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ORIGINAL ARTICLE

CONTENTS

Possibility of thromboaspiration method in treatment of embolic migration complication during arteriovenous malformation embolization of the head and neck localization

Igor V. Altman, Oleksandr L. Nikishyn, Iyad I. Al-Qashkish, Stanislav V. Konotopchyk
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ABSTRACT

Aim: To analyze the embolic migration complication during arteriovenous malformations (AVMs) embolization of the head and neck localization, and to demonstrate the possibility of tromboaspiration method in treatment of such complications in cerebrovascular region.

Materials and Methods: The endovascular intervention was performed in 116 patients with AVMs of the head and neck localization. We used a superselective catheterization of the external cerebral artery branches as a treatment method of AVMs embolization. During embolization of AVMs, the spherical and not spherical polyvinyl alcohol (PVA) emboli were implanted.

Results: The result of treatment was technically successful in 112 (96,6 %) patients with AVMs of the head and neck localization. There were 4 (3,5 %) cerebrovascular complications during AVMs embolization of the head and neck localization. In 2 cases a cerebrovascular complication arose during the AVMs embolization of head localizations. In those 2 cases the cerebrovascular complications were successfully treated conservatively. In other 2 cases cerebrovascular complications arose during the AVMs embolization of neck localizations. One patient died as result of a massive ischemic stroke in the vertebrobasilar zone. Another patient was successful treated by tromboaspiration method.

Conclusions: Any surgical intervention on the carotid arteries, including endovascular surgery, is associated with a risk to the health and life of the patient. A thorough angiographic diagnosis of the external and internal carotid and vertebral arteries is necessary before endovascular embolization. Modern endovascular technology, such as tromboaspiration, may be helpful to avoid embolic migration complication in cerebrovascular region.

KEY WORDS: arteriovenous malformation, cerebrovascular complication, tromboaspiration

Wiad Lek. 2024;77(5):881-886. doi: 10.36740/WLek202405101 DOI

INTRODUCTION

Arteriovenous malformations (AVMs) are congenital vascular malformations as result of genetic glitch of embryonic angiogenesis [1]. The most difficult is the diagnostic and treatment of patients with AVMs localization in the head and neck area. This is due to the anatomical features of the structure of this region [2, 3]. Endovascular embolization of head and neck AVMs always carry the risk of embolism of functionally important cerebral vessels [4, 5]. We analyzed the embolic migration complication during AVMs embolization of the head and neck localization, and demonstrated the possibility of tromboaspiration method in treatment of such complications in cerebrovascular region. We also presented a clinical case of ischemic stroke in the vertebrobasilar zone in a patient with an AVM in the neck region, which developed as a result of the embolus migration from the occipital artery to the vertebral artery through an abnormal shunt located in the AVM region, with subsequent thromboaspiration of clots from the vertebral artery system.

AIM

The aim of the study was to analyze the embolic migration complications during AVMs embolization of the head and neck localization, and to demonstrate the possibility of tromboaspiration method in treatment of such complications in cerebrovascular region.

MATERIALS AND METHODS

The endovascular interventions were performed in 2014-2024 for 116 patients with AVMs of the head and neck localization. There were 56 men (48,3 %) and 60 women (51,7 %). The average age of the patients was (mean ± standard deviation) 31,6 ± 3,7 years. There were 87 patients (75,0 %) with AVMs of head localization and 29 (25,0 %) – of neck localization. We used a superselective catheterization of the external cerebral artery branches as a treatment method of AVMs embolization. During embolization of AVMs, the spherical and non-spherical polyvinyl alcohol (PVA) emboli were implanted.

Fig. 1. A view of the patient's neck at 16-year-old. AVM in the neck region with purple vascular spots on, the nape and neck.

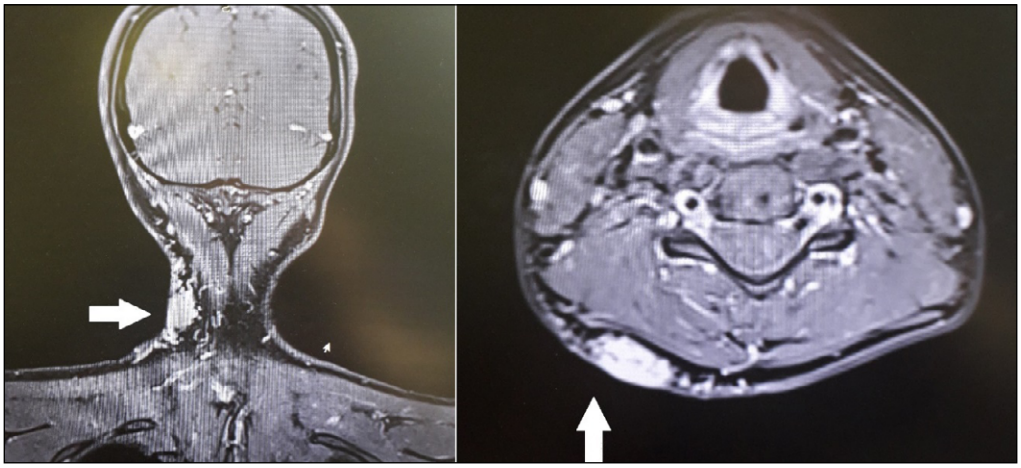

Fig. 2. MRI of the head and neck showed an AVM in the soft tissues in the occiput and neck region (white arrow).

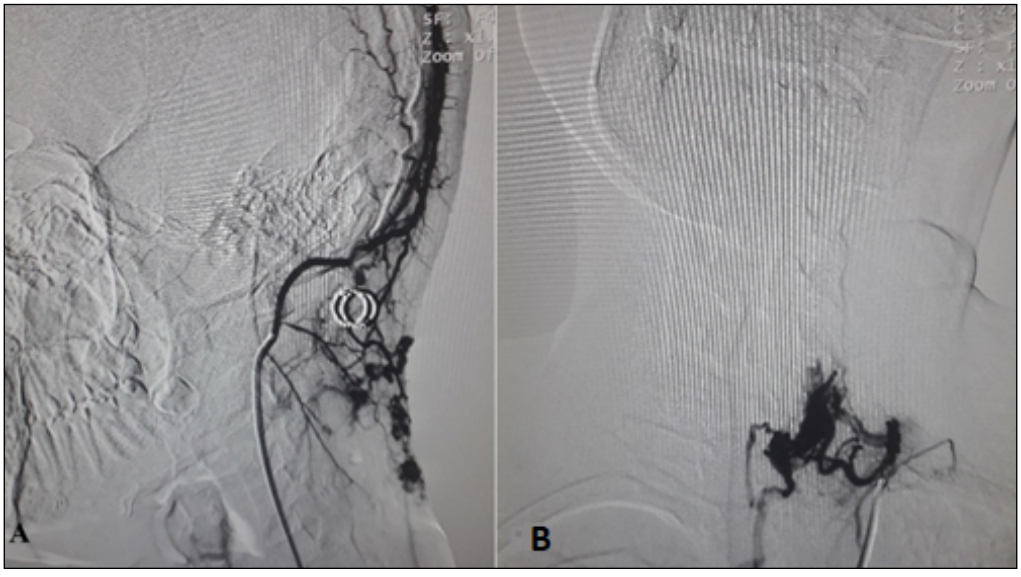

Fig. 3. The selective angiography of 16-year-old patient. The AVM of the soft tissues in the occiput and neck region: (A) – AVM filling from the left occipital artery; (B) – AVM filling from the left thyrocervical trunk.

Fig. 4. The selective angiography of 16-year-old patient. The AVM of the soft tissues in the occiput and neck region: (A) – the left vertebral artery; (B) – the right vertebral artery. Normal angiographic picture

Fig. 5. The selective angiography of 16-year-old patient. The AVM embolization from the left occipital artery: (A) – angiography before embolization; (B) – control angiogram. The beginning of shunting from the occipital artery into another arterial vessel (an arrow) was detected.

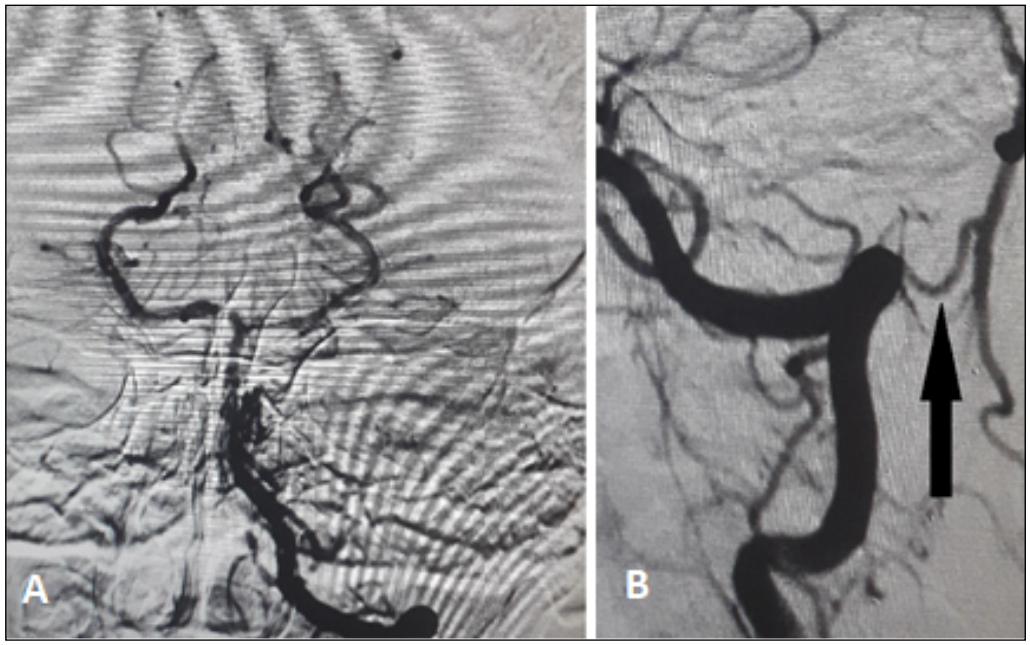

Fig. 6. The control vertebral artery angiography of 16-year-old patient: (A) – the angiogram revealed thrombosis of the basilar, superior cerebellar arteries on the right and left of the P1 segment and the posterior cerebral artery on the right and left; (B) – the thrombosis was due to the presence of a pathological arterial shunt between the left vertebral and left occipital arteries through the AVM area (an arrow).

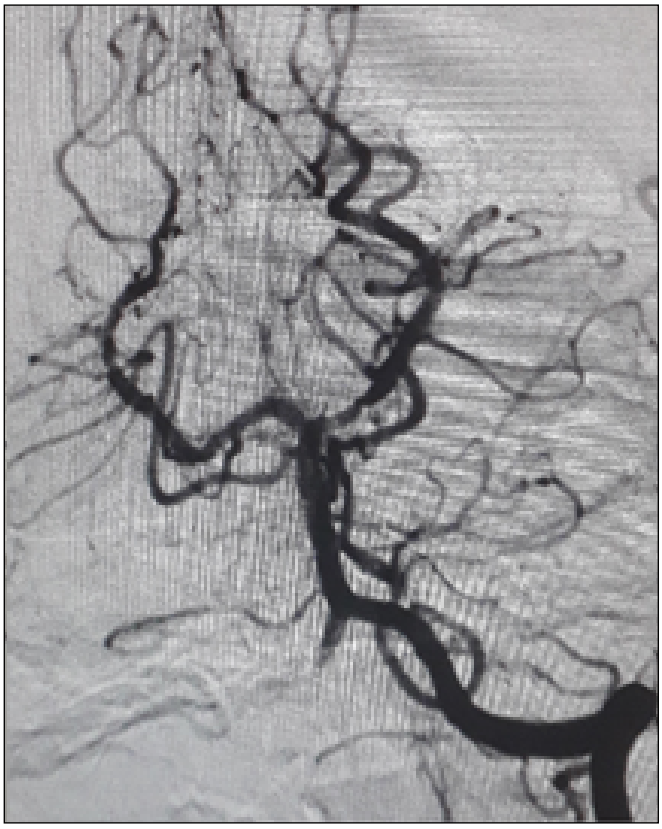

Fig. 7. The result of thromboaspiration performed in 16-year-old patients. The thromboaspiration favored the restoration of blood supply to the basilar, superior cerebellar arteries on the right and left and the posterior cerebral artery on the right and left.

Fig. 8. The 16-year-old patient. The result after rehabilitation.

This study was conducted in compliance with the principles of bioethics according to the Helsinki Declaration (1964) and the Universal Declaration on Bioethics and Human Rights (Paris, 2005). All patients signed informed consent to participate in the study.

RESULTS

The result of treatment was technically successful in 112 (96,6 %) patients with AVMs of the head and neck localization. There were 4 (3,5 %) cerebrovascular complications during AVMs embolization of the head and neck localization.

In 2 cases a cerebrovascular complication arose during the AVMs embolization of head localizations. They were conditioned by emboli migration from the external cerebral artery to the branches of internal cerebral artery. In those 2 cases the cerebrovascular complications were successful treated conservatively.

In other 2 cases cerebrovascular complications arose during the AVMs embolization of neck localizations. The analysis of complications showed, that ischemic stroke developed as result of the emboli migration through an abnormal arterial shunt between the occipital arteries and the vertebral artery, located in the AVM region. One patient died as result of a massive ischemic stroke in the vertebrobasilar zone. Another patient was successful treated by tromboaspiration method.

The following is a case of successful treatment of cerebrovascular complication after AVM embolization in 16-year-old girl. She was born with purple vascular spots on the nape and neck. The size of the spots has gradually been increasing (Fig. 1).

Patient was hospitalized in the endovascular neuroradiology clinic for angiographic examination, endovascular treatment with next surgical resection of AVM. The complex patient`s assessment included general clinical examination, electrocardiography, echocardiography, arterial Doppler ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), contrast magnetic resonance imaging (MRI-angiography).

The MRI of the head and neck showed a vascular malformation in the soft tissues in the occiput and neck region with signs of arteriovenous shunting (Fig. 2).

At the next step we performed the selective angiography of subclavian, external and internal carotid, vertebral arteries. The AVMs filling from the left occipital artery and left thyrocervical trunk was detected (Fig. 3).

The signs of connection of AVM with brain vessels were not detected (Fig. 4).

The decision to perform AVM embolization from the left occipital artery was made. Before an embolization, the patient was generally anesthetized with propofol. The superselective catheterization of the occipital artery was performed, and embolization of AVM with «Embocure» emboli (Poland) 125-250 microns was started. During an embolization, the shunting from the occipital artery and AVMs vessels to another arterial vessel was appeared on the control angiograms (Fig. 5).

At the end of embolization, it was noticed that the patient did not regain consciousness and reacted slightly to irritation. Urgently, the patient was again taken for angiography. Angiography of vertebral and internal carotid arteries was performed. The angiogram revealed thrombosis of the basilar, superior cerebellar arteries on the right and left of the P1 segment and the posterior cerebral artery on the right and left. The thrombosis was due to the presence of a pathological arterial shunt between the left vertebral and left occipital arteries through the AVM area (Fig. 6).

The urgent thromboaspiration was performed, allowing us to restore a blood supply to the basilar, superior cerebellar arteries on the right and left and the posterior cerebral artery on the right and left (Fig. 7).

Following the intervention, the conservative treatment of ischemic stroke was applied. The patient`s condition improved from coma 1-2 to complete recovery of movement, consciousness and speech at 3-weeks follow-up. Moreover, the patient completely returned to normal life after two months of rehabilitation (Fig. 8).

DISCUSSION

Any surgical intervention on the carotid arteries, including endovascular surgery, is associated with a risk to the health and life of the patient. Neurological ischemic complications can be caused by migration of the embolic materials into the cerebral arteries or the vessel supplying the cranial nerves. This may lead to mortality or severe neurological deficit. To prevent this, meticulous attention should be paid to the angiographic findings demonstrating the neural arteries. However, the anastomotic channels between the target arteries and the branches coming off from the internal carotid, vertebrobasilar, or ophthalmic arteries are not always visualized on conventional angiography [6]. Existing vascular collaterals of the external and internal carotid artery systems should also be taken into account. The branches of the occipital artery supply blood to the skin and muscles of the back of the head, the auricle, the mastoid process, and the dura mater in the region of the posterior cranial fossa. The distal branches of the vertebral artery penetrate through the dura mater and go to the large occipital foramen. Extracranial segments of the vertebral artery also give rise to branches that supply blood to the deep muscles of the neck and meninges. The posterior meningeal branch originates from the vertebral artery above the level of C1 and supplies blood to the cerebellar tent and the medial parts of the dura mater of the occipital fossa. Therefore, there may be natural anastomoses between the vertebral and occipital arteries at the level of the distal small branches. In addition, the presence of a congenital vascular anomaly in the head and neck region increases the risk of large pathological arterial shunts and anastomoses between the internal and external carotid artery systems, including in the basin of the vertebral and occipital arteries. Therefore, it is important to have sufficient knowledge about the functional anatomy of the head and neck arteries having anastomotic channels with cerebral arteries, for which the injection of liquid embolic material or small-sized particles is contraindicated. Requiring experience and special training from the doctor. The use of interventional radiology in the treatment of AVM of the head and neck localization is still an understudied problem that constantly opens up new perspectives for research. Modern endovascular technology, such as tromboaspiration, may be helpful to avoid embolic migration complication in cerebrovascular region.

