, especially in relation to bone and thyroid metabolism.

Materials and Methods: An exploratory cross-sectional study was carried out with participation of 66 women suffering from Polycystic Ovary Syndrome and 34 healthy controls. Measurements and results obtained were for serum levels of sclerostin, osteocalcin, and thyroid-stimulating hormone by using ELISA technique.

Results: Mean serum sclerostin levels were significantly elevated in Polycystic Ovary Syndrome group $12.5 \text{ ng/mL} \pm 4.8$ compared to controls $4.8 \text{ ng/mL} \pm 2.4$ with t-value having been recorded as 9.02 and $P=0.000$. Patients with Polycystic Ovary Syndrome showed significantly lower serum osteocalcin levels ($3.7 \pm 1.2 \text{ ng/mL}$ vs. $5.2 \pm 2.2 \text{ ng/mL}$, $P=0.000$) and higher TSH levels ($6.3 \pm 1.3 \text{ } \mu\text{IU/mL}$ vs. $3.4 \pm 0.8 \text{ } \mu\text{IU/mL}$, $P=0.000$). Pearson correlation analysis revealed a moderate negative correlation between osteocalcin and sclerostin ($r=-0.458$, $P=0.039$). ROC analysis of sclerostin exhibited a sensitivity of 79% and specificity of 62% which can be interpreted as moderate in terms of diagnostic accuracy.

Conclusions: Findings highlight that sclerostin is much raised in women with PCOS and could well be a useful biomarker of the syndrome's effects on bone and thyroid metabolism. Its moderate diagnostic performance however, further researches on its role in the pathophysiology of Polycystic Ovary Syndrome are needed.

KEY WORDS: sclerostin, osteocalcin, body mass index, polycystic ovary syndrome

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INTRODUCTION

Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder among women of reproductive age, characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology. While its impact on reproductive health is well recognized, recent research highlights its broader systemic effects, notably on bone metabolism. These effects arise from complex hormonal and metabolic alterations inherent to PCOS, including changes in androgens, insulin resistance, and thyroid hormones – particularly thyroid-stimulating hormone (TSH) [1]. Bone health in women with PCOS shows contradictory data. A recent meta-analysis reported a 25% increased risk of fractures among women with PCOS, although without statistical significance [2]. Factors such as body mass index (BMI), ovarian hormones, and commonly used medications like combined oral contraceptives and metformin may variably influence bone mineral density (BMD) [2]. For example, women with PCOS and BMI $<27 \text{ kg/m}^2$ were reported to have significantly lower spine and hip BMD and increased bone resorption markers, suggesting elevated skeletal fragility, whereas those with BMI $>27 \text{ kg/m}^2$ showed greater BMD, potentially reflecting a protective effect of excess weight [5]. Thyroid function adds another layer to this complexity. Altered TSH levels have been implicated as mediators between

PCOS and bone metabolism changes [3-4]. Since thyroid hormones are known regulators of bone turnover, abnormal TSH may contribute to shifts in bone remodeling dynamics in PCOS, although this interaction remains underexplored. Sclerostin, a glycoprotein secreted mainly by osteocytes, is a critical inhibitor of bone formation through its suppression of the Wnt/ β -catenin signaling pathway [6-7]. However, recent studies suggest sclerostin may also be influenced by metabolic and endocrine factors, including BMI and possibly thyroid status [6]. Measuring circulating sclerostin has clinical relevance, as its levels may help stratify fracture risk and monitor treatment response [8-10]. However, data on sclerostin in the context of PCOS – especially considering the interplay between bone and thyroid metabolism – remain limited. Therefore, the aim of this study is to evaluate the potential role of sclerostin in the pathophysiology of PCOS, with specifically focusing on its association with bone and thyroid metabolism. Clarifying this relationship may help identify new biomarkers or therapeutic targets to improve bone health in women affected by PCOS.

AIM

The aim of this study is to evaluate potential role of sclerostin in pathophysiology of Polycystic Ovary Syndrome, especially in relation to bone and thyroid metabolism.

MATERIALS AND METHODS

PATIENTS AND DATA COLLECTION

This cross-sectional case-control study was conducted at the Medical City Complex in Baghdad, Iraq, during the period from September 2024 to March 2025. Sixty-six females who had been diagnosed with polycystic ovary syndrome (PCOS) were included in the study; 34 healthy female controls, matched for age and without clinical or biochemical evidence of PCOS. All subjects were recruited from the outpatient gynecology and endocrinology clinics within the hospitals that are part of Medical City. The diagnosis of PCOS was based on Rotterdam criteria; however, relevant clinical data such as age and menstrual history, as well as anthropometric measurements, had to be obtained from medical records. The body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2) and categorized per World Health Organization classification [11-12].

MEASUREMENT OF TSH

Blood samples were drawn from study participants in the morning hours, generally between 8:00 and 10:00 AM, on the same day to reduce diurnal effects and keep conditions standardized. The serum was obtained by spinning at 3000 rpm for 10 minutes and stored at -80°C until tested. Measurement of Thyroid Stimulating Hormone (TSH) were done by the ELISA procedure from Humacount (Germany). Serum were prepared by centrifuging blood for 10 minutes at 3000 revolutions per minute, followed by separation of the serum. Analysis is done using the ELISA technique in which TSH binds to specific antibodies and a colorimetric linked secondary enzyme antibody produces a color that is measurable and proportional to the amount of TSH in the sample, hence quantifying TSH. Results are interpreted in terms of established reference ranges for normal thyroid function (generally 0.4-4.0 mIU/L for adults). Calibration and quality control have been carried out prior to this assay application, which is further looked at together with clinical symptoms and other tests on thyroid hormones.

MEASUREMENT OF OSTEOCALCIN

Levels of osteocalcin were determined using a commercial enzyme-linked immunosorbent assay (ELISA) kit for human osteocalcin (from My BioSource). The test used here is based on the sandwich type, where microtiter plates precoated with anti-osteocalcin antibodies enable binding to osteocalcin molecule present in serum samples. After incubation, unbound substances are washed off followed by addition of biotinylated detection antibody and then streptavidin-conjugated horseradish peroxidase (HRP). Color developed when substrate solution was added; the reaction was later stopped with a sulfuric or hydrochloric acid solution. Absorbance read at 450 nm in a microplate reader. Concentrations will be calculated by comparing their absorbance values to that of a standard curve made from known quantities of recombinant osteocalcin. All assays were done per the instructions provided by the manufacturer; internal standards and duplicates were

used as part of quality control to ensure accuracy and precision of the assay.

MEASUREMENT OF SCLEROSTIN

Sclerostin levels in serum were measured using a commercial Enzyme Linked Immuno Sorbent Assay (ELISA) kit from Humacount, Germany, which was performed according to the instructions of the manufacturer. Blood samples were taken under standardized conditions in the morning after an overnight fast to minimize circadian effects on hormone levels. The collected blood was allowed to stand at room temperature and then centrifuged for 10 minutes at 3000 rpm to obtain serum. In order to keep protein integrity, aliquoted serum samples were stored at -80°C until analysis and not thawed more than once. Humacount's sclerostin ELISA uses sandwich immunoset microplate wells pre-coated with monoclonal human sclerostin-specific antibody. All sclerostin present in the samples binds to capture antibody after addition of sample onto plate wells. Then a biotin-linked second antibody against another epitope of sclerostin is added followed by streptavidin-HRP conjugate. Incubation followed by washing to remove unbound substances is done. A chromogenic substrate (usually TMB) is added which gives color that is proportional to the amount of sclerostin in the sample. An acidic stop solution halts the reaction and absorbance measured at 450 nm using a microplate reader that has been calibrated. Calculations involved were based on a standard curve obtained from known concentrations of recombinant human sclerostin, with each sample run in duplicate under conditions where both intra- and inter-assay coefficients of variation were kept under 10% so as to ensure high reproducibility as well as accuracy for the assay.

STATISTICAL ANALYSIS

The data was analyzed using SPSS Statistics software, version 26.0 (SPSS, Chicago). Normality of parametric data was checked using the Kolmogorov-Smirnov test. Those data which showed normal distribution have been expressed as mean $\pm$ standard deviation and were subjected to independent t-test for comparison in studied markers (sclerostin, osteocalcin and TSH). The predictive ability of sclerostin in predicting relapses among patients with PCOS can be tested by applying the area under the curve (AUC) test. Statistical significance was set at a P-value <0.05 .

ETHICS APPROVAL

The protocol in this study was approved by the ethical committee of the College of Medicine in the University of Baghdad (No. 232 in 2025).

CONSENT TO PARTICIPATE

Before collection of samples, the patients involved in the protocol were asked to write a consent for their participation

RESULTS

In the current study, age comparison between patients with PCOS and controls showed no significant difference in age distribution ($P=0.86$), the largest group among patients

Table 1. Frequency and percentage of demographic data for patients (PCOS) and control groups

Items	Rating	Patients N=66		Control N=34		Chi Square (P-value)
Age		Freq.	[%]	Freq.	[%]	0.72(0.86) NS
	25-34	11	20	12	32.5	
	35-44	10	35.71	9	42.5	
	45-54	8	22.86	6	10	
	55-64	5	21.43	7	15	
Mean ± SD 48.27 ± 18.55						
BMI	Normal	14	37.14	18	5	11.55(0.009)
	Overweight	24	31.43	10	70	
	Obese	16	25.71	4	20	
	Over Obese	12	5.71	2	5	

NS: Non-Significant at $P>0.05$

Source: Own materials

Table 2. Serum levels of osteocalcin and TSH in in patients with PCOS

Items	Patients N=66		Control N=34		T-Test (P-value)
	Mean	SD	Mean	SD	
Osteocalcin (ng/ml)	3.7	1.2	5.2	2.2	4.42(0.000) HS
TSH mIU/L	6.3	1.3	3.4	0.8	5.63 (0.000) HS

SD: Standard Deviation, HS: High Significant at $P<0.01$

Source: Own materials

being 35-44 years (35.71%) and the same group among controls at 42.5%, anyhow ruling out age as a confounding factor, the mean age was (48.27 $\pm$ 18.55). On the other hand, a marked difference was noted in the categories of body mass index (BMI) ($P=0.009$), where 31.43% of patients with PCOS were classified as overweight and 25.71% were obese, compared to just 10% and 20% in the control group, respectively; these results give evidence for increased prevalence of raised BMI in PCOS patients, giving further evidence to an already well-documented link between obesity and the actual pathology of PCOS (Table 1).

Serum biomarkers analysis shows mean serum osteocalcin levels to be markedly lower in PCOS patients (3.7 $\pm$ 1.2 ng/mL) compared to controls (5.2 $\pm$ 2.2 ng/mL), which thus turned out to be highly significant ($P=0.000$). Mean serum levels of thyroid-stimulating hormone (μ IU/mL) were significantly elevated in the PCOS group (6.3 $\pm$ 1.3 μ IU/mL) as compared to the control group (3.4 $\pm$ 0.8 μ IU/mL), P -value also being highly significant (0.000). It can therefore be implied that PCOS is related with altered bone turnover and thyroid function, possibly contributing other endocrine and metabolic dissociations typically found in such individuals (Table 2).

The results above show a statistically significant difference between serum sclerostin levels in women with PCOS and healthy controls. Mean sclerostin concentration in the PCOS group was 12.5 $\pm$ 4.8 ng/ml, much higher than that of the control group, which had a mean of 4.8 $\pm$ 2.4 ng/ml. The

difference was highly significant with t-test value = 9.02 and p -value = 0.000 indicating strong evidence against the null hypothesis; it suggests raised sclerostin levels could be associated with PCOS and thus possibly used as a diagnostic biomarker or indicator of pathophysiological involvement (Fig. 1).

From the Pearson correlation analysis, a statistically significant moderate negative correlation was seen between osteocalcin and sclerostin ($r=-0.458$, $P=0.039$) which implies that as osteocalcin levels go decreased, sclerostin associated with it increases. On the other hand, TSH exhibited a weak positive correlation ($r=0.234$) which was not significant statistically ($P=0.06$), thereby implying no meaningful linear association in this case. These results underscore the possible applicability of osteocalcin as a more sensitive biomarker in the context under study (Table 3).

The biomarker sclerostin has moderate levels of diagnostic capability for polycystic ovary syndrome (PCOS) with an area under the curve of 0.76 which therefore means that it has fairly good ability to discriminate between those with and without the condition. The statistically significant p -value of 0.045 adds further weight to the credibility of the findings. At a cut-off point of 4.9, sclerostin shows a sensitivity of 79% and specificity of 62%, meaning that it probably detects true positives better than it does true negatives. These results potentially place sclerostin in useful waters as a supportive biomarker when running

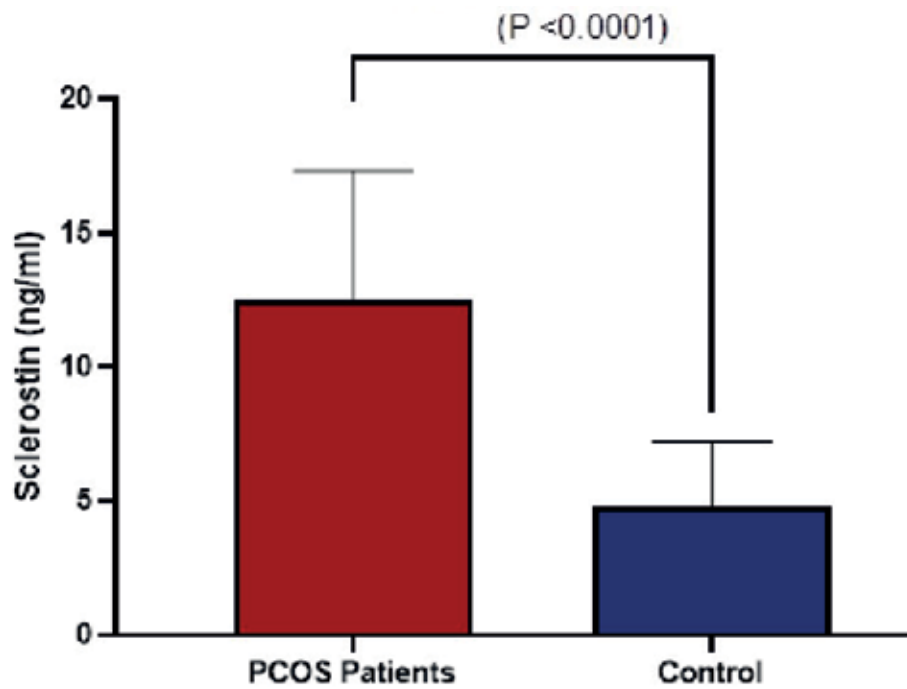


Fig. 1. Differences in serum sclerostin (ng/mL) levels between PCOS patients and healthy groups

Source: Own materials

Table 3. Correlation between sclerostin and other markers

Biomarker	r	P-value	Sig.
Osteocalcin (ng/ml)	-0.458	0.039	S
TSH (mIU/L)	0.234	0.06	NS

S: Significant at $P < 0.05$, NS: Non-Significant at $P > 0.05$

Source: Own materials

Table 4. Sensitivity and specificity of sclerostin for the diagnosis of OP

Biomarkers	(AUC)	Sig. P-value	Cut-off Point	Sensitivity (%)	Specificity (%)
Sclerostin	0.76	0.045	4.9	0.79	0.62

AUC: Area Under the Curve

Source: Own materials

diagnostics for PCOS but real tests in bigger cohorts are needed to nail down its clinical use (Table 4 and Fig. 2).

DISCUSSION

The present study highlights the association between elevated circulating sclerostin levels and polycystic ovary syndrome (PCOS), emphasizing its potential role at the intersection of bone and thyroid metabolism. Emerging evidence increasingly recognizes sclerostin, a potent inhibitor of bone formation, as a key biomarker in PCOS pathophysiology, particularly through its links with metabolic status and bone remodeling dynamics. Multiple studies have reported elevated sclerostin levels in women with PCOS, especially in the context of higher

body mass index (BMI). For instance, Bertizlioğlu et al. (2023) conducted a cross-sectional study and identified a significant positive correlation between serum sclerostin and BMI, waist, and hip circumference, suggesting that adiposity could stimulate sclerostin expression in PCOS patients [13]. Complementing these findings, Wyskida et al. (2020) reported higher sclerostin concentrations among obese PCOS patients and those with insulin resistance, while notably finding no association with classic hormonal disturbances. This implies that sclerostin levels in PCOS may be predominantly modulated by metabolic rather than endocrine factors [14]. However, contrasting data have been reported. Bilen et al. (2022) did not detect significant differences in sclerostin levels between PCOS patients and

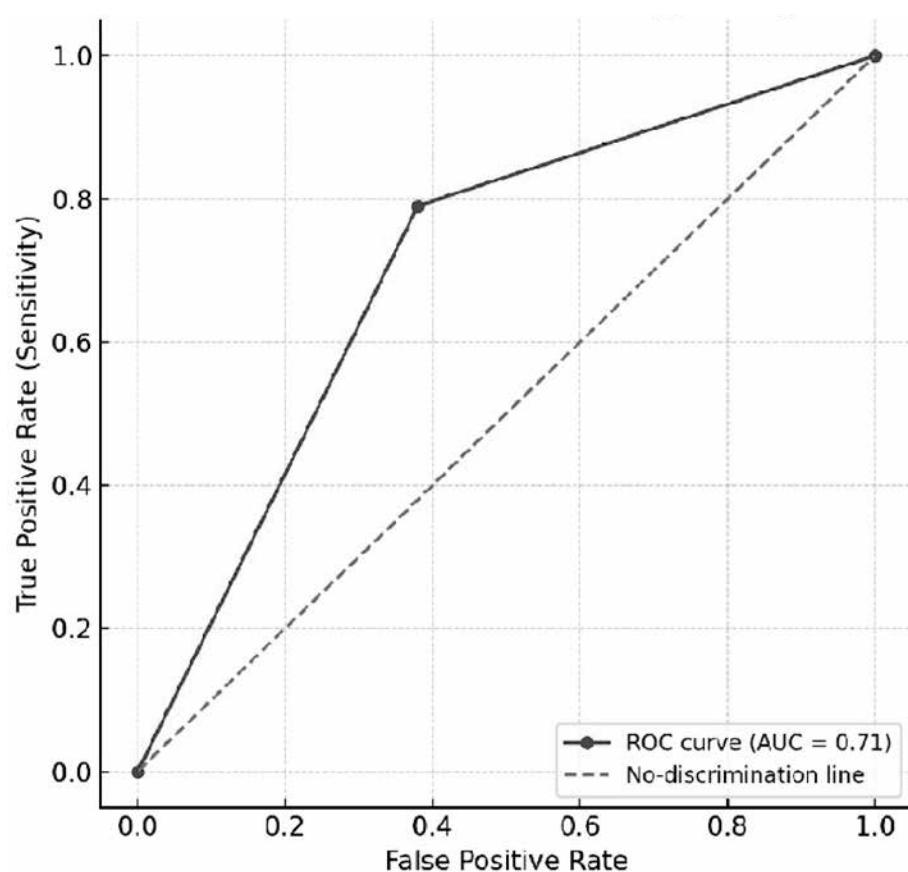


Fig. 2. ROC curve for sclerostin in the diagnosis of PCOS

Source: Own materials

healthy controls, despite higher mean BMI among the PCOS group. These discrepancies could reflect differences in study design, population characteristics, or unmeasured confounding factors [15]. Furthermore, Çintesun et al. (2021) demonstrated higher sclerostin levels in PCOS patients across phenotypes compared to controls; however, the study did not establish a clear relationship between sclerostin and subclinical atherosclerosis, underscoring the complexity of sclerostin's systemic roles beyond bone metabolism [16]. The current study's observation of a significant moderate negative correlation between osteocalcin and sclerostin ($r = -0.458$, $P = 0.039$) aligns with sclerostin's established inhibitory function on bone formation. Osteocalcin, a marker of osteoblastic activity, is expected to inversely relate to sclerostin levels, reflecting the balance between bone formation and inhibition. Regarding thyroid metabolism, the study found a weak positive correlation between sclerostin and thyroid-stimulating hormone (TSH) ($r = 0.234$). Thyroid hormones critically regulate bone turnover, and the interplay among TSH, sclerostin, and osteocalcin represents an area of growing interest. Mihaljević et al. reported that hyperthyroid patients exhibited significantly higher serum sclerostin and osteocalcin levels and lower TSH, while hypothyroid patients showed reduced sclerostin and elevated TSH, suggesting that thyroid status may directly or indirectly influence bone metabolism through sclerostin

modulation [17]. Similarly, Rija et al. (2021) corroborated these associations, observing increased sclerostin and decreased osteocalcin in hyperthyroid patients, whereas hypothyroid patients displayed elevated TSH and sclerostin but reduced osteocalcin, reinforcing the notion of TSH's suppressive influence on bone turnover [18]. Further mechanistic insights come from Zygmunt et al. (2021), who investigated recombinant human TSH administration in post-thyroidectomy patients. They documented that TSH elevation was associated with significant decreases in both sclerostin and osteocalcin ($r = -0.672$ and -0.405 , respectively), indicating a potential inhibitory role of TSH on bone metabolism independent of thyroid hormone levels [19]. Bjerkreim et al. also found an inverse relationship between TSH and osteocalcin ($\rho = -0.24$, $p < 0.05$) in hypothyroid patients under substitution therapy, supporting the hypothesis that TSH itself may directly modulate bone turnover [20]. Collectively, these findings suggest that sclerostin acts as an integrative marker at the intersection of metabolic status, bone remodeling, and thyroid function in PCOS. The observed correlations reinforce the relevance of including sclerostin, along with osteocalcin and TSH, in assessing bone health risk in PCOS patients, particularly given the complex interplay among adiposity, endocrine factors, and bone metabolism. Future studies with larger cohorts and mechanistic designs are warranted to clarify

causality and therapeutic implications, potentially guiding individualized interventions to mitigate fracture risk in women with PCOS.

CONCLUSIONS

Findings highlight that sclerostin is much raised in women with PCOS and could well be a useful biomarker of the syndrome's effects on bone and thyroid metabolism. Its moderate diagnostic performance however, further

researches on its role in the pathophysiology of PCOS are needed.

ABBREVIATIONS

PCOS:	Polycystic Ovarian Syndrome
TSH:	Thyroid-Stimulating Hormone
BMI:	Body Mass Index
BMD:	Bone Mineral Density
HRP:	Horseradish Peroxidase

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CONFLICT OF INTEREST

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The impact of extreme conditions of service activities on the functional and psycho-emotional state of law enforcement officers

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ABSTRACT

Aim: The aim is to study the impact of extreme conditions of service activities of varying intensity during martial law on the dynamics of indicators of the functional and psycho-emotional state of law enforcement officers.

Materials and Methods: The research, which was conducted in 2022-2024, involved 227 male police officers with different service experience (up to 3 years n=52, 4-5 years n=59, 6-10 years n=56, over 10 years n=60). Indicators of the functional and psycho-emotional state of law enforcement officers were assessed before and after their tours of duty of different duration (3 and 6 months) to the combat zone using the following indicators: body mass index (BMI), vital index (VI), double product index (DPI), emotional state index (ESI), psychological state index (PSI)

Results: The deterioration of indicators of the functional and psycho-emotional state of law enforcement officers with different professional experiences during tours of duty of different durations (intensity) was revealed. The difference between the BMI indicators before and after a tour of duty lasting 3 and 6 months is 0.34-0.93 and 1.09-1.61 kg/m², VI indicators 1.63-2.49 and 2.27-2.84 ml/kg, DPI indicators 2.26-2.94 and 3.07-3.42 c.u., ESI indicators 0.78-0.59 and 1.16-0.93 points, DPI indicators 2.26-2.94 and 3.07-3.42 c.u., PSI indicators 13.50-9.94 and 18.16-13.09 points, respectively

Conclusions: It was found that the longer the duration of the tour of duty, the more pronounced negative changes occurred in the studied indicators. The negative impact of extreme conditions of service activities on the dynamics of indicators of the functional and psycho-emotional state of law enforcement officers was proved

KEY WORDS: law enforcement officers, functional state, martial law, psycho-emotional state, extreme conditions

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INTRODUCTION

During martial law, which was introduced in connection with the invasion of our country by the Russian aggressor, almost all state institutions have changed their powers, competencies, rights and obligations, policies, and procedures. The National Police is no exception, and the service activities of law enforcement officers, which are multifunctional, responsible, involve a risk to the life and health of law enforcement officers and are accompanied by several negative factors, are recognized by many scholars [1, 2] as extreme. With the introduction of martial law in Ukraine, the range of tasks and powers of law enforcement officers has significantly expanded, which has further increased the level of extremity of the conditions of service activities of law enforcement officers [3, 4].

According to scientists [5, 6], law enforcement officers' service activities in extreme conditions are constantly accompanied by significant psycho-emotional tension, professional stress and risk, and psychological trauma. The stressful nature of law enforcement officers' activities and the negative determinants of their service under martial law inevitably lead to the emergence of a negative phenomenon

– emotional burnout. The consequence of their activities in extreme conditions of constant exposure to stress factors is the loss of positive professional motivation, the manifestation of various neurotic reactions, and mental and physical health disorders [7, 8]. According to experts [9, 10], under the principle of feedback, this problem can lead to poor quality of performance of operational and service tasks, the possibility of law enforcement officers being injured and wounded, and sometimes even killed. Therefore, the study of indicators of law enforcement officers' functional and psycho-emotional state in extreme conditions of service activities of varying intensity during martial law is relevant.

AIM

The aim is to study the impact of extreme conditions of service activities of varying intensity during martial law on the dynamics of indicators of the functional and psycho-emotional state of law enforcement officers.

MATERIALS AND METHODS

The research, which was conducted in 2022-2024 at Odesa State University of Internal Affairs (Odesa, Ukraine)

ra National Academy of Internal Affairs (Kyiv, Ukraine), involved 227 male police officers with different service experience (up to 3 years – $n = 52$ (special rank – lieutenant – captain), 4-5 years – $n = 59$ (special rank – senior lieutenant – captain), 6-10 years – $n = 56$ (special rank – captain – major), over 10 years – $n = 60$ (special rank – major – colonel)). Indicators of the functional and psycho-emotional state of law enforcement officers were assessed before and after their tours of duty of different duration (3 and 6 months) to the combat zone using the following indicators: body mass index, vital index, double product index, emotional state index, psychological state index.

Research methods: analysis and generalization of literature sources, medical and biological methods, methods of psychodiagnostic, biostatistical methods. The body mass index (BMI) was determined by the ratio of body weight to body length squared, the vital index (VI) by the ratio of lung capacity to body weight, and the double product index (DPI) by the product of blood pressure and pulse. Indicators of the functional state of law enforcement officers were determined by medical staff in the academies' clinics.

The emotional state index (ESI) was determined by the method referred to as "Self-Assessment of Emotional State" on a ten-point scale, as the arithmetic mean of four indicators determined by law enforcement officers according to the following sets of statements (scales): "Resilience-anxiety", "Vigor-fatigue", "Elation-depression", "Self-confidence-helplessness". If the ESI was in the range of 8-10 points, it was interpreted as very good; 6-7 points – good; 4-5 points – poor; 1-3 points – bad. The psychological state index (PSI) was assessed using the "Scaled Self-Assessment of Psychological State". Law enforcement officers were asked to assess various characteristics of their state at the time of the examination, marking the appropriate place on the scales: well-being, proactive attitude, mood,

working capacity, and self-confidence. The assessment was performed on a 100-point scale. Scores from 1 to 20 points corresponded to a low level of psychophysiological state; from 21 to 40 points – below average; from 41 to 60 points – average; from 61 to 80 points – above average; from 81 to 100 points – high.

The biostatistical methods were used to process the data obtained. The compliance of the sample data distribution with the Gauss' law was assessed using the Shapiro-Wilk W test. All the data had a normal distribution, and therefore a Student's t-test was chosen to check the reliability of the difference in the comparison groups. The reliability of the difference was set at $p < 0.05$. All statistical analyses were performed using SPSS software, version 10.0, adapted for medical and biological research. The procedure for organizing the study and the topic of the article were previously agreed with the committee on compliance with Academic Integrity and Ethics of the Odesa State University of Internal Affairs. Also this study followed the regulations of the World Medical Association Declaration of Helsinki. Informed consent was received from all participants who took part in this study.

RESULTS

The analysis of the dynamics of the BMI shows that its value tends to deteriorate in the course of service activities of law enforcement officers with different professional experiences during their tours of duty lasting both 3 and 6 months. However, a more pronounced and reliable ($p < 0.05-0.01$) deterioration in the BMI was found in law enforcement officers of all study groups after a 6-month tour of duty (Table 1).

The difference between the indicators before and after a tour of duty lasting 3 months is 0.34, 0.48, 0.75 and 0.93 kg/m², respectively, in law enforcement officers

Table 1. Dynamics of the BMI in law enforcement officers before and after their tours of duty of different intensity (Mean $\pm$ m, $n=227$, kg/m²)

Groups of law enforcement officers with different experience	n	Stages of the research		Reliability of the difference	
		Before the tour of duty	After the tour of duty	The difference	t; p
Tour of duty lasting 3 months					
up to 3 years	27	24.85±0.35	25.19±0.38	0.34	0.74; >0.05
4-5 years	31	25.12±0.36	25.60±0.37	0.48	0.93; >0.05
6-10 years	29	24.93±0.33	25.68±0.36	0.75	1.54; >0.05
over 10 years	34	24.79±0.31	25.72±0.34	0.93	2.02; <0.05
Tour of duty lasting 6 months					
up to 3 years	25	24.94±0.37	26.03±0.38	1.09	2.06; <0.05
4-5 years	28	24.76±0.35	26.11±0.37	1.35	2.65; <0.05
6-10 years	27	24.81±0.36	26.23±0.38	1.42	2.71; <0.05
over 10 years	26	24.88±0.36	26.49±0.35	1.61	3.21; <0.01

Legend: n – sample size; Mean – arithmetic mean; m – standard error; t – Student's t-test value; p – p-value

Source: compiled by the authors of this study

with experience up to 3 years, 4-5 years, 6-10 years and over 10 years. However, significant changes are observed only in law enforcement officers with experience over 10 years ($p < 0.05$). But after a tour of duty lasting 6 months, BMI indicators significantly ($p < 0.05-0.01$) worsened in all studied groups of law enforcement officers. The difference between the indicators before and after a tour of duty lasting 6 months is 1.09, 1.35, 1.42 and 1.61 kg/m², respectively, in law enforcement officers with experience up to 3 years, 4-5 years, 6-10 years and over 10 years. It has also been found that law enforcement officers with more professional experience (over 10 years) have the largest difference between pre- and post-tour indicators (the amount of weight gain is the largest). This is because the vast majority of law enforcement officers in this group performed special tasks at headquarters and command posts in managerial positions, which is associated with their low motor activity, performing tasks in a sitting position, under time pressure, and high nervous tension.

The research revealed a significant ($p < 0.05$) deterioration in the VI of law enforcement officers of all study groups (except for law enforcement officers with up to 3 years of experience after a 3-month tour of duty) both after a 3-month tour of duty to the combat zone and after a 6-month tour (Table 2).

It has been established that after a 6-month tour of duty, changes in the indicators of the VI in law enforcement officers of all groups are more negatively expressed compared to those after a 3-month tour of duty. The difference between the VI indicators before and after a tour of duty lasting 6 months is 2.27, 2.65, 2.51 and 2.84 ml/kg, respectively, in law enforcement officers with experience up to 3 years, 4-5 years, 6-10 years and over 10 years. This indicates that with an increase in the duration of a tour of duty to the combat zone (with an increase in its intensity), extreme conditions

of service activities have a more negative impact on the state of the respiratory system of law enforcement officers. The most pronounced changes in the VI indicators were found in law enforcement officers with 6-10 years and over 10 years of experience, which indicates a decrease in the body's resistance to the effects of negative factors of service activities with age, and therefore with increasing experience.