CONCLUSIONS

1. Any surgical intervention on the carotid arteries, including endovascular surgery, is associated with a risk to the health and life of the patient.
2. A thorough angiographic diagnosis of the external and internal carotid and vertebral arteries is necessary before endovascular embolization.
3. Modern endovascular technology, such as tromboaspiration, may be helpful to avoid embolic migration complication in cerebrovascular region.

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The study was conducted as a fragment of the complex scientific project «To provide new and improve current approaches to the treatment of patients with traumatic and congenital arteriovenous fistulas of different location» (code NAMS – 2P.24; state registration number 0123U103185; PPCE – Programmatic Classification of Expenditures Codes – 6561040).

CONFLICT OF INTEREST

The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

The specifics of the interpretation of non-performance or improper performance by medical or pharmaceutical employees of their professional duties, taking into account the practice of the ECHR

Anzhela B. Berzina[1], Alina O. Pletenetska[1], Polina P. Marshall[2], Inna V. Berdnik[3], Olena H. Kozynets[3]

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ABSTRACT

Aim: To find out the specifics of the interpretation of non-performance or improper performance by medical or pharmaceutical employees of their professional duties, taking into account the practice of the ECHR.

Materials and Methods: This article is based on the analysis of the international legal acts, the practice of the ECHR, national judicial practice, court statistics, criminal and medical law legal doctrine, official statistics of the Office of the Prosecutor General of Ukraine, analytical data based on the results of cooperation with the "Main Bureau of Forensic Medical Examination of the Ministry of Health of Ukraine". Dialectical, comparative, analytical, synthetic and system analysis research, hermeneutic methods were used.

Results: In each specific case it is necessary to establish whether there is non-performance or improper performance of professional duties by medical or pharmaceutical employees, the result of which is the failure to fulfil his direct professional duties, provided for by regulatory and legal acts, job instructions, qualification requirements and standards of treatment. The patient's right to health care is not ensured by the guarantees provided for by national legislation, so patients file complaints with the ECHR.

Conclusions: A single approach to the interpretation of such terms as "non-performance or improper performance by a medical or pharmaceutical employee his professional duties" is a guarantee of the uniformity of their enforcement and the formation of stable judicial practice in this category of criminal cases.

KEY WORDS: patient rights, criminal offences, ECHR practice, criminal proceedings

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INTRODUCTION

Every person has a natural, inalienable and inviolable right to health care. The priority of health care is a basic guideline both at the level of international legal regulation and at the national level. However, if the patient did not receive an adequate level of medical care or was faced with the inaction of medical or pharmaceutical employees, he or his relatives, other persons to whom this right is granted by law has the possibility of applying to the court for the protection of the violated right. In case of impossibility of achieving such protection at the national level, there is a mechanism of appeal to the European Court of Human Rights (hereinafter – ECHR).

Ukraine, having ratified [1] the European Convention on Human Rights and Fundamental Freedoms (hereinafter – the Convention) [2], undertook the obligation to implement the decisions of the ECHR, to introduce European standards of human rights into the Ukrainian judiciary and administrative practice. The ECHR's decision is binding for Ukraine to implement, in accordance with Article 46 of the Convention. The legal positions of the ECHR are mandatory not only for the legislation of Ukraine, but also for most EU countries. Systematic interpretations of non-performance or improper performance of professional duties by medical or pharmaceutical employees in the decisions of the ECHR are aimed, among others, at clarifying the importance and relevance of which measures of state influence should be taken at the national level to reduce the number of violations by medical and pharmaceutical employees.

AIM

The aim of the article is to find out the specifics of the interpretation of non-performance or improper per-

formance by medical or pharmaceutical employees of their professional duties, taking into account the practice of the ECHR.

MATERIALS AND METHODS

This article is based on the analysis of the international legal acts, in particular, the European Convention on Human Rights and Fundamental Freedoms, as well as the practice of the ECHR, national judicial practice, statistics on the number of criminal proceedings in the courts of Ukraine, criminal and medical law legal doctrine (41 normative legal acts and 57 court judgments), official statistical data of the Office of the Prosecutor General of Ukraine, analytical data based on the results of cooperation with the "Main Bureau of Forensic Medical Examination of the Ministry of Health of Ukraine". Dialectical, hermeneutic, comparative, analytical, synthetic and system analysis research methods were used.

RESULTS

Non-performance of professional duties means that medical or pharmaceutical employees does not perform a set of actions, the performance of which is mandatory for them. Non-performance of professional duties should be distinguished from improper performance of professional duties; here we are talking about situations when employees still perform their duties, but not fully, carelessly, both once and systematically. For example, untimely and/or incorrect doctor's diagnosis; violation by the pharmacist of the temperature regime for the storage of medicinal products; leaving foreign objects in the patient's body, etc. It is necessary to take into account that the choice of treatment methods, which are preceded by the establishment of a diagnosis or work with medicinal products, prescriptions, also depends on other factors, such as the individual characteristics of the patient's body, the medical equipment available or absent in the hospital, etc. Therefore, in each specific case, it is necessary to establish whether there is improper performance of professional duties, that is such actions of medical or pharmaceutical employees, the result of which is the failure to fulfil their direct professional duties, provided for by regulatory and legal acts, job instructions, qualification requirements and standards of treatment, excluding randomness and cases. As for non-performance of professional duties by medical or pharmaceutical employees, this should be understood as the inactivity of these categories of persons. When investigating such criminal proceedings, the competent authorities must understand the correctness or falsity of the actions or existing inactivity of medical or pharmaceutical employees, using special medical knowledge, involving experts, removing medical documentation in order to determine the compliance of the actual actions of these categories of employees with the requirements of regulatory acts (orders, instructions, recommendations, etc.).

We submitted a request to the Prosecutor's General Office of Ukraine to obtain official statistical data on the number of criminal proceedings sent to court under Article 140 of the Criminal Code of Ukraine for the period from 2013 to 2022 (Table 1).

The analysis of this data gives reason to claim that there is a clearly disproportionate number of victims' statements for investigation of the facts of non-performance or improper performance of professional duties by medical or pharmaceutical employees with the number of criminal offenses that are sent to court. In most cases, the pre-trial investigation is carried out inefficiently or too slowly. The more time elapses from the moment of registration of a crime report, the less likely it is that the victim will have a positive outcome of the investigation, at least in the form of the transfer of criminal proceedings materials to the court. As a result, the patients' request for protection of their right to health care is not satisfied, and the guarantees provided by the national legislation for a quick, complete and impartial investigation of the criminal offense are not provided.

Taking into account the statistical indicators for the previous 5 years regarding the number of considerations by courts of first instance in Ukraine of materials of criminal proceedings under Article 140 of the Criminal Code of Ukraine, we note to a greater extent the similarity of the indicators of the number of criminal proceedings with some decrease over the last few years (Table 2).

It is interesting that the number of criminal proceedings that are closed in Ukraine is almost twice as high as the number of verdicts passed in these categories of cases. Such statistical indicators are caused primarily by the difficulty of collecting the evidence base, proving a causal connection between a specific action by medical or pharmaceutical employees and the consequences that have occurred. The medical reform that has been ongoing in Ukraine since 2014 unfortunately has done little to improve the situation with the protection of violated rights and freedoms of patients. Many regions of the state are not provided with diagnostic tools and medical equipment to the same extent, there are systematic staff reductions, which leads to an increase in the burden on other

Table 1. Data on criminal offenses registered during 2013-2022 (proceedings) according to Art. 140 of the Criminal Code of Ukraine "Improper performance of professional duty by a member of medical or pharmaceutical profession" and the results of their pre-trial investigation

Year	Registered criminal offenses in the reporting period	Criminal offenses in which proceedings are closed	Criminal offenses accounted for in the reporting period	Criminal offenses for which proceedings are referred to the court
2013	1333	677	656	14
2014	692	256	436	5
2015	758	209	549	3
2016	850	208	642	1
2017	959	234	725	2
2018	906	251	655	3
2019	965	296	669	1
2020	966	313	654	2
2021	876	310	566	0
2022	510	183	327	2

Table 2. Statistics of consideration by courts of the first instance in Ukraine of materials of criminal proceedings under Art. 140 of the Criminal Code of Ukraine "Improper performance of professional duty by a member of medical or pharmaceutical profession"

Year	The number of proceedings under consideration	The number of proceedings received for consideration in the reporting year	The number of considered proceedings	Number of proceedings with a verdict	The number of closed proceedings in the case
2023	129	31	38	**15**	23
2022	134	25	34	**9**	22
2021	152	41	37	**12**	21
2020	143	52	33	**10**	17
2019	124	43	30	**11**	17

employees, etc. For example, the Criminal Cassation Court of Ukraine as part of the Supreme Court pointed out (Case No. 369/3248/17 from 14.12.2021) that in the case when serious consequences for the patient are not related to non-performance or improper performance by a medical employee of his professional duties, and occurred as a result of other circumstances, for example, a late request for medical help or a patient's refusal to follow the doctor's medical prescriptions, a patient's violation of the regime established for him, as well as cases when serious consequences for the patient occurred as a result of other circumstances, responsibility for Art. 140 of the Criminal Code is excluded [3]. The lack of an opportunity to analyse a significant number of verdicts under Article 140 of the Criminal Code of Ukraine also affects the ability to generalize the practice of the ECHR. However, we have examples when, in their complaints to the ECHR against Ukraine, the applicants claimed that they were not properly provided with medical care as one of several violations committed against them as part of criminal proceedings. We are talking about the improper performance of professional duties by medical employees in relation to patients who are kept in custody or in penal institutions. In the Case "Kushnir v. Ukraine" [4], the applicant, among other things, complained about his health and inadequate medical care during his detention, stating that "he was not provided with adequate medical care". The applicant also "stated that he "as a result of unsuccessful treatment [at the place of serving his sentence] ... was sent for treatment at [his] place of residence ...". Having studied the materials of the complaint, medical documentation and arguments of the applicant, the ECHR recognized a violation of Art. 3 of the Convention (in connection with the improper performance adequate medical care and treatment).

It should be noted that the majority of Ukrainians' applications to the ECHR regarding the receipt of poor-quality, inappropriate medical care are appeals against the decisions of national courts in civil cases. An example is the case "Tsmokalov v. Ukraine" [5]. This case "essentially concerns the failure of the state authorities to provide the applicant with adequate compensation for the improper performance of professional duties by medical employees during treatment in state hospitals". In the statement, the applicant complained that "he was falsely diagnosed with Behçet's syndrome", although in fact he had tuberculosis, and for about three months he received inappropriate

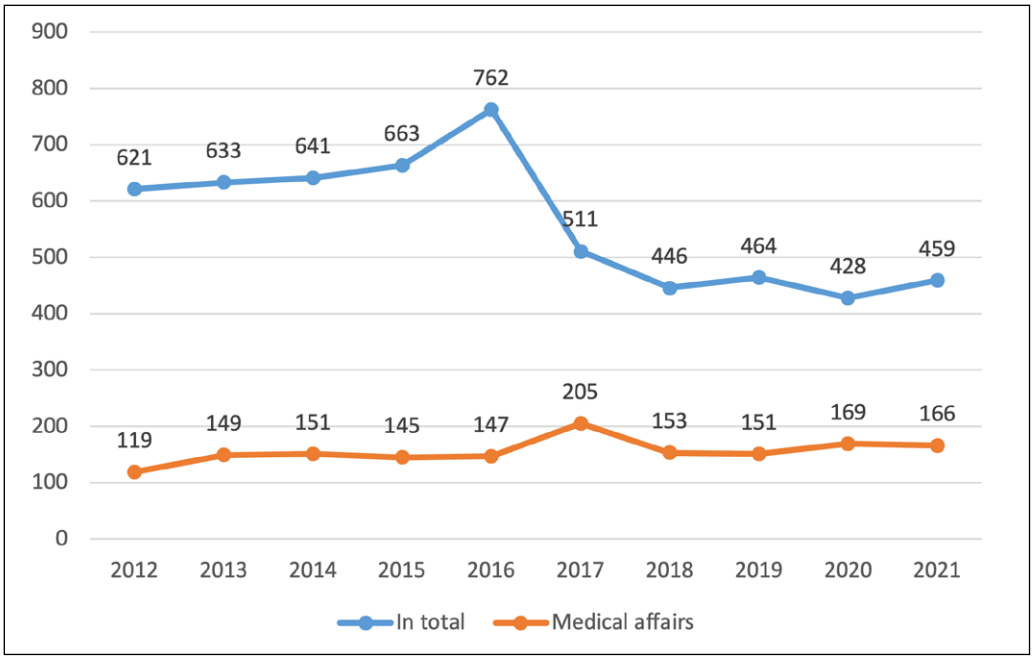

Fig. 1. Quantitative characteristics of commission forensic medical examinations conducted by the "Main Bureau of Forensic Medical Examination of the Ministry of Health of Ukraine" in 2012-2021.

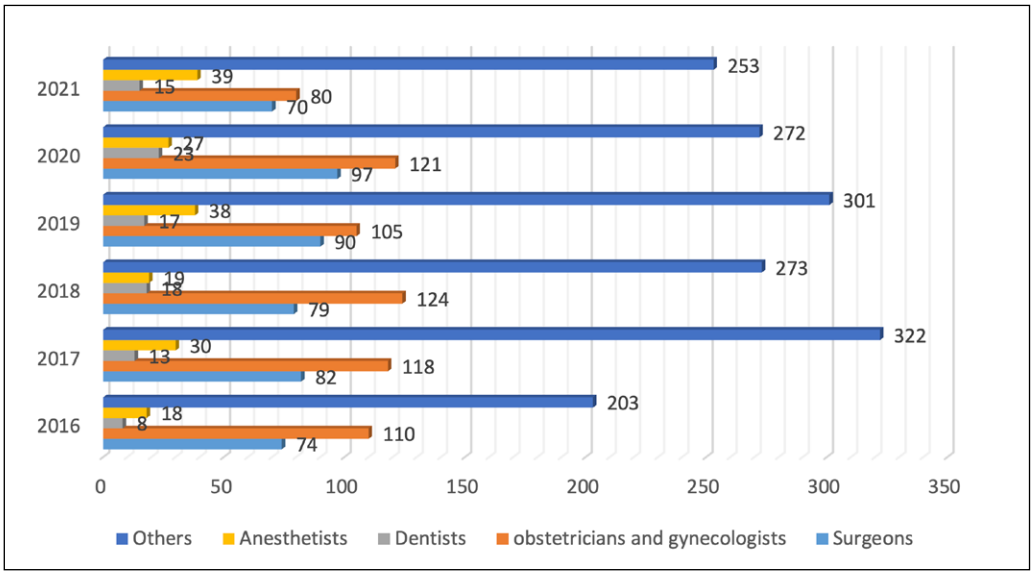

Fig. 2. Distribution of re-examinations conducted by the "Main Bureau of Forensic Medical Examination of the Ministry of Health of Ukraine" during 2016-2021, by medical affairs by doctors of various specialties.

treatment, including unregistered medicinal products, which caused a significant deterioration in his health and increased the progression of tuberculosis. During treatment at one of the hospitals, the applicant was undressed (as he claimed against his will) and shown to medical students and clinical residents as a "patient with a rare disease". Based on the results of the case review, ECHR ruled on the violation of Art. 8 of the Convention, paragraph 1 of Art. 6 of the Convention (in connection with the duration of the proceedings on compensation for damage).

Proving similar categories of cases in the framework of criminal proceedings, it is relevant to request to experts, as they are persons with special medical knowledge. Statistically we have calculated how many commission forensic medical examinations in general were conducted by the "Main Bureau of Forensic Medical Examination of the Ministry of Health of Ukraine" in 2012-2021, and how many of them related to medical affairs. And how many of them are sent for re-examination (Fig. 1, Fig. 2).

DISCUSSION

Negligence is the breach of a legal duty to care. It means carelessness in a matter in which the law mandates carefulness. A breach of this duty gives a patient the right to initiate action against negligence. Persons who offer medical advice and treatment implicitly state that they have the skill and knowledge to do so, to decide

the treatment, and to administer that treatment [6]. Medical negligence is considered as «a very common negative social phenomenon in the world. Legal liability for medical negligence is a necessary part of this mechanism, but it should not be only criminal, but also civil or disciplinary» [7].

The established procedure for the performance of duties by medical and pharmaceutical workers does not mean that the patient is guaranteed to receive the appropriate level of medical and pharmaceutical care. Health risks are always relevant [8, 9]. The complexity and in many cases unpredictability, or low predictability of pathological processes of the human body cause a high level of risk of medical activity. At the same time, the death of a patient or causing significant harm to his health is the result of medical mistakes [7]. Investigating such categories of cases, there is a subjective factor [10], therefore "the non-performance or improper performance of professional duties by a medical or pharmaceutical worker is a consequence of a negligent or dishonest attitude towards them, which should be understood as bad, indifferent, without due diligence, careless, sloppy, negligent execution of them" [11].

According to the national legislation of Ukraine, the Criminal Code of Ukraine contains Article 140 – Non-performance of professional duties by a medical or pharmaceutical employee [12]. This article, like other articles of the Criminal Code of Ukraine, does not contain the concept of "medical error"; it is not fixed at the level of national legislation in Ukraine. When resolving the issue of medical errors, judges of national courts in Ukraine most often turn to experts, as persons with special medical knowledge [13]. It is very important for both parties, as well as for society, to have a clear, unified mechanism that would help to establish the presence or absence of a medical error in the actions of doctor and/or junior medical personnel [14]. A medical error is defined as a poor-quality provision of medical services, which was committed as a result of improper performance or non-performance of professional duties, which was committed due to certain objective or subjective reasons, and it is in no way related to negligent and dishonest attitude towards one's duties, which, as a result, caused harm to the patient's health [15]. In the decisions of the ECHR, medical error has repeatedly been the subject of consideration, for example, the Case "Gray v. Germany" [16] from May 22, 2014; "Altug and others v. Turkey" [17] of 30 June 2015, etc. Thus, in the ECHR Case "Altug and others v. Turkey" the court ruled that the authorities did not ensure proper implementation of the relevant legislative and regulatory procedure aimed at protecting patients' right to life (the obligation to interview patients or their families about their medical history to inform them of possible allergic reactions and obtain consent for the introduction of a medical device).

Both medical and legal sciences are still far from the unity of views on the concept of "medical error", differentiating it from other concepts, such as "accident", "conscientious misconception", "adverse outcome of treatment", as well as crimes involving medical professionals, such as "illicit medical activity", "improper performance of professional duties that have caused the person to contract the human immunodeficiency virus or other incurable disease", "failure to provide assistance to a person in a life-threatening condition", "failure to assist a patient by medical staff", "violation of the patient's rights", etc. [18].

CONCLUSIONS

1. A single approach to the interpretation of such terms as "non-performance or improper performance by a medical or pharmaceutical employee his professional duties" is a guarantee of the uniformity of their enforcement and the formation of stable judicial practice in this category of criminal cases. It provides an opportunity for the investigator, the prosecutor to better prepare for conducting investigative (search) actions, for example, for the questioning of witnesses, by formulating more precise and appropriate questions, etc. And also contributes to a better understanding by the prosecution of the content of the act of a criminal offense, which must be established in the process of proof at the stage of the pre-trial investigation of this category of crimes.
2. In Ukraine, the patient's civil legal protection of his right to quality and proper professional medical care remains a more effective and realistic way to obtain the appropriate satisfaction.
3. The problems of pre-trial investigation of non-performance or improper performance by a medical or pharmaceutical employees their professional duties remain urgent, they require more analysis and a comprehensive approach to their solution. The systematization and generalization of the practice of the ECHR in cases based on claims of injured patients as a result of non-performance or improper performance of professional duties by medical or pharmaceutical employees will also make it possible to better study the experience of foreign countries in the investigation of these violations and, if appropriate, to adopt it.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Epidemiology of healthcare-associated endometritis after surgical abortion in Ukraine: results a multicenter study

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ABSTRACT

Aim: To determine the current prevalence of healthcare-associated endometritis after surgical abortion and antimicrobial resistance of responsible pathogens in Ukraine.

Materials and Methods: We performed a prospective, multicentre cohort study was based on surveillance data of healthcare-associated endometritis after legal induced surgical abortion. Women who underwent induced surgical abortion at gynecological departments of 16 regional hospitals between 2020 and 2022 are included in the study. Definitions of endometritis were adapted from the CDC/NHSN. Antibiotic susceptibility was done by the disc diffusion test as recommended by EUCAST.

Results: Among 18,328 women who underwent surgical abortion, 5,023 (27.4%) endometritis were observed. Of all post-abortion endometritis cases, 95.3% were detected after hospital discharge. The prevalence of endometritis in different types surgical abortion was: after vacuum aspiration at < 14 weeks, 23.8%, and after dilatation and evacuation at ≥ 14 weeks, 32%. The most responsible pathogens of post-abortion endometritis are *Escherichia coli* (24.1%), *Enterococcus* spp. (14.3%), *Enterobacter* spp. (12,8%), *Pseudomonas aeruginosa* (8.3%), *Proteus mirabilis* (6.6%), *Serratia marcescens* (6.2%), *Staphylococcus aureus* (5.9%), and *Stenotrophomonas maltophilia* (5.7%). A significant proportion these pathogens developed resistance to several antimicrobials, varying widely depending on the bacterial species, antimicrobial group.

Conclusions: Results this study suggest a high prevalence of endometritis after surgical abortion in Ukraine. A significant proportion of women were affected by endometritis caused by bacteria developed resistance to several antimicrobials. Optimizing the antibiotic prophylaxis may reduce the burden of endometritis after surgical abortion, but prevention is the key element.

KEY WORDS: surgical abortion, vacuum aspiration, dilatation and evacuation, endometritis, responsible pathogens, antimicrobial resistance, Ukraine

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INTRODUCTION

An induced abortion is one of the most common gynecological procedures in worldwide. Between 1990-2019, the global unintended pregnancy rate has declined, whereas the proportion of unintended pregnancies ending in abortion has increased. Abortion is sought and needed even in settings where it is restricted—that is, in countries where it is prohibited altogether or is allowed only to save the women's life or to preserve her physical or mental health. Unintended pregnancy rates are highest in countries that restrict abortion access and lowest in countries where abortion is broadly legal. As a result, abortion rates are similar in countries where abortion is restricted and those where the procedure is broadly legal (i.e., where it is available on request or on socioeconomic grounds) [1].

Despite well-developed abortion methods, there are known risks and adverse effects that must be considered. One known complication of induced abortion is infection, which is relatively uncommon in the current era of safe, surgical abortion. Potential complications related to abortions include pain, bleeding, an incom-

plete abortion, or an infection in the upper genital tract that causes endometritis, oophoritis, parametritis, and salpingitis [2, 3]. The reported incidence of post-abortion infections in world varies between studies, likely depending on local differences in diagnostics, the study population, laws and regulations, and the prevalence of sexually transmitted diseases.

According to the literature, infections related to abortions are often caused by an ascending bacterial infection such as chlamydia, gonorrhea, mycoplasma and bacterial vaginosis that proceeds from the lower genitals and moves through the cervix to the uterus [4]. The infection, if untreated, can spread to the fallopian tubes and may lead to infertility [2, 5, 6].

The World Health organization (WHO) recommends antibiotic prophylaxis to prevent infectious complications associated with abortions. However, the WHO points out that there is only evidence for prophylactic antibiotics performing a surgical abortion when the risk of infections is more evident [7]. Additionally, antibiotic prophylaxis for all women undergoing abortion procedures likely results in overuse of antibiotics, which is associated with antibiotic resistance [8]. Antibiotic treatment is given if/when a bacterial infection is identified, which could be before, during, or after the abortion. Prior research indicated that the timing of antibiotic administration relative to the timing of the abortion does not affect the rate of post-abortion infection [9,10]. Surgical abortion is one of the most common gynecological procedures in Ukraine, but there is still little knowledge about the epidemiology and microbiology of post-abortion endometritis.

AIM

The aim this study to determine the current prevalence of healthcare-associated endometritis after surgical abortion in women and antimicrobial resistance of responsible pathogens in Ukraine.

MATERIALS AND METHODS

STUDY DESIGN, SETTING AND POPULATION

We performed a prospective, multicentre cohort study was based on surveillance data of healthcare-associated endometritis after legal induced surgical abortion. Women who underwent induced surgical abortion at gynecological department of 16 regional hospitals between 2020 and 2022 are included in the study. Bacterial screening for chlamydia, gonorrhea, mycoplasma, and bacterial vaginosis was performed prior to the abortions. The eligibility criteria for the study were: being a woman aged 15–49; being a resident of the study site. Exclusion criteria: women after of medical abortion, chlamydial infections, syphilis or other sexually transmitted bacterial infections, patients with diagnosis of bacterial vaginosis, candidiasis and trichomoniasis, participation in a clinical trial using antibiotics or genital microbicides.

DEFINITION

The criteria for healthcare-associated endometritis after surgical abortion were adapted from the Centers for Disease Control and Prevention's (CDC) and National Healthcare Safety Network's (NHSN) case definitions. In this study abortion— Disruption of an embryo or fetus implanted in the uterus. A pregnancy does not begin until after the implantation of the blastocyst, ~7 d after fertilization. Abortions may be spontaneous or induced. Induced abortion—An abortion that is deliberately caused for elective or therapeutic medical reasons. Incomplete abortion—An abortion in which some, but not all, of the products of conception (including placenta and amniotic membranes) remain in the uterus. Surgical methods of abortion (surgical abortion)— Use of transcervical procedures for terminating pregnancy, including vacuum aspiration, and dilatation and evacuation (D&E). Vacuum aspiration (electrical or manual; EVA or MVA) — Vacuum aspiration involves evacuation of the contents of the uterus through a plastic or metal cannula, attached to a vacuum source. Electric vacuum aspiration (EVA) employs an electric vacuum pump. The healthcare provider dilates (widens) the cervix and inserts a tube attached to a vacuum and pump. It uses suction to remove tissue from the uterus. With manual vacuum aspiration (MVA), the vacuum is created using a handheld, hand-activated, plastic 60 ml aspirator (also called a syringe). D&E is used after 12–14 weeks of pregnancy. D&E requires preparation of the cervix using osmotic dilators and/or pharmacological agents, and evacuating the uterus primarily with forceps orceps, using vacuum aspiration to remove to remove any remaining blood or tissue. Gestational age (duration of pregnancy) — The number of days or weeks since the first day of the woman's last normal menstrual period (LMP) in women with regular cycles. For women with irregular cycles or when LMP is unknown, gestational age is the size of the uterus, estimated in weeks, based on clinical examination or ultrasound, that corresponds to a pregnant uterus of the same gestational age dated by LMP [11].

DATA COLLECTION

Abortion complications, categorized as healthcare-associated endometritis were assessed in women who

Table 1. Distribution of 5,023 healthcare-associated endometritis after surgical abortion in Ukrainian hospitals, 2020-2022

Type of procedure	Number of patients	Endometritis		95% CI
		n	%	
Vacuum aspiration at < 14 weeks	10,216	2,431	23,8	23,5-24.1
Dilatation and evacuation at ≥ 14 weeks	8,112	2,592	32	31,5-32.5
Total	18,328	5,023	27,4	27,1-27.7

Table 2. Distribution of pathogens isolated from women with healthcare-associated endometritis after surgical abortion in Ukrainian hospitals, 2020-2022

Microorganisms	Number of isolates (n)	Percentage (%)
Gram-positive cocci	1,906	28.1
Staphylococcus aureus	397	5.9
Coagulase-negative staphylococci	287	4.2
Enterococcus spp.	968	14.3
Streptococcus spp.	254	3.7
Gram-negative bacilli	4,878	71.9
Escherichia coli	1,637	24.1
Enterobacter spp.	868	12.8
Proteus mirabilis	451	6.6
Serratia marcescens	422	6.2
Stenotrophomonas maltophilia	388	5.7
Citrobacter spp.	281	4.1
Pseudomonas aeruginosa	564	8.3
Acinetobacter baumannii	267	3.9
Total	6,784	100.0

came in contact with the gynecological clinic within 30 days after the procedure. Required data collected through checklist containing demographic and clinical information such as patient age, gestational age, gestational history, length of hospital stay, cause of abortion, patient's symptoms, cervical condition, complications of abortion, instruments used in abortion if manipulated, microbiological and radiographic investigations, antibiotics usage, and culture and sensitivity of the clinical isolates, and the person performing the abortion. The discharged women were advised for ongoing follow-up care for a month after surgical abortion in the outpatient department. In this study information regarding the post-abortion period following discharge was obtained from the outpatient records and from records documenting follow-up by referring gynecologists.

MICROBIOLOGICAL METHODS

In this study all samples were obtained from women with clinical symptoms of endometritis. All microbial isolates were identified using standard microbiological techniques. Antibiotic susceptibility testing isolates was performed according to the recommendations of the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

ETHICS

In this study all patients gave written consent before the surgical abortion and the study was approved by the Ethics Committee of Shupyk National Healthcare University of Ukraine. Women were excluded if they did not give written consent for adult women and parental/caregiver informed consent and informed assent for women under the age of 18 and if there were no conditions for the interview to be conducted in privacy.

STATISTICAL ANALYSIS

Statistical analysis was performed using STATA 11.0 (StataCorp, College Station, TX) and SAS 9.2 (SAS Institute, Inc, Cary, NC). The data were described using frequencies and proportions. Descriptive statistics, Student's t test, $\chi 2$, and Fisher's exact test were performed as appropriate. The primary outcome, composite 30-day major postoperative infections, was analyzed as a dichotomous variable (Yes/No). Results our study

are expressed as median (range), mean ± standard deviation for continuous variables, and number and corresponding percentage for qualitative variables. The likelihood ratio test statistic was used to compared to the chi-squared distribution of the model and a p-value calculated. Only variables with a p-value of <0.05 based on likelihood ratio testing were included in the final model; therefore, some variables identified on univariate analysis were not included in the final regression model as they did not significantly impact the analysis.

RESULTS

PREVALENCE OF ENDOMETRITIS

A total of 18,328 first-trimester surgical abortions were performed during the study period (2020-2022). Of the 18,328 women evaluated, 10,216 (55.7%) underwent a vacuum aspiration at < 14 weeks and 8,112 (44.3%) underwent a dilatation and evacuation at ≥ 14 weeks. Endometritis cases were registered in 5,023 (27.4%, 95% CI 27.1-27.7%) of all surgical abortions. Of the total post-abortion endometritis cases, 95.3% were detected after hospital discharge. The prevalence of endometritis in different types surgical abortion was: after vacuum aspiration at < 14 weeks, 23.8% (95% CI 23.5-24.1%), and after dilatation and evacuation at ≥ 14 weeks, 32% (95% CI 31.5-32.5%). The distribution of endometritis after surgical abortion in Ukrainian hospitals is shown in Table 1.

The prevalence of endometritis after surgical abortion varied widely within Ukraine, from <10% in three (18.7%) of 16 regional hospitals to ≥20% in eight (50%), mostly in southern (Kherson, Odesa, Dnipro, Kropyvnytskyi, Zaporizhzhia), eastern (Kharkiv), and central (Kyiv, Zhytomyr) Ukraine. An increase in the incidence of post-abortion endometritis was observed in 9 (56.3%) out of 16 regional hospitals, mostly in southern (Kherson, Odesa, Dnipro, Kropyvnytskyi, Zaporizhzhia), eastern (Kharkiv), and central (Kyiv, Zhytomyr, Vinnitsia) Ukraine.

Preoperatively, in 97.6% patients used ultrasound and 78.4% gave perioperative antibiotics. Of all women who positive for one or several bacteria and therefore received antibiotics, 31.7% developed a post-abortion infection. At most hospitals, most surgical abortion was performed under combined local anesthesia and intravenous sedation (74.8%); only 6.2% indicated deep sedation or general anesthesia were used exclusively. Postoperatively, in 51.3% of patients performed immediate tissue examination and for 36.3% of women offered postabortion contraception on the same day as the abortion. Other assessed outcomes included medication regimens and cervical preparation, with a high degree of consistency among facilities and physicians.

RESPONSIBLE PATHOGENS AND ANTIMICROBIAL RESISTANCE

In total, 6,784 pathogens (Gram-negative and -positive bacteria) were isolated from patients with post-abortion endometritis. The predominant post-abortion endometritis pathogens were: *Escherichia coli* (24.1%), *Enterococcus* spp. (14.3%), *Enterobacter* spp. (12.8%), *Pseudomonas aeruginosa* (8.3%), *Proteus mirabilis* (6.6%), *Serratia marcescens* (6.2%), *Staphylococcus aureus* (5.9%), *Stenotrophomonas maltophilia* (5.7%), followed by coagulase-negative staphylococci (4.2%), *Citrobacter* spp. (4.1%), *Acinetobacter baumannii* (3.9%), and *Streptococcus* spp. (3.7%). Distribution of pathogens isolated from women with healthcare-associated endometritis after surgical abortion are presented in Table 2.

Antimicrobial susceptibility testing data were available for all pathogens causing healthcare-associated endometritis after surgical abortion. The antimicrobial resistance reported by Ukrainian hospitals varied widely, depending on the bacterial species, antimicrobial group and geographical region. In this study methicillin/oxacillin resistance was found in 14.8% of *S. aureus* (MRSA), and vancomycin resistance was found in 10.9% of enterococci. Antimicrobial resistance to third-generation cephalosporins was detected in 32.1% of all *Enterobacterales*, and was most common among *E. coli* (27.4%). Carbapenem resistance was found in 14.9% of *Enterobacterales*. Antimicrobial resistance to carbapenems was detected in 37.4% of all non-fermentative, Gram-negative bacteria, and was most common among *P. aeruginosa* (35.7%), and *A. baumannii* (44.2%).

DISCUSSION

This study, to the best of our knowledge the first largest prospective, controlled study to date, we evaluated the prevalence of endometritis after surgical abortion. Additionally, this was the first study of phenotypic characterization of antibiotic resistance of responsible pathogens isolated from patients with endometritis after surgical abortions. This study expands upon the previous reports and is the first study to publish prevalence healthcare-associated endometritis and antimicrobial resistance of responsible pathogens in Ukraine [3, 12].

Induced abortion is one of the most common surgical procedures in Ukraine. Abortion in Ukraine is legal on request during the first twelve weeks of pregnancy. Between 12 and 28 weeks, abortion is available on a

variety of grounds, including medical, social and personal grounds, and for any reason with the approval of a commission of physicians. As of 2010, the abortion rate was 21.2 abortions per 1000 women aged 15–44. In 2018, the abortion rate increased to 247 abortions per 1000 live births. Throughout 2019 almost 75 000 women had an abortion in Ukraine. According to the Ministry of Healthcare of Ukraine, the number of abortions in 2019 reached 74 606, including 727 abortions experienced by minor individuals.