A similar trend to the VI is observed in the analysis of the dynamics of the DPI indicators, which characterizes the functional state of the cardiovascular system of law enforcement officers. An increase in the index shows a deterioration in the functional state of this system. Thus, after a tour of duty of different duration, there was a significant ($p < 0.05$) deterioration in the DPI indicators in law enforcement officers of all groups. However, the negative changes are more pronounced after a 6-month tour of duty compared to the indicators after a 3-month tour (Table 3).

The difference between the DPI indicators before and after a tour of duty lasting 3 months is 2.56, 2.52, 2.73 and 2.94 c.u., respectively, in law enforcement officers with experience up to 3 years, 4-5 years, 6-10 years and over 10 years. The difference between the indicators before and after a tour of duty lasting 6 months increased to 3.07, 2.93, 3.17 and 3.42 c.u., respectively, in law enforcement officers with experience up to 3 years, 4-5 years, 6-10 years and over 10 years. Among the studied groups of law enforcement officers, the worst values of the DPI after returning from tours of duty of different intensities were found in the group with more than 10 years of experience, which confirms our previous findings regarding this category of law enforcement officers. The results also confirmed the conclusion that with the increase in the duration of the tour of duty, there is a more pronounced deterioration in the functional state of the cardiovascular system in law enforcement officers with any experience.

Table 2. Dynamics of the VI in law enforcement officers before and after their tours of duty of different intensity (Mean $\pm$ m, n=227, ml/kg)

Groups of law enforcement officers with different experience	n	Stages of the research		Reliability of the difference	
		Before the tour of duty	After the tour of duty	The difference	t; p
Tour of duty lasting 3 months					
up to 3 years	27	56.72±0.79	55.09±0.81	1.63	1.44; >0.05
4-5 years	31	56.35±0.75	54.17±0.78	2.18	2.01; <0.05
6-10 years	29	56.41±0.77	54.06±0.79	2.35	2.13; <0.05
over 10 years	34	56.17±0.73	53.68±0.76	2.49	2.36; <0.05
Tour of duty lasting 6 months					
up to 3 years	25	57.08±0.74	54.81±0.76	2.27	2.14; <0.05
4-5 years	28	56.57±0.72	53.92±0.75	2.65	2.55; <0.05
6-10 years	27	56.22±0.73	53.71±0.76	2.51	2.38; <0.05
over 10 years	26	56.11±0.75	53.27±0.77	2.84	2.64; <0.05

Legend: n – sample size; Mean – arithmetic mean; m – standard error; t – Student's t-test value; p – p-value

Source: compiled by the authors of this study

Table 3. Dynamics of the DPI in law enforcement officers before and after their tours of duty of different intensity (Mean $\pm$ m, n=227, c.u.)

Groups of law enforcement officers with different experience	n	Stages of the research		Reliability of the difference	
		Before the tour of duty	After the tour of duty	The difference	t; p
Tour of duty lasting 3 months					
up to 3 years	27	89.03±0.89	91.59±0.87	2.56	2.06; <0.05
4-5 years	31	90.56±0.85	93.08±0.86	2.52	2.02; <0.05
6-10 years	29	90.84±0.90	93.57±0.92	2.73	2.12; <0.05
over 10 years	34	91.15±0.86	94.09±0.88	2.94	2.39; <0.05
Tour of duty lasting 6 months					
up to 3 years	25	88.76±0.78	91.83±0.80	3.07	2.75; <0.05
4-5 years	28	89.21±0.81	93.14±0.83	2.93	2.53; <0.05
6-10 years	27	90.19±0.85	93.36±0.84	3.17	2.65; <0.05
over 10 years	26	91.46±0.88	94.88±0.87	3.42	2.76; <0.05

Legend: n – sample size; Mean – arithmetic mean; m – standard error; t – Student's t-test value; p – p-value

Source: compiled by the authors of this study

The analysis of the ESI showed that before the tour of duty for 3 and 6 months, the emotional state of law enforcement officers of all study groups was at a good level. During the performance of tasks in extreme conditions of service activities, the ESI deteriorated significantly ($p < 0.05-0.01$), but more pronounced negative changes occurred in law enforcement officers after a 6-month tour of duty (Table 4). At the same time, after returning from a tour of duty, all the studied groups of law enforcement officers assessed their ESI as worsened.

The difference between the ESI indicators before and after a tour of duty lasting 3 months is 0.78, 0.67, 0.68 and 0.59 points, respectively, in law enforcement officers with

experience up to 3 years, 4-5 years, 6-10 years and over 10 years. But the difference between the ESI indicators before and after a tour of duty lasting 6 months increased to 1.16, 1.05, 1.03 and 0.93 points, respectively, in law enforcement officers with experience up to 3 years, 4-5 years, 6-10 years and over 10 years. It was also found that the less experience law enforcement officers have in their professional activities, the more pronounced negative changes occurred in the ESI indicators. This is due to the insufficient psychological adaptation of law enforcement officers with little professional experience (up to 3 and 4-5 years) to the extreme conditions of work during a tour of duty to the combat zone.

Table 4. Dynamics of the ESI in law enforcement officers before and after their tours of duty of different intensity (Mean $\pm$ m, n=227, points)

Groups of law enforcement officers with different experience	n	Stages of the research		Reliability of the difference	
		Before the tour of duty	After the tour of duty	The difference	t; p
Tour of duty lasting 3 months					
up to 3 years	27	6.31±0.22	5.53±0.23	0.78	2.45; <0.05
4-5 years	31	6.45±0.20	5.78±0.21	0.67	2.31; <0.05
6-10 years	29	6.37±0.21	5.69±0.22	0.68	2.24; <0.05
over 10 years	34	6.24±0.19	5.65±0.21	0.59	2.08; <0.05
Tour of duty lasting 6 months					
up to 3 years	25	6.25±0.23	5.09±0.24	1.16	3.49; <0.01
up to 5 years	28	6.56±0.22	5.51±0.23	1.05	3.30; <0.01
up to 10 years	27	6.49±0.23	5.46±0.22	1.03	3.24; <0.01
over 10 years	26	6.61±0.24	5.58±0.23	0.93	2.80; <0.05

Legend: n – sample size; Mean – arithmetic mean; m – standard error; t – Student's t-test value; p – p-value

Source: compiled by the authors of this study

Table 5. Dynamics of the PCI in law enforcement officers before and after their tours of duty of different intensity (Mean±m, n=227, points)

Groups of law enforcement officers with different experience	n	Stages of the research		Reliability of the difference	
		Before the tour of duty	After the tour of duty	The difference	t; p
Tour of duty lasting 3 months					
up to 3 years	27	49.16±2.38	35.66±2.47	13.50	3.94; <0.001
4-5 years	31	51.55±2.27	39.15±2.36	12.40	3.79; <0.001
6-10 years	29	50.24±2.31	39.28±2.40	10.96	3.79; <0.01
over 10 years	34	49.63±2.29	38.69±2.38	9.94	3.01; <0.01
Tour of duty lasting 6 months					
up to 3 years	25	52.33±2.42	34.17±2.49	18.16	5.23; <0.001
up to 5 years	28	51.86±2.34	37.27±2.39	14.59	4.36; <0.001
up to 10 years	27	51.05±2.38	37.81±2.43	13.24	3.89; <0.001
over 10 years	26	50.74±2.41	37.65±2.48	13.09	3.79; <0.01

Legend: n – sample size; Mean – arithmetic mean; m – standard error; t – Student's t-test value; p – p-value

Source: compiled by the authors of this study

The PCI indicators also have a significant ($p < 0.01-0.001$) negative trend during tours of duty of different intensity in all studied groups of law enforcement officers, but after a 6-month tour of duty, more pronounced negative changes are observed (Table 5). At the same time, law enforcement officers with less professional experience have a more pronounced deterioration in their psychological state than those with more experience.

The difference between the PCI indicators before and after a tour of duty lasting 3 months is 13.50, 12.40, 10.96 and 9.94 points, respectively, in law enforcement officers with experience up to 3 years, 4-5 years, 6-10 years and over 10 years. The difference between the indicators before and after a tour of duty lasting 6 months increased to 18.16, 14.59, 13.24 and 13.09 points, respectively, in law enforcement officers with experience up to 3 years, 4-5 years, 6-10 years and over 10 years. This indicates more pronounced psychological signs of stress and a lower level of stress resistance in law enforcement officers of this category. It should be added that law enforcement officers of all study groups had an average level of PSI before tours of duty of varying intensity, and afterward, it dropped to below average. All this confirms the negative impact of extreme conditions of service activities during martial law on the psycho-emotional state of law enforcement officers.

DISCUSSION

Martial law is a special legal regime introduced in the event of armed aggression or threat of attack, a threat to Ukraine's independence and territorial integrity, and provides for the granting of the relevant state authorities, military command, and local self-government bodies with the powers necessary to avert the threat and ensure national security [11]. As our results demonstrate, the period of martial law, hostilities, and potential threats negatively

affect the course of official activities of authorized subjects, which is accompanied by changes in their functional and emotional state, and can lead to serious psychological and somatic problems.

Among the powers of the National Police of Ukraine, which have been significantly expanded during the period of martial law, experts [12, 13] identify the following: escorting persons detained on suspicion of committing a criminal offense, taken into custody, accused or sentenced to imprisonment, as well as guarding them in the courtroom; apprehension in temporary detention centers in cases provided for by law of persons detained for committing criminal or administrative offenses; persons subject to a preventive measure of detention; persons subject to administrative arrest; accused and convicted persons; carrying out demining of an operational nature (detection, neutralization and destruction of explosive devices); application of coercive measures to persons participating in the armed aggression against Ukraine without taking into account certain restrictions and prohibitions defined by law (in particular, it is allowed to apply coercive measures without warning, strike with special means without restrictions on the location of their application, as well as the use of firearms) and many others. As stated by I. Cieślak, A. Kielan, D. Olejniczak, K. Prontenko with colleagues, performing tasks in extreme conditions of service activities during martial law for a long time causes somatic changes and chronic stress in law enforcement officers, which can negatively affect their physical and mental health [14, 15]. This trend is confirmed by our research, as a more pronounced and significant deterioration in personal indicators was found in law enforcement officers of all studied groups with a longer period of tour to the combat zone (duration 6 months).

Y. K. Cheung, J. C. Li, N. Magnavita with colleagues [16, 17] have revealed the negative impact of chronic stress on the health of law enforcement officers, the quality of their

performance of official duties, relationships with colleagues and family, etc. Given this, we found that the less experience of professional activity of law enforcement officers, the more they are exposed to stressful situations, which is reflected both at the personal (physiological, cognitive, emotional), and at the functional and everyday levels. This is due to the insufficient psychological adaptation of law enforcement officers with little experience of professional activity (up to 3 and 4-5 years) to the extreme conditions of service and combat activity. As for changes in functional status (body mass index, double product index, etc.), as rightly noted by B. Qi, Y. K. Wu, A. Bisson Desrochers et al. [18, 19], law enforcement officers are in a state of high professional stress, and therefore are at risk of mental health disorders and various physiological manifestations (eating disorders, cardiological symptoms, etc.).

Our research expands and supplements the findings of many scientists [20-22] regarding the negative impact of extreme conditions of service activities during martial law of varying intensity on the functional and psycho-emotional state of law enforcement officers with different professional experiences. First of all, the service activities of law enforcement officers in wartime conditions radically change their usual way of life, making significant adjustments to the psycho-emotional background of work and life. At the same time, in the presence of systematic crisis states in the personality of a law enforcement officer, increased anxiety, fear, a sense of helplessness and loss of control over the situation may be observed. This requires the development of effective methods and programs of psychotherapeutic support for specialists experiencing war stress and traumatic events.

CONCLUSIONS

The negative impact of extreme conditions of service activities of varying intensity during martial law on the dynamics of indicators of the functional and psycho-emotional state of law enforcement officers was proved. The deterioration of indicators of the functional and

psycho-emotional state of law enforcement officers with different professional experiences during their tours of duty of different durations (intensity) for all studied indices was revealed. It was found that the longer the duration of the tour of duty, the more pronounced negative changes occurred in the studied indicators of law enforcement officers. The difference between the BMI indicators before and after a tour of duty lasting 3 and 6 months is 0.34-0.93 and 1.09-1.61 kg/m², VI indicators – 1.63-2.49 and 2.27-2.84 ml/kg, DPI indicators – 2.26-2.94 and 3.07-3.42 c.u., ESI indicators – 0.78-0.59 and 1.16-0.93 points, DPI indicators – 2.26-2.94 and 3.07-3.42 c.u., PSI indicators – 13.50-9.94 and 18.16-13.09 points, respectively. Such severity of functional and psycho-emotional exhaustion contributes to the development of inadequate emotional reactions, reduced interaction with colleagues, reduced quality of professional tasks, etc.

Depending on the experience of service activities, the worst indicators of the functional state after returning from a tour of duty were found in law enforcement officers with up to and over 10 years of experience, and the worst indicators of the psycho-emotional state – in law enforcement officers with up to 3 and 4-5 years of experience. This is due to the low amount of motor activity, performing tasks in a sitting position by law enforcement officers with more experience in managerial positions at headquarters and command posts, and insufficient stress resistance and adaptation to extreme conditions of activity by law enforcement officers with little experience in professional activities. The results of the research make it necessary to substantiate the methodology for maintaining and restoring the functional and psycho-emotional state of law enforcement officers in the course of their service activities in extreme conditions during martial law.

Prospects for further research are to study the impact of extreme conditions of service activities of varying intensity under martial law on the dynamics of indicators of the functional and psycho-emotional state of female law enforcement officers.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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Legal status of ayurveda in the healthcare system

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ABSTRACT

Aim: To determine the legal status of Ayurveda within traditional healthcare systems, to assess the regulatory classification of Ayurvedic medicinal products, and to identify and evaluate the potential health risks and benefits associated with the use of non-conventional treatment methods, with a particular focus on Ayurveda.

Materials and Methods: Based on an extensive review of literature, international and national regulatory documents, scientific studies, and expert opinions, this article offers guidance for understanding the influence of Ayurveda and traditional systems on the current concept of patient rights and freedoms in healthcare. The research is grounded in dialectical, comparative, analytical, synthetic, and comprehensive methodologies. A total of 302 PubMed-indexed articles on Ayurveda published in the past five years were analysed. It was concluded that the majority of positive assessments of Ayurveda came from researchers of Indian ethnic origin. The article also draws attention to the aggressive marketing of Ayurveda's implementation across Europe. The most significant research has been conducted in the last five years. The research used keywords such as Ayurveda, Ayurvedic products, Ayurvedic remedies, and Phytopreparations.

Conclusions: The study concludes that there is a pressing need to harmonise the Indian Pharmacopoeia with the Pharmacopoeias of the USA and the EU, as well as to further integrate Ayurveda into the framework of modern evidence-based medicine. The role of the World Health Organization in standardising Ayurveda and in defining core knowledge requirements for Ayurvedic practitioners is also discussed.

KEY WORDS: Ayurveda, Ayurvedic products, Ayurvedic remedies, herbal medicines, physician corruption

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INTRODUCTION

Ayurveda is a traditional Indian therapeutic concept that promotes a holistic approach to health through restoring balance within the body. It incorporates a wide range of practices – including personalised dietary regimens and herbal formulations – aimed at maintaining and improving health, spiritual well-being, and treating diseases. In many countries, Ayurvedic products are gaining increasing significance as part of complementary and alternative medicine systems [1].

However, the legal and regulatory attitudes toward Ayurveda as a form of healthcare – and consequently toward Ayurvedic products – vary widely across countries. These range from full legal recognition of Ayurveda alongside conventional medicine, to complete prohibition of its practice and exclusion of any reimbursement by national health insurance systems. The World Health Organization (WHO) recognises Ayurveda as one of the most widely used traditional health resources globally [2].

Remarkably, as early as 1978, WHO acknowledged the role of traditional, complementary, and alternative medicine systems in both developing and developed countries under the slogan “Health for All.” Later, this issue was further

addressed in WHO's Global Strategy on Traditional Medicine, covering various aspects such as herbal cultivation, product manufacturing, dosing, and official guidance [3].

In countries like India and Sri Lanka, Ayurvedic medicine is recognised and regulated by the state on par with conventional medicine. It is also an officially acknowledged component of healthcare in other South Asian countries, such as Nepal, the Maldives, and Bangladesh [4].

In contrast, Germany adopts a cautious stance regarding Ayurvedic products. According to the Federal Institute for Drugs and Medical Devices (BfArM), Ayurvedic items may be marketed as dietary supplements, detox products, teas, spices, drinks, herbs, and aromatic oils, often based on plant, animal, or mineral ingredients. These may be sold either as medicinal products (upon obtaining legal classification) or as food supplements. Notably, safety assessment is mandatory only for medicinal products, not for food supplements. No Ayurvedic remedy has been approved as a drug in Germany to date [5].

BfArM highlights the challenges in assessing these products, noting that data on their potential pharmacological effects are often lacking. In some cases, toxic substances or strong pharmacological agents may be intentionally added.

If a product is classified as a food supplement, authorities must assess whether it constitutes a dangerous food or misleading product [6].

Additionally, BfArM underscores that manufacturers and regional regulatory bodies often face difficulties in distinguishing legitimate medicinal products from the diverse and inconsistent range of Ayurvedic items available on the market [1]. Furthermore, considering India's ambitions to introduce Ayurvedic drugs worldwide, BfArM stresses the need for these products to meet established scientific and regulatory standards.

This approach is partly rooted in the Directive 2004/24/EC of the European Parliament and Council, which amended Directive 2001/83/EC concerning traditional herbal medicinal products [7]. The initial version of the directive, adopted in 2004, significantly limited the sale of herbal medicines throughout Europe and severely constrained the practice of Ayurveda across the continent.

Herbal medicinal products fall under the scope of Directive 2001/83/EC, which requires that any medicinal product marketed must obtain authorisation based on demonstrated quality, safety, and efficacy. The directive introduced a simplified registration process and a formal definition of traditional herbal medicines.

This regulatory change sparked concern in India, both from scientific and commercial standpoints. However, the full implications of these changes appear to be insufficiently addressed. Ayurvedic professionals expressed emotional opposition to the restrictions, but systematic and strategic responses have been lacking.

This raises important questions: Is the restriction justified? Should the EU include Ayurveda under its recognised complementary and alternative medicine practices? Or is this more of a trade barrier than a science-based decision? Although these concerns have been voiced, they may not have reached the appropriate policy-making levels.

As a result, most Ayurvedic products were banned in the EU as of 1 May 2011. Nevertheless, some countries like Germany and France stated that the EU directive would not harm their national regulatory frameworks [8].

In Ukraine, Ayurvedic products not officially registered as medicinal products are typically sold as dietary supplements or cosmetics, including via pharmacies. De jure, the use of Ayurveda in Ukraine is considered a form of folk healing rather than official medicine.

In contrast, in the United States, the practice of Ayurveda is legal and unregulated across all 50 states, but must comply with state-specific laws. Practitioners are advised to familiarise themselves with the relevant legal frameworks of their specific states [9].

For example, the California Association of Ayurvedic Medicine (CAAM) was founded in 1998. With the establishment of the first state-approved Ayurvedic educational institution in California – the first of its kind in the U.S. – it became clear that Ayurveda was on the path toward legal recognition as a professional practice. This development brought with it responsibilities such as defining educational standards, ethical values, and public trust in the viability of Ayurveda.

CAAM promotes Ayurveda on a local, state, and global level through training, events, and professional collaboration [10].

However, in the U.S., the FDA regulates Ayurvedic products as dietary supplements. Controversies have arisen due to heavy metals (e.g. lead, mercury) found in some preparations. In contrast, the EU applies stricter safety and quality regulations. The harmonisation of Ayurveda with modern regulatory frameworks remains a significant challenge [11].

Thus, national regulations governing the application of Ayurvedic medicine vary significantly from country to country, yet there remain serious legal barriers to both the use of Ayurvedic products and the professional practice of Indian Ayurvedic physicians, particularly those seeking to operate within Europe.

In this context, it is important to analyse the potential risks for patients associated with the use of Ayurvedic remedies and the provision of medical services by Ayurvedic practitioners. Furthermore, this paper will examine the reasons behind the divergent regulatory approaches to Ayurveda across different countries – especially in terms of the acceptance of Ayurvedic therapies as legitimate components of healthcare systems.

AIM

The objective of this article is to determine the legal status of Ayurveda within traditional healthcare systems, to assess the regulatory classification of Ayurvedic medicinal products, and to identify and evaluate the potential health risks and benefits associated with the use of non-conventional treatment methods, with a particular focus on Ayurveda.

MATERIALS AND METHODS

Based on an extensive review of literature, international and national regulatory documents, scientific studies, and expert opinions, this article offers guidance for understanding the influence of Ayurveda and traditional systems on the current concept of patient rights and freedoms in healthcare. The research is grounded in dialectical, comparative, analytical, synthetic, and comprehensive methodologies. A total of 302 PubMed-indexed articles on Ayurveda published in the past five years were analysed. It was concluded that the majority of positive assessments of Ayurveda came from researchers of Indian ethnic origin. The article also draws attention to the aggressive marketing of Ayurveda's implementation across Europe. The most significant research has been conducted in the last five years. The research used keywords such as Ayurveda, Ayurvedic products, Ayurvedic remedies, and Phytopreparations.

ETHICS

A citation agreement was obtained from the copyright holder.

FRAMEWORK

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REVIEW AND DISCUSSION

In South-East Asia, Ayurvedic medicines are a central component of the multimodal therapeutic model, particularly in outpatient settings. These products are prescribed in various formulations with notable regional variations. In practice, Ayurvedic practitioners – including physicians and psychotherapists – often select specific remedies based on individual school traditions or clinical presentations [1].

Given Ayurveda's growing popularity in certain countries [12], the World Health Organization (WHO) between 2019 and 2022 developed a standardised terminology for Ayurveda, including a glossary of English-language terms commonly used in Ayurvedic training and clinical practice [13].

Furthermore, in 2022, WHO published the “Benchmarks for Training in Ayurveda”, establishing core knowledge requirements for individuals involved in Ayurvedic practice or education. These benchmarks address issues related to clinical safety, the preparation of Ayurvedic formulations, and serve as a guidance document for national regulatory authorities aiming to establish or strengthen standards for qualified Ayurvedic education and practice. This initiative aligns with the WHO Traditional Medicine Strategy 2014–2023 and reflects a consensus among practitioners, policymakers, educators, and regulators [14].

India has also taken steps to standardise Ayurvedic pharmaceuticals through the creation of the Ayurvedic Pharmacopoeia of India, which outlines quality, purity, and efficacy standards for selected formulations produced and distributed nationwide. The first volume of the Ayurvedic Formulary of India was published in 1978 [15].

Despite these efforts, Ayurveda does not always lead to positive patient outcomes, and concerns remain regarding the toxicity of certain products due to heavy metal content. In the United States, a study analysing 252 Ayurvedic formulations found lead in 65%, mercury in 38%, and arsenic in 32% of the samples. Nearly half of the mercury-positive samples, 36% of those containing lead, and 39% of those with arsenic exceeded safe daily intake limits by several orders of magnitude [16].

In Germany, the Federal Consumer Association (Verbraucherzentrale) has warned that imported Ayurvedic products often contain lead, mercury, arsenic, tin, and iron – some of which are added intentionally through traditional processing (e.g., *rasa* or *rasaushadhi* methods). Reports from the Bavarian State Office for Health and Food Safety confirm these findings, with one analysis revealing toxic heavy metals in 60% of samples, including arsenic levels up to 49,000 times and mercury levels up to 7,800 times above safe thresholds [17].

In May 2022, *Arznei-telegramm* reported a case of severe lead poisoning in a 24-year-old man in Cologne after consuming an Ayurvedic dietary supplement that had been recommended for general health support [18]. According to the report, the man presented to the emergency department in Cologne with complaints of general malaise, cramping abdominal pain, anemia, and a pale-grey complexion. A previous inpatient examination did not yield a diagnosis. Upon further inquiry, the patient

revealed that he had been taking an Ayurvedic remedy for a month, recommended to him as generally beneficial for health. The product, which originated from India, was found to contain a toxic level of lead.

A similar case occurred in Canada and was published in the *Canadian Medical Association Journal* in August 2023 [19], highlighting that lead poisoning remains a serious issue, especially as it is becoming increasingly difficult to detect. In earlier times, lead poisoning was more common and its causes more obvious, such as lead pipes. During the investigation, the patient stated that she had been taking Ayurvedic products daily for over a year to treat infertility. Her regimen varied from a few to a dozen pills per day. She had stopped taking them prior to hospitalization due to abdominal pain but resumed use after discharge. Her blood lead level was found to be 55 µg/dL (normal < 2 µg/dL). Occupational and environmental exposure histories did not identify any other potential sources of lead.

In light of these cases, experts from the medical association highlighted the following key points:

The use of Ayurvedic products is relatively widespread; such medicines may be contaminated with lead and other heavy metals.

Clinicians should consider lead toxicity in patients with microcytic anemia of unknown cause, especially if basophilic stippling is present, or in patients presenting with abdominal pain, headache, fatigue, new or worsening cognitive impairment, and a suspicious exposure history.

Elevated blood lead levels confirm the diagnosis of lead toxicity.

Clinicians should notify public health agencies to identify and remove lead-contaminated Ayurvedic products from the market.

According to the U.S. Centers for Disease Control and Prevention, Ayurvedic products may contain herbs, minerals, metals, or animal-derived substances and are manufactured in both standardized and non-standardized formulations [20].

To assess the health deterioration or presence of improvement after the use of Ayurvedic products, we reviewed a substantial number of scientific publications, particularly 302 articles from the PubMed database over the past five years. We highlight several of them here [21–30].

Interestingly, Ayurveda as a method of treating diseases is viewed positively primarily by authors who are specialists of Indian origin. Negative experiences with Ayurvedic treatments are virtually absent in the works of Indian professionals.

However, we came across an article written by Indian specialists in which the possibility of contamination of certain herbal medicinal products with heavy metals is acknowledged, although not as a systemic practice in these remedies but as accidental contamination [31]. Another author, in earlier studies, acknowledges that controlled clinical trials are considered the highest level of evidence. Ayurveda significantly lags in the number and quality of randomized controlled clinical trials and systematic reviews in the field of scientific evidence [32].

An analysis of articles over the past five years dedicated to Ayurveda shows that this method of treatment is most widely used among patients in the United States and European countries in cases of hard-to-treat or incurable diseases. This primarily includes oncology, diabetes, and others.

Some EU researchers point out that even in countries where doctors can legally practice Ayurveda, treatment is usually not covered by national health systems and must be paid for by the patients themselves or through additional private insurance. Currently, complementary and alternative medicine (CAM) in general is under pressure in the EU. Homeopathy in particular faces the critical issue of whether active ingredients and their effectiveness can be measured. By comparison, Ayurveda, as an allopathic medicine, has clear advantages since its forms of therapy (such as manual, phytopharmacological, and nutritional therapy) are visible [33].

Meanwhile, in the EU, market inspections by official food safety authorities have repeatedly identified excessive levels of heavy metals in dietary supplements, as reported in the materials of the European Rapid Alert System for Food and Feed (RASFF) [34]. As a result, in 2023, Commission Regulation (EU) 2023/915 was introduced, which established maximum levels for certain contaminants in food products [35].

Despite large-scale preventive efforts and strict regulations, in 2011–2012 the New York City Department of Health and Mental Hygiene investigated six cases of lead poisoning related to the use of ten oral Ayurvedic products manufactured in India. Blood lead levels (BLL) ranged from 16 to 64 µg/dL. The lead concentration in the products reached 2.4%; some products also contained mercury or arsenic, which can also adversely affect health [36].

Thus, although the Indian government seeks to promote Ayurveda internationally as a holistic therapeutic concept, the evidence for the effectiveness of Ayurvedic treatments is generally not very reliable. Therefore, some researchers advise avoiding Ayurvedic treatment and recommend that diagnoses be made by qualified physicians of conventional medical practices [5]. Meanwhile, Indian researchers claim that Ayurvedic treatment methods have been criticized for several reasons. Firstly, some pharmaceutical companies produce falsified and improperly labeled drugs, and secondly, some doctors engage in illegal Ayurvedic practice [37]. Specialists also claim that one-fifth of Ayurvedic medicines, both of American and Indian manufacture, purchased online, contain lead, mercury, or arsenic in significant amounts. Among metal-containing products, 95% were sold through U.S. websites, and 75% claimed compliance with good manufacturing practices. All metal-containing products exceeded one or more standards for acceptable daily intake of toxic metals [38].

However, in the context of EU countries, experts assert that Ayurveda fills a gap in the European healthcare system, which is why patient demand for Ayurvedic treatments is only increasing. However, it requires quality training for Ayurvedic medical professionals and the admission of safe Ayurvedic products to the pharmaceutical market [33].

The European Ayurveda Association (EUAA) is actively promoting Ayurveda in Europe. It is an umbrella organization (founded in 2006) that supports Ayurvedic professionals and promotes Ayurveda to the public in Europe. It is a registered non-governmental organization that is politically, economically, and religiously independent. The organization conducts exclusively and directly non-profit activities and is registered and based in Germany [39].

It is important to note that some Ayurvedic methods are recognized in European countries, particularly Ayurvedic massage, phytotherapy, and dietetics. Specifically, state regulations for Ayurvedic therapists in the fields of massage, dietetics, and phytotherapy have been established in Austria, Switzerland, Italy, and Portugal. These regulations vary by country and govern the activities of Ayurveda graduates who seek to work in the paramedical field with Ayurveda, open their own centers and/or officially conduct Ayurvedic therapy under the supervision of a medical professional [33]. An analysis of various websites allows us to conclude that Ayurvedic treatment in Europe typically takes place through wellness procedures, massage, and fitness activities in hotels and at resorts [40].

For example, in France, Ayurveda is present in dietetics, wellness massage, and yoga [41–43].

Despite the clear distinction between Ayurvedic products as medicinal products and dietary supplements, it is possible to confidently assert that violations of national legislation occur in some European countries.

For example, a Polish-language online store aimed at Polish consumers sells Ayurvedic products advertised as intended for treatment. For instance, one such product is Cold Balm Balsam, among others, which are presented as treatments for various diseases, starting with the common cold [44]. However, the server address is located in India. A similar situation is observed in Ukraine, where Ayurvedic products are sold through online stores, and according to their instructions, they are also intended for treatment. One example is the product Fah Talai Jone (*Andrographis paniculata*). Other products are also intended for therapeutic purposes [45]. Furthermore, a social media survey of 248 individuals revealed that in 78 cases, certain doctors unofficially recommended various types of Ayurvedic products for treating different diseases through specific online stores.

However, for example, in Germany, an analysis of several websites confirmed the absence of violations of European legislation. The products sold through various online stores or internet pharmacies have a clear legal status without misleading advertisements that would indicate disease treatment when the product is categorized as herbal tea or a dietary supplement [46].

There is another hidden risk associated with the recommendation of Ayurvedic products by medical professionals, not directly related to patients' health. In some cases, such actions by physicians may bear signs of corruption. This occurs when the promotion of Ayurveda is tied to arrangements between doctors and product manufacturers or distributors. The latter may pay medical

professionals additional money to promote their products. In such cases, doctors may receive direct payments for each patient who purchases an Ayurvedic product or gain other benefits, privileges, and services for promoting these products (e.g., expenses for attending conferences, travel, or gifts provided by the manufacturer/distributor). Such cases are known as «marketing agreements» and, according to legislation such as that in Germany, are classified as corruption offenses. Ukraine is currently moving toward establishing criminal liability for such actions.