Infection after surgical abortion is considered a very dangerous complication, not only causing inflammation of the reproductive organs, leading to infertility but also life-threatening. However, recognizing signs of infection after abortion is still difficult, because these signs have many similarities with common symptoms.

It is important to understand the underlying physiology that makes post-abortion endometritis such a dangerous complication of pregnancy. Pregnancy begins with the implantation of the blastocyst into the endometrial lining of the uterus. The placenta develops at the point of implantation, becoming the primary interface with the woman's body and the seat of the fetal-maternal communication system that regulates pregnancy. The embryo/fetus develops inside a membranous sac within the uterine cavity. Endometritis occurs as a result of an infection in the lining of the uterus, known as the endometrium. Such infections may develop due to abnormal bacteria, or bacteria usually found in the vagina. The cervix is the opening to the uterus, and it usually keeps bacteria out of the uterus. However, bacteria can get in when the cervix is open. This may happen for various reasons, such as during childbirth or surgery. The infectious agents that produce endometritis after surgical abortion arise from the polymicrobial environment of the vagina and lower genital tract, reaching the uterine cavity through ascending infection. When bacteria gain access to the endometrium, they can spread rapidly to uterine cavity. Devitalized tissue is often present in the uterine cavity in surgical abortions, allowing bacteria to flourish. The confluence of these physiological and microbiological factors explains why infection of the endometrium can disease in such a post-abortion endometritis.

Once the amniotic membranes have ruptured, the risk of infections increases with increasing duration of rupture of the membranes [13, 14]. Incomplete abortion is a powerful risk factor for death from infection. The death-to-case ratio for women with incomplete abortion is over 50 times higher than that for those who have adequate evacuation of the products of conception; the comparative mortality ratio is approximately 18 times higher. Retained tissue provides a nidus for the development of local infection, which then leads to generalized sepsis [15].

Healthcare-associated endometritis after surgical abortion is one of the most important complications of pregnancy that can occur as a result of manipulation. In the literature there are few data on the incidence of clinically significant pelvic infection after surgical abortion. The most healthcare-associated infections after surgical abortion include endometritis, bacterial vaginitis, oophoritis, parametritis, cervicitis, adnexa utery, salpingitis, chorioamnionitis, and other reproductive tract infections [2, 3]. The reported incidence of post-abortion infections varies between studies, likely depending on local differences in diagnostics, the study population, laws and regulations. In Sweden a frequency of 2.4% for infectious complications from medical abortions and 4.9% from surgical abortions [9]. Another study conducted in Sweden and Norway investigated the infection rate after surgical abortions. They reported infections among 4.8% of the patients [10]. These patients had not received any prophylactic antibiotics. Several studies have shown that pre-abortion treatment for BV [10, 16] is effective in reducing the rate of post-abortion infections.

In procedures that access the endometrial cavity through the cervix, some bacterial contamination is inevitable. The reported infection rate following first trimester surgical abortion ranges widely due to various clinical practices and degrees of ascertainment and diagnostic biases. According to the literature, prevalence of healthcare - associated endometritis is estimated is between 9.7% [17] and 25.9% [3]. In our study, the total endometritis frequency after surgical abortions was 27.4%. Of all endometritis cases, 95.3% were detected after hospital discharge. The prevalence of endometritis in different types surgical abortion was: after vacuum aspiration at < 14 weeks, 23.8%, and after dilatation and evacuation at ≥ 14 weeks, 32%.

Endometritis after surgical abortion results from the ascension of bacteria from the cervix and vagina into the uterus. The uterus does not harbour microorganisms until the amniotic sac ruptures, which thus provides passage for bacteria to ascend into the uterus. Microorganisms tend to harbour in an endometrium that is then devitalized and injured. In any pelvic procedure, if proper asepsis is not maintained or if the woman has an untreated vaginal infection prior to a pelvic intervention such as dilatation, curettage, or endometrial aspiration, then the risk of endometritis is higher.

The most bacteria involved in post-abortion infections are found in the normal vaginal flora, which ascend to cause infections of the uterus and upper genital tract, if favorable conditions for growth are present [18, 19].

Cervical and uterine cultures, cultures of the placenta and of any evacuated products of conception.

According to the literature, the main responsible pathogens of healthcare-associated endometritis are *E. coli, Enterococcus* spp., *S. aureus, P. aeruginosa, Enterobacter* spp. [3, 12, 20]. Our results which is consistent with previous research.

Prompt diagnosis, speedy intervention, and rapid escalation of care are of critical importance. The internationally recognized standard of care is prompt intervention with broad-spectrum antibiotic coverage and removal of the products of conception to prevent infectious complications [21]. The selective use of antibiotics for prophylaxis is one of the key advances in infection control. Clinicians should understand when antibiotic prophylaxis is indicated and when it is not. Indeed, inappropriate use of antibiotics contributes to the development of antibiotic resistant bacteria and can therefore also lead to morbidity. The antimicrobial resistance of responsible pathogens reported by Ukrainian hospitals during study period varied widely, depending on the bacterial species, antimicrobial group and geographical region. Previous studies found a high prevalence of healthcare-associated reproductive tract infection caused by multidrug-resistant organisms in hospitals, varying on geographical region of Ukraine [3, 12, 17, 20, 22, 23]. These data underscore the importance of tracking antimicrobial resistance responsible pathogens of healthcare-associated endometritis.

STRENGTHS AND LIMITATIONS

One of the strengths in this study is the size of the study group. A total of 4945 induced abortions were included, which gave a fairly accurate depiction of the incidence of endometritis after surgical abortion. Another strength in this study is the prospective multicentre observational cohort study, based on endometritis after surgical abortions surveillance data and using CDC/NHSN methodology.

The limitations in this study included that it was performed in regional hospitals only. The prevalence of endometritis after surgical abortions and antimicrobial resistance of responsible pathogens in other hospitals was not investigated. Another limitation is that various individuals were involved in categorizing the endometritis after surgical abortions. This may have resulted in misdiagnosis. The timeline of 30 days regarding the follow-up of the patients proved to have disadvantages. Some patients did not contact the gynecological clinic for their post-abortion infections until after 30 days, which leads to an underestimation in the amount of infections. One limitation is that some patients may be missing in our statistics since they sought medical help somewhere other than at regional hospital. However, there are few private gynecological clinics in Ukraine, so it can be assumed that the majority of the infections are represented in this material.

CONCLUSIONS

When performing a surgical abortion, there is always a risk that bacteria from the lower genitals will be brought up to the uterus, causing endometritis. Results this study suggest a high prevalence of endometritis after surgical abortion in Ukraine. A significant proportion of women were affected by post-abortion endometritis caused by bacteria developed resistance to several antimicrobials, varying widely depending on the bacterial species, antimicrobial group. To reduce antimicrobial resistance of responsible pathogens of endometritis after surgical abortion, it is necessary to develop and implement advanced infection control measures based on surveillance data. Lack of evidence on the effect of routine antibiotic prophylaxis for prevention infections after surgical abortion and antimicrobial resistance calls for further research. Optimizing the antibiotic prophylaxis may reduce the burden of endometritis after surgical abortion, but prevention is the key element.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Characteristic features of patients with myopia depending on the expressiveness of anxiety/depression

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ABSTRACT

Aim: To determine the peculiarities of character traits of patients with myopia at different levels of anxiety and depression.

Materials and Methods: 30 patients with moderate myopia and mild myopic astigmatism in both eyes were examined. The "Kettel Test" was used to study the characteristics of the patient's character, and the Hospital Anxiety and Depression Scale was used to assess the levels of anxiety and depression. All examined patients were divided into 3 groups: the 1st group with a normal level of anxiety, the 2nd group with subclinical anxiety/depression, the 3rd group with clinically pronounced anxiety/depression. Mathematical processing of the research results was carried out using the methods of mathematical statistics.

Results: Characteristic features of patients with myopia include conservatism, restraint, subordination, anxiety, developed imagination and high self-control. In half of people with myopia, anxiety/depression is subclinically determined, and in a third – clinically expressed anxiety/depression is observed. In the absence of anxiety in patients with myopia, the main character traits were conservatism, restraint, subordination, sufficient normative behavior, high self-control, and self-confidence; in the presence of subclinical anxiety – sufficient self-control and normative behavior, sociability, developed imagination, conservatism; with clinically expressed anxiety and depression – developed imagination, anxiety, significant normative behavior, conservatism, restraint, subordination.

Conclusions: Studying the characteristic features of patients with myopia is necessary to clarify the peculiarities of the formation of the internal picture of the disease, the etiopathogenesis of the formation of nosogenies due to this pathology, and the development of individual psycho-corrective programs for such patients.

KEY WORDS: Character, anxiety, depression, myopia, etiopathogenesis, nosogenies, psycho-corrective programs

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INTRODUCTION

Some projections suggest that by the year 2050, nearly 50% of the world's population could be myopic, with around 10% highly myopic [1]. In addition, the prevalence of high and potentially pathological myopia over -6D of myopia is of the order of 10 to 20% [2]. Myopia has been traditionally viewed as a consequence of the interplay between genetic, ethnic, and environmental risk factors. The following section highlights these risk factors: younger age at myopia onset, age normal cutoffs, myopic parents, Asian ethnicity, binocular vision disorders, and visual environment [3, 4].

R. Kaiti et al. [5], considering modern concepts of the development of myopia, emphasize that diet, socio-economic status [6], intelligence, and geography [7] are important risk factors for myopia. Myopia is associated with personality introversion, greater intelligence and cognitive abilities, and higher socioeconomic standards [8]. Several systemic diseases (albinism, Down's syndrome, Marfan's syndrome, Stickler's syndrome, dental caries, and diabetes) are also risk factors for the development of myopia [5].

R. Van de Berg et al. [9] say, that personality is defined as the system of enduring characteristics that contribute to consistency in an individual's thoughts, feelings, and behavior. It is widely accepted that personality is influenced by genetic and environmental factors [9]. However, the literature is inconclusive on links between personality and myopia. Numerous studies report that myopic persons tend to differ from nonmyopic persons along personality dimensions such as introversion/extroversion, passivity/anxiety, and abstractness/practicality [9]. In a review of the literature was concluded that myopic persons tend to be more introverted, tolerant to anxiety, and overcontrolled than nonmyopic persons [9].

T. Yokoi et al. [10] sought to determine the incidence of depression and anxiety disorders in patients with high myopia, as well as factors that would predict the development of psychiatric complications and their impact on vision-related quality of life. 205 patients with pathological myopia were examined. The frequency of depression was 22,0 %, and anxiety disorders – 25,9 %.

Table 1. Character traits in different groups of patients with myopia

Character traits (points)	Patients with myopia (M±m)		
	1st group N=6	2nd group N=15	3rd group N=9
A- sociability-closedness	5,95±0,49	6,48±0,26	5,40±0,24*
B- intellect	6,20±0,53	6,34±0,18	6,09±0,34
C- emotional stability	5,78±0,74	6,37±0,31	5,20±0,30**
E- independence-subordination	5,46±0,63	5,67±0,32	5,27±0,34
F- safety-concern	4,58±0,45	5,15±0,30	4,01±0,32**
G- the expressive force of «I»- unprincipledness	6,86±0,29	6,75±0,32	6,94±0,20
H- courage-timidity	5,70±0,74	6,39±0,25	5,08±0,31**
I- flexibility-stiffness	5,22±0,16	4,97±0,36	5,47±0,28
L- suspiciousness-credulity	5,87±0,28	6,24±0,39	5,55±0,44
M- practicality-rich imagination	6,12±0,19	6,03±0,35	6,21±0,37
N- flexibility-straightness	5,73±0,62	5,03±0,27	6,40±0,31***
O- anxiety-calm	6,31±0,37	5,81±0,24	6,79±0,33
Q1- radicalism-conservatism	3,55±0,27	3,41±0,35	3,73±0,38
Q2- conformism-nonconformism	5,76±0,27	5,54±0,33	6,01±0,37
Q3- high-low self-control	6,63±0,23	6,81±0,19	6,421±0,17
Q4- tension-relaxation	5,25±0,16	5,29±0,23	5,24±0,24

Notes: 2nd-3rd group *-p<0,05; **-p<0,01; ***-p<0,001.

Between 22 and 26 % of patients with high myopia had psychiatric disorders that had a strong negative impact on vision-related quality of life [10]. On the other hand, J. Łazarczyk et al. [11], evaluating patients with and without refractive abnormalities, showed that both myopic and hyperopic patients showed significantly less nonspecific anxiety and hostility compared to healthy subjects. Even today, this question is debatable, which became the purpose of this study.

AIM

To determine the peculiarities of character traits of patients with myopia at different levels of anxiety and depression.

MATERIALS AND METHODS

30 patients with myopia were examined at the British Ophthalmological Center in Kyiv. The clinical diagnosis of myopia was established by the Order of the Ministry of Health of Ukraine No. 827 dated 08.12.2015 [12], IMI – Clinical Management Guidelines Report. [13], Myopia control strategies recommendations from the 2018 WHO/IAPB/BHVI Meeting on Myopia [14]. All the studies were conducted according to implemented guidelines in consideration of GCP-ICH and the Declaration of Helsinki and current Ukrainian regulations [15, 16]. The study protocol was approved by the ethics committee of the National Medical University named after O.O. Bogomolets, Ministry of Health of Ukraine. The written informed consent was obtained from all the patients [17].

30 patients with moderate myopia and mild myopic astigmatism in both eyes were examined. 12 men and 18 women aged (M±m) 31,3 ± 5,7 years participated in the study. Independent distance visual acuity of the patients was (M±m) 0,04 ± 0,01 IU, and the maximum corrected visual acuity was (M±m) 0,87 ± 0,13 IU. The optical indicators of the eye were determined in conditions of cycloplegia using autorefractometry. Spherical refraction was (M±m) -4,27 ± 0,734 Dptr., and cylindrical – (M±m) -0,68 ± 0,52 Dptr; length of the anterior-posterior axis of the eye – (M±m) 25,31 ± 0,80 mm; thickness of the cornea in the central point – (M±m) 544,18 ± 29,73 μm.

The "Kettel Test" [18, 19] was used to study the characteristics of the patient's character, and the Hospital Anxiety and Depression Scale (HADS) [20] was used to assess the levels of anxiety and depression. We studied such character traits: sociability-closedness (A), intellect (B), emotional stability (C), independence-subordination (E), safety-concern (F), the expressive force of «I»- unprincipled ness (G), courage-timidity (H), flexibility-stiffness (I), suspiciousness-credulity (L), flexibility-straightness (N), anxiety-calm (O), radicalism-conservatism (Q1),

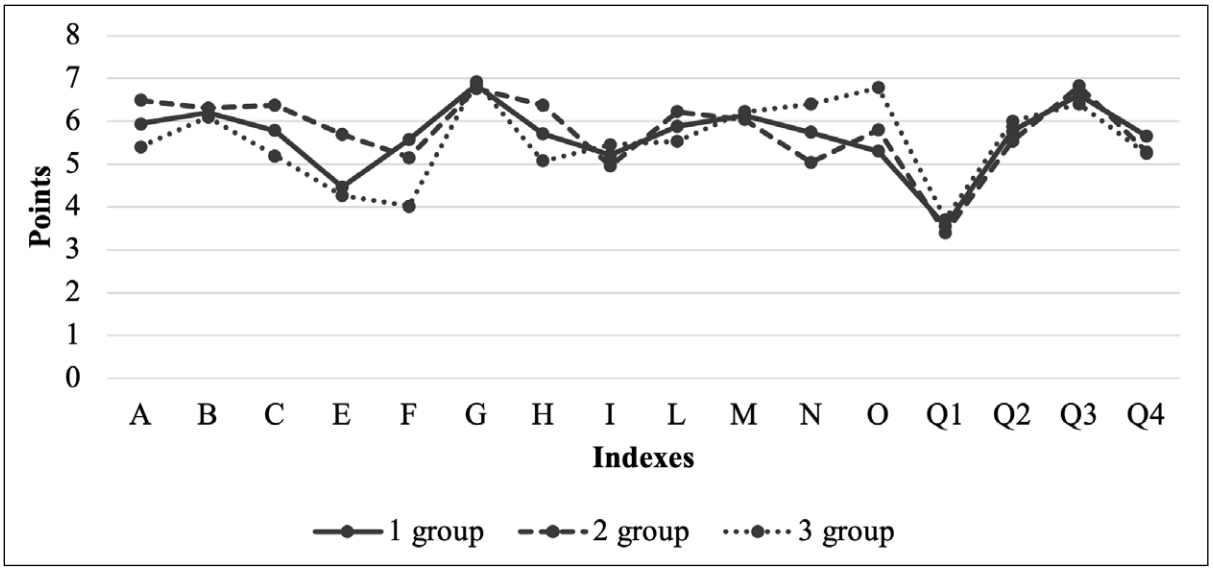

Fig. 1. Generalized profile of characterological features of patients of different groups with myopia

conformism-nonconformism (Q2), high-low self-control (Q3), tension-relaxation (Q4) [18, 19].

Depending on the level of anxiety/depression according to the Hospital Anxiety and Depression Scale (HADS), all examined patients were divided into 3 groups: the 1st group included 6 people (with a normal level of anxiety), the 2nd group involved 15 examined (with subclinical anxiety/depression), the 3rd group was made up of 9 patients (with clinically pronounced anxiety/depression).

Mathematical processing of the research results was carried out using the methods of mathematical statistics. The statistical description of the research indicators was carried out using the methods of primary statistical analysis [21]. We used the computer program «Statistica 7.0 for Windows». The quantitative indicators were presented as M±m. The quantitative data in the studied groups were compared by the use of the two-sample Student's t-test. It was considered that the average values of indicators differ significantly if the p-value did not exceed 0,05.

RESULTS

The generalized characterological profile of all patients with myopia was within the normal range and practically had neither low nor high scores. The highest indicators were +G (expressive strength of "I"-unprincipled), +Q3 (high-low self-control), +M (practicality-rich imagination); the lowest – -Q1 (radicalism-conservatism), -F (concern-security), -E (independence-subordination) (Table 1).

In all patients with myopia, conscious adherence to norms of behavior was observed, but sometimes there was a possibility of subordination to the case or circumstances (+G); discipline, accuracy in fulfilling social requirements, the ability to control one's emotions, take care of one's own public reputation (+Q3); sufficiently developed imagination, orientation to both the internal and external world, high creative potential (+M); conservatism, doubts about new ideas, tendency to moralize and preach (-Q1); prudence, caution, silence, tendency to complicate everything, some preoccupation, pessimistic perception of reality, expectation of failure, fears about the future (-F). That is, the leading characterological features of patients with myopia were conservatism, restraint, subordination, anxiety, developed imagination, and high self-control.

The 86,7 % of those examined had anxious thoughts, 80 % felt fear, 73,3 % complained of feelings of anxiety, 66,7 % felt internal tension, 53,3 % were not satisfied with life, 33,3 % – did not feel cheerful, 26,6 % – complained about slowness of actions, 30,0 % noted the lack of satisfaction with their affairs, 16,6 and 20,0 % – lack of meaning and job satisfaction In 20 % of patients, the level of anxiety/depression according to the Hospital Anxiety and Depression Scale (HADS) is 6,54 points, in 50 % – 8,73 points, in 30 % – 13,56 points. That is, 50 % of patients with myopia were diagnosed with subclinically expressed anxiety/depression, and 30 % with clinically expressed anxiety/depression.

In patients with myopia in the absence of anxiety and depression (the 1st group), the highest indicators were +G (expressive strength of «I» – unprincipled), +M (practicality – rich imagination), +Q3 (high-low self-control), and the lowest – -Q1 (radicalism-conservatism), -E (independence-subordination), -I (flexibility-rigidity) (Table 1).

They were characterized by compliance with norms and rules, which they sometimes violated under certain circumstances, efforts to act by their own value preferences (+G); sufficiently developed imagination, orientation to both the inner world and external reality, high creative potential (+M); discipline, strict adherence to social requirements and rules, the ability to control one's emotions, concern for one's own social reputation (+Q3); conservatism, resilience in the face of difficulties, doubts about new ideas, tendency to moralize and teach others (-Q1); shyness, tendency to give way to others, dependence, self-blame, tact, submissiveness, to complete passivity (-E); excessive self-confidence and independence, mannerism, skepticism, cynicism, pragmatism (-I).

The leading characterological features of such persons were conservatism, restraint, subordination, sufficient normativity of behavior, high self-control, and self-confidence.

In patients with subclinical anxiety/depression (50,0% of the examined – the 2nd group), the highest indicators were +Q3 (high-low self-control), +G (expressive strength of "I" – unprincipled), +A (sociability-closedness), +M (practicality-rich imagination); the lowest- Q1 (radicalism-conservatism) (Fig. 1).

Discipline, compliance with social requirements, the ability to control one's emotions, care for one's social reputation (+Q3); conscious observance of norms and rules of conduct, perseverance in achieving the goal, accuracy, responsibility, business orientation (+G); sociability, good-naturedness, openness, kind-heartedness, naturalness and ease of behavior, attentiveness, benevolence, sincerity in relationships, active in resolving conflicts, trustworthiness, experiencing bright emotions, lively response to any event (+A); sufficiently developed imagination, orientation to both the inner world and external reality, high creative potential (+M); conservatism, resilience in the face of difficulties, doubts about new ideas, tendency to moralize and teach others (-Q1).

The leading characterological features of these patients were high self-control, sufficient normativity of behavior, sociability, developed imagination and conservatism.

A third of the examined patients who were diagnosed with clinically significant anxiety/depression (the 3rd group) are characterized by +M (practicality-rich imagination), +O (anxiety-calm), +G (expressive strength of "I"- unprincipledness) and -Q1 (radicalism-conservatism), -E (independence-subordination), -F (concern-security) (Fig.). Persons with myopia and severe anxiety/depression had a statistically significant decrease in levels of A- sociability-closedness – on 16,7 % ($p<0,05$), C- emotional stability – on 18,3 % ($p<0,05$), F- safety-concern – on 22,1 % ($p<0,01$), H-courage-timidity – on 20,5 % ($p<0,01$), and increase of N- flexibility-straightness – on 27,2 % ($p<0,01$) (Table 1).

These individuals were distinguished by sufficiently developed attention, orientation both to the inner world and to external reality, sufficient creative potential (+M), insecurity, anxiety, depression, vulnerability (+O), a tendency to consciously observe norms and rules, but sometimes and to impulsive behavior, the desire to adhere to one's own's value guidelines (+G), conservatism, stability with traditional life difficulties, doubts about new ideas, a tendency to demoralize and teach (-Q1), shyness, a tendency to give way to others, dependence, preoccupation the possibility of mistakes, tact, submissiveness to complete passivity (-E), prudence, carefulness, silence, a tendency to complicate everything, preoccupation, pessimistic perception of reality, anxiety about the future, expectation of failure (-F).

The leading characterological features of patients with myopia and severe anxiety/depression included developed imagination, anxiety, significant normative behavior, conservatism, restraint, and subordination.

That is, the leading characterological features of patients with myopia were conservatism, restraint, subordination, anxiety, developed imagination, and high self-control.

50 % of patients with myopia were diagnosed with subclinically expressed anxiety/depression, and 30 % with clinically expressed anxiety/depression. 86,7 % of those examined had anxious thoughts, 80 % felt fear, 73,3 % complained of anxiety, 66,7 % felt internal tension, 53,3 % were not satisfied with life, 33,3 % did not feel cheerful, 26,6 % – complained about the slowness of actions, 30,0 % noted lack of satisfaction with their affairs, 16,6 and 20,0 % – lack of meaning and satisfaction from work.

The leading characterological traits of persons with myopia and a normal level of anxiety were conservatism, restraint, subordination, sufficient normative behavior, high self-control, and self-confidence.

Patients with myopia and subclinical anxiety/depression can be characterized as highly self-controlled, with sufficient normativity of behavior, sociable, with a developed imagination, and conservative. In the conducted study, we did not find statistically significant differences between persons with a normal level of anxiety and subclinically expressed anxiety depression, which may be related to the small size of the group.

In patients with myopia and severe anxiety/depression, it is possible to note a developed imagination, anxiety, significant normative behavior, conservatism,

restraint, and subordination. However, significant differences in character traits were observed in patients with myopia of 2nd and the 3rd groups. Persons with myopia and severe anxiety/depression had a statistically significant decrease in levels of A- sociability-closedness – on 16,7 %, C- emotional stability – on 18,3 %, F- safety-concern – on 22,1 %, H- courage-timidity – on 20,5 %, and increase of N- flexibility-straightness – on 27,2 %. The obtained results indicate the need for further research on the prevalence of mental and behavioral disorders in patients with myopia.

DISCUSSION

Globally 22,9 % of the population had myopia and 2,7 % had high myopia in 2000, and projects that these figures will increase to 49,7 % and 9,8 %, respectively by 2050. It is estimated that in 2020 2,6 billion live with myopia and is estimated to increase to 4,7 billion by 2050; almost half the global population [11, 22]. Myopia prevalence has significantly increased from 79,5 % to 87,7 %; moderate myopia (38,8 % to 45,7 %), severe myopia (7,9 % to 16,6 %), and terminal myopia (0,08 % to 0,92 %) [11, 22]. The statistics suggest an alarming increase in myopia prevalence globally, rendering it a burden in public health [11].

Trait anxiety is defined by Spielberger as a theoretical construct, that "is a motive or acquired behavioral disposition, that predisposes a person to perceive a wide range of objectively non-dangerous (physically or psychologically non-dangerous) circumstances as threatening to respond to these anxiety reactions disproportionate in intensity and magnitude of the objective danger" [9-11, 23].

Numerous reviews and studies have reported that people with myopia differ from people without myopia on personality parameters such as introversion/extroversion, passivity/anxiousness, and abstractness/practicality [11]. J. Łazarczyk et al. emphasize that R. Lanyon, J. Giddings found that myopic patients are more withdrawn, embarrassed and self-centered, and less open in their social relationships; they have fewer friends [11]. In the study of A. Kalkan et al. found that patients with myopia have statistically significant lower scores on the low traits of goal-directedness, willingness to cooperate, empathy, willingness to help, and compassion compared to normal patients [24]. Self-directedness, empathy, and willingness to help were significantly lower in patients with myopia compared to individuals with myopic astigmatism. However, other studies do not indicate significant differences in personality characteristics between myopic and non-myopic people [25].

A number of studies have shown that such eye diseases as amblyopia and strabismus negatively affect the mental state of patients. People with amblyopia had higher levels of somatization, obsessive-compulsive disorder, interpersonal sensitivity, depression, and anxiety compared to controls [11]. J. Horwood et al. indicate that the sense of victimhood that arose in early childhood can be associated with psychosocial maladjustment and causes anxiety, depression, loneliness, and low self-esteem. Visual defects, such as strabismus or amblyopia, have been associated with impaired interpersonal relationships and low self-esteem [11, 26, 27].

Anxiety disorders and depressive disorders are among the most common disorders experienced by young people and may later contribute to the development of anxiety disorders in adults [10]. T. Yokoi et al. sought to determine the incidence of depression and anxiety disorders in patients with high myopia, as well as factors that would predict the development of psychiatric complications and their impact on vision-related quality of life. The frequency of depression was 22,0 %, and anxiety disorders – 25,9 %. Between 22 and 26 % of patients with high myopia had psychiatric disorders that had a strong negative impact on vision-related quality of life [10].

CONCLUSIONS

1. Characteristic features of patients with myopia include conservatism, restraint, subordination, anxiety, developed imagination, and high self-control.
2. In half of people with myopia, anxiety/depression is subclinically determined, and in a third – clinically expressed anxiety/depression, is expressed in an increase in anxious thoughts, increased fear, a feeling of anxiety, and internal tension. Half of the patients were not satisfied with life, did not feel cheerful, and complained about the slowness of actions, lack of meaning, and satisfaction from work.
3. In the absence of anxiety in patients with myopia, the main character traits were conservatism, restraint, subordination, sufficient normative behavior, high self-control, and self-confidence; in the presence of subclinical anxiety – sufficient self-control and normative behavior, sociability, developed imagination, conservatism; with clinically expressed anxiety and depression – developed imagination, anxiety, significant normative behavior, conservatism, restraint, subordination.
4. There were significant differences in character traits were observed in patients with myopia of subclinical and severe anxiety/depression. Persons with myopia

and severe anxiety/depression had a statistically significant decrease in levels of sociability-closedness (A) – on 16,7 %, emotional stability (C) – on 18,3 %, safety-concern (F) – on 22,1 %, courage-timidity (H) – on 20,5 %, and increase of flexibility-straightness (N) – on 27,2 %.

5. Studying the peculiarities of the character of patients with myopia is necessary to clarify the etiopathogenesis of the formation of nosogenies due to this pathology, the peculiarities of the formation of the internal picture of the disease, and the development of individual psychocorrective programs for such patients.

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CONFLICT OF INTEREST
The Author declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Etiological differences in demographics, clinical course and consequences of acute pancreatitis: a retrospective study

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ABSTRACT

A**im:** The study is intended to consider acute pancreatitis from the point of view of its etiological structure, as well as demographic description, features of the clinical course, distribution of morphological forms, severity and consequences of the disease in different etiological variants.

Materials and Methods: The work was based on a retrospective analysis of the medical records of 677 patients with acute pancreatitis who underwent inpatient treatment from 2017 to 2022 in an emergency hospital and a tertiary regional hospital in Vinnytsia, Ukraine.

Results: The etiological structure of the general sample was as follows: the alimentary factors – 37,5% of cases, biliary – 18,6%, alcohol – 14,0% and postoperative – 7,8%, respectively. The oldest patients were observed in the group with biliary AP (age [median, interquartile range] 61 [46-72] years), the youngest – in the group with alcoholic AP (age [median, interquartile range] 40 [35-47] years). Men significantly predominated in the groups with alimentary and alcoholic AP. A significant predominance of women was observed in the group with biliary AP (62,7% vs. 37,3%, p=0,0003). The highest mortality was in the alcoholic AP group (22,1%), also here was a significantly lower rate of inpatient bed days (6,0). Edematous AP was dominant in all etiological variants. While infected necrotic pancreatitis was significantly more often found in patients with alcoholic genesis (7,4%).

Conclusions: The etiologic variations of acute pancreatitis differ by demographic and clinical indicators and require more detailed study to understand its prognosis, management, and development of effective prevention and treatment strategies.

KEY WORDS: acute pancreatitis, etiology, clinical course

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INTRODUCTION

Acute pancreatitis remains the subject of special attention and careful study. The frequency of occurrence of this pathology in recent decades does not tend to decrease both in the world and in Ukraine, and in cases of severe forms it can lead to significant complications and high mortality, which can reach 41% [1]. It is the high prevalence of acute pancreatitis throughout the world and its various etiological forms, which vary in different geographical regions, that make it the subject of intensive scientific research.

For today numerous clinical studies have studied the effect of etiology on the course of AP. According to the latest data, in 70% of cases acute pancreatitis today is caused by gallstone disease and alcohol abuse in the ratio of gallstone etiology to alcohol 2:1 [2-5]. A 2019 meta-analysis showed that gallstones are the leading cause of AP worldwide, and occur twice as often as alcohol, 95% confidence interval (CI) (42%, 39-44). Alcohol showed a slightly higher estimated mean effect than idiopathic AP, and their 95% CIs were similar (21%, 17-25 and 18%, 15-22, respectively) [6]. On the other hand, in the structure of the causes of AP, there is an increase in the share of idiopathic AP, which in some places reaches 25,6% [3].

In general, there is a potential relationship between the etiology, clinical course and consequences of acute pancreatitis, which was convincingly demonstrated in a systematic review and meta-analysis [7]. According to his data, the highest risk of moderately severe and severe course was found in hypertriglyceridemia-induced acute pancreatitis, followed by alcoholic, biliary and ERCP-induced. Patients with biliary AP had the lowest recurrence rate. The mortality rate was significantly higher in hypertriglyceridemia-induced acute pancreatitis compared with alcoholic and biliary pancreatitis (odds ratio (OR) = 1,72 and 1,50, 95% CI 1,04-2,84 and 0,96-2,35, respectively).

Thus, the development of acute pancreatitis can be based on various causative factors, from alcohol consumption to gallstone disease and other causes. Understanding the influence of various etiological factors on the course of AP and its consequences will allow effective management of this pathology, optimization of diagnosis and treatment, as well as development of prevention strategies.

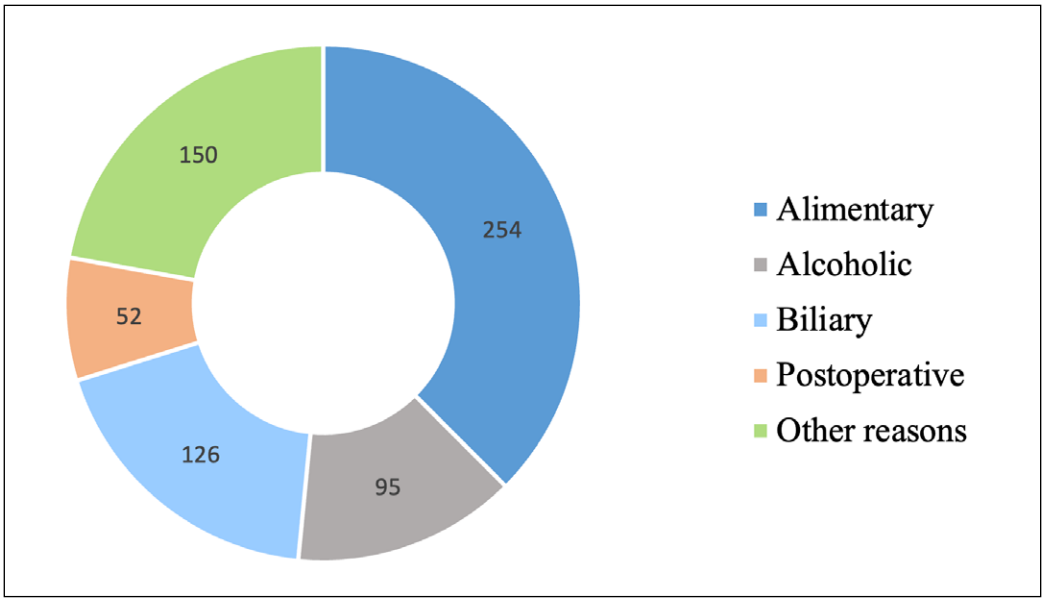

Fig. 1. Structural distribution of patients by etiology of acute pancreatitis.