Moreover, a recommendation from a physician to purchase Ayurvedic products for treatment is often perceived by the patient as a medical recommendation, even though it may be nothing more than hidden advertising. As a result, the patient's treatment proves ineffective, money is spent, and the doctor receives an indirect benefit – namely, that the patient keeps returning to them.

CONCLUSIONS

Despite the widespread use of Ayurveda as a method of treatment among patients worldwide, as well as the broad distribution of Ayurvedic products, it must be acknowledged that there is a significant body of evidence indicating serious health consequences associated with the use of Ayurvedic

products. Existing cases of treatment with Ayurveda are insufficient to confirm its overall effectiveness. In some instances, physicians' recommendations of such products may carry signs of corruption, which indicates the necessity of a legal prohibition on promoting Ayurvedic products where marketing agreements exist between the physician and the manufacturer/distributor.

At the same time, it must be recognized that in certain cases, the negative consequences of Ayurvedic treatment result from improperly labeled products, illegal or unauthorized practice of Ayurveda, and poor harmonization of Ayurvedic practice with conventional medicine. This highlights the need for adapting Ayurveda in line with modern conventional medicine. It may also be appropriate to propose the revision of the Indian Pharmacopoeia to align it with the European Pharmacopoeia and the United States Pharmacopoeia.

The distribution of Ayurvedic products in the U.S. and European markets should only be carried out either through the procedure of recognition as medicinal products under proper regulation or by recognizing them as dietary or food supplements, including herbal teas, etc.

It is also necessary to establish control over online stores that attempt to sell Ayurvedic products in certain European countries outside of official regulatory frameworks.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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Adverse Childhood Experiences and the psychopathogenesis of chronic pain: A narrative review

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ABSTRACT

Aim: To explore the influence of Adverse Childhood Experiences (ACEs), including abuse, neglect, and household dysfunction, on the development and persistence of chronic pain in adulthood. The review emphasizes psychopathogenetic and biopsychosocial mechanisms that mediate the relationship between early trauma and chronic pain syndromes.

Materials and Methods: This narrative review synthesizes data from 42 peer-reviewed clinical and experimental studies published between 1998 and 2025. Literature was retrieved from PubMed, Scopus, Web of Science, Google Scholar, ScienceDirect, and SpringerLink using keywords such as “childhood trauma,” “chronic pain,” “neurobiology of pain,” and “central sensitization.” Inclusion criteria focused on full-text articles addressing neuroendocrine, emotional, and behavioral consequences of ACEs. Special attention was given to mechanisms involving chronic stress, emotional dysregulation, altered pain perception, and maladaptive coping strategies.

Conclusions: ACEs are significant contributors to the psychopathogenesis of chronic pain. They disrupt neurobiological regulation, intensify emotional vulnerability, and alter pain processing pathways. The biopsychosocial model provides a comprehensive framework for understanding these interactions. Trauma-informed care and targeted education – centered on emotional awareness and conscious pain regulation – are essential for improving treatment outcomes and promoting holistic recovery. Recognizing the long-term impact of ACEs is vital for developing effective rehabilitation strategies and empowering affected individuals.

KEY WORDS: childhood trauma, chronic pain, emotional regulation

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INTRODUCTION

Chronic pain remains one of the most widespread and debilitating health conditions globally. Despite its prevalence, the complex interplay of biological, psychological, and social factors continues to challenge our understanding of its origins and persistence. One increasingly recognized influence is early-life adversity, commonly framed as Adverse Childhood Experiences (ACEs), which include abuse, neglect, and household dysfunction during formative years [1, 2].

Emerging evidence links ACEs with heightened vulnerability to chronic pain experienced later in life. Systematic reviews and meta-analyses report that exposure to even a single ACE increases the odds of adult chronic pain by approximately 30-50%, with a clear dose-response relationship observed as the number of ACEs rises [2, 3].

Biological pathways implicated in this connection include dysregulated neuroendocrine responses (especially hypothalamic-pituitary-adrenal [HPA] axis alterations), sustained inflammation, and central sensitization leading to hyperalgesia and multisite pain [1].

Neuroimmunological studies reveal that childhood trauma can program long-term changes such as elevated

cortisol levels, microglial activation, and upregulated pro-inflammatory cytokines – each contributing to altered nociceptive processing and lower pain thresholds [1, 4].

Central nervous system alterations are also evident: ACEs disrupt the functional connectivity of regions like the prefrontal cortex, amygdala, and hippocampus, which underlie central sensitization and emotional dysregulation [3-5].

In the psychological sphere, trauma-related cognitive processes such as hypervigilance, catastrophizing, and avoidance behaviors further amplify pain experiences and impede healthy coping. These maladaptive patterns reinforce a cycle of pain and distress, requiring a shift toward trauma-informed approaches in chronic pain treatment [6, 7].

This narrative review surveys the literature connecting ACEs with chronic pain syndromes, focusing on psychophysiological mechanisms and outlining the implications for trauma-informed, biopsychosocial pain management strategies [1, 7, 8].

AIM

To explore the influence of Adverse Childhood Experiences (ACEs), including abuse, neglect, and household dysfunction,

on the development and persistence of chronic pain in adulthood. The review emphasizes psychopathogenetic and biopsychosocial mechanisms that mediate the relationship between early trauma and chronic pain syndromes.

MATERIALS AND METHODS

This narrative review was conducted to explore the relationship between ACEs and the psychopathogenesis of chronic pain, with a focus on neurobiological, psychosocial, and behavioral mechanisms.

A comprehensive literature search was performed using the following databases: PubMed, Scopus, Web of Science, Google Scholar, ScienceDirect, and SpringerLink. The search strategy included combinations of the following English-language keywords: „Adverse Childhood Experiences“, „Chronic Pain“, „Pain Psychopathogenesis“, „Childhood Trauma“, „Neurobiology of Pain“, „Early Life Stress“, „Post-Traumatic Stress Disorder (PTSD) and Pain“, „Central Sensitization“, and „Trauma and Pain“.

The search covered publications from 1998 to September 2025, beginning with the foundational ACE study by Felitti et al. (1998) [9] and extending to the most recent peer-reviewed literature available.

The studies were selected based on the following inclusion criteria: peer-reviewed articles including original research, systematic reviews, meta-analyses, and narrative reviews; empirical or theoretical relevance to the link between ACEs and chronic pain; and coverage of biological, psychological, or social mechanisms underlying pain development in the context of early trauma. We excluded editorials, commentaries, conference abstracts without full text, as well as studies unrelated to ACEs or chronic pain.

The initial search yielded over 120 publications. After screening for relevance, quality, and accessibility, 42 articles were included in the final review.

ETHICS

Publicly available sources (reviewed articles, clinical guidelines, databases) were used. No patient-identifying data were used, and no primary data collection was performed. ICMJE and Helsinki Declaration standards were followed. All sources were properly cited; plagiarism and data fabrication were excluded.

REVIEW AND DISCUSSION

DEFINITION AND CLASSIFICATION OF ACEs

ACEs refer to various forms of trauma and chronic stress experienced before the age of 18, which has long-term effects on health and well-being. The original ACE study by Felitti et al. (1998) classified these experiences into three major domains: abuse, neglect, and household dysfunction [9]. These domains remain the foundation of ACE categorization in current research and clinical frameworks.

CORE ACE CATEGORIES:

- **Abuse:**
 - *Physical abuse*: intentional infliction of physical harm by a caregiver;

- *Emotional (psychological) abuse*: verbal threats, humiliation, or intimidation;
- *Sexual abuse*: any sexual contact or behavior imposed on a child;

- **Neglect:**

- *Physical neglect*: failure to provide basic physical needs such as food, shelter, or medical care;
- *Emotional neglect*: lack of emotional support, love, or attention;

- **Household dysfunction:**

- Exposure to domestic violence (e.g., one parent abusing another);
- Parental substance use or alcohol dependence;
- Mental illness in a parent or caregiver;
- Parental separation, divorce, or incarceration.

These categories have been validated across numerous international studies and are associated with cumulative effects on neurodevelopment, immune system functioning, and long-term psychosocial outcomes (Hughes et al., 2017; Merrick et al., 2019) [10, 11].

For example, in a large population study, Bellis et al. (2014) demonstrated that individuals with four or more ACEs were significantly more likely to experience chronic physical pain, substance dependence, and depressive disorders in adulthood compared to those with none [12]. Similarly, the CDC-Kaiser ACE Study showed a strong dose-response relationship between the number of ACEs and the risk of developing a wide array of chronic illnesses, including chronic pain syndromes (Felitti et al., 1998) [9].

Expanding on these traditional categories, contemporary frameworks now consider broader traumatic exposures such as community violence, peer victimization, and experiences of discrimination or poverty as *expanded ACEs* or *social adversities* (Cronholm et al., 2015; Wade et al., 2016) [13, 14]. These additions help contextualize ACEs in populations disproportionately exposed to structural or conflict-related trauma, including war-affected individuals [15, 16].

In the context of this review, understanding the classification and breadth of ACEs is crucial to identifying mechanisms that predispose individuals to chronic pain disorders and to designing trauma-informed interventions targeting both emotional and physiological dimensions of suffering [17, 18].

EPIDEMIOLOGICAL EVIDENCE LINKING ACEs TO CHRONIC PAIN

Recent epidemiological studies robustly associate ACEs with chronic pain. Individuals with ≥ 4 ACEs exhibit significantly elevated odds of developing conditions such as fibromyalgia, irritable bowel syndrome (IBS), and musculoskeletal pain [15–18]. A meta-analysis by Nicolson et al. (2023) reported a 2,7-fold increased risk of chronic pain among those with high ACE exposure [19].

More recent data reinforce this link. Namely, Bussi eres et al. (2023) conducted a meta-analysis (23 studies, $n \approx 826$ k) and found that cumulative ACE exposure increases the odds of adult chronic pain, with adjusted odds ratio

(OR) escalating from 1,29 for one ACE to 1,95 for four or more ACEs [2].

Recent large-scale cross-sectional studies provide compelling evidence of a dose-dependent association between ACEs and chronic pain across different age groups and populations [20].

Luo et al. (2024), analysing data from 9,923 Chinese adults in the China Health and Retirement Longitudinal Study (CHARLS), found that individuals with ≥ 5 ACEs had significantly higher odds of reporting pain at both single and multiple sites [21]. Most individual ACE indicators were associated with elevated risk for specific pain complaints (e.g. neck pain, back pain), and the association remained consistent regardless of physical activity levels, sex, education, or socioeconomic status.

Similarly, Groenewald et al. (2020) conducted a nationally representative study of 48,567 U.S. children aged 6-17 and found that those with ACE exposure had a markedly higher prevalence of chronic pain (8.7% vs. 4.8%). The odds of chronic pain increased with the number of ACEs (adjusted OR: 2.7 for ≥ 4 ACEs) [22]. Financial hardship, living with a mentally ill adult, and racial discrimination were among the strongest individual predictors.

Together, these studies underscore a robust, cumulative relationship between early-life adversity and the risk of chronic pain. This association is evident from childhood through late adulthood and appears independent of modifiable lifestyle or demographic factors. Together, these studies underscore a robust, cumulative relationship between early-life adversity and the risk of chronic pain. This association is evident from childhood through late adulthood and appears independent of modifiable lifestyle or demographic factors.

MILITARY POPULATIONS AND THE ACE-PAIN CONNECTION

The association between ACEs and chronic pain is particularly pronounced in military and veteran populations, who often report elevated exposure to both childhood and service-related trauma. Blossnich et al. (2014) [23], analyzing U.S. adult data ($n=10\,540$), found that 34% of individuals with chronic musculoskeletal pain had ≥ 4 ACEs, with an OR of 2,2 (95% confidence interval [CI]: 1,9-2,6), underscoring a strong cumulative risk.

Complementing these findings, Williamson et al. (2022) examined ACEs and military-specific adversities among 750 female Army veterans in the UK. A large proportion reported exposure to at least one ACE, most commonly emotional and physical abuse [24]. These early-life adversities were significantly associated with increased symptoms of PTSD in adulthood, as well as increased vulnerability to emotional bullying, sexual harassment, and assault during military service.

Together, these findings reinforce the need to assess ACE exposure as part of comprehensive clinical assessments in both general and military populations. Trauma-informed interventions should consider not only current psychosocial stressors but also the developmental origins of chronic pain vulnerability.

ADDITIONAL META-ANALYTIC EVIDENCE SUPPORTING THE ACE-PAIN LINK

Recent large-scale meta-analyses further substantiate the relationship between adverse childhood experiences and chronic pain outcomes. Bussi res et al. (2023) highlighted that specific forms of abuse – namely physical, sexual, and emotional – demonstrated significant associations with adult pain-related disability, with adjusted ORs ranging from 1,37 to 1,56 [20]. These findings emphasize the differential impact of distinct ACE types on somatic health trajectories in adulthood.

In an even broader review, Dalechek et al. (2024) synthesized findings from 52 studies spanning the last two decades, applying rigorous PRISMA guidelines and quality assessment via the Joanna Briggs Institute tool [26]. This systematic literature review and meta-analysis focused on the triadic relationship between ACEs, anxiety, and chronic pain. Among the studies, 79% demonstrated moderate to strong associations across these variables. Notably, individuals with a history of ACEs were nearly twice as likely to seek treatment for chronic pain in adulthood (OR = 1,99; 95% CI: 1,53-2,60; $p<0,01$).

Regarding the prevalence of specific ACE categories among chronic pain patients, the review reported the following:

- 50% experienced sexual abuse;
- 46% reported physical abuse;
- 33% emotional abuse;
- 25% emotional neglect;
- 23% physical neglect.

Statistical analysis revealed correlations (r) between anxiety and chronic pain ($r=0,30$; 95% CI: 0,14-0,45; $p<0,01$), and between ACEs and anxiety ($r=0,26$; 95% CI: 0,15-0,36; $p<0,01$), indicating that emotional sequelae of early trauma likely mediate or amplify chronic pain perception [26].

However, the authors acknowledged several limitations, including heterogeneity in ACE definitions and chronic pain types, cultural variability in samples, a narrow participant age range (mean age of approximately 44 years), and reliance on retrospective self-reports subject to recall or suppression bias [26]. Nonetheless, the evidence supports a robust interrelation among childhood adversity, emotional distress, and pain outcomes [27].

Finan and Garland (2022) reviewed how ACEs contribute to catastrophizing, hypervigilance, and emotional dysregulation in chronic pain populations. Their narrative review emphasizes the need to integrate trauma-informed strategies into pain treatment protocols [28]. Clinically, the authors recommend routine screening for ACEs in adults presenting with anxiety and chronic pain symptoms. They emphasize the importance of using standardized diagnostic tools for ACEs and psychological distress to enable cross-study comparisons and targeted interventions.

Integration of adversity-informed care could enhance the comprehensiveness and efficacy of chronic pain treatment. This approach may potentially improve long-term health trajectories for vulnerable individuals (Table 1).

Epidemiological data from diverse populations consistently show that higher ACE exposure significantly increases the risk of adult chronic pain. The dose-response

Table 1. Epidemiological Findings on ACEs and Chronic Pain

Study	Sample	Chronic Pain Type	% with ≥ 4 ACEs	OR (95% CI)
Nicolson et al. (2023) [19]	Meta-analysis (23 studies)	Various	~30%	2.7 (2.1-3.4)
Luo et al. (2024) [21]	CHARLS (n = 9923, China)	Body pain (multi-site)	Data not reported	Neck pain OR 1.11 (0.90-1.36); p<0.001 for trend
Bussi�eres et al. (2023) [20]	Meta-analysis (~826 000 adults)	Mixed chronic pain	–	Adjusted OR ~1.45-1.56 for direct ACEs
Blosnich et al. (2014) [23]	U.S. adults, n = 10 540	Musculoskeletal	34%	2.2 (1.9-2.6)
Williamson et al. (2022) [24]	UK female veterans, n = 750	Not specified	High prevalence of ≥1 ACE	– (qualitative associations)

Source: compiled by the authors of this study

effect, with ≥4 ACEs corresponding to nearly doubled odds of pain, underscores the importance of trauma-informed assessment in rehabilitation settings [25–28]. Notably, further large-scale studies and regional military samples (e.g., the Ukrainian cohort) are needed to elucidate the role of early-life trauma in vulnerability to chronic pain.

PSYCHOPATHOGENESIS OF CHRONIC PAIN FOLLOWING ACEs

Accumulating evidence supports a multifactorial model in which ACEs contribute to the long-term development of chronic pain through intertwined neurobiological, psychological, and behavioral mechanisms. These mechanisms operate across the lifespan, shaping both vulnerability and maintenance of pain syndromes.

THE KEY MECHANISMS LINKING ACEs TO CHRONIC PAIN INCLUDE THE FOLLOWING:

HPA Axis Dysregulation: Chronic early stress leads to sustained activation of HPA axis, resulting in prolonged cortisol release and reduced stress resilience. Altered cortisol dynamics interfere with endogenous pain regulation systems and amplify pain perception [19, 25,27-30];

Central Sensitization: Individuals exposed to ACEs often exhibit enhanced nociceptive processing, characterized by lowered pain thresholds and increased spinal cord excitability. These changes reflect central sensitization – a key feature of conditions like fibromyalgia and IBS [31, 32];

Structural and Functional Brain Changes: Neuroimaging studies show ACE-related reductions in grey matter volume in key brain regions such as the amygdala, hippocampus, and prefrontal cortex – areas involved in pain regulation, emotional processing, and threat perception [33-35]. Long-term trauma also alters functional connectivity within pain-related networks, contributing to heightened vigilance and pain catastrophizing [33, 34];

Psychological Comorbidities: ACEs are strongly associated with anxiety, depression, and PTSD, all of which increase chronic pain risk and severity. These conditions impair emotional regulation, promote hyperarousal, and interfere with adaptive coping [32, 36, 37];

Attachment Disturbances and Emotional Dysregulation: Early relational trauma often results in insecure attachment styles, alexithymia, and poor interoceptive awareness. These factors diminish emotional resilience and heighten sensitivity to bodily discomfort [38, 39];

Maladaptive Coping Strategies: Trauma survivors frequently adopt avoidance, hypervigilance, and catastrophizing – psychological processes that reinforce the pain experience and perpetuate distress [32, 36, 37, 40, 41].

Together, these mechanisms form a psychophysiological feedback loop, where disrupted brain-body communication, unresolved emotional trauma, and pain-related disability interact to sustain chronic pain (Table 2).

These findings align with the biopsychosocial and trauma-informed frameworks of chronic pain, which view pain not

Table 2. Neuropsychological Mechanisms Linking ACEs to Chronic Pain

Mechanism	Description	Supporting Evidence
HPA Axis Disruption	Chronic stress alters cortisol levels and pain modulation	[1, 5-7, 29, 33, 36]
Central Sensitization	Increased sensitivity in spinal and cortical pain pathways	[6, 8, 12, 33, 34, 39, 40]
Neuroplastic Changes	Altered brain connectivity and volume in pain-related regions	[4, 6, 8, 33, 34, 39, 40]
Emotional Dysregulation	Anxiety, depression, PTSD interfere with coping and worsen pain	[4, 5, 9, 10, 32, 38, 39]
Maladaptive Coping	Avoidance, hypervigilance, catastrophizing prolong the pain cycle	[32, 36, 37, 40, 41]

Source: compiled by the authors of this study

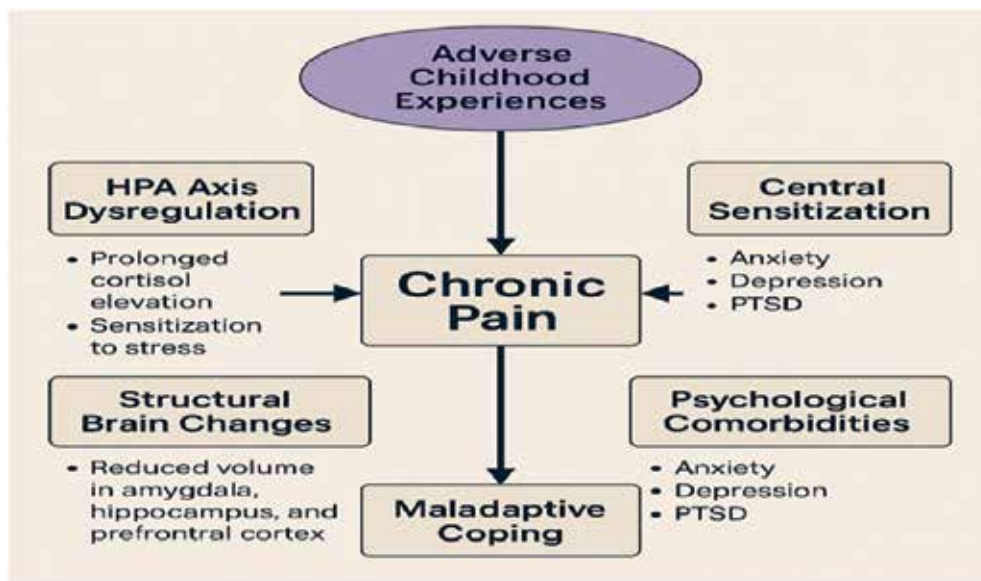


Fig. 1. Pathophysiological and Psychosocial Mechanisms Linking ACEs and Chronic Pain: Foundations for Multidisciplinary Rehabilitation

Picture taken by the authors

only as a physical symptom but also as a complex outcome of early adversity [3, 31], nervous system plasticity [10, 38, 42], and psychological dysregulation [40, 41]. Importantly, many of these mechanisms are modifiable, underscoring the importance of targeted psychological and somatic interventions in pain rehabilitation, particularly for individuals with histories of childhood trauma. Growing evidence indicates that ACEs are a significant risk factor for the development of chronic pain later in life. Fig. 1 illustrates the main psychopathogenetic pathways linking ACEs to persistent pain. Dysregulation of the HPA axis leads to prolonged elevations of cortisol and enhanced stress sensitization, while structural brain changes in the amygdala, hippocampus, and prefrontal cortex impair stress and pain regulation. Central sensitization further amplifies pain perception and exacerbates comorbid conditions such as anxiety, depression, and PTSD. Maladaptive coping strategies reinforce this cycle, creating a multidimensional mechanism through which ACEs shape chronic pain vulnerability [30–38].

TRAUMA-INFORMED PAIN MANAGEMENT

A trauma-informed approach plays a crucial role in addressing chronic pain among individuals with a history of adverse childhood experiences (ACEs) [1–6, 9–12, 19–22, 26–30, 32–36, 40, 41].

This model is grounded in four interrelated principles. First, it requires an in-depth understanding of how traumatic experiences shape neurobiological, psychological, and behavioral pain responses [1, 3, 4, 6, 8, 28, 30–33, 35–42]. Second, it emphasizes recognition of trauma-related symptoms that may complicate clinical presentations [2–5, 10–22, 28, 29, 42]. Third, it calls for an appropriate response, integrating trauma-focused interventions such as Cognitive Behavioral Therapy (CBT), Eye Movement Desensitization and Reprocessing (EMDR), and mindfulness

practices [3, 28, 36, 37, 42]. Finally, the principle of resisting re-traumatization underscores the importance of ensuring safety, building trust, and fostering patient empowerment throughout the therapeutic process [1–6, 9–12, 19–22, 26–30, 32–36, 40, 41].

At the same time, research indicates that not all individuals with a history of ACEs develop persistent dysfunction. Many demonstrate remarkable resilience, drawing on protective resources that buffer against the long-term consequences of trauma [1, 21, 36, 40]. Among the most significant protective factors are stable and supportive relationships with adults, timely access to psychological care, and engagement in psychoeducational or peer-based programs [1–6, 9–12, 19–22, 26–30, 32–36, 40, 41]. These elements enhance adaptive coping, reduce vulnerability to chronic pain, and facilitate more favorable rehabilitation outcomes.

Clinical observations in Ukrainian rehabilitation facilities are consistent with global data on the role of ACEs in chronic pain, but remain inconclusive due to limited local evidence [7, 38]. Evidence from international and military populations further supports the importance of addressing early trauma, psychological dysregulation, and somatic symptoms. These findings highlight the need to integrate trauma-informed biopsychosocial models with physical rehabilitation interventions within multidisciplinary rehabilitation programs, particularly for war-affected populations [7, 23, 24, 27, 38, 42].

The proposed model highlights the multidimensional pathways through which ACEs contribute to the development of chronic pain syndromes. Based on our survey [7, 38], we can assume that adverse early-life circumstances, combined with war-related stressors, may manifest as complex pain syndromes with accompanying psychological comorbidities.

Our previous studies [7, 38] also highlight the potential benefits of incorporating psychophysical components into trauma-informed approaches to rehabilitation and pain management. These insights will inform our future research aimed at developing integrative, multimodal rehabilitation strategies for high-risk populations.

Evidence from health care professionals [7, 38] reflects the broader psychosomatic impact of trauma, particularly when early adversity is exacerbated by war-related stressors. It also illustrates the clinical utility of integrating trauma-informed approaches with physical rehabilitation, using acupuncture and structured physical interventions, alongside educational and social work support, to improve pain outcomes. These findings indicate the need for systematic research.

Building on these observations, our future research will focus on integrating clinical, psychophysiological, and educational interventions into a comprehensive trauma-informed rehabilitation model.

FUTURE DIRECTIONS

Preliminary clinical observations from Ukrainian rehabilitation settings suggest a potential association between ACEs and chronic musculoskeletal pain in military personnel with combat-related injuries. These findings, though not yet systematically investigated, indicate cumulative and interactive effects of early and war-related trauma on pain expression and psychological comorbidities. Future studies should focus on confirming the prevalence

of ACEs in military and veteran populations, examining their associations with anxiety, depression, sleep disturbances, and pain duration, and integrating psychophysiological assessments alongside biomarker research. Particular attention should be paid to personalized rehabilitation strategies, including the use of trauma-informed multimodal interventions, digital health solutions and telemedicine platforms for remote monitoring and support.

Moreover, adaptive clinical trials and artificial intelligence-based analyses may enhance the precision of identifying risk subgroups and predicting rehabilitation outcomes. Ethical considerations such as accessibility, equity of care, and long-term sustainability must also be addressed.

Such research will provide the foundation for evidence-based, multidisciplinary rehabilitation models tailored to the unique needs of populations exposed to both early-life adversity and war-related trauma, with direct implications for clinical practice and national health policy.

CONCLUSIONS

ACEs are significant contributors to the psychopathogenesis of chronic pain. Understanding their long-term effects is crucial for developing trauma-informed care models and rehabilitation strategies. A biopsychosocial perspective enhances the effectiveness of interventions and supports holistic chronic pain management. Additionally, targeted education for individuals with ACEs – focused on emotional awareness and conscious pain regulation – is essential for empowering patients and improving long-term outcomes.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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Modern view on the epidemiology, risk factors, prevention and screening of pseudoexfoliation syndrome in the context of glaucoma prophylaxis

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ABSTRACT

Aim: The analysis of current data on the epidemiology of pseudoexfoliative syndrome (PES) and risk factors for its development, determination of the possibility of early detection of PES through screening to prevent the development of glaucoma.

Materials and Methods: The literature review was carried out using publications indexed in the scientometric databases PubMed and Scopus. A structured search was performed with the use of relevant keywords and their logical combinations, including: prevalence, morbidity, complications, pseudoexfoliation syndrome, glaucoma, pseudoexfoliative glaucoma, vision loss, blindness, risk factors, intraocular pressure, prevention, early diagnosis, differential diagnosis, screening, and others. The review is primarily based on recent studies; however, a significant proportion of earlier publications (dating back to 1997) was deliberately included to provide a historical perspective and to highlight the evolution of scientific knowledge in this field. Totally, 44 sources were analyzed. The analysis employed formal-logical and systemic-complex methods, ensuring a comprehensive and critical synthesis of the available evidence.

Conclusions: Early diagnosis of PES is necessary to prevent the development and progression of pseudoexfoliative glaucoma, which leads to blindness. Therefore, the development of a screening algorithm and its implementation for at-risk patients – people over 50 years old – is relevant. For patients diagnosed with PES, it is important to regularly visit an ophthalmologist to monitor the possible development of glaucoma.

KEY WORDS: pseudoexfoliation syndrome, glaucoma, epidemiology, prevention, screening

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INTRODUCTION

Pseudoexfoliation syndrome (PES) is characterized by the accumulation of abnormal fibrillar-granular protein, known as pseudoexfoliative material (PEM), primarily in the anterior structures of the eye, but also in various other tissues and organs. PES is a widespread systemic age-related disease and the most common cause of secondary open-angle glaucoma, specifically pseudoexfoliative glaucoma (PEG), which leads to rapid vision loss, severe optic neuropathy, and marked increases in intraocular pressure (IOP) [1].

In contrast to PES, exfoliation syndrome (ES) was first described in 1922 by Austrian ophthalmologist A. Elschnig in workers chronically exposed to high temperatures, particularly infrared radiation, such as glassblowers, blacksmiths, and steelworkers. ES is characterized by delamination of the anterior lens capsule, whose epithelial cells are particularly sensitive to heat. ES is largely asymptomatic and does not require treatment. Currently, the so-called 'glassblower's lens' is rare due to improvements in occupational eye protection. PES was first described by Czech ophthalmologist D. Dvorak-Theobald in 1954. Because true exfoliation had already been described, the new condition was termed 'pseudoexfoliation' to reflect its later discovery. ES differs from PES by the absence of fluffy gray-white exfoliative material (EM) on the lens and pupil, and by more distinct

lens capsule delamination. Unlike PES, ES does not increase the risk of glaucoma development [2].

Currently, numerous studies aim to elucidate the interactions of genetic, environmental, and lifestyle factors in the etiology and pathogenesis of PES, contributing to the development of novel preventive and therapeutic strategies. Public health approaches aimed at early detection of PES and PEG through screening may mitigate the socio-economic impact of the disease [3]. Patients diagnosed with PES should undergo regular ophthalmologic examinations to monitor for glaucoma development. For individuals without PES, preventive eye examinations are recommended starting at age 40, and subsequently every 1–2 years after age 65 [4].

AIM

The analysis of current data on the epidemiology of PES and risk factors for its development, determination of the possibility of early detection of PES through screening to prevent the development of glaucoma.

MATERIALS AND METHODS

The literature review was carried out using publications indexed in the scientometric databases PubMed and Scopus. A structured search was performed with the use of relevant keywords and their logical combinations, including: prevalence,

morbidity, complications, pseudoexfoliation syndrome, glaucoma, pseudoexfoliative glaucoma, vision loss, blindness, risk factors, intraocular pressure, prevention, early diagnosis, differential diagnosis, screening, and others. The review is primarily based on recent studies; however, a significant proportion of earlier publications (dating back to 1997) was deliberately included to provide a historical perspective and to highlight the evolution of scientific knowledge in this field. Totally, 44 sources were analyzed. The analysis employed formal-logical and systemic-complex methods, ensuring a comprehensive and critical synthesis of the available evidence.

ETHICAL APPROVAL

This review is based exclusively on the analysis of publicly available scientific evidence from peer-reviewed journals, clinical practice guidelines, and established databases. No patient-identifiable data were used, and no approval from an ethics committee was required, as the study did not involve new clinical interventions or the collection of primary patient data.

The authors confirm adherence to the ethical principles of the World Medical Association's Declaration of Helsinki and to the international standards for medical journal publications, including the recommendations of the International Committee of Medical Journal Editors (ICMJE). The manuscript contains no instances of plagiarism or data fabrication. All sources of information have been accurately cited and properly referenced.

FRAMEWORK

The research was conducted as part of the scientific project «Scientific Rationale for Improving Organizational Principles of the Healthcare System Under Modern Transformational Changes» (state registration number 0123U101432, registration date 03.03.2023).