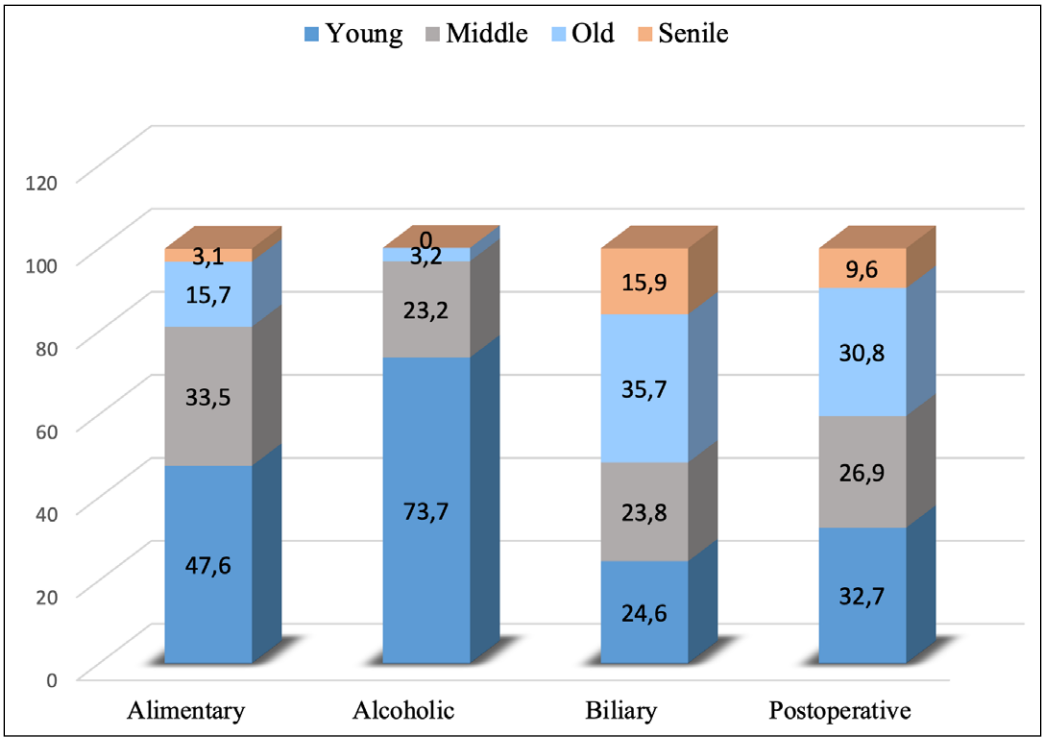

Fig. 2. Age distribution (in %) and median age depending on the etiological variant of acute pancreatitis.

AIM

The aim of our study is to determine the etiological factors of acute pancreatitis and to study their influence on the course of the disease.

MATERIALS AND METHODS

The analysis of clinical material was carried out on the basis of information from the medical records of inpatients who received treatment for acute pancreatitis from 2017 to 2022 in the Vinnytsia city clinical hospital of emergency medical care and the Vinnytsia regional clinical Pirogov memorial hospital. As part of the study, the data of 677 patients with acute pancreatitis were analyzed. Among them, the vast majority were men – 60,7% (411), women were 39,3% (266). All patients undergoing inpatient treatment gave their consent to the processing of their personal data and information obtained during examination and treatment. The collection and analysis of clinical and laboratory material was performed in accordance with all ethical standards defined in the Declaration of Helsinki.

Patients eligible for inclusion met specific criteria. Specifically, a diagnosis of acute pancreatitis based on the 2012 Atlantic Classification with any two of the following three symptoms: characteristic abdominal

Table 1. Groups of patients

Groups of patients	Number of patients	Median age
Alimentary AP	n=254	46,0 (37,0; 58,0)
Alcoholic AP	n=95	40,0 (35,0; 47,0)
Biliary AP	n=126	61,0 (46,0; 72,0)
Postoperative AP	n=52	53,0 (42,5; 66,5)
p1-2=0,001; p1-3<0,0001; p1-4=0,08; p2-3<0,0001; p2-4<0,0001; p3-4=0,03		
Young age p1-2<0,0001; p1-3<0,0001; p1-4=0,04; p2-3<0,0001; p2-4<0,0001; p3-4=0,27		
Middle age p1-2=0,06; p1-3=0,05; p1-4=0,35; p2-3=0,91; p2-4=0,61; p3-4=0,66		
Old age p1-2=0,001; p1-3<0,0001; p1-4=0,01; p2-3<0,0001; p2-4<0,0001; p3-4=0,52		
Senile age p1-2=0,08; p1-3<0,0001; p1-4=0,04; p2-3<0,0001; p2-4=0,002; p3-4=0,27		

Notes: 1. Intergroup difference %, calculated according to the $\chi 2$ criterion for independent samples; 2. The intergroup difference in age medians was calculated using the Kruskal-Wallis ANOVA test.

Table 2. Ratio of men to women in different groups (reliability calculated according to the $\chi 2$ criterion for one-group analyses)

1. Alimentary AP	2,0 to 1,0	$\chi 2$=58,2; p<0,0001
2. Alcoholic AP	7,6 to 1,0	$\chi 2$=112,2; p<0,0001
3. Biliary AP	0,6 to 1,0	$\chi 2$=16,3; p=0,0003
4. Postoperative AP	0,8 to 1,0	$\chi 2$=1,4; p=0,50
Men: p1-2=0,0001; p1-3<0,0001; p1-4=0,002; p2-3<0,0001; p2-4<0,001; p3-4=0,39		
Women: p1-2=0,0001; p1-3<0,0001; p1-4=0,002; p2-3<0,0001; p2-4<0,001; p3-4=0,39		

pain, serum lipase/amylase threefold above normal, and corresponding changes in the pancreas visualized on CT or US.

All patients were classified according to Atlanta 2012 criteria into three groups depending on severity. Mild acute pancreatitis was not characterized by organ failure and was not accompanied by local or systemic complications. Moderate acute pancreatitis was determined by the presence of transient organ failure and/or local complications. The severe course of acute pancreatitis was characterized by persistent organ failure, that is, organ failure lasting more than 48 hours [8].

Determination of the etiological factor of acute pancreatitis was carried out on the basis of a detailed collection of medical anamnesis. In cases of alcohol consumption before the onset of the disease, it was considered that acute pancreatitis has an alcoholic etiology. The biliary etiology of acute pancreatitis, not having a specific biochemical marker, was determined by visualization of calculi in the gallbladder and/or ducts, including microlithiasis, as well as in the presence of a history of biliary colic attacks and dysfunction of the sphincter of Oddi. The consumption of fatty and fried food before the onset of the disease was considered as an alimentary factor. Although in the modern classification of acute pancreatitis according to the recommendations of Atlanta 2012, there is no alimentary genesis, we consider that such an etiological factor is important and should be taken into account, based on a clear cause-and-effect relationship of the development of AP in patients after eating fatty, fried food. Postoperative pancreatitis was defined according to the definition proposed by ISGPS [9]. ERCP-induced pancreatitis was diagnosed on the basis of the method proposed by Cotton P. [10]. A rare cause of acute pancreatitis was the use of certain medications by patients. In the absence of visible causes in the medical history, the etiological factor was considered unknown.

Statistical analysis of the obtained material was carried out using SPSS software (version 20, from IBM). Quantitative values are presented in the form of the median and interquartile range (25 and 75 percentiles) in the case of non-normal distribution of the value of the indicators, which is determined by the W-test (Shapiro-Wilk test) and in the form of the mean value (M) ± standard deviation of the mean (σ) in with normal

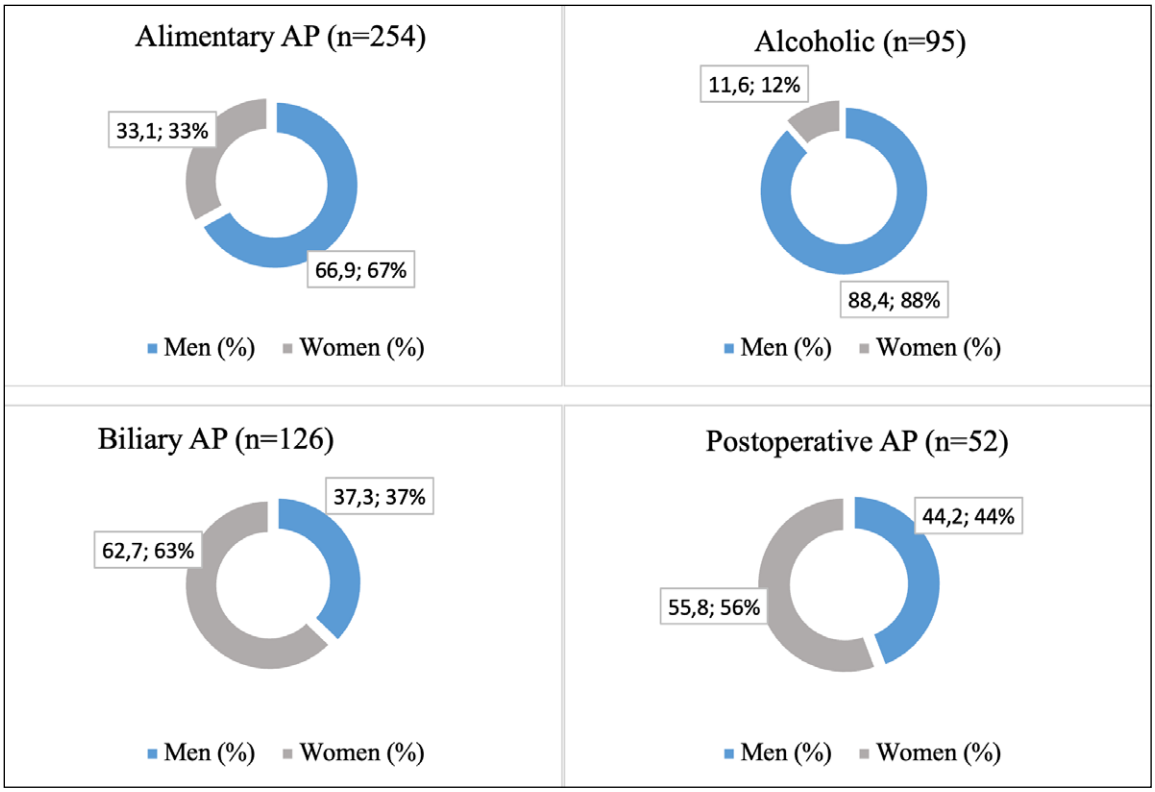

Fig. 3. Distribution (in %) by gender depending on the etiological variant of acute pancreatitis.
Note. Between-group distribution by gender, carried out according to the χ2 test for independent samples.

distribution – p by W-test > 0,05. The reliability of the difference in the number of indicators was calculated for the median by Kruskal-Wallis ANOVA & Median test, for the average value – by one-way ANOVA & LSD-test. The level of significance was set at the 95% level, and the p value was considered statistically significant if it was less than 0,05.

RESULTS

Among all etiological factors of acute pancreatitis, alimentary was dominant – 254 (37,5%) cases, biliary factor was found in second place, which accounted for 126 (18,6%), alcoholic factor was the third most frequent – 95 (14,0%) and fourth place in the etiological structure of acute pancreatitis was taken by the postoperative factor – 52 (7,8%) cases. Another 150 (22,2%) patients had other causes of acute pancreatitis, which included post-traumatic, drug-induced acute pancreatitis, stress-induced acute pancreatitis, and in 134 (19,8%) patients, the cause of acute pancreatitis could not be determined (Fig. 1).

Analysis of the age characteristics of patients with acute pancreatitis depending on the cause of the disease showed (Fig. 2) that in the group with biliary AP (n=126) the oldest patients were observed, which was statistically significant compared to other groups of patients (median age 61,0 vs. 46,0, 40,0 and 53,0 years, p<0,0001, p<0,0001 and p=0,03, respectively). In addition, this group had the most elderly (37,5%) and senile (15,9%) patients, and the least young (24,6%) and middle-aged (23,8%) patients. Therefore, the proportion of young patients was significantly lower (24,6% versus 47,6% and 73,7%, p<0,0001 and p<0,0001, respectively), while the proportion of elderly patients (35,7% versus 15,7 % and 3,2%, p<0,0001 and p<0,0001, respectively) and elderly (15,9% vs. 3,1% and 0, p<0,0001 and p<0,0001, respectively) age turned out to be more compared to groups of alimentary and alcoholic AP.

In the group with alcoholic AP, the youngest patients were observed (40,0 vs. 46,0, 61,0, and 53,0 years, p=0,001, p<0,0001, and p<0,0001, respectively). Also, this group had the most young patients (73,7% vs. 47,6%, 24,6% and 32,7%, p<0,0001; p<0,0001 and p<0,0001, respectively) and the least elderly patients (3,2% versus 15,7%, 35,7% and 30,8%, p=0,001; p<0,0001 and p<0,0001, respectively) compared to other groups of patients. There were no elderly patients in the group with alcoholic AP (0 vs. 3,1%, 15,9% and 9,6%, respectively, p=0,08; p<0,0001 and p=0,002, respectively).

It is worth noting that patients with alimentary and postoperative AP had an intermediate position with a slightly

Table 3. Mortality, duration of treatment, time factor and department of hospitalization depending on the etiological variant of acute pancreatitis

Clinical characteristics	Etiological variant of AP				Intergroup reliability (p) of the difference in results		
	Alimentary	Alcoholic	Biliary	Postoperative	1-2 1-3	1-4 2-3	2-4 3-4
Total (n=527)	1 group (n=254)	2 group (n=95)	3 group (n=126)	4 group (n=52)			
Lethal result, number (%) 44 (8,3 %)	16 (6,3 %)	21 (22,1 %)	7 (5,6 %)	0 (0)	<0,0001 0,77	0,06 0,0003	0,0003 0,08
Bed-day, days 8,0 (5,0; 12,0)	8,0 (5,0; 12,0)	6,0 (4,0; 9,0)	9,0 (6,0; 13,0)	10,0 (7,5; 14,5)	0,0009 1,00	0,43 <0,0001	0,0001 1,00
Time from the onset of the disease to hospitalization							
Up to 6 hours, number (%) 49 (9,3 %)	24 (9,4 %)	13 (13,7 %)	10 (7,9 %)	2 (3,8 %)	0,25 0,63	0,19 0,17	0,06 0,32
6-24 hours, number (%) 179 (34,0 %)	90 (35,4 %)	27 (28,4 %)	38 (30,2 %)	24 (46,2 %)	0,22 0,31	0,15 0,78	0,03 0,04
24-48 hours, number (%) 140 (26,6 %)	71 (28,0 %)	28 (29,5 %)	33 (26,2 %)	8 (15,4 %)	0,78 0,72	0,06 0,59	0,06 0,12
> 48 hours, number (%) 158 (30,0 %)	69 (27,2 %)	27 (28,4 %)	44 (34,9 %)	18 (34,6 %)	0,82 0,12	0,28 0,31	0,44 0,97
The department of patient's hospitalization							
Surgical, number (%) 456 (86,5 %)	224 (88,2 %)	66 (69,5 %)	114 (90,5 %)	52 (100,0 %)	<0,0001 0,50	0,009 0,0001	<0,0001 0,02
Intensive care unit, number (%) 66 (12,5 %)	27 (10,6 %)	27 (28,4 %)	12 (9,5 %)	0 (0)	<0,0001 0,74	0,01 0,0003	<0,0001 0,02
Another, number (%) 5 (0,9%)	3 (1,2 %)	2 (2,1 %)	0 (0)	0 (0)	0,52 0,22	0,43 0,10	0,29 -

Notes:

1. Quantitative data are presented in the form of median and interquartile range (from the 25th to the 75th percentile) due to detection of non-normal distribution using the W-test (Shapiro-Wilk) and expressed as a percentage;
2. The reliability of the difference between quantitative indicators is given using the Kruskal-Wallis ANOVA & Median test in percentages – according to the $\chi 2$ criterion.

higher median age in the group with postoperative AP – 53,0 vs. 46,0 years, respectively (p=0,08). In addition, the family with postoperative AP had fewer young problems (32,7% vs. 47,6%, p=0,04) and used more elderly (30,8% vs. 15,7%, p=0 ,01) and older age (9,6% vs. 3,1%, p=0,04) compared to the alimentary AP (Fig. 2, Table 1).

Analysis by gender showed a significant predominance of men in the groups with alimentary and alcoholic AP (66,9% vs. 33,1% and 88,4% vs. 11,6%, p<0,0001 and p<0,0001, respectively) (Fig. 3, Table 2). Moreover, the largest proportion of men was found in the group with alcoholic AP and had statistical significance in comparison with other groups of patients (88,4% versus 66,9%, 37,3% and 44,2%, p=0,0001, p< 0,0001 and p<0,0001, respectively). The ratio of men to women in the group with alcoholic AP was 7,6 to 1,0.

A significant predominance of women was observed in the group of patients with biliary AP (62,7% vs. 37,3%, p=0,0003), in comparison with the group of patients with postoperative pancreatitis, where the gender distribution is almost equal (55,8% women versus 44,2% of men, p=0,50). The share of women in the group with biliary AP was the largest, which had statistical significance compared to alimentary and alcoholic (62,7% vs. 33,1% and 11,6%, p<0,0001 and p<0,0001, respectively).

In the course of treatment, 44 out of 527 (8,3%) patients died (Table 3). The highest percentage of mortality was in the group with alcoholic AP, which had statistical significance compared to all other groups of patients (22,1% versus 6,3%, 5,6% and 0, p<0,0001, p=0,0003 and p=0,003, respectively). In comparison with patients with postoperative pancreatitis, the mortality rate was higher in the group of patients with alimentary genesis, which tended to be significant (6,3% versus 0, p=0,06).