REVIEW AND DISCUSSION

PES can be found all over the world, its prevalence varies significantly from region to region, but the reason for such significant territorial differences is still unknown. The most common age group at the time of first presentation for PES was the seventh decade of life – 40,89% of patients [5]. The average age of patients with PES was 66,2 years, and the prevalence of PES increased with age (10,1% in the 41-50 age group and 28,8% in the over 81 age group) [6]. In general, worldwide, PES occurs in approximately 10-20% of the population over 50 years of age, with prevalence ranging from 1,5% to 40,9%, in Europe – from 3,6% to 34,2%, in Asia - from 1,5% to 22,1%, in African countries - from 1,5% to 40%. Other data show that the frequency of PES varies from 0,3% to 18% depending not only on the region but also on the examination method [7]. The global prevalence of PES is increasing, with approximately 70 million people living with this condition, and many patients with this condition may be undiagnosed. PES is more common in Finland, Scandinavia, Greece and Turkey, and the difference in rates can be explained by genetic, environmental or unknown factors [8]. In Scandinavian countries, the highest prevalence has been recorded, where

approximately half of open-angle glaucoma cases are associated with PES [9]. It has been reported that in northern Sweden, PES affects every fourth person who reaches the age of 66 [10]. The prevalence of PES in Croatia was 3,6% [11]. In a study conducted in Jordan, the frequency of PES among patients over 50 years of age was 4,9% [12]. The prevalence rate among the population of Pakistan aged 45 and older was 6,45% [13]. In the defined population of the state of Minnesota (USA), the age- and sex-standardized incidence of PES was 25,9 per 100 000 population [14]. The prevalence of PES in the Indian state of Kashmir among individuals aged 49 to 89 years was 26,32% [15]. In Turkey, the prevalence of PES among patients over 40 years old was 5,0% [16]. Thus, it is obvious that the prevalence of PES depends on geographic location, ethnicity, as well as many other factors (environmental, demographic, and genetic).

No differences were found between PES-positive and PES-negative individuals in age- and sex-standardized median life expectancy and all-cause mortality rates [17].

It is worth noting that epidemiological studies conducted in different countries and at various times often lack consistency and are difficult to compare due to the involvement of populations of varying sizes and age-sex structures. On the other hand, this population-based approach to studying PES epidemiology is justified, as the prevalence of PES is different in each population. Thanks to population studies, it is possible to determine the individual needs of the population regarding the diagnosis and treatment of PES, and therefore, resources in this population can be used more effectively [18].

The epidemiological characteristics of PES include age and gender factors. All researchers agree that the prevalence of PES increases with age, although there are exceptions, such as reports of a 27-year-old man [19] and a 28-year-old woman [20] diagnosed with PES, albeit against the background of ocular diseases requiring surgical intervention. The prevalence of PES by gender varies in different regions; however, some researchers report a higher prevalence among men [5, 12, 15, 21]. For example, it has been stated that men were affected more frequently than women (55,2% and 44,8%, respectively).

In addition, PES is commonly observed among patients who have undergone cataract extraction surgery [6]. Overall prevalence is higher among individuals with lower socioeconomic status and retirees [5].

PES is associated with numerous genetic risk variants across different gene loci [22], and the syndrome exhibits a hereditary component [23]. Familial aggregation of PES and PEG indicates a genetic inheritance pattern, although the magnitude of risk varies among populations [24]. However, a purely genetic explanation is unlikely to account for certain characteristics of the disease, such as its progressive course, asymmetric ocular manifestations, age-related onset, and the development of PEG in only a subset of individuals with PES [25]. It appears that the development of PES is influenced by a combination of genetic predisposition and environmental factors; thus, further research into these external influences may improve understanding of PES pathogenesis and inform more effective, targeted therapeutic strategies [7].

Currently, the pathogenetic concept describes PES as an elastic microfibrilopathy, with key factors including transforming growth factor beta-1 (TGF- β 1), oxidative stress, and impaired cellular defense mechanisms [26].

Environmental risk factors include residence in regions with high annual sunlight exposure, proximity to the equator, and higher altitudes. Prolonged outdoor exposure – due to work, leisure, or rural living – may increase risk via excessive ultraviolet (UV) radiation. Even in northern regions with low temperatures, UV exposure can occur due to sunlight reflected from snow or water surfaces [7, 15, 27].

Dietary influences may also play a role. Chronic alcohol consumption and high intake of coffee or tea can elevate homocysteine levels, which may also result from deficiencies in vitamins B6, B12, or folate [8, 28, 29].

Population-based studies indicate that PES and PEG may be associated with systemic conditions, particularly vascular diseases, inguinal hernia, and pelvic organ prolapse in women [30]. Additional reports suggest links between PES and hypertension, hearing loss, and the use of medications for cardiovascular and mental health disorders [16, 31]. Associations with heart failure and age-related macular degeneration further support a potential vascular contribution to the development of PES [31].

Patients with PES are frequently affected by cataracts, the most common type being nuclear sclerosis [15]. Cataracts were diagnosed in 65% of patients with PES [32], and cataract extraction surgery was performed in 25,9% of eyes with PES [5].

One of the serious consequences or complications of PES is recognized to be open-angle glaucoma. Patients with this syndrome have a tenfold higher risk of developing glaucoma compared to those without PES [8]. According to other data, glaucoma occurs 20 times more frequently in patients with PES than in the general population of the same age, which is why PES can be considered a true trigger for glaucoma development [33].

The guidelines of the European Glaucoma Society state that PEG develops in approximately 15-26% of eyes with PES over a five-year period [30]. However, data on the prevalence of PEG among patients with PES vary greatly. The age- and sex-standardized incidence of PEG was reported as 9,9 cases per 100,000 population in India [14]. In a Swedish study, the prevalence of PEG was 2,1% [10]. According to other data, PEG was present in one-quarter of patients, primarily in those with clinically bilateral PES [12].

Among patients with bilateral PES (65,2% of cases), glaucoma was registered in 34,7%, while among patients with unilateral PES, glaucoma was present in 45,0% [34]. Another study reported that PES was predominantly unilateral, with glaucoma detected in one-quarter of the affected eyes [5]. It has been established that the prevalence of glaucoma in patients with PES is 15,3% [35], while other researchers reported PEG in 26% of PES patients aged 59-90 years [36], and even 30,3% in some cases [32].

PEG accounts for 23,6% of all cases of open-angle glaucoma [11]. It is considered the most aggressive form of secondary glaucoma and is difficult to manage. A quarter of PEG

patients are blind in one eye, and 7% are blind in both eyes [33]. The progression of PEG occurs approximately three times faster than that of primary open-angle glaucoma [30].

However, not every patient with PES will inevitably develop glaucoma, and it is impossible to accurately predict which individuals with PES will experience optic nerve damage and, ultimately, vision loss [23].

Knowledge of the characteristic ophthalmologic clinical signs of PES and PEG is essential for early detection. One of the most common manifestations of PES is elevated intraocular pressure (IOP), which is associated with the accumulation of pathological material within ocular structures, thereby disrupting the normal outflow of aqueous humor. In turn, increased IOP may lead to optic nerve damage and the development of glaucoma.

Normotensive fellow eyes of patients with unilateral hypertensive PEG carry a significant risk of glaucomatous damage, which is associated with the level and range of IOP fluctuations [37]. Eyes with PES are approximately six times more likely to exhibit elevated IOP compared to eyes without PES [10], and elevated IOP has been recorded in 9% of patients with PES [35].

At the time of PES diagnosis, elevated IOP and its diurnal fluctuations are usually observed [34], with the range of IOP fluctuations in PES being broader than in primary open-angle glaucoma [8]. Other studies have also confirmed an epidemiological link between PES and elevated IOP [13, 23, 31].

Patients with PES commonly exhibit diurnal IOP fluctuations: higher values in the morning and evening hours (28,8% of eyes) and normal IOP readings during the daytime (71,2% of eyes), which underscores the importance of IOP monitoring [36].

When measuring IOP, higher values (29-34 mmHg) were observed in patients with features of anterior chamber angle blockage (such as angle narrowing or closure, increased pigmentation, and the presence of confluent exfoliative conglomerates) [33].

An important manifestation of ocular pathology is undoubtedly reduced visual acuity. In patients with PES, visual acuity was significantly lower compared to patients without PES [15]. According to another study, mild visual impairment or its complete absence was observed in 70% and 20% of eyes with PES, respectively [5].

For early diagnosis, knowledge of the micro-symptoms of the disease is essential. In particular, an accurate diagnosis of PES can be made by detecting the presence and location of PEM [8]. PEM accumulates on the anterior lens capsule in a characteristic pattern known as the "moth-eaten pupil" due to pigment loss along the pupillary margin, which becomes more visible after pupil dilation [30]. The most common locations of PEM were the pupil (81,01% of eyes) and the iris (19,15%) [5].

Thus, patients with PES represent a high-risk group for vision impairment, primarily due to the development of glaucoma. Glaucoma is a major cause of vision loss in the elderly, making the early identification of such patients crucial for slowing glaucoma progression. Due to the subtle and uneven progression of PES, glaucoma is often diagnosed at an advanced stage [23].

The need for glaucoma screening in the elderly has been discussed for over 40 years, with proposed methods including intraocular pressure measurement, visual field testing, and optic disc evaluation. It was hypothesized that with the use of these early diagnostic techniques combined with effective treatment, significant progress in preventing blindness could be achieved [38].

Fifteen years later, a broader range of laboratory methods became available, including light and electron microscopy, as well as immunohistochemical and molecular-biological approaches. It was emphasized that clinical diagnosis relies on biomicroscopy, biocytology, and laser Tyndallometry [39]. Early forms of PES were found to be more frequently detected than expected in eyes with cataracts. Therefore, alongside biomicroscopy – which remains a valuable tool for early detection – there is a need to refine clinical criteria for the early diagnosis of PES [40].

Currently, to reduce glaucomatous damage in patients with PES, extended evaluation of the anterior segment is recommended to prevent missed early-stage diagnoses [1]. Monitoring the retinal nerve fiber layer (NFL) thickness and the average peripapillary retinal nerve fiber layer (RNFL) thickness in eyes with PES using optical coherence tomography (OCT) may aid in the early detection of eyes at risk of developing PEG [36]. Early identification of retinal damage provides clinically significant information for detecting initial glaucomatous changes in patients with PES [41].

OCT studies have revealed significant thinning of the retinal nerve fiber layer in patients with PES, with even more pronounced thinning in patients with PEG [33]. The diagnostic value of a portable pupillometer for differentiating eyes with PES from healthy controls by measuring pupil diameter was found to be low (sensitivity 14%, specificity 94%) [42]. Diagnostic errors in PES are also reported in pseudophakic patients, which may have significant consequences for future treatment. Therefore, precise attention to the anatomy of the pupillary margins and thorough gonioscopic evaluation of the iridocorneal angle are essential for accurate diagnosis [43].

Ophthalmologists should perform annual examinations of patients with PES and properly inform them, as the risk

of glaucoma development may persist throughout life and increases with age [4, 34, 35]. Due to the increased incidence of cataract and postoperative complications associated with PES, careful preoperative clinical evaluation of patients is necessary to ensure the effectiveness of surgical intervention [15].

Public health strategies aimed at screening for PES and early detection of PEG may be important in alleviating the socio-economic burden of the syndrome, as it has been shown that eye care costs in patients with PEG are 27% higher than in patients with primary open-angle glaucoma due to additional costs for multiple ophthalmological visits, surgical interventions, and treatment of possible complications [3]. The experience of early diagnosis of PES in Sweden has been interesting. It is suggested that the possibility of diagnosing PES by primary care optometrists should be considered to reduce unnecessary referrals to secondary ophthalmology departments and to make wise use of limited health care resources. At the same time, the risk of missing glaucoma in its early stages can be reduced, even in patients with mildly elevated IOP [44].

CONCLUSIONS

An increasing number of individual population studies on the prevalence of PES and its etiological relationship with PEG provide a clearer picture of the global epidemiological process. Recent research has improved understanding of the roles of genetic, environmental, and lifestyle factors in the development of PES, which may contribute to the design of more targeted treatment strategies. Evidence of systemic associations between PES and cardiovascular and cerebrovascular pathologies has grown, and knowledge of the pathophysiology of affected tissues has expanded through analysis of PES composition. Studying the effects of PES on ocular tissues allows for the refinement of diagnostic criteria, optimization of clinical management and treatment regimens, and reduction of surgical complications. However, prevention of PES remains an unresolved issue. Screening of at-risk populations – particularly individuals over 50 years old – remains the primary strategy to prevent the development of pseudoexfoliative glaucoma.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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Cost-benefit analysis of mobile dental clinics in remote areas of Ukraine

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ABSTRACT

Aim: To evaluate the cost–benefit of mobile dental clinics as a strategy to improve access to dental care in Ukraine’s remote rural areas. This review quantifies anticipated costs for equipment and operations against the benefits of expanded service coverage, improved oral health outcomes, and cost savings from prevention.

Materials and Methods: A narrative review was conducted using secondary data from scientific literature and national health reports. Searches were performed in PubMed (Medline) and Scopus for publications from 2010 to 2025, with emphasis on the most recent data. Keywords included “mobile dental clinic cost analysis,” “rural dental care Ukraine,” “dental clinic access disparities,” and “mobile health cost–benefit.” Approximately 60 publications were retrieved; after screening for relevance and quality, 14 key sources were included in the analysis. International case studies and Ukrainian health statistics were compared to evaluate the costs and outcomes of mobile dental units versus fixed dental clinics. No new clinical research was conducted.

Conclusions: Mobile dental clinics are a feasible and cost-effective strategy to reduce urban-rural disparities in oral health. They bring essential care to isolated populations, improve quality of life, and are justified by projected health gains and cost savings. Pilot deployment of mobile dental clinics in high-need areas, integrated with existing referral networks, is recommended as a sustainable approach to improve oral healthcare access in Ukraine.

KEY WORDS: health units, cost-benefit analysis, dental services

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INTRODUCTION

Ukraine faces a significant gap in oral healthcare access between urban centers and remote rural areas [1–3]. The dental disease burden is high: studies report that 98% of Ukrainians have dental problems, and childhood caries rates exceed 70% [2]. Yet dental care resources are concentrated in cities. On average, Ukraine has only about 3,5–4 dentists per 10,000 people, far below Western countries (for comparison, the U.S. has ~6 per 10,000) [2]. Crucially, rural communities are severely underserved: for example, in the Lviv region, only ~10% of licensed dentists practice in rural areas, while ~90% work in cities [2]. Nationally, most private clinics are urban, and “very few fully qualified dentists” serve the countryside [2–3]. Rural dental offices that do exist often lack modern equipment and can provide only basic extractions and emergency care [2]. This urban-rural disparity leaves many village residents with essentially no access to preventive or restorative dental care, contributing to untreated decay, tooth loss, and worsened overall health.

Remote areas of Ukraine – such as the Carpathian highlands in the west and sparsely populated northern provinces – pose particular challenges for dental service delivery. Low population density makes it infeasible to maintain full-time fixed clinics, and poor roads or transportation infrastructure limit villagers’ ability to travel for care [2].

The ongoing conflict has further strained access: in war-affected eastern regions, many clinics have been destroyed or abandoned. Mobile dental units deployed near the front lines have become “really necessary” to treat soldiers and civilians in isolated villages where no regular dentist is available [4].

In these conditions, the introduction of mobile dental clinics – self-contained dental offices on wheels – is proposed as an innovative solution to bridge the access gap. Mobile clinics can travel to remote communities, bringing dentistry directly to underserved populations. Programs in other countries have shown that mobile units can deliver a wide range of treatments (from exams and fillings to extractions) with quality comparable to fixed offices [1]. This article examines the costs and benefits of implementing mobile dental clinics in Ukraine’s remote areas. Using secondary data from published studies and international experiences, we analyse whether the investment in mobile clinics is justified by expected health gains and cost efficiencies, and identify key factors for successful deployment in the Ukrainian context.

AIM

The primary aim of this review is to evaluate the cost-benefit of mobile dental clinics as a strategy to improve

dental care access in Ukraine's remote rural areas. We seek to quantify, using available data, the anticipated costs (capital and operational) of mobile clinic programs versus their benefits in terms of increased service coverage, improved oral health outcomes, and potential cost savings (e.g., prevention of advanced disease or emergency treatments). Specific objectives include: (1) describing the current distribution of dental services across Ukraine and the scope of unmet need in rural communities; (2) assessing the cost-efficiency of mobile dental units relative to fixed clinics, drawing on case studies and economic evaluations; and (3) examining the broader benefits of mobile clinics – such as reductions in travel barriers, earlier disease detection, and quality-of-life improvements – especially for vulnerable groups like rural elderly, children, and conflict-affected populations. By synthesizing evidence on costs and outcomes, we aim to inform policymakers whether mobile dental clinics represent a cost-effective intervention and how they might be optimally implemented in Ukraine's healthcare system.

MATERIALS AND METHODS

This analysis is designed as a narrative review based on secondary data gathered from scientific literature, health statistics, and relevant case studies. The methodology did not involve any new clinical trial or field survey; instead, we aggregated existing evidence in a descriptive cost-benefit analysis format. The search and selection of sources were conducted as follows:

Databases Searched: We performed a literature search in PubMed/Medline and Scopus to identify studies and reports on mobile dental clinics, cost-effectiveness comparisons, and oral health access disparities in Ukraine or similar settings. Additional sources from international organizations and news agencies were also considered for context (e.g., World Bank data, health system reports, and media coverage of mobile clinics in Ukraine).

Search Period: The search covered publications from 2010 up to 2025, focusing on the most recent data available (including early 2025 publications). This period was chosen to capture the last 15 years of developments, which encompasses contemporary mobile health implementations and Ukraine's evolving healthcare context (including pre- and post-2014 conflict impacts).

Keywords: We used combinations of keywords such as “mobile dental clinic cost analysis”, “rural dental care Ukraine”, “dental clinic access disparities”, “mobile health unit cost-benefit”, and “mobile dentistry outcomes”. Both English-language sources and any available Ukrainian-language health statistics were included. References within relevant articles were also reviewed to identify additional sources (snowball technique).

Selection of Sources: The initial search identified approximately 60 relevant publications and reports. Titles and abstracts were screened for relevance to the cost-benefit of mobile vs. fixed dental services and for data specific to Ukraine or comparable health systems. After removing duplicates and excluding sources not directly pertinent, about 20 full-text sources were examined in detail. Of these, 14 key sources (including research studies, official statistics,

and case reports) were deemed most relevant and are cited in this article. These sources provided quantitative data on dental workforce distribution, cost figures for mobile clinics, outcomes of mobile dental programs, and contextual information on Ukraine's healthcare disparities.

Data on current dental access in Ukraine were obtained from publications by Ukrainian health authorities and researchers, including regional statistics on dentist distribution and service provision [2-3]. These provided insight into how many dentists and clinics serve rural populations versus urban, and the prevalence of untreated dental disease. For evaluating mobile clinics, we extracted data from case reports and studies of mobile dental programs in various countries (e.g., India, South Africa, United States, Eastern Europe), noting any reported costs (capital costs of vehicles/equipment, operating expenses), outputs (number of patients treated, procedures performed), and outcomes (oral health improvements, patient satisfaction, return on investment). Where available, we recorded economic metrics such as cost per patient, cost per procedure, or return on investment (ROI) for mobile clinics.

To compare costs with fixed clinics, we utilized published estimates for establishing and running a conventional dental clinic versus a mobile unit. A simple cost comparison was performed using available data from U.S. clinics to evaluate the expenses of operating a small fixed dental practice versus a two-chair mobile clinic. Additionally, we reviewed literature on the benefits of mobile clinics – for example, prevention of more serious disease, reduction of emergency dental visits, and intangible benefits like increased access equity and patient convenience.

Given that our sources span different contexts, all cost figures were interpreted with caution for applicability to Ukraine (adjusting qualitatively for differences in labor costs, infrastructure, etc.). Wherever possible, findings specific to Eastern Europe or middle-income countries were prioritized. We also considered special considerations for Ukraine: the impact of the war (which has created acute needs in some remote areas) and the existing health system structure (the need for integration with public services). All information is cited from source materials to ensure accuracy and allow verification.

ETHICS

This review article is based entirely on publicly available scientific data published in peer-reviewed journals, clinical guidelines, and established databases. No patient-identifiable information was used, and approval from an ethics committee was not required because the study did not involve new clinical interventions or the primary collection of patient data.

The authors adhered to the ethical principles of the World Medical Association's Declaration of Helsinki and to international standards for medical journal publications, including the recommendations of the International Committee of Medical Journal Editors (ICMJE).

No part of this work contains plagiarism or data fabrication. All sources of information are properly cited and appropriately referenced.

FRAMEWORK

This study was carried out as part of a planned research project at Donetsk National Medical University (Kropyvnytskyi, Ukraine), focused on improving access to dental care in underserved regions (state registration № 0125U100327; dates: 2024-2027). The research did not receive specific external funding; it was conducted as an initiative within the academic and clinical duties of the authors.

REVIEW AND DISCUSSION

CURRENT DENTAL CARE ACCESS IN REMOTE AREAS

Data confirm a pronounced disparity in oral healthcare availability between Ukraine's urban and rural populations. Nationally, Ukraine had roughly 19,000 dentists in 2021, equating to about 3.5-4 dentists per 10,000 people - a modest supply compared to Western countries [2]. However, this national average masks a skewed distribution. Over 90% of dentists practice in cities or towns, while rural areas (where about 30% of the population lives) are served by under 10% of dentists [2]. In practical terms, many villages have no resident dentist at all. A 2015 health system review noted *"very few fully qualified dentists"* serving rural areas, and a reliance on outdated public dental cabinets in those locales [3]. Public rural clinics often struggle with aging equipment and limited services - for instance, lacking X-ray machines or restorative materials [2]. Preventive care is scarce; rural residents may only seek care for severe toothaches, often leading to extractions as the main solution. This is reflected in utilization patterns: in some districts, tooth extractions outnumber fillings, indicating late presentation of disease and lack of conservative treatment options. Table 1 summarizes a cost component comparison between a mobile clinic and a small fixed rural clinic (using approximate U.S. figures as a reference point).

Geographically, the access gap is greatest in Ukraine's western highlands and certain northern rural regions, which have high rural population shares (in some western oblasts, over 50% rural) but very few dental providers. By contrast, some eastern oblasts, such as Donetsk or Kharkiv, have more dentists overall; however, these are primarily concentrated in urban centers [3]. The ongoing conflict since 2014 has further exacerbated disparities: in Ukraine's conflict zones, volunteer mobile dentists from non-governmental organizations, such as "Ukrop Dental" and the Life Saving Center, have operated makeshift or donated mobile clinics since around 2015. Soldiers and villagers welcomed these services; one soldier noted that, without the mobile unit coming near his position, he "wouldn't have the time or opportunity" to receive treatment, and that field dentistry was critical for maintaining combat readiness [4]. Despite these efforts, large swaths of rural Ukraine remain effectively without regular dental care.

EVIDENCE ON MOBILE CLINICS

– COSTS AND OUTPUTS

Multiple international programs demonstrate that mobile dental clinics can provide a broad scope of services with outcomes comparable to fixed clinics [1]. In a South African public-sector mobile clinic, for example, a cost-efficiency study found the mobile unit delivered 1,64 times the value of care relative to its operating costs [1]. Another analysis from the United States reported that mobile clinics yielded high returns by preventing costlier downstream treatments – essentially, every \$1 invested in mobile care saved several dollars in avoided emergency procedures and complications [5]. Typical costs for a dental van (outfitted with two chairs and necessary equipment) include the vehicle purchase or retrofit, dental instruments, and ongoing expenses for staff,

Table 1. Comparison of cost components for a mobile dental clinic versus a small fixed clinic in a rural area (costs in USD, approximate)

Cost Category	Mobile Dental Clinic (approximate)	Fixed Dental Clinic (approximate)
Initial Setup Costs	Custom mobile van purchase and outfitting: ~\$450k; dental equipment & instruments: ~\$50k; No building needed. Total ≈ \$500k	Clinic facility construction or setup: ~\$500–600k if new; dental equipment & instruments: ~\$100k+. Total ≈ \$600k
Annual Operating Costs	Staff salaries (e.g. 1 dentist, 2 assistants): ~\$200k/yr; fuel & vehicle maintenance: \$10-20k/yr; dental supplies: ~\$15k/yr. Total ≈ \$250k per year	Staff salaries (dentist, assistants, admin): ~\$250k/yr; utilities & facility upkeep: ~\$15k/yr; dental supplies: ~\$30k/yr; rent or mortgage (if applicable): ~\$30k/yr. Total ≈ \$325k–350k per year
Service Reach	Serves ~1,500-2,000 patients per year (rotating through multiple villages)	Serves ~3,000–4,000 patients per year (at a single location in town or large village)
Cost per Patient	Roughly \$120–\$170 per patient (higher due to travel time and lower patient volume)	Roughly \$80–\$120 per patient (lower with higher volume in a populated area)
Estimated ROI	High return through prevention: e.g. \$20–\$23 saved per \$1 spent (due to avoided emergencies and complications). One program showed mobile units delivered ~1.6× the value of their cost in care provided [1]	Standard care delivery – essential services but no significant net savings beyond the value of treatments provided (approximately \$1 saved per \$1 spent, i.e. ROI ~1:1)

Notes: The mobile clinic avoids building costs but incurs vehicle-related expenses, whereas the fixed clinic requires facility infrastructure. Annual operating costs for both models include staffing and maintenance. Cost figures are derived from U.S. clinic data comparing an approximately two-chair mobile dental unit with a three-chair fixed clinic. ROI indicates return on investment based on program reports

Source: compiled by the authors of this study

fuel, and maintenance. One U.S. estimate put the capital cost around \$300 000 and annual operating costs around \$250 000 for a two-chair mobile clinic [5], though these figures vary by setting and scale. Notably, mobile clinics often prioritize preventive and primary care services which, while less lucrative than specialized procedures, yield significant public health benefits by intercepting disease early [5].

Our comparative review indicates that when serving low-density areas, mobile units can be more cost-effective than establishing a permanent clinic. Fixed clinics entail construction or rental costs, utilities, and staff who may be underutilized in sparsely populated regions. By contrast, a mobile clinic maximizes utilization by moving between communities. In one analysis, a single mobile unit could serve multiple villages on a rotating schedule, reaching a combined population that would never justify individual stationary clinics [5-6]. The flexibility to relocate means the expensive equipment (dental chair, X-ray, sterilizer, etc.) is used more efficiently. Additionally, mobile services reduce indirect costs for patients (travel time, transportation expenses), which is significant in rural Ukraine where public transport may be infrequent and roads are poor.

Community feedback from pilot programs has been positive; patients appreciate receiving care “at their doorstep” and report improved oral health awareness after visits. In Ukraine’s recent context, international donors have recognized this need: in 2022-2023, at least five fully equipped mobile dental units were donated to Ukraine’s Ministry of Health to bolster frontline and rural care capacity [7]. Thousands of patients – soldiers and civilians – have received dental treatment from these units, who otherwise would have had no access to care [4].

BROADER BENEFITS

Beyond direct financial metrics, mobile dental clinics confer social and health benefits that are harder to quantify but critically important. They greatly improve access for vulnerable groups – for example, elderly people with limited mobility, children in remote schools, or communities affected by conflict (internally displaced persons, etc.). Regular visits by a mobile clinic can also instill preventive dental habits (such as daily brushing and fluoride use) through on-site education sessions conducted alongside treatments [6]. Early intervention by mobile teams (e.g., filling a cavity when it’s small) can avert more serious infections or tooth loss that would require costly specialist care later. Moreover, by providing services in underserved areas, mobile clinics help reduce inequalities in health status between urban and rural populations, contributing to a fairer healthcare system overall. During humanitarian crises, such as the ongoing war, these mobile clinics have a clear advantage of being deployable to wherever needs are greatest, including near conflict zones as mentioned. For instance, mobile units near the front line have been able to treat urgent dental issues for military personnel, which is also a factor in maintaining force readiness and morale [4]. Such outcomes not only improve individual health but also contribute to the social cohesion and resilience of Ukrainian communities. The

evidence suggests that this modern approach to an age-old problem can yield healthier teeth and brighter futures for Ukraine’s rural population, at a cost that society can afford and justify in the long run.

The findings from this cost-benefit review indicate that mobile dental clinics present a feasible and advantageous strategy to improve oral health access in remote areas of Ukraine. The cost analysis suggests that while mobile units require upfront investment, they can operate cost-effectively, especially when serving widely dispersed populations that cannot support permanent clinics. International case studies reinforce that mobile clinics can achieve a favorable cost-to-benefit ratio – for instance, South Africa’s mobile clinic delivered ~1,64 times the value of care relative to its costs [1], and U.S. programs showed high ROI from prevented downstream costs [5]. In Ukraine’s context, where public resources are limited, investing in mobile clinics could be justified by the preventive savings (reducing advanced dental treatments and related complications) and by alleviating strain on urban clinics. It is plausible that some rural patients who currently flood city hospitals for emergency dental issues would instead be treated earlier in their communities, easing the burden on higher-level facilities [8, 9].

However, implementation challenges must be considered, and integration into the health system ensured. A known potential pitfall of mobile programs is operating in isolation. It is crucial that mobile dental units coordinate with local healthcare providers and refer patients requiring complex care to fixed clinics or hospitals, ensuring a “dental home” for ongoing care [5]. Continuity of care and community trust are essential – without follow-up, initial gains could be lost. Therefore, mobile clinics in Ukraine should be linked to the national health service network. For example, after a mobile visit, clear referral pathways should exist to the nearest district dental clinic for procedures that cannot be performed on the van (such as dentures, root canals, or oral surgery), with possible subsidies or transportation support for referred rural patients. Additionally, mobile units should maintain health records that can be shared with or integrated into patients’ existing medical records at stationary facilities [8]. Another consideration is the sustainability and operational logistics. Mobile dental clinics will require dedicated budgets for maintenance – vehicles operating on Ukraine’s rural terrain may face tough conditions (mud, snow, rough roads), necessitating robust 4x4 platforms and frequent repairs. Fuel costs can be significant given the long distances between villages. Government support or donor funding will be needed for these recurring costs. Training staff in mobile clinic operations and having backup plans for technical issues are also important. Early experiences in some programs noted that initial phases had “*several missed workdays owing to technical and mechanical issues*,” though reliability improved over time [8]. Ensuring a supply chain for spare parts and technical support for dental equipment (compressors, suction pumps, portable X-ray units) on the van is vital for uninterrupted service.

Workforce capacity represents a potential bottleneck. Encouraging dentists to participate in mobile clinics and rural rotations may require incentives, such as hardship pay or crediting service toward mandatory practice for new graduates. The concept of mandatory rural service rotations for new dental graduates, as piloted in some countries, could be explored [3]. Such measures could channel young practitioners into rural outreach via mobile clinics, at least temporarily, while providing exposure to community dentistry. Furthermore, deploying teams of oral health auxiliary workers – hygienists and dental therapists – can extend the reach of mobile clinics cost-effectively [8]. These mid-level providers can deliver preventive care and perform basic procedures (such as cleanings, fluoride treatments, and simple restorations), freeing dentists to focus on more complex treatments during mobile clinic visits. Given Ukraine's dental education capacity, partnering with universities could be mutually beneficial; for example, a dental school could implement a mobile clinic rotation for students, supervised by faculty, to both improve rural care and enrich student training, as has been done elsewhere [10, 11]. It is also important to manage expectations about the scope of services. Mobile clinics typically do not handle advanced surgical cases or very lengthy procedures that are better done in a fully equipped clinic or hospital setting [5]. They are best suited for primary dental care and urgent basic treatments. This means mobile units significantly contribute to prevention and routine care, but they are *complementary* to fixed clinics, not a replacement for the entire dental infrastructure [5]. Stakeholders should thus view mobile dentistry as one component in a multi-tiered approach: preventive and primary care via mobile units, with secondary/tertiary dental care handled at regional centers. Notably, the presence of mobile services may actually increase demand for certain advanced treatments, as previously unmet needs are identified. For example, if a mobile clinic identifies many patients in need of orthodontics or complex oral surgery, referrals will spike. The health system should anticipate this and perhaps plan periodic transport or special clinics for referred patients (or eventually deploy specialized mobile units for services like prosthodontics).

Quality control and patient safety must be ensured. Mobile clinics must adhere to infection control and quality standards just like any brick-and-mortar clinic. Evidence from existing programs indicates they can indeed maintain high standards – one frontline dentist working in a Ukrainian mobile unit near the war zone noted, *“we are operating here at the level of a premium clinic. Not all city clinics have what we have here,”* referring to the modern equipment in their donated mobile truck [12]. Nonetheless, regular monitoring, strict sterilization protocols, and licensing oversight are needed to ensure that care in the mobile setting meets professional standards. Privacy considerations (the van should have a partitioned treatment area) and patient comfort (managing anxiety in an unusual setting) are also important for acceptance [10].

Finally, the socio-political context appears favorable for such innovations. Ukrainian healthcare reforms emphasize

increasing access and efficiency, and international donors have shown willingness to fund mobile solutions (as evidenced by the donation of mobile clinics during the war). Public acceptance of mobile clinics in Ukraine seems positive – both civilians and military personnel have expressed gratitude and even relief when these services arrive [13]. Thus, scaling up mobile dental clinics could also boost public morale and trust in the healthcare system's responsiveness [9].

One limitation of this analysis is that it relies on diverse sources, some of which are not specific to Ukraine regarding cost data. Actual costs in Ukraine may vary; for example, vehicle procurement could be higher due to import taxes and customization requirements, whereas labor costs (salaries) are lower than in Western settings. We did not perform a formal economic evaluation (such as net present value or cost-utility analysis) due to the lack of granular local cost data. Future research could collect Ukraine-specific data by piloting a mobile clinic in several districts and tracking its costs, utilization, and patient outcomes over time [10]. Additionally, while we have qualitatively addressed benefits, quantifying health outcomes (e.g., number of cavities prevented or quality-adjusted life years gained) would further strengthen the economic case. Nonetheless, the available evidence strongly suggests that the benefits – both quantifiable and qualitative – outweigh the costs of this intervention in rural Ukraine. This review provides a foundational argument that can be refined as more local data become available [11, 14].

CONCLUSIONS

Introducing mobile dental clinics in remote areas of Ukraine is a practical, evidence-based, and cost-effective strategy to reduce disparities in oral healthcare between urban and rural populations. Mobile clinics can deliver comprehensive preventive and therapeutic dental services directly to underserved communities, overcoming barriers of distance, transportation, and affordability that traditionally limit access to care. By providing regular examinations, preventive treatments, and timely management of dental disease, these clinics reduce the risk of severe complications and the need for emergency interventions, ultimately improving oral health outcomes and quality of life.

A phased national implementation is recommended. Pilot projects should begin in high-need rural regions and be staffed by rotating dental professionals supported through public health programs and incentive mechanisms. Integration of mobile dental services into the existing healthcare infrastructure is essential, with clear referral and follow-up pathways for complex cases, standardized clinical protocols, and continuous quality monitoring. Sustainable financing – through a combination of government funding, partnerships with dental universities, non-governmental organizations, and international donors – will help ensure stable operations.

Beyond routine service delivery, mobile dental clinics enhance the resilience of Ukraine's health system. Their mobility allows rapid response to emergencies, such as armed conflict or natural disasters, maintaining essential oral

healthcare when fixed facilities are disrupted. By expanding access, preventing advanced dental disease, and promoting equitable health outcomes, mobile dental services represent

a forward-looking public health intervention that benefits individuals, communities, and the national healthcare system as a whole.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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Common signs, uncommon condition: A case report of a 41-year-old woman with a large left-sided esophageal hiatus hernia and a benign esophageal leiomyoma

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ABSTRACT

Benign esophagus tumors are lesions rarely found in the general population. Leiomyomas, the most common of them, arise from the submucosal muscularis propria of the esophagus. They remain asymptomatic for a long time. The lack of typical symptoms, the non-specific abdominal complaints, and the very rare occurrence of these tumors in the population lead to diagnostic failures. This article describes a case of 41-year-old female patient diagnosed with a round lesion found in the chest X-ray. The CT scan revealed a large esophageal hiatal hernia extending to the left ventricular wall. She was qualified for surgical treatment. During the preparation of the abdominal part of the esophagus, a solid tumor, covering half of the esophageal circumference, was found in its wall. The neoplasm was resected. The histopathological examination revealed Leiomyoma. To summarize: benign esophageal tumors are lesions that can cause many diagnostic challenges in routine medical practice. In addition, they may not be visible in imaging studies, especially when located circumferentially or intramurally. In clinical practice, non-specific symptoms affecting the upper gastrointestinal tract are frequently encountered. These symptoms are typically caused by common and non-serious underlying conditions. The objective of this article is to highlight the rare causes of these symptoms, with the aim of reducing the risk of misdiagnosis in the future.

KEY WORDS: esophageal neoplasms, leiomyoma, hiatal hernia, abdominal pain

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INTRODUCTION

Benign tumors of the esophagus are uncommon growths that continue to be a diagnostic challenge. This category encompasses leiomyomas, lipomas, gastrointestinal stromal tumors (GIST), schwannoma, and granular cell tumors [1]. Among these, leiomyomas are the most prevalent lesions, which develop from smooth muscle cells [1, 2]. Despite ongoing research, misdiagnoses of leiomyomas still occur. There are a few reports on leiomyomas describing the cases of diagnostic misses. Hatch et al. found that the preoperative diagnosis of leiomyoma was accurate in only 53% of cases [3]. These tumors can be asymptomatic or present with nonspecific symptoms, which constitutes a significant diagnostic challenge. Furthermore, according to Pan W. et al., leiomyomas may occur simultaneously in multiple sites or with other esophageal abnormalities, such as hiatal hernia or granular cell tumors [4].

This report of a 41-year-old woman with a large left-sided esophageal hiatus hernia and a benign esophageal leiomyoma. In the case described in this paper, failure to

diagnose leiomyoma resulted from the coexistence of an esophageal hiatal hernia.

AIM

The main purpose of this work is to highlight leiomyomas as a rare cause of nonspecific gastrointestinal complaints.

CASE REPORT

A 41-year-old female patient was admitted to the Nephrology Department because of an indeterminate lung lesion found in an outpatient chest radiograph. Upon admission, she complained of a chronic cough lasting for approximately 2-3 months, and nonspecific abdominal pain, not related to food intake or body position.

Initially, she was diagnosed by primary care physician, who discontinued the ACE (Angiotensin-converting-enzyme) inhibitor (ramipril), originally prescribed due to subnephrotic proteinuria and hypertension in the course of IgA nephropathy. Afterwards the doctor ordered a chest X-ray which showed an ambiguous change in the left

Table 1. Laboratory tests

Nephrology Department		Patient's value													
		Surgery Department													
		Day of hospitalization													
Parameter	Normal value	1	3	4	5	6	7	8	9	11	14				
WBC [G/l]	4-10	16,51	22,07	18,93	14,2	11,12	11,4	13,48	20,59	20,77	16,69				
RBC [T/l]	4,0-5,0	4,44	3,19	2,91	2,87	2,71	2,76	2,84	3,17	3,08	3,17				
Hb [mmol/l]	7,7-10,0	8,6	6,4	5,8	5,7	5,3	5,5	5,7	6,4	6,00	6,3				
PLT [G/l]	150-400	350	249	242	263	276	313	374	540	635	720				
ESR [mm/h]	3-15	10	-	-	-	-	-	-	-	-	-				
Creatinin [mg/dl]	0,5-0,9	1,13	1,73	1,36	1,00	0,92	0,92	0,77	0,86	0,81	0,92				
eGFR [ml/min/1,73m²]	80-120	60	36	48	69	77	77	95	83	90	77				
Urea [mg/dl]	12,8-42,8	26,7	-	-	44,2	-	-	-	-	-	29,8				
Sodium [mmol/l]	136-145	140	142	146	143	142	143	142	138	138	139				
Potassium [mmol/l]	3,5-5,1	4,8	4,43	4,11	3,5	3,67	3,03	3,2	3,92	3,75	3,36				
PCT ng/ml	<0,05	-	2,2	1,53	0,89	-	0,29	-	0,18	0,17	0,11				
CRP [mg/l]	<5	-	291,14	172,33	82,77	37,17	19,89	-	27,22	20,29	12,79				
ALT [U/l]	<33	91	-	-	30	-	-	-	-	27	-				
AST [U/l]	<32	111	-	-	26	-	-	-	-	22	-				
Total bilirubin [mg/dl]	0,1-1,2	0,86	-	-	-	-	-	-	-	0,09	-				
Albumin [g/l]	35,6-46,1	37	-	-	27	-	-	-	-	-	-				
ACR [mg/g crea]	<30	682	-	-	-	-	-	-	-	1287	794				
24-Hour Urine Protein Test [mg/day]	<150	438	-	-	-	-	-	-	-	-	-				
Erythrocyturia [RBC/HPF]	<3	1-3	-	-	-	-	-	-	-	30-65	10-30				
WBC – white blood cells; RBC – red blood cells; Hb – hemoglobin; PLT – platelets; ESR - Erythrocyte Sedimentation Rate; eGFR – estimated glomerular filtration rate; PCT - Procalcitonin; CRP – C reactive protein; ALT – alanine transferase; AST - aspartate transferase; ACR - albumin-to-creatinine ratio; RBC /HPF - red blood cells per high power field															

WBC – white blood cells; RBC – red blood cells; Hb – hemoglobin; PLT – platelets; ESR – Erythrocyte Sedimentation Rate; eGFR – estimated glomerular filtration rate; PCT – Procalcitonin; CRP – C reactive protein; ALT – alanine transferase; AST – aspartate transferase; ACR – albumin-to-creatinine ratio; RBC/HPF - red blood cells per high power field

Source: Own materials



Fig. 1. A large hiatal hernia, and esophagus without strictures and pathological masses. The examination shows a large hiatal hernia involving most of the stomach (red arrow). The hernia causes modeling of the distal part of the esophagus (blue arrow) – CT scan, coronal section of thorax

Source: Own materials



Fig. 2. A part of the stomach (red arrow) displaced into the chest through the diaphragmatic hiatus. The hernia is adjacent to the surrounding mediastinal structures. – CT scan, oblique section of the thorax

Source: Own materials



Fig. 3. The image shows part of the stomach that has displaced above the diaphragm into the mediastinum (red arrow). The hernia is so large that it is adjacent to the heart wall (green arrow). – CT scan, a sagittal section of the thorax

Source: Own materials

lung that required further imaging. Due to an elevated creatinine level and a decreased eGFR (estimated glomerular filtration rate), to prevent contrast induced nephropathy, the patient was directed to the nephrology department to perform a contrast enhanced CT (computed tomography) scan of the chest.

On admission, the patient complained of cough and abdominal pain. On the Numerical Rating Scale (NRS), the patient rated the pain as 3/10. She described it as upper abdominal discomfort. The patient did not report any other complaints. She denied chest pain, gastrointestinal bleeding, postprandial pain, unexplained weight loss, hemoptysis, dysphagia, and odynophagia. She was not taking any medications. Physical examination did not reveal any abnormalities except for obesity.

Laboratory tests revealed increased creatinine levels, decreased eGFR, hematuria without active urine sediment, and an increased the albumin-to-creatinine (ACR) ratio – all tests were stable relative to previous measurements (Table 1).

No abnormalities were found in the abdominal ultrasound. Contrast-enhanced thoracic CT scan was performed and post-contrast nephropathy prophylaxis was applied. The examination revealed a rather large hiatal hernia involving most of the stomach with dimensions of 52x50x55mm. The hernia caused modeling of the wall of the distal part of the esophagus, adhering to the mediastinal structures, especially to the left ventricle (Figure 1-3). No enlarged lymph nodes were identified in the mediastinum. There were no other abnormalities observed in the esophagus. Additionally, the examination revealed atelectatic thickening of the pulmonary parenchyma in the lower lobe of the left lung.

Following the surgical consultation, the patient was qualified for the Nissen fundoplication procedure. Considering the patient's typical complaints and the unambiguous appearance on chest CT scan, the decision was made to proceed with surgical intervention without first obtaining further imaging or endoscopic tests. Considering the likely association of the cough with a hiatal hernia and gastroesophageal reflux, Ramipril was reinitiated at a dosage of 5mg per day.

After three months, the patient attended a planned follow-up appointment at the surgical department. The patient was hospitalized for elective planned surgical intervention. During the preparation of the abdominal part of the esophagus displaced to the mediastinum, a large (5x4x4 cm) solid tumor covering half of the esophageal circumference was found in its wall. The tumor was removed through resection, and combined (anterior-posterior) crurorrhaphy was performed during operative procedure. Due to unexpected tumorectomy, initially planned Nissen fundoplication was converted to a 180-degree anterior

fundoplication, known as the Dor fundoplication. On the first postoperative day, the patient complained of pain in the surgical wound. Due to the unexpected need to modify (expand) the procedure, the decision was made to expand the diagnostics. At our surgical centre, it is standard protocol for each patient to undergo a contrast examination of the oesophagus on the first postoperative day. The purpose of this examination is to rule out the possibility of any complications, including anastomotic leakage. In this particular case, the diagnostic process was initiated by the aforementioned examination, which revealed the presence of contrast medium leakage. Revision surgery was performed on the same day. During relaparotomy, methylene blue was administered, exposing the leakage through the suture line, which was subsequently sealed with single stitches. Following a further examination of the area, conducted using dye, no further leakage was identified. A small sample of fluid was collected from the area for microbiological analysis. Following surgical intervention, blood cultures were obtained and the patient was started on antibiotics. Piperacillin with tazobactam was administered at a dosage adjusted according to the estimated glomerular filtration rate (eGFR). A microbiological examination of fluid obtained from the pleural cavity identified the presence of *Staphylococcus aureus* MSSA and *Streptococcus anginosus*. Following a consultation with the hospital microbiologist, antibiotic therapy was converted on the sixth day. Piperacillin/tazobactam was replaced with metronidazole, cloxacillin and ceftriaxone, which were administered for an additional ten days. Fluid therapy and parenteral nutrition were included. Oral nutrition was gradually added during hospitalization. On the eighth day of hospitalization, it was determined that the patient exhibited satisfactory tolerance to drinking water, and from the ninth day, a liquid diet enriched with Nutridrinks was initiated. In the early postoperative period, the patient reported discomfort at the site of the surgical incision. However, following the administration of analgesia, comprising buprenorphine and metamizole, these symptoms resolved. The doses of analgesic medications were progressively reduced until their complete cessation. The patient remained in good general condition throughout. She was discharged home after 16 days of hospital stay. Two weeks after being discharged from hospital, the patient was admitted to the Surgical Outpatient Clinic. Appropriate wound healing and adequate tolerance of a balanced diet were observed.

The tumor lesion was sent for pathological analysis. Bundles of spindle-shaped cells, minimal atypia and no necrosis were observed within the tumor on histopathologic examination. The immunohistological staining showed a positive result for desmin and smooth muscle actin (SMA), but staining for CD117 was negative. The study confirmed the diagnosis of leiomyoma.

The patient is currently under the care of the Nephrology Clinic, due to a diagnosis of IgA nephropathy. Following several years of observation, no symptoms related to the upper part of the gastrointestinal tract have been reported.

DISCUSSION

The main purpose of this work is to focus on the uncommon causes of non-specific gastrointestinal symptoms. The authors conducted a literature review to systematize the current knowledge about the rare esophageal neoplasm called leiomyoma.

Benign esophagus tumors are rare lesions representing less than 1% of all esophagus neoplasms [5]. Leiomyomas, being the most common, represent 60-70% of them [3]. Autopsy studies showed a population prevalence of 0.06 to 0.1% [6]. These tumors are usually diagnosed in people between the age of 20-50, more often in males [6]. Most frequently (around 60%), they are situated in the distal third of the esophagus [7].

Leiomyomas, especially those below 2cm, are asymptomatic [8]. Symptoms such as dysphagia, postprandial vomiting, regurgitation, upper gastrointestinal bleeding, weight loss, and non-specific chest pain usually appear when the tumor is larger than 5 cm in diameter. Moreover, these tumors can grow to considerable sizes [10]. Leiomyoma with diameter larger than 10 cm are defined as a giant leiomyoma [11].

Leiomyomas may malign into leiomyosarcomas, although this phenomenon is rare [12]. Some authors suggest that ultrasonographic features such as a tumor diameter of 3 cm or more, ulceration, nodular shape, a heterogeneous internal echo, and the presence of an anechoic area may suggest the occurrence of a malignant myogenetic tumor [13].

The diagnostic process should include a barium esophagogram, esophagoscopy, endoscopic ultrasound, and computed tomography [14]. Esophageal tumors can be seen in roentgenography as a crescent-shaped or rounded filling defects in the barium column, however this examination is not accurate and other tests should be considered. The CT scan can be valuable in identifying esophageal lesions and determining their location and size [3]. Jehangir et al. suggested that calcifications within the tumor visible on CT may be characteristic for leiomyomas, but their appearance is very rare [15]. On the other hand, this study has some limitations: lesions that are localized circumferential or intramural cannot be visualized [16]. Recent investigations suggest that endoscopic ultrasonography (EUS) is a superior diagnostic tool for esophageal tumors due to its ability to provide better visualization of the location, structure, and size of the lesion. Therefore, it can be considered the gold standard for diagnosis [17]. Leiomyomas on EUS examination are imaged as hypoechoic areas with smooth borders in the esophageal wall [16]. The mucosa is intact which helps to distinguish them from malignancies [17]. Endoscopy can be used for biopsy sampling. It has been proven that endoscopic ultrasound-guided fine needle biopsy for gastrointestinal subepithelial tumors has become a common diagnostic method with acceptable effectiveness (87.9%). [18]. However, according to current knowledge, this procedure is not recommended due to the potential for complications such as hemorrhage, infection, and increased risk of mucosal perforation during surgical treatment and should be implemented just in case of a diagnostic problem [19].

On the other hand, Qu J. et al. suggested that the use of MRI in the staging of oesophageal tumours allows for more accurate assessment of the disease's extent and the status of adjacent organs compared with other imaging modalities, including CT and esophageal endoscopy. The presence of leiomyoma is challenging to discern due to its comparable intensity to that of the muscularis propria on the T2-weighted imaging. Furthermore, no diffusion restriction is evident on the contrast-enhanced T1-weighted image, and the enhancement is slightly homogeneous. As posited by the authors of the study, the potential for enhanced visualisation of leiomyomas is suggested to be optimised through the implementation of magnetic resonance imaging MRI. This review emphasises the imaging features that differentiate between esophageal masses and proves the critical role of MRI in the diagnostic process [20].

The histological diagnosis of leiomyoma should not be problematic due to its characteristic morphology. GIST and schwannoma should be considered in the differential diagnosis. Immunohistochemical tests of leiomyoma are positive for SMA and desmin, while they are negative for CD 117, CD 34, or S100. Positive staining for CD117 and CD 34 are characteristic of GIST while positive staining for S100 indicates schwannoma [21].

It is possible that several different conditions may result in similar or identical clinical symptoms and/or a similar radiological presentation as that observed in a leiomyoma. These include, for example, achalasia, esophageal cancer, esophageal diverticula, esophageal hemorrhage, esophageal lymphoma, esophageal motor dysfunction, esophageal spasm, esophageal stricture, esophageal varices, esophagitis, and foreign body. It is important to take all of these into consideration when undertaking a differential diagnosis [22].

Treatment options include observation, endoscopic tumor removal, by thoracotomy or laparotomy, and minimally invasive techniques such as laparoscopic or thoracoscopic surgery like VATS (video-assisted thoracic surgery). The choice depends on the location, shape, and size of the tumor [23].

Leiomyoma enucleation by thoracotomy is the most traditional approach. Thoracoscopic or laparoscopic surgery is also an effective and safe treatment option, especially for tumors between 1 and 5 cm in diameter, however, recent studies have demonstrated that alterations exceeding 5 cm can be effectively managed by this method [23]. Samphire et al. proved, that a video-assisted thoracoscopic surgery (VATS) was associated with shorter hospitalization, reduced need for pain medications, better cosmetic results, and faster return to normal daily activities [24]. On the other hand, in recent years more authors have suggested that robotic surgery may be the best surgical method compared to existing methods. A three-dimensional vision, restoration of the natural eye-hand axis, and enhanced dexterity due to articulated instruments are listed as main advantages. Gadelkarim et al., also highlight the merits of the robotic approach for a leiomyoma in this location. According to the authors, the robotic approach offers distinct advantages, including its ability to perform intricate movements with

precision, utilize three-dimensional vision, and efficiently navigate confined and delicate spaces, which might be challenging with conventional video-assisted thoracoscopic surgery (VATS). Moreover, the ergonomic comfort it affords is particularly advantageous for surgeons operating on patients with a large body habitus. In the videos provided, the author systematically demonstrates the sequential phases of the procedure, elucidating the benefits of this methodology [25]. According to Inderhees et al., the robotic enucleation is associated with less mucosal damage, less complications during and after the surgery, and shorter hospitalization in comparison to thoracoscopic enucleation [26].

The occurrence of leiomyoma rarely requires total esophageal resection. According to recent studies, resection should be performed for lesions greater than 8cm or those with an annular shape [3]. However, the unequivocal guidelines are still unclear. For example, Samphire et al. mention 4 additional indications: 1) large size of the lesion that cannot be resected by minimally invasive techniques, 2) major ulceration or destruction of esophageal mucosa which cannot be repaired, 3) multiple leiomyomas or diffuse leiomyomatosis, 4) suspicion of a malignant lesion [24].

Leiomyomas originating from the lamina muscularis mucosae can be treated with endoscopic resection which avoids complications associated with major surgery such as incision size, postoperative trauma, longer hospitalization, and postoperative pain [27]. The maximum tumor size that can be effectively removed during endoscopy has not been clearly established. Endoscopic submucosal dissection is suggested as the most accurate method for lesions measuring less than 3 cm [24]. However, He et al. demonstrated in their study that this procedure can be successful even in the case of larger lesions with a diameter smaller than 5 cm [12].

The management of small and asymptomatic leiomyomas is controversial. Some authors are of the opinion that their removal is unwarranted because of the uncertain correlation between the presence of leiomyomas and the shortening of the patient's life [28]. Moreover, deaths due to the presence of the tumor are very rare, and surgery is associated with the risk of complications [24]. On the other hand, Hatch et al. suggest that even small and asymptomatic tumors should be removed because of the risk of tumor growth, malignancy, and the appearance of symptoms [3]. Current research indicates that leiomyomas do not recur after surgical removal [2]. In conclusion, the management of leiomyomas is still a controversial subject. Further research is needed to establish unequivocal standards of care.

In the presented case, the proper diagnosis of leiomyoma was missed in the chest CT due to atypical symptoms and a coincidence of hiatal hernia. Because the symptoms were thought to be caused by a hiatal hernia, no other imaging studies were performed for diagnosis. In this case, incorporating endoscopic ultrasound (EUS) into the diagnostic process could provide more detailed information to tailor the surgical procedure to the specific needs of the patient and minimize the potential risk of complications during and after surgery.

The esophageal lesion was a borderline size of about 5x5x5cm. However, many publications report that tumors of this size can cause symptoms [26]. Therefore, surgeon decided to remove it. In addition, the procedure had just been performed. Leaving the tumor during surgery would have required a second procedure, putting the patient at additional risk of surgical complications. It was not possible to remove the lesion during endoscopy due to its mediastinal location. The tumor was removed so that it could be submitted for a histopathological examination and to establish a diagnosis.

In comparison, Jehangir et al. described the case of a patient who also had a hiatal hernia and an esophageal tumor like our patient. However, in the case described, the tumor was visualized on CT scan due to its large size and the presence of calcifications within the tumor. The diagnosis was completed by endoscopic examination, which visualized a lesion that seemed to grow from the muscularis propria, which helped in the choice of surgical method [15]. In our case, the identification of the leiomyoma occurred concomitantly with the hiatal hernia repair procedure, leading to its resection within the confines of the surgery. Beside the fact the enucleation is a treatment of choice there are no contraindications to simultaneous surgery for esophageal hiatal hernia and leiomyoma removal [28]. Padhy et al. describe the case of a 26-year-old female patient with a hiatal hernia and a large esophageal tumor found on imaging. The patient underwent right posterolateral thoracotomy for removal of the tumor and Nissen fundoplication for the hiatal hernia. The author points out that leiomyoma and hiatal hernia are rare, but if they are present, tumor resection and hiatal diaphragm surgery should be considered [28]. Samphire et

al. also reported in their paper that 2 patients underwent leiomyoma resection using the Collis-Nissen method due to coexisting hiatal hernia and reflux disease [24]. In our case the Dor fundoplication was presented. This surgical method is rarely chosen in Poland as a first-line treatment. It is an effective procedure for the surgical treatment of gastroesophageal reflux and is associated with a high rate of patient satisfaction at late follow-up. It has also been used as an adjunct to Heller's cardiomyotomy in the treatment of achalasia. In addition to preventing postoperative reflux, it provides coverage of the esophageal mucosa and esophagus exposed at the site of the muscularis propria transection. However, they may have a higher risk of recurrent reflux than Nissen fundoplication, but a lower rate of adverse effects [29].

CONCLUSIONS

In conclusion, benign tumors of the esophagus are rare lesions and according to the available studies some patients are diagnosed for months before a proper diagnosis is made. For this reason, it is important to include the presence of primary esophageal tumors in the differential diagnosis. Diagnostic procedures such as Barium swallow or EUS may improve the diagnostic process of patients with nonspecific gastrointestinal symptoms, and reduce the frequency of surgical interventions and associated complications. Due to the rare nature of these cancers in the general population, surgery guidelines are not clear. The size of the tumor that needs to be removed is not clearly defined, and some authors suggest that tumor resection is unnecessary in the case of small size and suspected leiomyoma. In conclusion, leiomyomas are rare esophageal tumors that demand further examination to enhance diagnostic and treatment methods.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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CLINICAL CASE

Autoimmune encephalitis with LGI1 antibodies: a report of two cases

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ABSTRACT

Autoimmune encephalitis associated with anti-LGI1 antibodies (ang. leucine-rich glioma- inactivated 1) is one of the most common forms of limbic encephalitis. The aim of this paper was to present two cases of this disease with different clinical course and prognosis. We described the medical history of a 64-year-old man and a 75-year-old woman in whom the presence of anti-LGI1 antibodies in serum and/or cerebrospinal fluid was detected. Both patients had typical facial-brachial dystonic seizures, memory impairment and hyponatremia. In the first case, in the early phase of the disease, MRI showed bilateral changes in the temporal lobes (mainly in the hippocampi), while in the second case, neuroimaging did not show typical changes for autoimmune encephalitis – vascular and atrophic changes dominated. In the first case, combined therapy (steroids and intravenous immunoglobulins) was used and significant improvement was achieved. In the second case, only intravenous immunoglobulins were used. Differential diagnosis of rapidly progressing neurological disorders should include autoimmune encephalitis. One of the forms of this disease is autoimmune encephalitis with the presence of anti-LGI1 antibodies, which should always be suspected in patients with dystonic facial-brachial seizures and memory disorders, especially with concomitant hyponatremia. Determination of antineuronal antibodies should be a standard procedure in such cases. Fast and accurate diagnosis allows for the initiation of effective treatment. Oncological vigilance should also be maintained – in some patients the presence of cancer is detected.

KEY WORDS: autoimmune encephalitis, anti-LGI1; hyponatremia, dystonic seizures, immunotherapy, case report

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INTRODUCTION

Autoimmune encephalitis associated with anti-LGI1 antibodies (leucine-rich glioma- inactivated 1) is one of the most common forms of limbic encephalitis caused by antibodies against voltage-gated potassium channel (VGKC) proteins [1]. This disease most often occurs in the age group of 30-80 years, with a clear predominance of disease in men in the sixth and seventh decades of life [2]. Typical symptoms include: memory impairment (mainly short-term) and other cognitive functions, behavioral disorders (disorientation, apathy, aggression, personality disorders) and faciobrachial dystonic seizures (FBDS) [3,4]. It is often accompanied by refractory hyponatremia, probably resulting from the syndrome of inappropriate antidiuretic hormone secretion (SIADH) associated with damage to the hypothalamus [5, 6]. In contrast to the most common autoimmune encephalitis with the presence of anti-NMDAR antibodies, which in young women often coexists with ovarian teratoma, encephalopathy associated with anti-LGI1 antibodies is rarely a paraneoplastic syndrome, although cases of coexistence with neoplasms such as lung cancer,

thymoma or colon cancer have been reported [7, 8]. Diagnosis consists of confirming the presence of anti-LGI1 antibodies in blood and cerebrospinal fluid and excluding other causes. It should be remembered that in 25-60% of patients, standard magnetic resonance imaging (MRI) of the head does not show any abnormalities in the acute phase of the disease. In the remaining patients, characteristic hyperintense changes are observed in the medial temporal lobe structures (mainly in the hippocampus and amygdala), visible in T2/FLAIR sequences [9, 10]. The sensitivity of laboratory tests varies depending on the method used – anti-LGI1 antibodies are detected in serum in the vast majority of patients (over 90%), while in the cerebrospinal fluid the detection rate is lower and is approximately 60-80% using standard commercial tests [11, 12]. In EEG examinations in patients with autoimmune encephalitis associated with anti-LGI1 antibodies, epileptic discharges (57.3%) and focal disturbances, such as slowed waves (59.3%) and focal discharges (53.5%), typically located in the temporal lobes [13]. The goal of therapy is the fastest and strongest possible suppression of the autoimmune

response. The first-line treatment is high-dose corticosteroids (e.g. intravenous methylprednisolone). In the absence of improvement or contraindications to steroid therapy, second-line therapy should be implemented: intravenous immunoglobulins (IVIG) or plasmapheresis [4]. The literature also emphasizes the role of other immunosuppressants (rituximab, azathioprine, mycophenolate mofetil) in patients with relapses or poor response to initial treatment [14].

The prognosis for this condition is generally good – most patients (approx. 80-90%) respond to immunotherapy and achieve improvement, but older age, initial severe course and the presence of anti-LGI1 antibodies in the cerebrospinal fluid may be associated with a poor course [4, 15].

AIM

The aim of this study was to present two cases of autoimmune encephalitis with the presence of anti-LGI1 antibodies with different clinical course and prognosis.