The duration of inpatient treatment in the total sample was 8,0 (5,0; 12,0) days. Despite the high mortality in the group with alcoholic AP, these patients had significantly

Table 4. Distribution of morphological forms and accompanying pathology depending on the etiological variant of acute pancreatitis

Morphological form of AP	Etiological variant of AP				Intergroup reliability (p) of the difference in results		
	Alimentary	Alcoholic	Biliary	Postoperative	1-2 1-3	1-4 2-3	2-4 3-4
Total (n=527)	1 group (n=254)	2 group (n=95)	3 group (n=126)	4 group (n=52)			
Morphological forms of AP							
Edema form, number (%) 396 (75,1 %)	191 (75,2 %)	65 (68,4 %)	98 (77,8 %)	42 (80,8 %)	0,20 0,58	0,39 0,12	0,11 0,66
Aseptic necrotic pancreatitis, number (%) 102 (19,4 %)	48 (18,9 %)	22 (23,2 %)	22 (17,5 %)	10 (19,2 %)	0,38 0,73	0,96 0,29	0,58 0,78
Infected necrotic pancreatitis, number (%) 28 (5,3 %)	15 (5,9 %)	7 (7,4 %)	6 (4,8 %)	0 (0)	0,62 0,65	0,07 0,41	0,04 0,11
Accompanying pathology							
Diagnosed accompanying pathology, number (%) 451 (85,6 %)	218 (85,8 %)	75 (78,9 %)	122 (96,8 %)	36 (69,2 %)w	0,12 0,001	0,004 <0,0001	0,19 <0,0001
Pathology of the stomach and duodenum, number (%) 210 (39,8 %)	114 (44,9 %)	33 (34,7 %)	54 (42,9 %)	9 (17,3 %)	0,09 0,71	0,0002 0,22	0,03 0,001
Cardiovascular pathology, number (%) 77 (14,6 %)	36 (14,2 %)	20 (21,1 %)	5 (4,0 %)	16 (30,8 %)	0,12 0,003	0,004 0,0001	0,19 <0,0001
Diabetes, number (%) 41 (7,8 %)	20 (7,9 %)	8 (8,4 %)	13 (10,3 %)	0 (0)	0,87 0,43	0,04 0,63	0,03 0,02
Gallstone disease, number (%) 119 (22,6 %)	12 (4,7 %)	1 (1,1 %)	93 (73,8 %)	13 (25,0 %)	0,11 <0,0001	<0,0001 <0,0001	<0,0001 <0,0001
Adiposity, number (%) 43 (8,2 %)	18 (7,1 %)	2 (2,1 %)	20 (15,9 %)	3 (5,8 %)	0,07 0,007	0,73 0,0007	0,24 0,07
Another pathology, number (%) 178 (33,8 %)	74 (29,1 %)	35 (36,8 %)	45 (35,7 %)	24 (46,2 %)	0,17 0,19	0,02 0,86	0,27 0,19
Number of accompanying diseases, 1,0 (0; 1,0)	1,0 (0; 1,0)	1,0 (0; 1,0)	2,0 (1,0; 2,0)	1,0 (0; 1,0)	1,00 <0,0001	1,00 <0,0001	1,00 <0,0001

less bed days compared to all other groups of patients (6,0 vs. 8,0, 9,0, and 10,0 days, respectively, p=0,0009, p<0,0001 and p=0,0001, respectively) (Table 3).

Analysis of the time from the onset of the disease to hospitalization of patients in the hospital in the general sample showed that in most cases this interval lasted from 6 hours and was the highest during the first day (from 6 to 24 hours – 34,0%). Intergroup analysis showed a significant prevalence of patients with postoperative pancreatitis who were hospitalized within 6-24 hours compared to alcoholic and biliary genesis (46,2% compared to 28,4% and 30,2%, respectively, p=0,03 and p=0,04, respectively).

86,5% (456) of patients with AP of the general sample were hospitalized for inpatient treatment in the surgical department. All patients with postoperative pancreatitis (100%) were hospitalized in the same department, as well as the majority of patients with alimentary (88,2%) and biliary genesis (90,5%). The smallest number of patients with AP who were hospitalized for treatment in the surgical department was the group with alcoholic genesis. This difference was statistically significant compared to other patient groups (69,5% vs. 88,2%, 90,5%, and 100%, respectively, p<0,0001, p=0,0001, and p<0,0001, respectively).

Instead, 12,5% (66) of patients were hospitalized immediately to the intensive care unit. Among them, there

Table 5. Distribution of complications depending on the etiological variant of acute pancreatitis

Complication of acute pancreatitis	Etiological variant of AP				Intergroup reliability (p) of the difference in results		
	Alimentary	Alcoholic	Biliary	Postoperative	1-2	1-4	2-4
Total (n=527)	1 group (n=254)	2 group (n=95)	3 group (n=126)	4 group (n=52)	1-3	2-3	3-4
Diagnosed complications, number (%) 184 (34,9 %)	86 (33,9 %)	37 (38,9 %)	53 (42,1 %)	8 (15,4 %)	0,38 0,12	0,009 0,64	0,003 0,0006
Fluid accumulations, number (%) 41 (7,8 %)	22 (8,7 %)	5 (5,3 %)	13 (10,3 %)	1 (1,9 %)	0,29 0,60	0,09 0,17	0,33 0,06
Phlegmon of the retroperitoneal space, number (%) 16 (3,0 %)	10 (3,9 %)	4 (4,2 %)	2 (1,6 %)	0 (0)	0,91 0,22	0,15 0,23	0,13 0,36
Parapancreatic abscess, number (%) 9 (1,7 %)	8 (3,1 %)	1 (1,1 %)	0 (0)	0 (0)	0,27 0,04	0,19 0,25	0,46 -
Diabetes mellitus, type II, (%) 11 (2,1 %)	8 (3,1 %)	1 (1,1 %)	2 (1,6 %)	0 (0)	0,27 0,37	0,19 0,73	0,46 0,36
Peritonitis, number (%) 24 (4,6 %)	11 (4,3 %)	9 (9,5 %)	3 (2,4 %)	1 (1,9 %)	0,07 0,34	0,41 0,02	0,08 0,85
Pseudocyst, number (%) 23 (4,4 %)	14 (5,5 %)	4 (4,2 %)	5 (4,0 %)	0 (0)	0,62 0,52	0,08 0,93	0,13 0,15
Pleurisy, number (%) 62 (11,8 %)	34 (13,4 %)	13 (13,7 %)	13 (10,3 %)	2 (3,8 %)	0,94 0,39	0,05 0,44	0,06 0,16
POPF, number (%) 2 (0,4 %)	1 (0,4 %)	0 (0)	0 (0)	1 (1,9 %)	0,54 0,48	0,21 -	0,18 0,12
Other, number (%) 116 (22,0 %)	46 (18,1 %)	29 (30,5 %)	34 (27,0 %)	7 (13,5 %)	0,01 0,04	0,42 0,56	0,02 0,05
Total number of complications 0 (0; 1)	0 (0; 1)	0 (0; 1)	0 (0; 1)	0 (0; 0)	1,00 1,00	0,13 1,00	0,07 0,06

were the most patients with alcoholic genesis of AP, which significantly outweighed the number of patients alimentary, biliary, and postoperative AP (28,4% versus 10,6%, 9,5% and 0 respectively, p<0,0001, p=0,0003, p<0,0001, respectively) (Table 3).

The main morphological form of AP was edematous in all etiological variants of AP: alimentary – 75,2%, alcoholic – 68,4%, biliary – 77,8%, postoperative – 80,8%, respectively (p>0,10). Aseptic necrotic pancreatitis occurred in 19,4% of patients in the general group and did not differ significantly in different etiological forms of AP: 18,9%, 23,2%, 17,5% and 19,2%, respectively (p>0,20). While infected necrotic pancreatitis, as the most severe form of pancreatitis, was significantly more often detected in patients with alcoholic genesis, in particular compared to postoperative, in which this form was not detected in any case (7,4% vs. 0, p=0,04) (Table 4).

In 85,6% of patients with AP, a concomitant pathology was diagnosed, and it was found significantly more often in patients with biliary etiology of AP compared to other etiological forms (96,8% compared to 85,8%, 78,9% and 69,2% respectively; p=0,001, p<0,0001 and p<0,0001 respectively). In addition, in patients with alimentary AP, concomitant pathology was detected significantly more often than in patients with postoperative AP (85,8% compared to 69,2%; p=0,004). Thus, concomitant pathology was most often detected in patients with biliary genesis of AP, and least often - in patients with postoperative AP (Table 4).

The total number of complications in patients with AP was 34,9%. The most common among them were fluid accumulation (7,8%) and pleurisy (11,8%). It should be noted that in the group with postoperative pancreatitis the number of complications was significantly lower than in other etiological forms of AP (15,4% compared to 33,9%, 38,9% and 42,1%, respectively; p=0,009, p =0,003 and p=0,0006). Also, in this same group, there was a trend towards a significant decrease in the number of cases of fluid accumulation compared to biliary AP (1,9% compared to 10,3%; p=0,06) (Table 5).

Pancreatic fluid collections and pseudocysts were found significantly more often in patients with moderate and severe disease compared to those with mild disease (18,2% and 18,6% vs. 0,3%, respectively;

p <0,0001 in in both cases, and 12,0% and 6,2% vs. 0,3%; p <0,0001 in both cases). On the other hand, phlegmon of the retroperitoneal space, parapancreatic abscesses, and type II diabetes were detected in the group with a severe course significantly more often than in those with a mild or moderately severe course (19,4% vs. 0% and 0,5%, respectively; p < 0,0001 in both cases; 10,1% vs. 0% and 0,5%; p < 0,0001 in both cases; and 8,5% vs. 0,3% and 1,6%; p < 0,0001 and p=0,003, respectively). Logically, the total number of complications was significantly higher in patients with severe disease and significantly lower in those with mild disease (2,0, 1,0, and 0, respectively; p <0,0001 in all cases).

DISCUSSION

This study showed significant variations of AP in gender distribution, age, time, laboratory and clinical, as well as different distribution of etiological groups according to the severity of the course and the results of treatment in different etiological variants of this pathology, which requires their careful study. Based on the latest understanding of the features of pathogenetic mechanisms and clinical features in each individual etiological variant of AP, it can help identify risk groups and determine the appropriate approach to each patient.

In recent years, more and more studies have appeared in which the authors tried to divide all causes of AP into two groups (biliary and non-biliary genesis) depending on their interaction with the biliary system. However, in our opinion, despite the convenience and simplicity of performing statistical processing in the case of two etiological groups, such a division is inherently limited.

The absence of an alimentary etiological variant of pancreatitis in modern classifications is, in our opinion, a misunderstanding of the importance of this factor in the development of acute pancreatitis. After all, in the dominant part of the patients analysed by us – 37,5% (254), a clear connection was noted with the intake of fatty, fried food on the eve of the disease in the absence of other causative factors, including any biliary factor.

In contrast to the current study, which was conducted in Ukraine, and according to the results of which the biliary factor of AP was in the second place and amounted to 18,6% (126), Alkareemy, E.A.R. et al., 2020, published the results of their study, in which the biliary factor was dominant in patients from Egypt and accounted for more than half of all cases – 56% [11]. Similar data, where the biliary factor of AP was dominant in the vast majority of patients, were published in a number of other studies. In particular, a 2020 study by Matta B, et al., whose final analysis included 1612 patients with AP, demonstrated the predominance of the biliary factor of AP in India – in 45% of patients, in Latin America – in 78% of patients, respectively [12]. This can be explained by the geographical variations of this disease, in which different regions and countries may have differences in the causative factors of the development of acute pancreatitis, such as nutrition, alcohol consumption, infections, genetic aspects, etc.

Regarding the age structure, patients with biliary AP were characterized by the highest age (median 61,0 years), while patients with alcoholic AP were the youngest (median 40,0 years). Elderly patients with alcoholic genesis of AP were not identified at all. The highest age at biliary genesis is predictable, because the frequency of gallstone formation increases with age, which is confirmed by many studies. In particular, a Chinese study found that the presence of gallstones are independent risk factors for the development of AP in people older than 55 years [13].

Men significantly predominated in the groups with food and alcohol genesis, especially in the last one (the ratio of men to women was 7,6 to 1,0). However, this trend suddenly changed in favor of a significant preponderance of women in the case of biliary AP, which corresponds to the results of other studies [14, 15], while in the postoperative variant the ratio of men to women was almost equal.

Of the 44 reported deaths among the 527 patients examined (8,3%), the highest mortality rate was recorded in the alcoholic AP group (22,1%), while there were no deaths in the postoperative AP group (0).

The mean length of hospital stay for all patients with AP was 8,0 (5,0; 12,0) days, with the shortest duration of treatment recorded in the group with the alcoholic variant of AP (median 6,0 days). 86,5% of patients with AP were hospitalized in the surgical department, 100% of them with postoperative AP and the vast majority with alimentary (88,2%) and biliary (90,5%). The largest number of cases of treatment in the intensive care and intensive care unit amounted to 28,4% and was registered in patients with an alcoholic etiology of AP.

The edematous form prevailed in all etiological variants of AP. However, infected necrotic pancreatitis, as the most severe form of pathology, was diagnosed significantly more often in patients with the alcoholic variant of AP (7,4%). This echoes data from a meta-analysis, which also revealed a more frequent development of necrotic AP in patients with alcoholic compared to biliary AP (OR = 1,58, 95% DI 1,08-2,30) [7]. In our opinion, this may be related to deeper metabolic intracellular changes under the influence of alcohol than in other forms [16].

In addition to pancreatitis, another pathology was also detected in 85,6% of the examined. This was much more common in patients with biliary AP and

significantly less often in patients with postoperative AP. In our opinion, the biliary variant of AP should be considered as a polymorbid disease, since more than two concomitant diseases were observed in almost half of the cases.

Complications of AP were detected in 34,9% of patients. The most common among them were fluid accumulation (7,8%) and pleurisy (11,8%). The group with postoperative AP had the lowest number of complications. In our opinion, the latter is related to the fact that patients who underwent surgical interventions received postoperative treatment, including infusion therapy, nonsteroidal anti-inflammatory drugs, what reduce the risk of complications in patients with postoperative acute pancreatitis.

CONCLUSIONS

This study showed significant variations in gender distribution, age characteristics, pre-hospital duration of the pathological process, morphological forms, clinical course, complications and consequences of acute pancreatitis depending on its etiology. Among the most common causes of AP were consumption of fatty foods, alcohol and the presence of gallstones. Acute alcoholic pancreatitis occurred more often in men, while acute biliary pancreatitis occurred more often in women. Differences by sex in the manifestation of the disease, time of onset, course, diagnosis, severity and consequences should be taken into account when developing treatment tactics, taking into account the etiological variant of the pathology.

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CONFLICT OF INTEREST
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ORIGINAL ARTICLE

CONTENTS

Modern approaches to ultrasonographic assessment of carotid plaque in terms of its potential instability

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ABSTRACT

Aim: To identify potentially adverse characteristics of atherosclerotic carotid plaque in terms of stroke risk.

Materials and Methods: The study is based on the analysis of US data obtained from 96 patients aged 47 to 84 years diagnosed with carotid stenosis. The patients were divided into 2 groups depending on the presence or absence of ischemic events. Examination methods: clinical, duplex US, brain MRI, statistical. In addition to the standard US criteria for the evaluation of carotid stenoses, superb microvascular imaging (SMI) and shear wave elastography (SWE) are used.

Results: Statistically significant association of the following characteristics of plaques with the presence of ipsilateral ischemia focus was established: maximum thickness ($p = 0,04$), presence of microvascularization according to SMI data ($p = 0,02$), degree of carotid stenosis (statistically significant in the right carotid circulation [$p = 0,04$]), stiffness of the plaque according to SWE data (significantly in the right carotid circulation [$p = 0,001$]), type of plaque echogenicity according to Gray-Weale-Geroulakos classification (on the right carotid artery; $p = 0,04$).

Conclusions: The presence of microvascularization according to SMI data and the low stiffness of the plaque according to SWE data can characterize the potential instability of the carotid plaque. These criteria should be added to the traditional US assessment of carotid plaques.

KEY WORDS: carotid plaque, carotid stenosis, ultrasound, superb microvascular imaging, shear wave elastography

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INTRODUCTION

Among radiological methods of diagnosing carotid stenoses, the leading role belongs to an ultrasonographic (US) study, and not only as the first link or screening in the assessment of this pathology. The complex of US criteria formed today allows to carry out quantitative and qualitative characterization of the arterial lesion area and its blood supply, as well as determine the indications for revascularization. Indications for carotid revascularization are based on the assessment of the patient's symptomatic status and the degree of ipsilateral stenosis. According to various prospective studies, ipsilateral 50-99% carotid stenosis was responsible for ischemic stroke in 8%-12.5% of patients [1]. Recently, it is believed that the degree of luminal stenosis is not the best predictive indicator of stroke risk, as the morphology of the plaque plays a significant role. The clinical guidelines of the European Society of Vascular Surgery note the importance of assessing plaque vulnerability [1].

Histopathological factors of unstable atherosclerotic plaque (AP) are thinning of the fibrous cap, ulceration and violation of the cap with the formation of blood clots on the surface, the predominance of atheromatosis over fibrosis, the presence of a lipid (necrotic) nucleus, hemorrhage in the plaque, the presence of neoplastic vessels. In vivo detection of this kind of signs a priority of new diagnostic methods [2].