CASE REPORT 1

A 64-year-old man, not suffering from chronic diseases so far, was admitted to the clinical neurology department. A month earlier, he had been hospitalized in the neurology department of the district hospital due to sudden onset of memory and orientation disorders. MRI of the brain showed asymmetric, bilateral hyperintense areas in the medial temporal lobes (mainly in the hippocampi) in T2/FLAIR images. The patient was also tested for anti-neuronal antibodies in the serum – anti-LGI1 and anti-titin antibodies were found. The general CSF examination was normal. A focal neoplastic process was excluded (CT of the chest and mediastinum, and abdominal ultrasound were unchanged). The patient was suspected of having limbic encephalitis and was given intravenous methylprednisolone (1 g/day for 5 days), which resulted in improvement in the level of consciousness disorders. After completing the treatment, the patient was discharged home. Shortly after discharge, the patient began to experience dystonic attacks several times a day involving the left side of the face and the left upper limb. Two weeks later, the patient was admitted to the clinical neurology department. On admission, the patient was conscious, auto- and allopsychologically oriented, with postural and intentional tremor of the upper limbs, and no other focal or meningeal symptoms. Laboratory tests revealed mild hyponatremia (134.6 mmol/l), hypercholesterolemia, and slight hyperglycemia; other results (morphology, CRP, liver function tests, creatinine, tumor markers) were within the laboratory norm. Follow-up MRI of the head showed a reduction in the previously observed changes in the temporal lobes; there were no signs of focal contrast enhancement or diffusion restriction. Minor vascular changes in the white matter and mild, generalized cortical atrophy (GCA scale 1) and partial atrophy of the temporal lobes were noted. On the third day of hospitalization, a neuropsychological consultation was performed. The patient presented with a slowing of psychomotor drive, irritability and inappropriate mood. The Addenbrooke's Cognitive Examination-III (ACE-III)

test revealed a decrease in working memory function, immediate memory and concentration. The Rey–Osterrieth task on visual material indicated significant difficulties in planning and organizing visual activities. Cognitive dysfunction at the level of mild dementia was found. The patient did not remember previous hospitalization in the district hospital. The EEG examination recorded abundant alpha rhythm activity (8–10 Hz) with an admixture of sporadic fast waves; the basic bioelectric activity was slightly slowed. No seizures were observed during the video-EEG examination, nor were any seizure changes recorded in the EEG. During hospitalization, the patient continued to experience several-second dystonic seizures of the left half of the body with a frequency of up to a dozen per hour. Due to the diagnosis of autoimmune encephalitis with the presence of anti-LGI1, the patient was given intravenous immunoglobulins at a dose of 0.4 g / kg body weight / day for 5 days. Additionally, gabapentin was included in the treatment. In the following days, a significant decrease in the frequency of seizures was noted – from a dozen to several per hour. The patient was discharged in a good general condition with a recommendation for rehabilitation and continuation of outpatient treatment. A control hospitalization was planned after a month.

During the next hospitalization, the patient's neurological condition did not deteriorate. However, he still reported persistent memory disorders and sporadic dystonic seizures of the face and left limb. Control MRI of the head showed a stable image. The EEG and video-EEG examination did not reveal any focal discharges or other changes compared to the previous recording. The repeated neuropsychological assessment showed significant improvement in cognitive functions – restored attention, working and direct memory, and improved verbal fluency and visual-spatial functions.

Due to the impossibility of using immunoglobulins, it was decided to repeat intravenous treatment with methylprednisolone (1 g/day for 5 days). During this treatment, the frequency of dystonic attacks decreased to 4 per day. Oral prednisone therapy (60 mg/day) was then initiated with a planned gradual withdrawal over 6 months. The patient remains under outpatient neurological monitoring, his condition is stable.

CASE REPORT 2

A 75-year-old woman was admitted to the clinical neurology department due to recurrent dystonic seizures of the face and right upper limb. Three months earlier, she had been hospitalized in the neurology department of the district hospital due to similar seizures. At that time, epilepsy with focal seizures was diagnosed and the antiepileptic drug levetiracetam was included in the treatment. During further diagnostics, recurrent hyponatremia and dehydration were found, after which the patient was referred to the internal medicine department. There, hyponatremia was confirmed, and hypertension, hyperlipidemia and vitamin D3 deficiency were also diagnosed. Due to the deterioration of the patient's general condition and excessive sleepiness, levetiracetam treatment was discontinued.

On admission to the clinical neurology department, the patient was in good general condition, conscious and oriented auto- and allopsychologically. Neurological examination did not reveal meningeal symptoms. Muscle strength in the upper limbs was normal, but weakened in the lower limbs. The tendon reflexes in the upper limbs were lively and symmetrical, but they were not evoked in the lower limbs. A positive Babinski sign was found bilaterally and a positive Sterling sign on the right side. The patient performed the associative tests correctly. No disturbances in superficial or deep sensation were observed. The gait was uncertain and required support. During the examination, two dystonic attacks occurred: the patient suddenly turned her head to the left and twisted her lips; the attacks lasted a few seconds and subsided spontaneously. On the second day of hospitalization, the patient's consciousness disorders increased – the patient was drowsy and allopsychically disoriented. Laboratory tests confirmed persistent hyponatremia (124–132 mmol/l). No abnormalities were found in the remaining laboratory tests (morphology, CRP, ESR, transaminases, creatinine, CEA, CA19-9, CA125, thyroid hormones, vitamin B12, rheumatoid factor, antinuclear antibodies). MRI of the head was performed: the image indicated advanced leukoaraiosis and vascular brain damage (grade 3 on the Fazekas scale) and slight generalized cortical atrophy (grade 1 on the GCA scale). In addition, there were numerous small foci in the white matter of the brain and cerebellum, corresponding to past microbleeds; no foci of pathological contrast enhancement were found. Computed tomography angiography (angio-CT) revealed the following changes: occlusion of the left vertebral artery (segment V1/V2), short-segment occlusion of the left posterior cerebral artery (segment P1), and extensive atherosclerosis of the extra- and intracranial vessels. To assess the condition of the spine, an MRI of the lumbar-thoracic spine was performed – it revealed a fracture of the L1 vertebral body and spondylosis of the thoracic spine, without signs of compression of the nervous structures. On the second day of hospitalization, a neuropsychological consultation was performed. The patient had a slowed psychomotor drive, flat affect and possible fluctuations of consciousness. In the psychological examination (Mini Mental State Examination, MMSE) she obtained a result of 20/30 points. A significant deterioration of working memory, episodic memory and visual-spatial functions (difficulty in planning and organizing tasks) was observed. The results suggested mild dementia; however, due to the general condition of the patient and attention disorders, they were interpreted with great caution. The EEG recording was disturbed by the patient's movements; a reduced background activity was recorded with slow theta waves in the range of 4–6 Hz with medium amplitude, scattered in all leads. No clear reaction to photostimulation or hyperventilation was noted. No paroxysmal discharges or epileptic seizures were observed in video-EEG monitoring.

No significant deviations were found in the cerebrospinal fluid test (protein 38.6 mg/dl, glucose 48 mg/dl, cytosis 1 cell/ μ l). Due to the suspicion of autoimmune encephalitis, a

panel of antineuronal antibodies was determined. The result was positive: anti-LGI1 antibodies were detected in both serum and CSF. On this basis, a diagnosis of autoimmune encephalitis with anti-LGI1 antibodies was made.

Due to contraindications to steroid therapy (concomitant arterial hypertension), immunomodulating treatment was implemented: human immunoglobulins were administered intravenously in a total dose of 2 g/kg of body weight for 5 days. At the same time, the antiepileptic treatment was modified – lamotrigine was included in the treatment. The patient was discharged home with recommendations for rehabilitation and further neurological monitoring.

DISCUSSION

The presented cases illustrate the broad clinical spectrum of autoimmune encephalitis with anti-LGI1 antibodies. The patients presented showed characteristic features of this disease – sudden or subacute onset of memory impairment and dystonic facial-brachial attacks [1, 4]. At the same time, both were diagnosed with hyponatremia, which confirms the frequency of this symptom (according to the literature, 60–88% of cases) [5, 6]. In the woman (case 2), hyponatremia was much more severe (in the range of 124–132 mmol/l) and, despite the treatment, it persisted for a long time, which is often described in the available literature in this disease [5, 6]. In both cases, hyponatremia was not associated with the use of diuretics or another metabolic disease, thus indicating an endogenous cause (SIADH) [5, 6].

Despite some similar symptoms, the clinical course in both cases was different. In the man (case 1), the disease initially manifested itself mainly in memory and consciousness disorders, while typical dystonic attacks appeared only after several weeks. In turn, the patient (case 2) had dystonic attacks in the face and limbs (initially diagnosed as epilepsy) and fluctuations of consciousness from the beginning of the disease. In the first case, bilateral changes in the hippocampi occurred in the early phase, which were visible on MRI (which is typical for limbic encephalitis). These changes resolved after immunomodulatory treatment. In the second case, MRI did not show typical changes for autoimmune encephalitis – vascular and atrophic changes dominated, which could mask the picture of the evolution of inflammatory processes. The presence of pyramidal symptoms in the described patient was also associated with these changes. The therapeutic approach in both cases included first-line immunotherapy. In case 1, both steroids and intravenous immunoglobulins (IVIG) were used, which contributed to the reduction of the frequency of attacks and improvement in cognitive functions. This strategy is in line with the recommendations – the literature indicates that combined therapy (steroids and IVIG or plasmapheresis) is highly effective (according to the literature, the effectiveness of remission is about 96% with combined therapy) [14]. In case 2, on the other hand, only IVIG was used (due to existing contraindications), which could have contributed to the less spectacular therapeutic effect. Some retrospective studies suggest that steroid monotherapy may give better results

in the short term than IVIG monotherapy [4], therefore the optimal approach is combined therapy. In case 2, maintenance therapy (oral steroids – prednisone) was used, which probably contributed to maintaining symptom control. Such treatment seems justified, as the symptoms of autoimmune encephalitis with anti-LGI1 antibodies may recur [16]. In the case of lack of effectiveness of first-line drugs, other immunosuppressive drugs (azathioprine, rituximab, cyclophosphamide, mycophenolate mofetil) may also be used in the treatment. Significant improvement in the man (64 years old) and persistence of symptoms in the woman (75 years old) may also be related to age and multiple morbidities. According to available literature data, older age and initial significant cognitive dysfunction have an impact on poorer prognosis [15]. In the patient, the prognosis could additionally be worsened by existing significant vascular changes in the brain. It is worth emphasizing that in autoimmune encephalitis with anti-LGI1 antibodies, it is precisely the rapid initiation of immunotherapy that is one of the positive prognostic factors – while delaying treatment increases the risk of relapses and permanent neurogenic damage [16]. One retrospective study found that patients who started immunological treatment early had a lower rate of disease relapse [16]. Both case reports also emphasize the importance of rehabilitation and monitoring of cognitive functions. Case 1, despite the initial diagnosis

of cognitive dysfunction at the level of mild dementia, showed a high capacity for improvement after therapy (psychological test results significantly improved). Similarly, the literature reports that many patients experience remission of cognitive deficits under the influence of treatment [17]. On the other hand, it should be remembered that even after the acute phase has subsided, some patients may have subtle impairments in working and executive memory [4, 15], which requires further observation.

The differential diagnosis of autoimmune encephalitis should mainly include paraneoplastic syndromes, brain tumors (especially gliomas), primary psychoses and catatonic syndrome.

CONCLUSIONS

Differential diagnosis of rapidly progressing neurological disorders should include autoimmune encephalitis. One form of this disease is autoimmune encephalitis with the presence of anti-LGI1 antibodies, which should always be suspected in patients with facial-brachial dystonic seizures and memory disorders, especially with concomitant hyponatremia. Determination of antineuronal antibodies should be a standard procedure in such cases. Fast and accurate diagnosis allows for the initiation of effective treatment. Oncological vigilance should also be maintained – in some patients the presence of cancer is detected.

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Language-dependent performance of large language models in medical diagnostics: A comparative study of ChatGPT-4o and Claude 3.5 Sonnet

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ABSTRACT

Aim: The aim for this study was to evaluate the efficacy of ChatGPT-4o and Claude 3.5 Sonnet in diagnosing diseases from clinical case descriptions presented in various languages.

Materials and Methods: The study used 50 clinical case descriptions provided by both LLMs in three languages – English, Arabic and Ukrainian. Diagnostic results were assessed by a panel of clinicians according to standard criteria, and statistical methods were employed to determine the significance of the difference between the obtained indicators.

Results: The overall diagnostic accuracy for ChatGPT-4o was $62.00\% \pm 15.62\%$, with performance significantly differing by language: $72.00\% \pm 10.00\%$ in English, $44.00\% \pm 12.00\%$ in Arabic, and $70.00\% \pm 9.00\%$ in Ukrainian. A similar pattern was observed in Claude 3.5 Sonnet, which had a mean accuracy of $60.67\% \pm 14.50\%$. Both models performed significantly worse in Arabic compared to English and Ukrainian ($p < 0.05$).

Both models showed reduced, but significant, accuracy for cases published in 2024–2025 vs. 2023 ($p > 0.05$).

Conclusions: No significant differences in diagnostic accuracy were found between the LLMs; rather, the discrepancies were primarily related to the languages used. In multilingual healthcare settings, such as those involving Arabic, various underlying factors—particularly language complexity, cultural context, and the type of clinical cases—affect their performance. Further research is essential to improve the capabilities of LLMs, ensuring equitable healthcare access for diverse linguistically representative populations.

KEY WORDS: diagnostic accuracy, multilingual healthcare, Arabic, English, Ukrainian

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INTRODUCTION

Dynamic advanced reforms of Large Language Models (LLMs) have transformed many areas considerably, while healthcare being the most promising area of application. Their ability to support the diagnostic process through clinical decision is progressively recognized [1, 2]. However, the clinical diagnostic accuracy of these models in different languages remains an important field that raises concerns about their credibility in a multilingual setting.

The LLM has exhibited significant potential capacity in medical applications, which helps in making clinical decisions to improve the patient's commitment. Maida et al. (2024) discovered the usefulness of LLMs in gastroenterology clinical diagnosis, while Wang and Zhang (2024) highlighted their progress in general medical practice [1, 2]. Despite these promising developments, the current research mainly focuses on the performance of LLM in the context of the English language, leaving its credibility in other languages. This oversight raises concerns about their effectiveness in a multilingual and multicultural healthcare environment, where linguistic variety is an important factor.

Language plays a crucial role in healthcare diagnostics, as accurate communication is fundamental to effective patient

care. Studies have identified significant LLM inconsistency in delivering accurate medical information in non-English languages. Soto-Chavez et al. (2024) revealed that ChatGPT encountered limitations with medical information terminology in Spanish. Similarly, Chen et al. (2024) compared GPT-4 and GPT-3.5 on Taiwan's pulmonologist exam, demonstrating GPT-4's superior performance in a non-English context [3, 4]. These findings underscore the necessity of evaluating LLMs in diverse linguistic settings to ensure their reliability in these diverse healthcare contexts.

While some studies suggest that newer LLMs, such as GPT-4, outperform their predecessors in diagnostic accuracy, others reveal notable persistent limitations in non-English contexts. Chen et al. (2024) demonstrated that GPT-4 achieved superior results on Taiwan's Pulmonologist Exam compared to GPT-3.5, whereas Kılıç (2023) found that ChatGPT-3.5 struggled with Turkish medical exam questions [4, 5]. These inconsistent findings highlight the need for further refinement of LLMs to meet the rigorous standards required for medical education and practice.

The global nature of healthcare services necessitates tools that enhance reliability and efficiency across linguistic and cultural boundaries. Strika et al. (2025) and Tong et al.

(2023) have drawn attention to the cultural and linguistic biases in LLMs, particularly in healthcare systems, which have led to inaccuracies and disparities in non-English contexts [6, 7]. Addressing these biases is not only essential for improving diagnostic accuracy but also a critical step toward developing culturally and linguistically relevant LLM tools that can enhance access to healthcare services and promote global health equity.

As emphasized by A-Abbasi et al. (2024) and Bautista et al. (2023), further research into the cross-linguistic capabilities of AI models, particularly in underserved languages, are imperative [8, 9].

AIM

The aim for this study was to evaluate the efficacy of ChatGPT-4o and Claude 3.5 Sonnet in diagnosing diseases from clinical case descriptions presented in various languages.

MATERIALS AND METHODS

We evaluated the diagnostic accuracy of ChatGPT-4o and Claude 3.5 Sonnet, using on a standardized cohort of 50 pre-diagnosed medical clinical case descriptions pulled from Medscape Case Challenges series. 35 of them were published in 2023 and 15 between December 2024 and January 2025. The original English case scenarios were translated into Arabic and Ukrainian, using automated translation tools, then reviewed and revised by medical professionals familiar with the target languages, to ensure not only linguistic accuracy but also to reflect the precise medical terminology and nuances required.

150 diagnostic evaluations were performed for each LLM, balanced evenly across three languages (50 per language). The test cases were based on various medical conditions, such as cardiovascular, respiratory, and gastrointestinal diseases, etc... to provide a thorough evaluation of the LLMs' capability. The outputs were clinically evaluated using predetermined diagnostic criteria, and results were reviewed by a clinician panel.

The data are represented as M±SD. The Mann-Whitney U-Test was used to compare the mean values. The difference between proportions was determined using Fisher's Exact Two-Tailed test. Wilson's method was utilized to compute 95% confidence intervals (CI) for proportions. The difference was considered statistically significant at p<0.05.

RESULTS

The average performance of ChatGPT-4o in establishing a correct diagnosis was 62.00±15.62% (Table 1).

Its productivity was almost the same when providing cases in English and Ukrainian languages (p>0.05). However, for cases presented in Arabic, the performance was 1.6 times lower compared to the English and Ukrainian versions (p<0.05).

The overall productivity of Claude 3.5 Sonnet (60.67±19.73%) was slightly lower compared to ChatGPT-4o, but the difference was statistically insignificant (p>0.05). It showed the highest diagnosing performance when providing a description in the Ukrainian language. As in the case of ChatGPT-4o, when clinical case descriptions were given in Arabic, this LLM's efficiency was significantly lower (p<0.05).

Both LLMs showed almost the same performance when providing clinical case descriptions in English and Ukrainian (p>0.05). However, the efficacy of Claude 3.5 Sonnet was slightly lower than ChatGPT-4o when the tasks were in Arabic, although the difference was not statistically significant (p>0.05).

For case specific, the analysis was focused on the percentage of cases each model answered correctly in one, two, or all three languages, as well as the percentage of cases where both models failed to provide a correct diagnosis in any language.

ChatGPT-4o made the correct diagnosis in all tested languages in 19 cases (38.00%, 95% CI: 25.86-51.85%) and in two languages in 16 cases (32.00%, 95% CI: 20.76-45.81%), most of which (14) were in English and Ukrainian. In only 4 cases (8.00% 95% CI: 3.16-18.84%), this LLM was able to diagnose the disease correctly in any one language. In 22.00% of cases (95% CI: 12.75-35.24%), ChatGPT-4o failed to provide a correct diagnosis regardless of the description's language.

The performance of Claude 3.5 Sonnet in this aspect was almost the same as that of ChatGPT-4o (p>0.05). Thus, the correct diagnosis in all languages was established in 16 cases (32.00%, 95% CI: 20.76-45.81%), in two and one language – in 19 (38.00, 95% CI: 25.86-51.85%) and 5 cases (10.00%, 95% CI: 4.35-21.36%) respectively. Claude 3.5 Sonnet failed to diagnose the disease in 20% (95% CI: 11.24-33.04%) of cases independently of the description's language, which was comparable to the ChatGPT-4o's results (p>0.05).

The diagnostic performance of ChatGPT-4o and Claude 3.5 Sonnet was further analyzed based on the publication period of the clinical cases across three languages (Table 2).

For clinical cases published in Period 1, the average performance of ChatGPT-4o was 63.81±13.50%. When providing descriptions in English and Ukrainian, the frequency of correct diagnosis was almost the same (p>0.05). However,

Table 1. Total performance of LLMs in diagnosing diseases, % (95% CI)

Language	ChatGPT-4o	Claude 3.5 Sonnet
English	72.00 (58.33-82.53)	70.00 (56.25-80.90)
Arabic	44.00 (31.16-57.69)*	38.00 (25.86-51.85)*
Ukrainian	70.00 (56.25-80.90)	74.00 (60.45-84.13)

Note: * – the difference is statistically significant compared to English and Ukrainian languages (p < 0.05)

Source: compiled by the authors of this study

Table 2. The LLMs' efficacy depending on the period of clinical case publishing, % (95% CI)

Period of publication	Language	ChatGPT-4o	Claude 3.5 Sonnet
Period 1	English	74.29 (57.93-85.84)	71.43 (54.95-83.67)
	Arabic	48.57 (32.99-64.43)*	40.00 (25.55-56.43)*#
	Ukrainian	68.57 (52.02-81.45)	77.14 (60.98-87.93)
Period 2	English	66.67 (41.71-84.82)	66.67 (41.71-84.82)
	Arabic	33.33 (15.18-58.29)	33.33 (15.18-58.29)
	Ukrainian	73.33 (48.05-89.10)	66.67 (41.71-84.82)

Note: * - the difference is statistically significant compared to the English language ($p < 0.05$). # - the difference is statistically significant compared to the Ukrainian language ($p < 0.05$).

Source: compiled by the authors of this study

when cases were provided in Arabic, the efficiency was significantly lower ($p < 0.05$).

The average efficiency of ChatGPT-4o when working with clinical cases from Period 2 was slightly lower compared to Period 1 ($57.78 \pm 21.43\%$, $p > 0.05$). It showed the highest performance for descriptions in Ukrainian and the lowest in Arabic. However, the difference was statistically insignificant ($p > 0.05$).

The average diagnostic performance of Claude 3.5 Sonnet for clinical cases from Period 1 was comparable to that of ChatGPT-4o in the same period ($62.86 \pm 20.00\%$, $p > 0.05$). Depending on the language, the productivity was highest for Ukrainian and lowest for Arabic ($p < 0.05$). The performance for cases from Period 2 decreased slightly ($55.56 \pm 19.25\%$, $p > 0.05$). Although the rate of correct diagnosis in Arabic was lower compared to other languages, this difference was not statistically significant ($p > 0.05$).

A pairwise comparison of the effectiveness of both LLMs depending on language revealed no statistically significant differences for any publication period ($p > 0.05$).

DISCUSSION

This research reveals important findings about the accuracy of Large Language Models (LLMs) in multilingual health settings through an analysis of ChatGPT-4o and Claude 3.5 Sonnet performance. The results highlight both the potential and limitations of these models across English, Ukrainian, and Arabic languages, underscoring the need for further refinement to ensure their reliability in diverse linguistic and cultural contexts.

When the performance was compared for both models, ChatGPT-4o demonstrated a slightly higher overall accuracy (62.00%) compared to Claude 3.5 Sonnet (60.67%). This difference was not statistically significant ($p > 0.05$). The outcomes are both anticipated and alarming for current LLMs. Although the differences for ChatGPT-4o and Claude 3.5 Sonnet seem more manageable regarding incremental differences for LLMs (Shah-Mohammadi et al., 2024), the absolute accuracy (approximately 60-62%) of both models is a long way below the accuracy of human clinicians (generally over 90% in controlled diagnostic tasks) [10]. This reflects findings from Takita et al. (2025) where even the best performing

LLMs are still not able to match physician accuracy within the context of multilingual medical QA, particularly for non-English languages [11]. As indicated by the lack of significance ($p > 0.05$), neither model establishes a clear or meaningful advantage clinically within this study. These findings reflect larger trends in LLM performance differences by language or generally performance trends in Arabic where limitations were most notable for both models.

This finding echoes the observations of Shah-Mohammadi et al. (2024), who noted marginal improvements in newer LLM iterations like ChatGPT-4 over their predecessors. However, their research also indicated a decline in accuracy at a more granular level, particularly for rare or complex medical conditions [10]. The consistent struggle of both models with Arabic diagnostic tasks suggests that advancements in general LLM architecture alone may be insufficient to overcome linguistic biases. Addressing these disparities necessitates targeted strategies focused on enriching training datasets with diverse linguistic and cultural data.

When it comes to diagnostic performance across languages, a notable disparity in diagnostic accuracy has emerged. Both LLMs demonstrated significantly reduced performance when processing Arabic text compared to English and Ukrainian. The shortcomings in Arabic are widely acknowledged in the literature. For instance, Ghazawi et al. (2025) showed that LLMs like GPT-4 tended to score 15-20% lower on Arabic essay grading than English, with the authors attributed this to differences in cultural adaptation and dialectal language use [12]. Robinson et al (2025) showed a consistent drop in accuracy for dialectal Arabic in medical QA tasks, arguing that this was due to tokenization biases and lack of sufficient training data for dialectal Arabic [13]. Our findings confirmed these observations and highlight that Arabic's morphological complexity and low - resource status during LLM training compounded the performance gap.

The results corroborate previous findings which emphasize that LLMs experience substantial difficulties when working with non-English languages. For instance, Gulati et al. (2024) demonstrated limitations in ChatGPT's ability to handle medical terminology in Hindi and Russian, while Schluskel et al. (2024) concluded that while GPT-4 shows promise as a supplementary tool for patient education,

but it requires further refinement and validation before integration into clinical care [14, 15]. The pronounced underperformance in Arabic likely stems from a combination of factors: the inherent linguistic complexity of Arabic, the potential scarcity of Arabic healthcare data in LLM training datasets, and the inadequate representation of cultural nuances relevant to Arabic-speaking healthcare contexts. This highlights a critical need for the development of LLMs that are genuinely multilingual, particularly given the digital resource disparities faced by many languages globally. Clinically, this means LLM diagnostic reliability is inherently unstable for Arabic-speaking populations, risking misdiagnosis or underdiagnosis in real-world settings where language-specific nuances are critical.

The observed ~20% failure rate across languages indicates that there are some cases that are problematic for current LLMs, and cannot be improved with translation to different dialects or languages. These issues may pertain to: 1) the complexity of the case or the way it is presented (e.g., rare conditions with ambiguous or vague symptoms); 2) the constraints on reasoning LLMs have for whatever reason, as reported in Huang et al (2025), where hallucinations are reported at rates of 15-30% in a clinical task [16]. Significantly, the language independence of errors indicates LLMs are struggling with medical reasoning more than the processing of language translation.

The aim of this study was also to investigate the way the period in which a case study was published would affect its diagnostic performance. Both models exhibited a decline in performance for cases published in 2024-2025 compared to 2023 ($p > 0.05$). This temporal decline could be attributed to increased complexity in contemporary healthcare cases or evolving evaluation standards. The decrease could be a consequence of the training data cutoff for LLMs (e.g., at the time of this study, ChatGPT's knowledge cuts off in June 2024), or it could also be a result of increased case complexity associated with more recent studies. However, it does present a similar finding as Chen et al. (2024) found that LLMs exhibited delays in synthesizing novel medical knowledge post-training [17], highlighting the need for dynamic fine-tuning to keep up with medical knowledge advancement [8]. Additionally, the better performance by LLMs in English, as compared to Arabic, highlights another pressing ethical dilemma: LLMs may unintentionally contribute to subsequent healthcare disparities, as there are currently 400 million Arabic speakers unless we prioritize equitable distribution of data and bias mitigation efforts.

Alternatively, it could be a fundamental limitation of the ability of LLMs to effectively process authentic new or fast-paced medical knowledge. This point is closely related to the concerns raised by Al-Garadi et al. (2025) and Clusmann et al. (2023) advocating for responsible implementation frameworks of LLMs [18, 19], which offer strategies to promote responsible implementation, such as fine-tuning, prompt-engineering and EHR integration, among others, while also providing recommendations for future work aimed to protect data privacy, reduce bias, adhere to regulations, and promote computational sustainability.

These findings highlight the urgent necessity for continued updating and fine-tuning of LLMs in order to keep pace with medical change. This study has serious implications for global healthcare, where languages and cultural approaches to care are intrinsic variations in care delivery. The result that LLMs performed poorly in Arabic demonstrates an important divide in equitable access to AI-powered diagnostic tools for many non-English speaking populations. This disparity may worsen existing health inequities in settings already suffering healthcare shortages. As highlighted by Zhong et al. (2024) and Kapil et al. (2024), the challenge of mitigating this bias lies not only in technical means, but is also a moral obligation in promoting global health equity [20, 21].

Despite the strengths of this study, there are some limitations that need to be acknowledged. The automated translation, which was subsequently reviewed by medical experts, may have produced minor inconsistencies (i.e. errors) in the Arabic and Ukrainian case scenarios. The sample size, while substantial, is not meant to be all-encompassing, and ongoing potential variability in medical cases from these other language contexts may not have been reflected. Future studies can also compare overall performance of LLMs across other languages and medical specialized areas with both larger and more inclusionary datasets. Developing training protocols for LLMs to exercise cultural and linguistic sensitivity should be addressed in research to assist with the accuracy and reliability of LLMs in global healthcare infrastructures usually in multiple languages.

Substantially, this study identifies the immense utility of LLMs in clinical decision-making in translated case scenarios, and equally demonstrates the glaring challenges for languages that are not English. This concludes an immediate need for continued research and development aimed at reducing language and cultural biases while improving diagnostic performance. Ultimately, achieving equitable access to AI-based healthcare tools will require a collective effort by AI developers, physicians, and language experts. In such multi-disciplinary collaboration, we

can aspire to build more inclusive LLMs, in turn creating better care for patients and expanding global health equity.

CONCLUSIONS

In this study, large variations in the measures of diagnostic accuracy were recorded for both ChatGPT-4o and Claude 3.5 Sonnet depending on the language of clinical case descriptions with lower of accuracy in Arabic compared to English and Ukrainian. Language biases in model performance, limited language training datasets for non-English languages, and decreasing accuracy in relation to newer medical case descriptions were the key limitations. The nature of the language and cultural aspects of the case descriptions, and relevance of the medical knowledge for newer medical cases, were statistically associated with the measures of accuracy and misdiagnosis. Further research across language training datasets will aid in developing more accurate models, improving specifications, and developing bias and mitigations for uses of LLMs in global healthcare settings.

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Application of the medicine GPT model in diagnosing rare diseases in the emergency department

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ABSTRACT

Aim: Evaluation of the diagnostic accuracy and clinical utility of the Medicine GPT model in identifying and managing rare diseases in the emergency department.

Materials and Methods: A retrospective study was conducted using 100 published rare case reports retrieved from PubMed. Cases were selected based on three common complaints: chest pain ($n = 50$), abdominal pain ($n = 30$), and shortness of breath ($n = 20$). Each case's clinical presentation was input into Medicine GPT, which then generated a leading diagnosis. The primary outcome was the proportion of correct diagnoses. Cohen's Kappa (κ) was calculated to determine inter-rater reliability.

Diagnostic accuracy varied by symptom category: chest pain (92%, $\kappa = 0.84$), abdominal pain (87%, $\kappa = 0.81$), and shortness of breath (90%, $\kappa = 0.875$). Based on full clinical presentations, overall diagnostic agreement reached 90% ($\kappa = 0.84$), indicating substantial to almost perfect consistency.

Conclusions: Medicine GPT demonstrated substantial diagnostic accuracy for rare emergency department presentations, indicating potential to enhance clinical decision-making. It may serve as a foundation for refining future AI models in real-world settings, but always should remain only as an assistive tool for professional clinical judgment.

KEY WORDS: emergency medicine, differential diagnosis, artificial intelligence, clinical decision-making

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INTRODUCTION

Artificial intelligence (AI) is increasingly transforming the landscape of modern medicine. Initially implemented in tasks such as medical image interpretation and pattern recognition [1], AI has now expanded into more sophisticated domains including clinical decision support, patient data synthesis, and disease diagnosis [2]. As these systems evolve, their integration with comprehensive medical databases such as PubMed, clinical practice guidelines, and high-impact peer-reviewed journals is becoming more seamless. This allows AI models to function not only as repositories of information but as active diagnostic agents capable of offering clinical recommendations [3]. These systems are now incorporating diagnostic algorithms that use patient-specific variables – such as age, sex, ethnicity, geographical location, and clinical presentation – to formulate highly tailored and evidence-based differential diagnoses [4]. Advanced models are capable of asking dynamic, patient-specific follow-up questions, mimicking the approach of human clinicians. Such adaptive features enhance diagnostic precision, especially when dealing with complex or atypical symptom presentations [5]. With access to electronic health records (EHRs), laboratory data, and imaging studies, AI tools can rapidly analyze and cross-reference patient data with the latest medical evidence, thereby reducing diagnostic time and cognitive load on physicians [6]. The utility of AI becomes even more apparent

in high-pressure settings such as emergency departments, where the gap between demand and available medical staff continues to widen. Time-sensitive decision-making, heavy workloads, and increasing case complexity put tremendous strain on emergency physicians [7]. Incorporating AI into such environments could yield numerous benefits – streamlining workflow, supporting triage and diagnosis, and minimizing diagnostic errors. Of particular importance is the management of rare clinical conditions, which often pose significant diagnostic challenges and carry a higher risk of medical error. Given the potentially severe consequences of misdiagnosis in such cases, the ability of AI systems to quickly and accurately narrow down differential diagnoses offers a critical advantage [8]. Recent years have witnessed the development of general-purpose models such as ChatGPT 3.5 and 4.0, which have shown varying degrees of diagnostic accuracy in clinical simulations [9]. While promising, these models are not specifically trained to handle the nuances and complexity of real-world medical cases. As such, there has been a growing interest in building domain-specific models with medical expertise. One such innovation is Medicine GPT – a next-generation AI model specifically designed to simulate clinical reasoning and provide diagnostic support. Medicine GPT differs fundamentally from its predecessors by being fine-tuned on a diverse array of clinical data, including case reports, guidelines from global health authorities, as well as

disease-specific literature. Its interactive capabilities allow it to behave like a digital clinician: interpreting symptoms, asking relevant follow-up questions, suggesting investigations, and recommending management plans – all rooted in evidence-based guidelines. Medicine GPT's strength lies in its design to replicate structured diagnostic reasoning pathways. This makes it particularly advantageous in emergency settings, where decisions must be made swiftly and accurately [7]. Unlike generalized AI platforms, Medicine GPT is optimized to provide clinically sound suggestions based on the latest medical standards and is especially suited for identifying and managing rare or complex conditions [8]. This reflects a broader trend toward the convergence of human clinical expertise and high-performance machine intelligence in healthcare delivery [10]. Despite its promising features, there is currently a lack of empirical research assessing the performance of Medicine GPT in real-world or simulated clinical environments. Thus, its diagnostic utility remains largely theoretical. This study aims to bridge that gap by evaluating the diagnostic accuracy of Medicine GPT in managing rare clinical conditions encountered in the emergency department. The goal is to determine whether Medicine GPT can offer a reliable and practical tool for clinicians operating in high-stakes, time-constrained settings.

AIM

This study aims to assess the diagnostic accuracy and practical applicability of Medicine GPT – domain-specific AI model trained on clinical data – in identifying rare and complex conditions in emergency department settings, with particular emphasis on its ability to simulate structured clinical reasoning, support time-sensitive decision-making, and reduce diagnostic error under real-world constraints.

MATERIALS AND METHODS

CLINICAL CASE VIGNETTES

To test the accuracy of Medicine GPT, 100 case reports were retrieved from PubMed using the keywords “rare case report + presenting complaint.” We evaluated 50 cases of chest pain, 30 cases of abdominal pain, and 20 cases of shortness of breath – three common symptoms presented in the emergency room.

DIAGNOSTIC ASSESSMENT USING MEDICINE GPT

The clinical presentations from each case report were input into Medicine GPT without revealing the final diagnosis. The model was asked to generate a differential diagnosis based on the symptoms, and its leading diagnosis was recorded (Fig. 1). The accuracy of Medicine GPT was then evaluated by comparing its leading diagnosis to the confirmed final diagnosis in the published case reports.

STATISTICAL ANALYSIS

To assess the accuracy of Medicine GPT in resolving case reports, inter-rater reliability was measured using Cohen's Kappa (κ) (Table 1). This test evaluates the level of agreement between diagnostic assessments of AI and those provided in the case report, while accounting for agreement occurring by chance.

REVIEW AND DISCUSSION

Medicine GPT demonstrated high diagnostic accuracy across different symptom categories (Table 2). For patients presenting with chest pain, the AI correctly identified the diagnosis in 46 out of 50 cases (92%), with $\kappa=0.84$, (almost perfect agreement). In abdominal pain cases, accuracy was 26 out of 30 (87%), with $\kappa=0.81$ (almost perfect agreement). For shortness of breath, the correct diagnosis was achieved in 18 out of 20 cases (90%), with $\kappa=0.875$ (almost perfect agreement). Overall, Medicine GPT resolved 90 out of 100 rare clinical cases (90%), with $\kappa=0.84$ (almost perfect agreement).

In this study, we evaluated the diagnostic accuracy of Medicine GPT in resolving case reports across different symptom categories. Overall accuracy was 90%, with $\kappa = 0.84$. These findings suggest that AI systems can support clinical decision-making with to near-perfect agreement with the case report final diagnosis.

COMPARISON

Our findings align with earlier investigations demonstrating the diagnostic potential of AI in clinical contexts [11, 12]. The observed κ values ranging from 0.81 to 0.875 underscore the reliability of Medicine GPT in structured diagnostic tasks. The model demonstrated the capacity to integrate and apply current clinical guidelines to confirm likely diagnoses and recommend appropriate treatment strategies [11-13].

POTENTIAL IMPLICATIONS FOR CLINICAL PRACTICE

Medicine GPT represents a significant advancement in the use of conversational AI for clinical decision support, particularly in the emergency setting. This environment demands rapid and accurate clinical reasoning, and Medicine GPT's ability to generate a structured differential diagnosis based on input symptoms can support clinicians in initial triage and decision-making [14-16]. Because it draws from a large corpus of up-to-date clinical guidelines and evidence-based literature, Medicine GPT ensures consistency and accuracy in its diagnostic suggestions [17, 18]. Integrating such systems into electronic health records (EHRs) or hospital information systems (HIS) could allow for real-time diagnostic support during patient encounters. This can promote standardized care, reduce diagnostic variability, and reinforce best practices [19]. In resource-constrained environments facing physician shortages, Medicine GPT may reduce clinician workload by partially automating symptom assessment, differential generation, and initial triage [20]. This could result in shorter waiting times, more efficient patient throughput, and a reduction in diagnostic delays in overcrowded departments. Furthermore, its high diagnostic accuracy makes it a valuable tool for managing complex presentations where human error may be more likely [21, 22]. By minimizing discrepancies and enhancing clinical confidence, the use of AI in this manner can contribute to improved patient safety and health outcomes [23]. As digital transformation accelerates within healthcare systems globally, AI-powered systems like Medicine GPT could support the creation of intelligent, adaptive, and resilient clinical infrastructures [24]. Their ability to interface with existing digital tools will be key to successful implementation across care settings [24].



Medicine GPT

Autor: Dr Jamshed Moidu

Ultimate guide for all medical conditions.

Take me to 'AI Medical Hub' ?

Differential Diagnosis for chest pain ?

Prepare me USMLE/PLAB/NEET/ or other major...

Diagnosis and management of MI ?

An obese 62-year-old female patient, with a 3-day history of chest pain, was admitted to the hospital with a suspected acute coronary event. She had been diagnosed with high-grade bladder cancer 6 months before. After the transurethral electroresection of the tumor 5 months before and subsequent chemotherapy (gemcitabine and cisplatin), the patient was qualified for the next cancer surgery. On admission, the patient remained without chest pain. The ECG record demonstrated inverted T waves in the leads from above the anterior and lateral wall. The coronarography demonstrated minor atherosclerotic changes in the coronary arteries.

The most likely diagnosis in this case is **Takotsubo cardiomyopathy (TTC)**, also known as **stress-induced cardiomyopathy** or "**broken heart syndrome**."

Reasoning for Diagnosis:

1. **Clinical Presentation:**

- The patient is a 62-year-old obese female, a demographic commonly affected by Takotsubo cardiomyopathy.
- She presented with chest pain suggestive of an acute coronary event.
- She has a history of **high-grade bladder cancer and recent chemotherapy**, which can act as a physiological and emotional stressor, a known trigger for Takotsubo cardiomyopathy.

Fig. 1. Example of Medicine GPT correct leading diagnosis based on the clinical presentation provided from a case report.

Sources: <https://chatgpt.com/g/g-rgWJmXVhn-medicine-gpt>;

Zalewska-Adamiec M, Klonowska P, Małyszko J, Kuźma Ł, Bachorzewska-Gajewska H, Dobrzycki S. Primary Takotsubo Syndrome as a Complication of Bladder Cancer Treatment in a 62-Year-Old Woman. *Am J Case Rep.* 2021 Apr 20;22:e930090. doi: 10.12659/AJCR.930090.

Table 1. Interpretation of Cohen's Kappa coefficient according to Landis and Koch (1966).

κ Value	Interpretation according to Landis & Koch (1966)
<0,00	No agreement
0,00-0,20	Slight agreement
0,21-0,40	Fair agreement
0,41-0,60	Moderate agreement
0,61-0,80	Substantial agreement
0,81-1,00	Almost perfect agreement

Source: McHugh ML. Interrater reliability: the kappa statistic. *Biochem Med (Zagreb).* 2012;22(3):276-82.

Table 2. Diagnostic accuracy of Medicine GPT across different symptom categories, including the number of accurate diagnoses, total cases, accuracy percentage, and Cohen's Kappa coefficient.

Symptom	Accurate Diagnoses	Total Diagnoses	Accuracy (%)	Cohen's Kappa
Chest pain	46	50	92%	0.84
Abdominal Pain	26	30	87%	0.81
Shortness of breath	18	20	90%	0.875
Total	90	100	90%	0.84

Source: Own materials

LIMITATIONS

Despite the encouraging findings, several limitations must be considered. The study relied on retrospective case reports, which do not fully capture the complexity and variability of real-time patient encounters. Real-life clinical scenarios are often less structured and more nuanced, presenting challenges that pre-prepared case reports may fail to replicate [16]. Additionally, retrospective analysis limits the capacity to evaluate decision-making under time pressure, a critical aspect of emergency medicine [18]. While Cohen's Kappa is a reliable indicator of inter-rater agreement, it does not account for the clinical significance of specific diagnostic errors [25]. An AI system may perform well statistically yet still fail in high-risk scenarios where accuracy is most crucial. Furthermore, the scope of the sample may have affected the generalizability of the. To enhance the robustness of future evaluations, studies should employ larger, more diverse clinical datasets collected across multiple healthcare settings. Inclusion of real-world clinical workflows, prospective designs, and geographic variability will improve the external validity of subsequent analyses [19].

FUTURE DIRECTIONS

Further research should prioritize real-world validation of AI diagnostic models in clinical environments where diagnostic accuracy has direct implications for patient outcomes. Emergency departments would benefit from tools that provide rapid,

accurate, and reliable diagnostic support under pressure [20]. In addition to technical validation, ethical, legal, and safety considerations must be explored, particularly regarding liability in cases of diagnostic error [23]. Studies should also focus on the model's ability to correctly identify and manage high-acuity conditions such as stroke, sepsis, and pulmonary embolism [22]. Emerging conversational AI systems like Medicine GPT, with their interactive and context-aware capabilities, show potential for dynamic clinical dialogue. These systems could gather relevant information by asking targeted follow-up questions and iteratively refining the differential diagnosis. Future work should examine diagnostic accuracy in scenarios where AI interacts directly with patients or clinicians using natural language inputs [11, 12, 24]. Such approaches could facilitate broader integration in primary care, emergency departments, and telemedicine settings [13].

CONCLUSIONS

This study demonstrates the substantial diagnostic accuracy of Medicine GPT across different symptom categories, with promising agreement ($\kappa = 0.81\text{--}0.875$) compared to final case report diagnosis. These findings highlight AI's potential only to support clinical decision-making; however, AI should always be seen as an adjunct rather than a replacement for human expertise, as real-world challenges such as atypical presentations, missing data, and complex clinical reasoning remain limitations.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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Artificial intelligence in the value system of future doctors

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ABSTRACT

Aim: To analyze the significance of modern computer technologies within the value systems of teachers and students at medical universities. Through expert assessments, it explores the advantages and risks associated with artificial intelligence. Special attention is given to the impact of the ongoing war on the value orientations of future doctors and the organization of professional training under new conditions.

Materials and Methods: The research employed modern methods of analysis, synthesis, generalization, and comparison, alongside expert assessments and creative essays. It also drew upon the experience of Ukrainian and Polish colleagues in creatively integrating AI into the educational process, particularly in training future doctors for effective patient communication during anamnesis-taking and for understanding the risks of iatrogenesis. To achieve the research goals, a digital information search was conducted using the scientometric database Scopus.

Conclusions: In the face of new challenges, there is an increasing need to examine the dynamics of professional self-development, motivation, and the value systems of future doctors. Given the innovative nature of AI, its potential applications in medicine, its significant benefits, and its possible risks, it is essential to study this issue in depth and systematically prepare medical students for the rational use of modern information technologies. The importance of international collaboration, comparative research, and the practical implementation of the Club of Rome's recommendations on integral thinking continues to grow.

KEY WORDS: medicine, professional training, values, creativity, artificial intelligence, communication, medical history, iatrogenics

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INTRODUCTION

The problem of improving the quality of modern doctors' training is gradually becoming a priority. It is no coincidence that in all sociological studies the issue of health occupies one of the priority places. It is necessary to realize that this is a complex, complicated problem that does not have a linear solution. When solving most of the current issues of medicine, the personality of the doctor and the personality of the patient remain in the first roles. That is why the issues of values do not lose their relevance. This is also evidenced by numerous studies of recent years [1, 2].

We have singled out the problem of values, since it is this aspect that directly affects motivation, planning of professional self-improvement, empathy, communication with patients, relatives of a sick person, colleagues. Confirmation of the relevance of the research topic is the fact that in September 2024 the tenth scientific forum of researchers from Ukraine and Poland was held with the eloquent title "Education for the Digital Transformation of Society". Systemic changes in the globalized world, new challenges, the spread of information technologies require new approaches in the medical education system [3, 4]. We note the incredible rate of change. If in the middle of the last century the first theoretical works devoted to the issues of artificial intelligence were published, then in recent years we have witnessed an avalanche-like growth of information flows [5, 6]. It is no coincidence that Polish

authors in their outstanding work "Pedagogical Encyclopedia of the 21st Century" consider the issue of information stress and even "information flood". We emphasize the importance of continued collaboration between Polish and Ukrainian researchers. On June 30, 2025, the website of the Ternopil National Medical University published information about the visit of Associate Professor of the Department of General Surgery A.V. Pavlyshyn to the Opole Polytechnic (Poland) for the purpose of „participation in the international research project „Application of Artificial Intelligence (AI) in Medicine". The project is aimed at creating, verifying and implementing the latest effective artificial intelligence technologies for analyzing visual markers of wounds and the wound process, identifying and analyzing types of damage to various types of tissues (skin, subcutaneous fat, muscles, fascia, bones, etc.). The study includes the formation of unique databases of different types of wounds, unified scales for visual assessment of wound defects, combat and civilian injuries. The result of this study will be the creation of a prototype of an intelligent telemedical decision support system for optimal strategies for identifying, sorting and treating civilian and combat injuries at different stages of pre-medical and medical care. The main goal of the research is to develop, test and implement effective artificial intelligence technologies for identifying various types of wounds, combat and civilian injuries based on automated analysis of photo and video

data" [7]. It should be noted that this is only one example of multifaceted, systematic cooperation between scientists. The importance of research aimed at studying the advantages and disadvantages of artificial intelligence is growing. In particular, significant advantages have been established in finding sources of information, speed, successful review of author's texts, ordering and visualization of significant amounts of information using tables and graphs. At the same time, significant difficulties are observed in artificial intelligence when performing creative tasks, inability to recognize elements of irony, insufficient consideration of individual characteristics.

AIM

To analyze the significance of modern computer technologies within the value systems of teachers and students at medical universities. Through expert assessments, it explores the advantages and risks associated with artificial intelligence. Special attention is given to the impact of the ongoing war on the value orientations of future doctors and the organization of professional training under new conditions.

MATERIALS AND METHODS

The study used modern methods of scientific research, in particular, analytical review of sources, generalization, comparison of data according to the requirements of comparative studies. Special attention was paid to expert assessments, creative essays, achievements of Ukrainian and Polish colleagues in the creative use of artificial intelligence in the educational process, development of empathy, training of future doctors for effective communication with patients in the process of anamnesis, understanding the threats of iatrogenics. To achieve the goal of the study, we used a digital information search tool in the Scopus scientometric database, used an information search method that reflects the content of interconnected professional values of medical students. Based on the data obtained on 22,823 documents (published in 1963-2025), we used the method of content analysis of the works of authors who published the most articles on this topic, which helped to identify promising directions for the development of professional values of medical students. To achieve the goal of the study, we used a digital information search tool in the scientometric database Scopus, creating an original system of concepts that reflects the content of different and at the same time interconnected professional values of medical students: ALL („values,“) OR ALL („professional values of doctor,“) OR ALL („interpersonal communication skills,“) AND ALL („medical students,“) OR ALL („medical education,“) OR ALL („ethical,“) OR ALL („abortion,“) AND ALL („empathy,“). We obtained data on 22,823 documents published in the scientometric database Scopus during 1963-2025. With the help of this digital tool, we were able to obtain generalizing information according to various indicators: chronological, geographical, source-related, etc. Further research involves conducting a content analysis of the works of authors who published the most

works on the topic of interest to us, and determining the system of professional values of medical students, using the concordance coefficient to compare the qualitative characteristics of the studied phenomena.

FRAMEWORK

The work was carried out according to the research work of I. Horbachevsky Ternopil National Medical University "0125U000116 Medical rhetoric and communication in the system of professional linguistic didactics" (state registration number 0125U000116).

REVIEW

The systemic challenges of our time pose a number of problems for medical workers: a pandemic, a war in Ukraine with mass casualties, a deterioration in the mental health of the population, professional burnout, childhood diseases, etc. In order for doctors to adequately respond to these and other challenges, they must be ready to solve professional tasks in conditions of uncertainty, in unforeseen circumstances. To do this, it is necessary to form a system of values for medical students in medical universities, which will provide clear principles and guidelines for their future professional activities. At the same time, such a system of values must be based on fundamental foundations that treat a person, his life, health, safety and dignity as the highest values.

In the current conditions of the development of world science, it is important to use the advantages of modern information technologies effectively, to understand their advantages and threats. Therefore, we consider it necessary, firstly, to show the vision of the professional values of medical students through the eyes of the most active scientists from different countries of the world, and, secondly, to share the experience of using a digital information search tool, the specifics of the scientometric database Scopus, which contributes to determining the priority values of modern medical education and improving curricula at medical universities.

Nowadays, the following questions are relevant in the international scientific discourse: ways to improve the quality of medical education in distance learning, the role of artificial intelligence as an academic and professional value for future doctors, new methods for forming communication skills of medical students, etc. In the context of these problems, one can observe the process of development and/or transformation of the value system of medical students in the 21st century. The results of the study by Öñöral & Kurtulmus-Yilmaz (2020) confirm the need for special attention to the formation of practical skills of future doctors in online learning [8]. As emphasized by AlGerafi, & Zhang (2021), who studied the perception of online learning by foreign students using the example of Chinese medical schools, in general, students did not feel confident in e-learning, because such conditions did not provide comfortable learning, preparation for communication with patients. The authors noted that technical difficulties and comprehension problems prevented international students from accepting medical education through

online learning in China, so efforts should be made to adapt them to this new reality [9]. However, if distance learning remains relevant in certain periods (for example, during a global pandemic or during a war, as is currently the case in Ukraine), then the impact of technological innovations on education seems inevitable and natural; and this requires appropriate scientific justification for their effective implementation in the educational process.

Therefore, it is important to consider, in particular, the results of the Milton et al. study that AI tools for developing written communication skills of future medical students are useful and effective means of creating academic texts. Meanwhile, their use can negatively affect the development of independent writing skills of medical students [10]. Thus, pedagogical support is needed to teach students the ethical and optimal use of AI tools as tools that facilitate, rather than replace, independent work of students. Naseer et al. (2025) note certain expectations and reservations regarding the use of AI in medical higher education institutions in general. On the one hand, they emphasize the potential of AI to improve the training and research of future doctors, and on the other hand, they are concerned about the risk of students becoming overly dependent on AI, as well as about ethical problems that may arise due to the lack of confidentiality in matters of patient health. We agree with their opinion on the need to develop ethical principles for the responsible use of AI in medical education [11]. As Almarzouki et al. (2025), who investigated the realization of medical students' interests in AI, claim, it is necessary to ensure that educational programs for future doctors foster literacy in working with AI and an understanding of how to use it appropriately in the medical profession [12]. As Rädcl-Ablas et al. emphasize, this can be achieved through innovative training methods that incorporate AI. For example, the development and use of a chatbot as a tool for educational role-playing games based on AI, which contributes to the development of patient interview

skills [13]. In addition, in the conditions of war in Ukraine, the requirements for the communicative competence of doctors are increasing, who, on the one hand, need to develop their skills in communicating with war participants, their families, and, on the other hand, English-speaking communication in the international medical community for joint solutions to modern challenges. In this regard, the study by Gutor & Sodomora (2024) highlights digital storytelling as a progressive approach to the communicative training of medical students. This method contributes to the integration of developing students' communicative and English language skills, enhances their professional thinking, and increases their mastery of medical vocabulary and terminology [14]. The aforementioned works reflect a scientific discussion about important problems of modern medical education; at the same time, it is worth objectively tracing what academic and professional values of medical students are being formed (need to be formed) in the context of addressing these pressing issues.

The results of the study show that in the second half of the twentieth century, the issue of values in the context of medical education and practice was actually not presented in scientific publications that were included in the Scopus scientometric database. And only since the beginning of the 2000s have we observed the dynamics of the growth of relevant publications. Approximately from 2009-2011 we have seen a sharp increase in scientific works devoted to the issues of values of future doctors (Fig. 1). In fact, over the past twelve years their number has increased sixfold (from 500 to 3000 units). This indicates the growing attention of modern scientists to ethical and bioethical problems, in connection with a new round of acute public discussions about the dilemma of abortion, euthanasia, the moral responsibility of doctors, the quality of medical services in the field of mental health, which is especially relevant for modern society (and not only in Ukraine, where the war is ongoing).

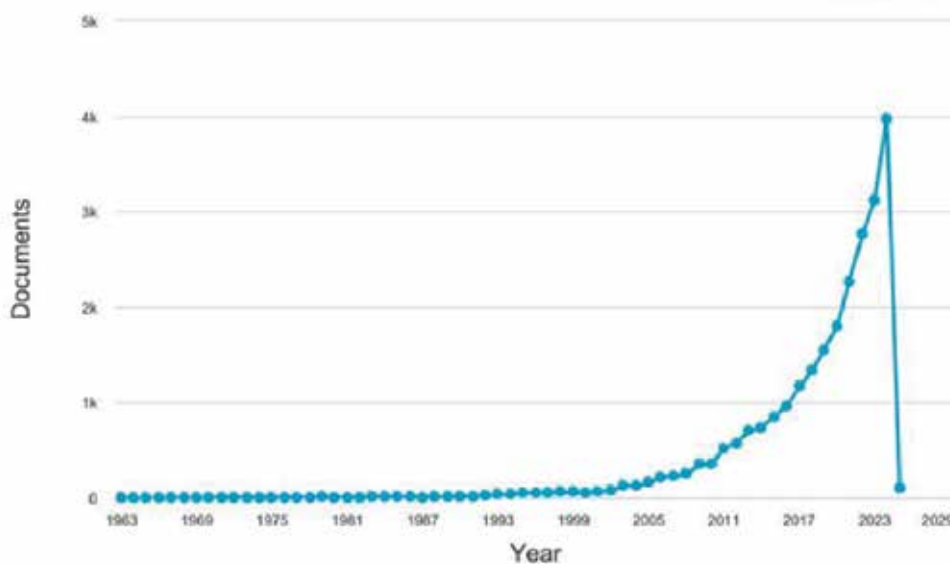


Fig. 1. Dynamics of publication of scientific research on the values of medical students

Source: Scopus

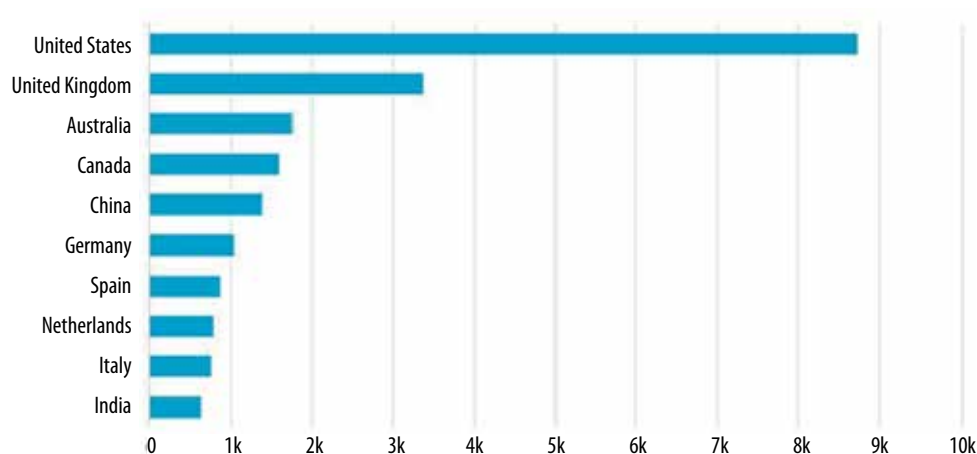


Fig 2. Geography of scientific research on the values of medical students

Source: Scopus

A eloquent „map” of scientific research on the problems of forming and implementing a system of values in the environment of medical education and the healthcare sector is presented in Fig. 2.

Thus, the largest share of scientific publications is from the USA, followed by the UK, Australia, and Canada. The next positions are occupied by China, Germany, Spain, the Netherlands, Italy, and India, where only a small number of researchers study the values of medical students.

Analyzing the data on available scientific publications by field of knowledge (Fig. 3), we see that the largest number of documents on the topic of values in medical education and practice are published in journals in the Social Sciences (24.8%). Publications in Medicine rank second (13.6%), followed by Psychology (12.0%), Arts and Humanities (11.3%), and Business and Management (10.4%). The remaining research is published in relatively small quantities (less than 5%) in fields such as Nursing, Economics, Computer Science, Environmental Studies, and Engineering.

These results will allow researchers to make adjustments to the topics of their works and will be important in the work of graduate students when writing their dissertations.

DISCUSSION

Every year, researchers increasingly recognize the importance of expert assessments of the phenomena under study. Over the past two years, we have explored the opinions of students and teachers at Ternopil National Medical University regarding the advantages and threats of using artificial intelligence in training future doctors. The results are quite revealing. According to the teachers, the advantages include: the speed of processing large amounts of information; increased efficiency, especially when performing monotonous tasks, which allows for more rational use of time; high accuracy when using algorithms; elements of creativity; access to distance learning; support for the automation of labor-intensive tasks; and the possibility of organizing competitions

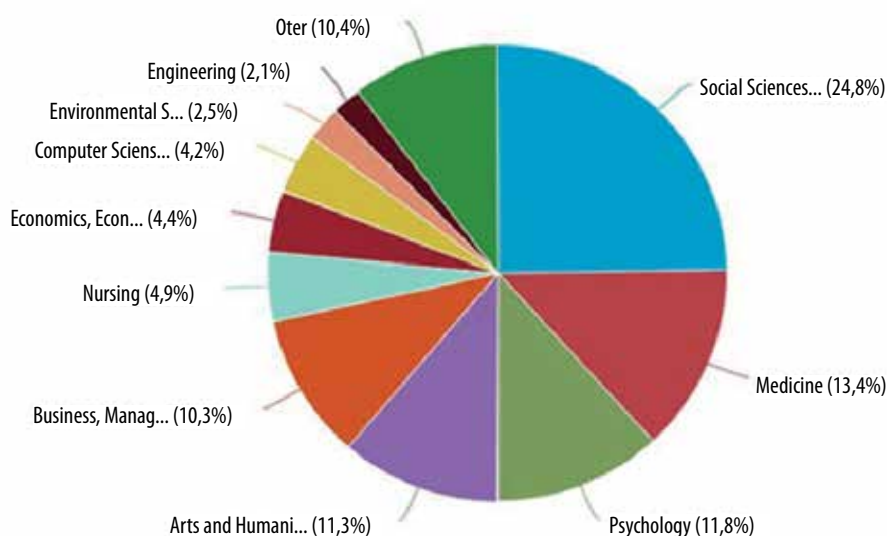


Fig. 3. Scientific research on the values of medical students by subject area

Source: Scopus

between student groups and AI in solving important professional and creative tasks. Equally interesting is the list of perceived threats: insufficient consideration of individuals' unique characteristics, which may lead to erroneous decisions; the potential for addiction; a decline in independent thinking; a lack of critical evaluation of information; violations of academic integrity; and significant costs for technical support.

The opinions of students – future doctors – who wrote creative essays on this topic at Ternopil National Medical University are of great interest. Regarding the advantages, the following views were most common: AI helps with learning, as one of the main benefits of online platforms (such as ChatGPT, Google Gemini, Grammarly, and Bing) is the ability to quickly find answers to complex questions, translate texts, and correct errors; it saves time, as AI allows for rapid processing of large amounts of information, enabling students to spend less time on routine tasks and more on understanding complex topics; and it provides convenience in everyday life, as voice assistants like Siri and Google Assistant can offer reminders, answer questions, and help plan daily activities.

The conclusions about the threats of artificial intelligence were equally thought-provoking. Students identified the following concerns: disinformation – AI can fabricate sources and information, and create fake videos and images; loss of people's ability to think critically and develop creative skills; loss of control over AI (the "machine uprising" scenario); privacy issues, since using AI services often means that personal data can be stored and used without users' knowledge, increasing the risk of information leaks; replacement of human labor, as the automation of many professions could lead to unemployment; and the potential for manipulation, because AI can be used to create fake news, manipulative content, or even synthetic voices and images.

Students draw interesting conclusions. One student noted: "From personal experience, I can say that artificial intelligence has repeatedly helped me in life and studies, saving time and making the process of acquiring knowledge somewhat simpler and more convenient. It is worth using AI as a smart tool, rather than relying entirely on it. First, try to understand the necessary material yourself, and only then turn to artificial intelligence to clarify the information."

Continuing such research – including comparing the opinions of teachers, students, doctors, and professional experts, and using the concordance coefficient for the mathematical processing of information – will help to partially offset the shortcomings and promote the rational use of AI's advantages.

In our opinion, the assessment of the capabilities of artificial intelligence in the context of theoretical foundations and practical use of the advantages of a didactic game is promising. We note the insufficient attention paid to these issues. It is enough to recall that even such a work by Nobel laureate Hermann Hesse as *The Glass Bead Game* did not find proper use in the didactics of higher medical education. Incidentally,

we note that we (A.V. Vykhreshch) have identified 12 most important aspects of this unique methodology: 1) representatives of many sciences and arts, including specialists in mathematics and music, participate in the creation of the game. The task of the interdisciplinary approach is an attempt to combine "the living beauty of spirituality and art with the magical power of formulas of exact disciplines"; 2) the theme of each game is unique, selected after discussing diverse projects on a competitive basis, and the winner receives recognition from the community; 3) among mathematicians, the game acquired great "flexibility, the ability to turn into creativity and even a certain awareness of itself and its capabilities"; 4) the game is popular among the elite of intellectual youth, who got "great pleasure" from the game; 5) gradually, the game moved to the level of synthesis; 6) the game, which was once "a professional entertainment of mathematicians, philologists, and musicians, began to increasingly attract all true intellectuals"; 7) the idea of the dynamic nature of the game, which in the process of development became "the embodiment of a spiritual and aesthetic ideal, a high cult, a mystical unity of the scattered members of the *universitas litterarum*. In our life it has taken on partly the role of art, and partly the role of abstract philosophy"; 8) interesting are the theses about the importance of contemplation and meditation in the game; 9) the game reaches an international level, gradually becoming a "public holiday"; 10) there is information about the technology of the game, which could begin with "a certain astronomical configuration, or the theme of a Bach fugue, or a phrase from Leibniz, or from the Upanishads, and then, depending on the intention and talent of the player, the leading idea called to life either developed and spread, or enriched its expressiveness with the consonances of related concepts"; 11) the game involved comparison, contrast, and harmonious combination (thesis – antithesis – synthesis); 12) as an example of choosing a game theme, G. Hesse offers an ancient ritual scheme of a Chinese manor with its orientation to the cardinal points, with a gate, a wall of spirits, the relationship and purpose of residential and utility buildings, subordinating them to the celestial bodies, the calendar, and family life, with the symbolism and rules of garden planning" [15].

Further study is required to address the problem of periodization of the development of didactic systems [16] with the identification of issues specific to medical universities. It is important to study the opinions of different age groups using the example of Poland. For example, in 2024, CBOS specialists published the results of original studies "Artificial Intelligence in the Opinion of Poles" [17] and "Artificial Intelligence – Feelings, Technology and Medical Diagnostics" [17]. This best practice should be used in European countries to obtain comparative characteristics.

CONCLUSIONS

Personality remains a determining factor in the development of society. In December 2017, experts from

the Club of Rome identified a promising area for further research, calling it integral thinking. A modern doctor is a person with a high level of empathy – a specialist who understands the patterns, causes, and consequences of disease and recovery, and who successfully uses modern information technologies, including artificial intelligence.

The “early scientific start” methodology we have developed provides for the systematic preparation of future doctors for research work, beginning from the first year. The focus is on the student’s value system, the search for original topics, the study of literary sources, and preparation for communication with senior colleagues. It is important that students are aware of the advantages and threats of modern computer systems, demonstrate civic resilience in times of war, and are committed to professional self-improvement to ensure effective help to people. The mass volunteer movement among students confirms the unity of word and deed.

A peculiar problem of modernity is the use of numerous new concepts that do not always correspond to the essence of the problem being analyzed. It is enough to recall such mythologemes as “neurolinguistic programming,” “clip thinking,” “mosaic thinking,” and a significant number of foreign terms. At first glance, everything seems logical: new challenges of modernity require new concepts. At the same time, inaccuracy in words causes inaccuracy in determining ways to solve issues and effectively achieve desired results. It is obvious that the problem being studied exists, but to understand it, a systematic analysis based on interdisciplinary scientific approaches is necessary. A new generation of students has entered university auditoriums. Using the example of a medical university, we can say that these are young people with a high level of information culture, ready to solve creative problems, with an established system of values, familiarity with foreign experience, and a developed sense of self-esteem and critical thinking.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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Functionality and protection of personal data when using Ukrainian-language mHealth apps

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ABSTRACT

Aim: to assess the functionality of mHealth apps with a Ukrainian interface and their compliance with personal data processing requirements.

Materials and Methods: we employed methods such as Overview, Data Retrieval and Analysis. The study is also based on overviewing and analyzing data of 40 mHealth apps.

Results: a study of 40 Ukrainian-language mHealth apps was conducted: 27.5% work only on Android, 72.5% on Android and iOS. There were identified 24 functions, among which the most common are arranging an appointment with a doctor (in 17 apps), online doctor consultation (in 12 apps), searching and reserving medicines (in 12 apps). Only 20 apps have a privacy policy, but most do not provide sufficient details on data processing. Only 9 apps have requirements for user data deletion, and 12 have mechanisms for withdrawing consent to data processing.

Conclusions: as a result of the study, there were detected risks for users of mHealth apps due to insufficient transparency of privacy policies, the lack of precise mechanisms for transferring personal data to third parties, withdrawal of personal data processing consent, and data deletion requirements.

KEY WORDS: e-health, human rights, digital technologies, Ukraine

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INTRODUCTION

The term «mobile health» (mHealth) is commonly employed to describe the use of mobile telecommunication technologies that are necessary to provide health care and maintain proper health condition [1-2]. The use of mHealth apps allows solving many problems that exist in the field of health care: from fighting chronic diseases to increasing the availability of quality medical care for everyone who needs it [3]. According to data from Statista, during the third quarter of 2022, Android users had access to 3.55 million apps in the Google Play App Store, whereas the App Store had approximately 1.6 million available apps during the same period [4]. It can be stated here that the share of mHealth apps among the total number of all apps is notable, since the data indicate that in the USA, 56% of doctors have discussed mHealth apps with their patients, and 26% of patients have asked their doctors about mHealth apps [5].

Attention should be drawn to the fact that «mHealth apps are classified into 2 large groups: apps for health personnel and apps for general public» [6]. In the first case, we are talking about mHealth apps that can help to establish communication directly among health personnel to analyze various situations that arise in practical activities, in the second case – about mHealth apps, which, firstly, can improve communication between health personnel and patients, and, secondly, provide users of such apps with the necessary information on

vital parameters. In addition, heed is also paid to the fact that mHealth apps can be useful for developing users' healthy habits [7].

The negative side of using mHealth apps can be considered the receiving of incorrect information by users of such apps [8], insufficient feedback between developers of mHealth apps and their users [9] and quality of the respective mHealth app [10].

AIM

This study aims to analyze Ukrainian-language mHealth apps, their functionality, and privacy policies. As part of the privacy policy research, we want to examine what user data is processed, whether it is transferred to third parties, how consent to personal data processing can be withdrawn, and how user data can be deleted.

MATERIALS AND METHODS

In the course of our study method of overviewing was employed, in order to overview mHealth apps that have the Ukrainian-language interface.

We searched for information about the Ukrainian-language mHealth apps through analyzing virtual stores of mobile apps, scientific literature and websites. To find mHealth apps in virtual stores of mobile apps we used the Google Play and App Store platforms, which are the most popular in Ukraine. Scientific literature was searched with the help of such databases as Scopus, Web of Science Core Collection,

PubMed, Google Scholar. The Google Search Engine was employed to find information about websites.

To search for mHealth apps on Google Play and Apple Store platforms, we selected the category «Medicine» and conducted an empirical study of mobile apps which were presented in these categories.

To work with scientific literature we chose keywords in Ukrainian and English for searching mHealth apps which were suitable for us. In terms of chronology we used only those articles which were published as of the end of 2022.

Key words we used:

- keywords related to health: health care, electronic health care system, medical services, telemedicine, diagnostics, patient, doctor;
- keywords related to the use of mHealth apps: mHealth, mobile apps, mobile software, electronic means, medical information system, treatment results;
- keywords which enable one to localize the search results regarding the Ukrainian-language mHealth apps: MoH (Ministry of Health of Ukraine), NHSU (National Health System of Ukraine), HELSI, eZdorovya.

Eligibility criteria for mHealth apps were determined as follows: only apps with the Ukrainian-language interface were studied. For this purpose, we explored information about such apps in virtual mobile application stores. We did not consider those apps that have the Ukrainian-language interface, but access to which is paid. Such criteria allowed us to study 40 mHealth apps.

We resorted to the method of data retrieval and analysis in order to determine functions of mHealth apps and study the privacy policy of mHealth apps (Table 1).

The selected apps were studied by us in view of the presence of privacy policy. As a result, 20 of the 40 apps did not have privacy policy. In addition, apps with privacy policy were analyzed by us concerning the presence of the following data:

- what data are processed;
- whether the data about the user are transferred to third parties;
- if it is possible to withdraw consent to the processing of personal data;
- when a user's data will be deleted.

RESULTS

We analyzed 40 Ukrainian-language mHealth apps. 11 out of 40 apps (27.5%) can be installed and used only with the help of Android. 0 out of 40 apps (0%) can be installed and used with the help of iOS. Instead, 29 out of 40 apps (72.5%) can be installed and used on both systems (Fig. 1).

DETERMINING FUNCTIONS OF MHEALTH APPS

We conducted a detailed analysis of each of the 40 mHealth apps and identified their functions. As a result, we were able to identify 24 functions of mHealth apps. Among the most common functions are the following: 1) arranging an appointment with a doctor (found in 17 apps); 2) doctor's online consultation (found in 12 apps); 3) searching and reserving medicines (found in 12 apps); 4)

obtaining medical information (found in 9 apps); 5) viewing the medical records (found in 8 apps) (Fig. 2).

The following functions of the analyzed mHealth apps occur most rarely, one time: 1) adding to the blood donor reserve list; 2) searching for defective batches of medicinal products; 3) chatting with a pharmacist; 4) viewing a doctor's prescription; 5) information on first aid provision; 6) information on actions in case of emergency situations; 7) generating a report for a doctor. A complete list of frequency of functions in mHealth apps is provided in Figure 2.

The Study of Privacy Policy of mHealth Apps. Each app was studied taking into account the presence of privacy policy. As a result, 20 out of 40 apps did not contain privacy policy. We analyzed the apps that had privacy policy with regard to the following data:

- what data about the app users are processed;
- whether the data of the app user are transferred to third parties, if yes, whether third parties, to whom the data are transferred, have been determined;
- if it is possible to withdraw consent to the processing of personal data, and if yes, in what way;
- when the app user's data will be deleted.

WHAT DATA OF THE APP USERS ARE PROCESSED?

Here we divided the data into two categories: 1) data that help to identify a person, 2) medical data.

The apps under study collect the following data which help to identify a person: name, gender, date of birth, passport data, registration number of the taxpayer's account card, place of registration / residence, photo, e-mail address, phone number, IP-address, information on the terms of the insurance policy, information on allowances, password, correspondence record, records of any bookings or advertisements, payment card or bank account details, details of the app visits, location information, information that is displayed in a social network account, occupational information, income status, ethnicity, information provided when chatting with other users, information about the device on which the apps is installed, full URLs of visit history including date and time, cookie data, marital status, referrer data. Below you can find the chart listing the data and indicating the number of apps that collect such data (Fig. 3).

As seen, data about the name (in 15 apps), phone number (in 13 apps), e-mail address (in 12 apps) are collected most frequently.

The examined apps collected the following medical data: medical information, information about medicinal products, information on the attending doctor, information on appointments with the doctor, feedback on a doctor's call, the fact of referring to the doctor (Fig. 4).

As shown, in the case with medical data, the examined apps most often collected medical information (in 6 apps), which, in particular, includes information on a patient's state of health, history of illnesses, and treatment methods. All other types of medical data occurred no more frequently than twice, as in the case with information about medicinal products.

In addition, in some apps we found unspecified formulations that do not allow us to accurately determine

Table 1. General information about mHealth apps

App Name	Creator	OC	Privacy Policy
Helsi	helsi.me	Both	Yes
Liki Control (Medication Control)	Liki Control	Both	No
DocRadar	LLC «DocRadar»	Both	Yes
OnelImpact Ukraine	Dure Technologies	Both	Yes
Doc.ua	LLC «DOC.UA»	Both	Yes
Tabletki.ua	Tabletki.ua	Both	Yes
Liki24	Liki24 Ltd	Both	Yes
Apteki.ua	Morion	Both	No
Medcard24	Medstar Solutions	Both	Yes
Persha Dopomoha (First Aid)	IFRC	Only Android	No
Likari24/7	LLC «Advanter Health»	Only Android	No
Likar Online	LLC «Likar Online»	Both	Yes
Moi Tabletki (My Pills)	level38	Only Android	No
MCA Ukraine	MCA Ukraine	Both	No
Diabetes Tracker	Axel Stein	Both	No
Apteka ANC (Pharmacy ANC)	Apteka ANC Ltd	Both	No
Apteka911	LCC «Apteka911.ua»	Both	Yes
Health24	Health24	Both	Yes
Medics	Medics	Both	No
DILA	ML DILA	Both	Yes
Odrex. Patient Room	LLC «House of Medicine»	Only Android	Yes
Apteka D.S. (Pharmacy D.S.)	Market Universal Ltd	Both	No
eLikari	IT Cerebrum	Both	Yes
MedPortal	E-life	Only Android	No
NE PIU (NO DRINK)	VITA KOD Vinnytsia	Both	No
Dobrobut (Well-being)	Dobrobut	Both	No
Apteka (Pharmacy)	eApteka	Only Android	No
Blood Preassure	aadhk	Only Android	No
Period Calendar	Simple Design Ltd.	Only Android	No
Pregnancy Calendar	Pregnancy App BabyInside	Both	No
MedUA	Maryna Dolzhenko	Both	Yes
MedexPlus	Medex Plus	Both	Yes
Bennett Test	Aliaksandr Uvarau	Only Android	Yes
My Doctor	Medstream Ltd	Both	Yes
Askep	Astwellsoft	Both	Yes
Pills Time	Mobile Creatures	Only Android	No
DobroDoc+	Domus	Both	Yes
DoctorOnline	LeoMed inc	Both	No
LadyTimer	Vipos Apps	Both	No
DostupniLiki (Affordable Medicines)	EMAIL WORLD	Only Android	Yes

Source: compiled by the authors of this study

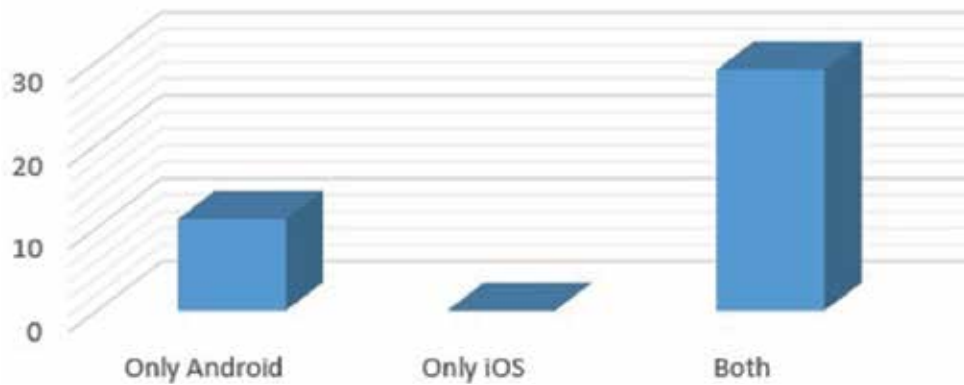


Fig. 1. Characteristics of mobile medical applications with a Ukrainian interface

Picture taken by the authors

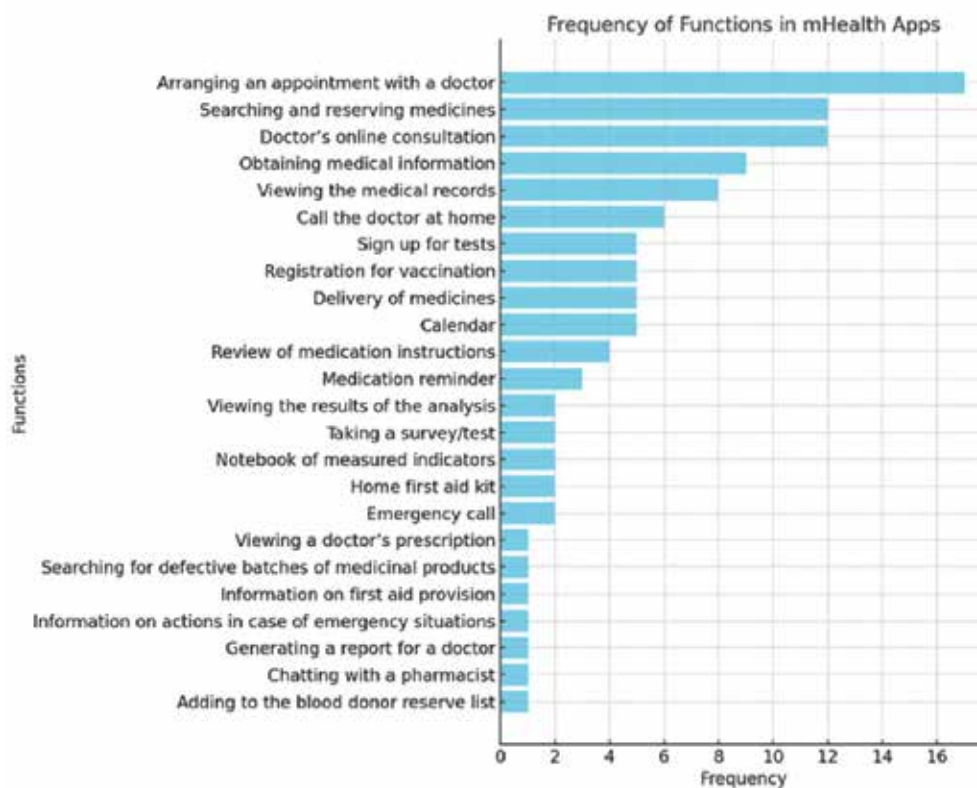


Fig. 2. Frequency of Functions in mHealth apps

Picture taken by the authors

what data are meant. In particular, the following formulations are found in the analyzed apps: «other data», «information on actions carried out in the system», «data on related persons» (it is not indicated who these related persons are), «details of the app visits», «other health-related information».

Admittedly, after the list of user data processed by the application, such words as «etcetera» and «so forth» are found.

The 3 apps that have privacy policies do not detail exactly what information is collected.

With regard to 20 apps having no privacy policy, they were analyzed in view of user data these apps collect. We revealed that 14 out of 20 apps, which do not have

privacy policy, collect data about app users. Such data include: name, date of birth, gender, residence place, phone number, e-mail access, geolocation, appointments with a doctor, health indicators, vaccinations and medication.

ARE THE DATA OF THE APP USER TRANSFERRED TO THIRD PARTIES? IF YES, HAVE THIRD PARTIES, TO WHOM THE DATA ARE TRANSFERRED, BEEN DETERMINED?

20 apps with privacy policies were analyzed to see if they transfer user data to third parties. It was discovered that 4 out of 20 apps clearly identified third parties to whom data about app users would be transferred. 9 out

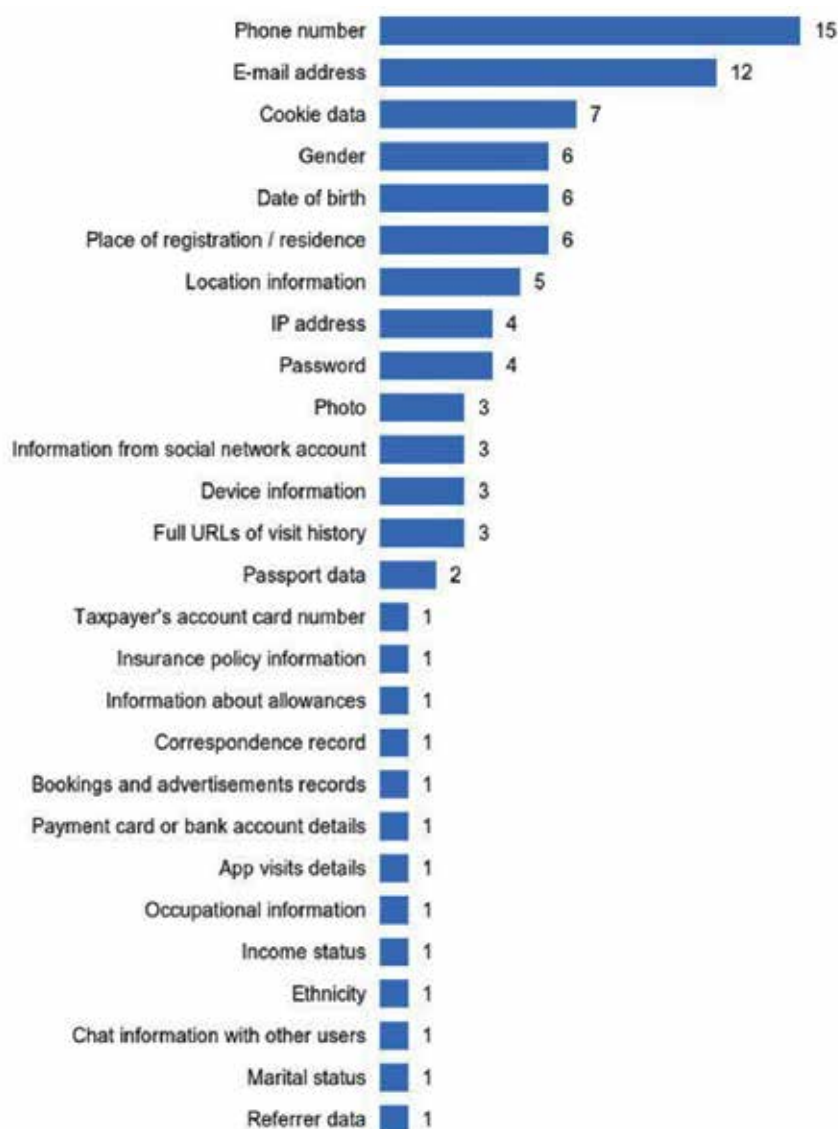


Fig. 3. Data that help to identify a person

Picture taken by the authors

of 20 apps envisage the possibility of transferring data to third parties, but at the same time it is not clear to whom exactly these data will be transferred. In 1 out of 20 apps, a list of third parties, to whom data about the user will be transferred, is defined, however, the possibility of transferring such data to other persons (which cannot be specified) is assumed. In 2 out of 20 apps it is indicated that the data are not transferred to third parties. Notably, in 4 out of 20 apps there is no mentioning whether the data are transferred to third persons (Fig. 5).

We were unable to determine whether 20 apps without privacy policies transfer the data to third parties.

CAN CONSENT TO THE PROCESSING OF PERSONAL DATA BE WITHDRAWN, AND IF YES, IN WHAT WAY?

We have determined how the issue of withdrawing consent to the processing of personal data is regulated in 20 apps that have privacy policies. 12 out of 20 apps

contain information on how to withdraw consent to the personal data processing.

There were determined ways of withdrawing the consent in 12 apps which contain information on the consent withdrawal: 1) filling out the feedback form (found in 2 apps), 2) sending a letter to the email address (found in 5 apps), 3) sending a letter to the registration address (found in 7 apps), 4) unchecking the appropriate box in a participant's account, 5) clicking on the unsubscribe link, 6) contacting the support service (Fig. 6).

1 out of 12 apps contains information about the possibility of submitting a request for data deletion but the way of doing it is not detailed.

No information about withdrawing consent to personal data processing was identified in 8 out of 20 apps which have privacy policies.

We could not determine whether it is possible to withdraw consent to personal data processing in 20 apps with no privacy policy.

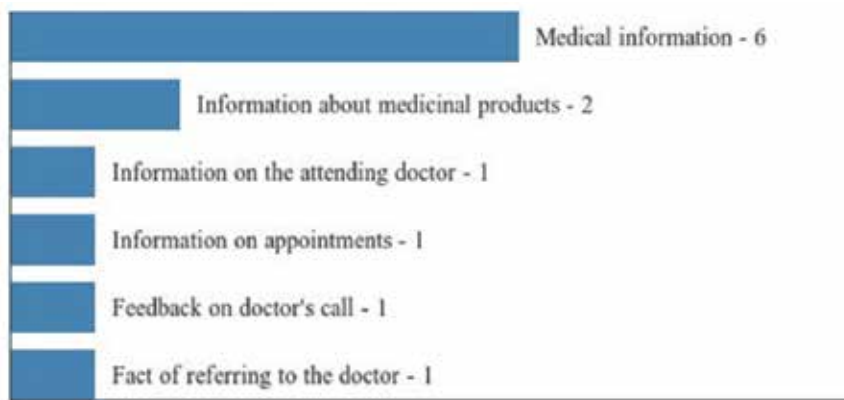


Fig. 4. Medical information

Picture taken by the authors

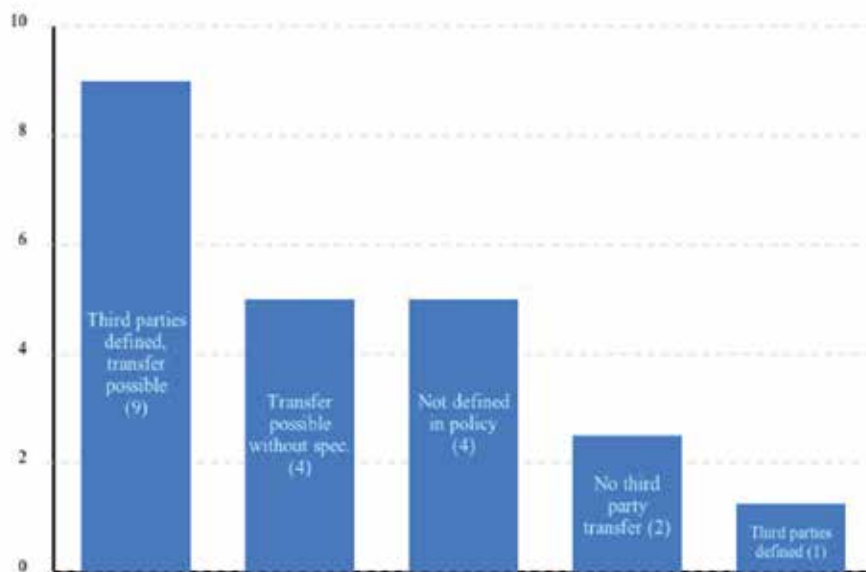


Fig. 5. Transfer of data to third parties

Picture taken by the authors

AT WHAT MOMENT WILL THE APP USER'S DATA BE DELETED?

Only 9 out of 20 apps that have privacy policies contain information about the app user data deletion. It is determined in these 9 apps that the user's personal data can be deleted: 1) 5 years after a user / a doctor last accessed the data; 2) no later than 10 years from the moment of closing access to the account or the date when the account was blocked; 3) until the moment of submitting a request to delete the account and its data; 4) after withdrawal of consent to data processing (found in 3 apps); 5) if the data are no longer needed for the original purposes; 6) in case of objection to data processing; 7) if the data were processed illegally; 8) if the data must be deleted to fulfill a legal obligation;

9) after the removal of the application (found in 2 apps); 10) from the moment of deleting user data.

We have not managed to clarify the issue with the period of the application user data deletion in 20 apps that do not have privacy policies.

DISCUSSION

After studying mHealth apps that have the Ukrainian-language interface, we can state that there are a number of problems with ensuring the privacy and protection of users' personal data in these apps, since 20 out of 40 studied mHealth apps did not have privacy policies at all. One of the reasons for this state of affairs is the lack of proper legal regulation in Ukraine, which would allow

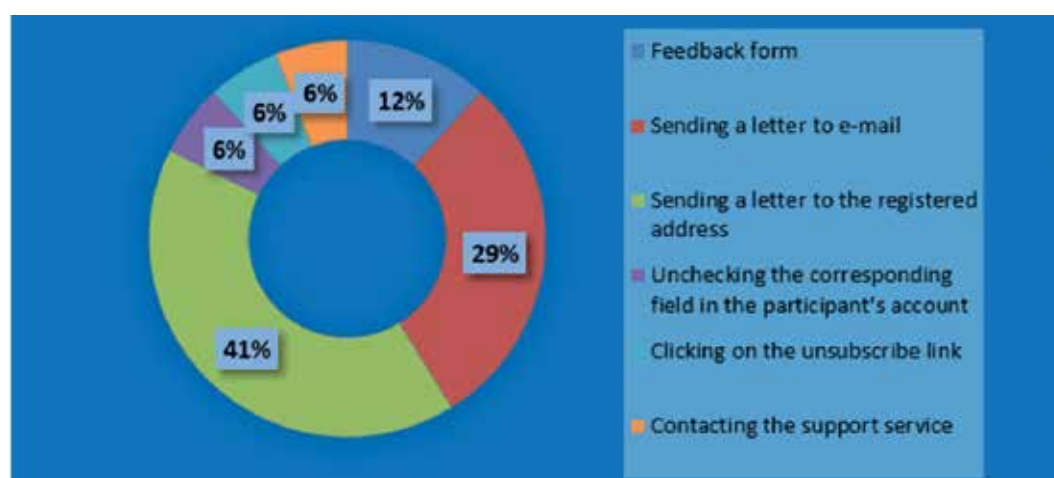


Fig. 6. How to withdraw consent to data processing?

Picture taken by the authors

determining the standards for handling personal data of mHealth app users. That is why there is an obvious need to develop and implement a regulatory framework for mHealth apps.

We have discovered that the mHealth apps, which we studied, collect a variety of user data. 20 of the considered 40 mHealth apps that have privacy policies collect sensitive information about users, such as information about the attending doctor, information about appointments with a doctor, medical information, whose leakage could cause significant harm to users. Among those 20 out of 40 mHealth apps that have no privacy policies, are 14 ones which also collect sensitive information about users. In the case of these 14 mHealth apps, it is not at all clear how this sensitive information is used. Therefore, the risks for the users of these mHealth apps are extremely high, which can lead to the violation of the dignity, honor and damage to a user's business reputation.

It is also worth emphasizing that information about users of mHealth apps can be transferred to third parties without their consent, which directly violates the Law of Ukraine «On Protection of Personal Data», since the user of mHealth apps as a subject of personal data has the right «to receive information about the conditions of granting access to personal data, in particular information about third parties to whom his / her personal data is transferred» [11]. Based on the analysis of the privacy policies of 10 mHealth apps, it has been identified that the data collected by the application may be transferred to third parties, but without a direct reference to these third parties. In addition, there are 4 mHealth apps that do not have information in their privacy policy about whether their data are transferred to third parties. In this regard, it is necessary that mHealth apps clearly state to which third parties data about mHealth app users can be transferred.

The issue also is that mHealth apps do not specify whether consent to the processing of personal data can be withdrawn. It is exactly the situation we encountered when analyzing 8 out of 20 mHealth apps that have privacy policies. This is

despite the fact that the corresponding right is enshrined in the Law of Ukraine «On Protection of Personal Data». Thus, the user of the respective application is not aware of how he needs to inform the owner of personal data. In this case, mHealth apps must clearly define such a way of withdrawing consent to the processing of personal data, which will require the subject of personal data to perform such a scope of actions that does not exceed the scope of actions at the time of giving consent to the processing of personal data.

Determining the moment when personal data will be deleted is also important, given that until the moment of deletion, such data may continue to be used for the specified purposes. In this regard, the owners of personal data must clearly define the grounds for deletion of data in the privacy policy, so that in the event of such grounds, personal data could be deleted without any delay.

It should be stressed that the mHealth apps we examined have a lot of text in their privacy policies, which does not encourage users to spend a lot of time figuring out how the mHealth apps will use their personal data. That is why users will be inclined to agree to the privacy policy without reading it. [6, 12-13].

Notably, the mHealth apps studied by us do not contain such important information as the method of data encryption, protection using a password or two-factor authentication, the possibility of data backup, as well as security audits to avoid possible threats of personal data leakage.

The lack of such important information in the studied mHealth apps is due to the fact that there is no proper monitoring of the privacy policies of such apps. This leads to the fact that the only tools which can influence mHealth app developers to improve privacy policies are user ratings and feedback in mobile app stores Google Play and App Store.

CONCLUSIONS

An analysis of 40 mHealth apps found that 20 of them lacked a privacy policy, which is a serious problem because

such apps collect user data, including data that helps identify a person and medical data. Of the apps with a privacy policy, only 3 clearly detailed what data was collected, and 9 enabled the data transfer to third parties without indicating who they were. A total of 9 apps with a privacy policy included information about the possibility of deleting

user data. 12 apps that featured a privacy policy specified ways of withdrawing consent to personal data processing, but none of the apps without a privacy policy contained information on this. The lack of a privacy policy in 20 of the 40 mHealth apps studied threatens the protection of user data and increases the risk of its misuse.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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