According to US criteria, echo-transparent AP (hypoechogenic plaques of types 1 and 2 according to Gray-Weale classification) are traditionally considered to be unstable, as they occur more frequently in patients with symptomatic carotid stenosis. The irregularity of the surface of the plaque, the presence of ulceration, are also suggested as an ultrasound marker of an unstable plaque and an increased risk of stroke [3].

The recently proposed Plaque-RADS classification presents a system for reporting the composition and morphology of carotid plaques obtained through various imaging techniques such as US, CT and MRI. The categories of plaque evaluation include maximum wall thickness, fibrous cap, intraplaque hemorrhage, lipid-saturated/lipid-rich necrotic nucleus, ulcerated plaque, as well as "ancillary features", namely plaque inflammation and neovascularization, plaque burden,

positive carotid remodeling, stenosis progression, and calcification. Of the 4 categories of plaque severity, categories from 2 to 3a can be diagnosed by US, the rest are determined with the help of MRI and CT [4]. However, new US techniques are able to complement the traditional assessment of AP.

Neovascularization in atherosclerotic plaque plays an important role in plaque vulnerability and is a major source of intra-plaque hemorrhage. Imaging of neogenic intra-plaque vessels has recently been considered to be a possible factor of its instability [5]. Conventional Doppler examinations filter out low-flow signals and prevent small vessel imaging. Contrast-enhanced ultrasound (CEUS) is useful in assessing the neovascularization of the carotid plaque as recommended by the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB, 2017), but requires the use of a contrast agent. Superb microvascular imaging (SMI) is a novel technique which can depict microvascular blood flow signals without the use of contrast agents [2]; the SMI technique is available in certain US diagnostic systems (Canon Medical Systems Corporation Otawara, Japan), demonstrated good sensitivity compared to CEUS as well as correlation with clinical symptoms. AP with higher SMI levels showed correlation with more neovessels in histological examination, as well as with hypoechogenic lesions compared to echogenic ones [5, 6].

Shear Wave Elastography (SWE) is a potential tool for the improvement of detection of vulnerable plaques and therefore it can improve the stratification of atherothrombotic stroke risk. Studies show good reproducibility and the potential clinical benefit of the Young's modulus (YM), its correlation with the qualitative assessment of the B-mode plaque (Gray-Weale classification), which helps to improve the diagnostic characteristics of the vulnerability of carotid plaques [7]. It was demonstrated that a lower mean YM is associated with focal neurological symptoms: transient ischemic attack (TIA), transient mononuclear blindness or stroke. Additionally, significantly lower YM was found in plaques where intra-plaque hemorrhage or thrombus was present, and in plaques with increased amount of foam cells [8]. Studies have revealed a lower mean YM for vulnerable plaque, although values vary between studies, e.g. 50 kPa versus 79 kPa for vulnerable and stable AP [8]; 62 kPa vs. 88 kPa respectively [2]; as well as 81 kPa vs 115 kPa [9].

Thus, advanced US SMI and SWE techniques can be promising in non-invasive identification of unstable carotid plaque and stratification of patients at risk of ischemic events.

AIM

To identify potentially adverse ultrasonographic characteristics of atherosclerotic carotid plaque in terms of stroke risk.

MATERIALS AND METHODS

The study included 96 patients aged 47 to 84 years, (22 women, 74 men), who underwent examination and treatment at the State Institution «National Scientific Center «The M.D. Strazhesko Institute of Cardiology, Clinical and Regenerative Medicine» of the National Academy of Medical Sciences of Ukraine» ("Sonolife" Medical Center) and the Municipal Non-Profit Enterprise of Kyiv Regional Council "Kyiv Regional Clinical Hospital." The set of studies included the assessment of clinical and anamnestic data, results of brain MRI, ultrasound of the main vessels of the neck and head using Toshiba Aplio 400 and Canon i800 ultrasound systems. All patients were diagnosed with carotid stenosis. Attention was paid to internal carotid artery (ICA) stenoses, assessment was carried out according to the standard duplex scanning procedure with determination of the degree of stenosis according to the NASCET protocol [1].

Morphological assessment of the types of ASP was carried out according to Gray-Weale-Geroulakos classification *[10*] 5 types of AP were evaluated: type 1 – hypoechogenic plaques with a thin hyperechogenic cap, type 2 – mainly hypoechogenic plaques with small hyperechogenic areas, type 3 – mainly hyperechogenic plaques with small hypoechogenic areas, type 4 – homogeneous hyperechogenic plaques, type 5 – plaques that cannot be classified due to strong calcification and acoustic shadows.

We applied new techniques for estimating AP in addition to traditional gray scale, color and spectral Doppler modes. The technique of SMI, which is in the software of the ultrasound systems we used, is aimed at finding newly formed vessels in the structure of the plaque. We used SMI in all the patients in two modes: monochrome (shades of gray) and color. To obtain high-quality images, image parameters were corrected: the speed scale was set to less than 2.5 cm/s, color gain was increased to improve sensitivity, smoothing time was increased, which improved temporal resolution due to the accumulation of blood flow signals [11].

SWE technique was also used to determine the density of the plaque, a Jung modulus of kPa was estimated. To obtain optimal visualization, the proposed recommendations were followed Standardized scanner settings for SWE: color range (0-180 kPa); acoustic power (0,0); gain (70-90%); The SWE Area of Interest (ROI) was adjusted to cover the entire plaque with carotid artery

Table 1. US characteristics of carotid stenoses in groups

Criterion	Groups, number of patients		Comparison in groups: U; p
	Group 1	Group 2	
AP thickness, mm, Me (IQR) on the right	3.3 (2.5–3.9), n=49	2.7 (2.1–3.3), n=36	U=680.0; p=0.02
on the left	3.0 (2.3–3.7), n=48	3.0 (2.3–3.4), n=43	U=959.5; p=0.56
Degree of stenosis, % Me (IQR) on the right	45 (30-60), n=49	30 (20–50), n=36	U=601.5; p=0.01
on the left	35 (25-60), n=48	35 (25–50), n=43	U=944.0; p=0.48

Table 2. US assessment of plaque structure in patient groups

Components	Groups				Comparison in groups
	Group 1		Group 2		
	right	left	right	left	χ^2; U; p;
Gray-Weale-Geroulakos AP type, quantity (%)					
1	4 (8.0)	5 (10.4)	1 (2.5)	0	right
2	16 (32.0)	13 (27.1)	2 (5.0)	5 (11.6)	χ^2=19.4; p=0.001
3	18 (36.0)	13 (27.1)	14 (35.0)	14 (32.6)	left
4	10 (20.0)	15 (31.3)	23 (57.5)	24(55.8)	χ^2=12.4; p=0.01
5	2 (4.0)	2 (4.2)	0	0	
Surface ulceration, n/N, quantity (%)	6/49 (12.2)	7/48 (14.6)	2/36 (5.6)	2/43 (4.7)	right χ^2=1.1; p=0.29; left χ^2=2.5; p=0.11
Presence of microvascularization n/N, quantity (%)	30/49 (61.2)	29/48 (60.4)	14/36 (38.8)	17/43 (39.5)	right χ^2=4,2; p=0.04 left χ^2=4,0; p=0.05
AP stiffness, kPa, Me (IQR)	70.0 (57.0–80.0)	72.0 (60.0–79.0)	82.0 (77.5–89.0)	85.0 (74.0–94.0)	Right U=390; p=0.001 left U=380; p=0.001

wall and soft tissue nearby at about two to three times the size of the plaque. To evaluate the SWE color map, the following options were selected: the blue color on the elastogram displayed a low YM (soft), the red color showed a high YM (hard). For the assessment, a film loop with about 10 frames was used. To stabilize the SWE image and facilitate inter-frame variability, the first two SWE frames were discarded due to operator arm movements, five frames were randomly selected to evaluate the plaque YM [7]. Thus, the assessment of carotid plaques was carried out according to a set of criteria: the maximum thickness of AP in mm, the degree of stenosis of ICA in% (NASCET protocol), the presence of local changes in the linear blood flow rate (CBF rate) in the stenosis zone, the morphological assessment of AP types in accordance with Gray-Weale-Geroulakos classification, presence of ulcers, presence of microvascularization according to SMI data, stiffness assessment according to SWE data. The observation group did not include patients with heart rhythm disorders in order to exclude the cardioembolic subtype of ischemic stroke.

Statistical analysis was carried out with the help of MS Office and Statistica 6 software package. The statistical significance of the difference between the groups was assessed taking into account the discrepancy between the data with the parameters of the normal distribution; for the comparison of quantitative indicators – according to the Mann-Whitney U-criterion, for qualitative indicators – according to the χ^2 criterion. The association between two binary variables was assessed by φ coefficient. The relative risk (RR) (with 95 % confidence interval [CI]) of the factor influence on the development of the event was determined. The level of significance was estimated as $p<0.05$.

The research was carried out in accordance with the principles of the Helsinki Declaration of the World Medical Association (1964-2000) and the "Council of Europe Convention on Human Rights and Biomedicine" within the framework of the dissertation research program approved by the Ethics Commission of the Shupyk National Healthcare University of Ukraine.

Table 3. Characteristics of carotid stenosis according to the formation of ipsilateral foci of ischemia

Characteristics of carotid stenosis	Right carotid circulation		Left carotid circulation	
	Foci of ischemia		Foci of ischemia	
	Are present	Not detected	Are present	Not detected
Degree of stenosis, %; Me (IQR)	50.0 40.0-60.0	35.0 25.0-55.0	40.0 30.0-60.0	35.0 20.0-60.0
U; p	169.0; 0.04		174.5; 0.07	
AP thickness, mm; Me (IQR)	3.7 2.9-4.0	3.0 2.5-3.5	3,3 2.5-3.7	2,4 2.1-3.0
U; p	180.5; 0.04		166.0; 0.04	
AP stiffness, kPa; Me (IQR)	59.0 53.0-71.0	80.0 70.5-87.5	70.5; 57.5-77.8	74.0 67.0-83.5
U; p	62.0; 0.001		109.0; 0.14	
Gray-Weale-Geroulakos AP type, χ^2; p	9.78; 0.04		8.88; 0.06	
Presence of microvascular quantity (%)	21(75.0)	8(42.1)	20 (74.1)	7(36.8)
χ^2; p; φ; RR (95% CI)	5.18; 0.02; 0.33; 1.8 (1.0-3.1)		6.38; 0.01; 0.37; 2.0 (1.1-3.8)	
Increasing blood velocity in stenosis zone, quantity (%)	15 (53.6)	5 (23.8)	13 (48.1)	5 (22.7)
χ^2; p; φ; RR (95% CI)	4.40; 0.04; 0.30; 2.3 (1.0-5.2)		3.40; 0.07	
AP Ulceration, quantity (%)	5 (17.9)	1 (5.3)	5(18.5)	1 (5.3)
χ^2; p	1.61; 0.20		1.73; 0.19	

RESULTS

According to the results of the clinical and instrumental data analysis, patients were divided into 2 age-matched groups. Group 1 included of 51 patients with symptomatic carotid stenosis; patients` age was (median [Me], interquartile range [IQR]) 68 (61-74) years. Patients of group 1 showed signs of ischemic events in the carotid circulation during the last 6 months: ischemic stroke – in 49 cases, transient ischemic attack in 2 observations. The ischemic focus (larger than 1.5 cm) in the right carotid circulation occurred in 22 patients, in the left – in 21, and in both carotid blood supply territories – in 6. Group 2 was formed by 45 patients with asymptomatic carotid stenosis, patients' age was (Me [IQR]) 67 (56-74) years. According to MRI, signs of discirculatory changes in the brain predominated in group 2. In all patients studied, II-III degree arterial hypertension (AH) was established: in group 1 – II degree AH in 15 (29.4%) observations, III degree – in 36 (70.6%), in group 2 – II degree AH in 23 (51.1%), and III degree – in 22 (48.9%). Diabetes mellitus in group 1 occurred in 10 (19.6%) patients, in group 2 – in 6 (13.3%).

ICA stenoses in the vast majority of patients were bilateral; in the group 1 only right-sided stenosis occurred in 3 patients, only left-sided in 2, in group 2 only right-sided stenosis was observed in 2 cases, only left-sided – in 9. The maximum thickness of the AP in group 1 was statistically significantly greater, reliable difference in the observation groups was established by the right ICA (U = 680.0; p=0.02). Comparison in the groups indicates a higher percentage of ICA stenosis in the group of patients with ischemic events, a significant difference in the right ICA was noted (U = 601.5; p=0.01) (Table 1). Group 1 showed a higher number of observations with a stenosis degree of ≥50% accompanied with increasing of blood velocity in the stenosis zone, (right 23 (46.9%) against 10 (27.8%), left 19 (39.5%) against 12 (27.9%), but with an unreliable difference in the groups (right $\chi^2 = 3.21$; p=0.07; left $\chi^2 = 1.4$; p = 0.24) (Table 1).

When evaluating the morphological structure of AP in gray scale mode, according to 5 types according to the Gray-Weale-Geroulakos classification, the predominance of heterogeneous AP of type 2 and 3 was established in group 1, and AP of type 3 and type 4 were more often detected in group 2. The occurrence of conventionally unstable plaques of low echogenicity (type 1) was small and was 8.1% in group 1 – 10.4% on the right and left respectively, 2.8% in group 2 only on the right. The difference in groups by type of AP was statystically significant in the right ($\chi^2 = 19.4$; p = 0.001) and left ICA ($\chi^2 = 12.4$; p = 0.01) (Table 2).

Complications of AP in the form of surface ulceration did not reveal significant differences in the groups. In the 1st group, ulceration was registered in only 6 and

7 plaques respectively on the right and left, in the 2nd group – in 2 cases on the right and left, ($\chi^2 = 1.1$; p = 0.30 in the right ICA and $\chi^2 = 2.5$; p = 0.11 in the left ICA). It should be noted that the use of the SMI mode significantly improves the assessment of the plaque surface and ulceration.

Evaluation of SMI mode data revealed the presence of microvascularization mainly in type 2 and 3 plaques, microvascular loci were less common in type 4 AP. A significant prevalence of findings in the group of patients with ischemic events ($\chi^2 = 4.2$; p = 0.04 in the right ICA and $\chi^2 = 4.0$; p = 0.05 in the left ICA). In calcified AP behind calcification sites, a flicker artifact was recorded that simulated the presence of microvascularization, so we selected areas without calcification for evaluation.

AP stiffness determination with the help of SWE made it possible to isolate plaques with YM from 34 to 102 kPa. We did not use SWE to evaluate plaques with pronounced calcification (5 type by Gray-Weale) and thickness less than 2 mm. The level of stiffness was significantly lower in the group of patients with ischemic events (Me = 70.0, IQR: 57,0–80,0 kPa in right ICA, Me = 72.0, IQR: 60.0–79.0 in left ICA) compared to the asymptomatic stenosis group (Me=82.0, IQR: 77.5–89.0 kPa in right ICA, p = 0.001; Me = 85.0, IQR: 74.0–94.0 in left ICA, p = 0.001) (Table 3).

Thus, significant differences in the characteristics of the AP in the observation groups were established according to the following indicators: plaque thickness and stenosis degree (in the right ICA), types of plaques according to the Gray-Weale-Geroulakos classification, the presence of microvascularization according to SMI data, plaque stiffness according to SWE data.

Further data analysis was carried out in the direction of comparison of the nature of carotid stenosis on the side of ischemia lesions (foci) formation according to MRI ("symptomatic" stenosis) compared to stenoses on the side without ischemia foci ("asymptomatic" stenosis) corresponding to the definition of a pathogenetic subtype of stroke according to TOAST classification criteria. Thus, the influence of qualitative and quantitative parameters of AP on the development of an ischemic event was determined. The analysis was perfomed in a group of patients with a stroke, there were foci on the right carotid territory in 28 cases, on the left carotid territory in 27, including patients with ischemic foci in both carotid circulations. The data are presented in Table 3.

Based on the results of statistical data processing, a significant association of characteristics of AP with the presence of ipsilateral ischemic focus ("symptomatic AP") was established. Among the quantitative parameters, the maximal thickness of the plaque (p=0,04 in the right and left carotid circulation), the degree of stenosis (statistically significant on the right side, p=0.04, close to significant on the left side, p=0.07), the stiffness of the plaque according to SWE data (statistically significant only on the right side, p=0.001), were determined. Among the qualitative characteristics are the presence of local disorders of blood flow velocity in the stenosis zone (on the right ICA, p=0.04, RR increases by 2.3 times), the presence of microvascularization according to SMI data (p=0,02 i p=0,01 according to the right and left sides, RR increases by 1.8-2,0 times), as well as types of plaques according to the Gray-Weale-Geroulakos classification (p=0,04 in the right ICA, p=0,06 in the left ICA).

The characteristics of carotid plaques that demonstrated a valid association with ischemic events can be taken into account in predicting stroke risk in a complex of other clinical indicators, as well as applied to a personalized approach in the planning of treatment tactics.

DISCUSSION

In recent years, many studies have been presented that have tried to identify the characteristic ultrasonic signs of unstable atherosclerotic plaque. However, it was not possible to determine any separate characteristic that could reliably predict the instability and risk of ipsilateral stroke. In our study, we analyzed both the traditional Doppler and gray-scale characteristics of plaques, as well as the signs found with modern ultrasound techniques such as SMI and SWE.

According to traditional parameters (degree of stenosis according to NASCET, plaque thickness, hemodynamic disorders in the stenosis zone, structure of the plaque according to the Gray-Weale-Geroulakos classification), we obtained the expected results, namely a significant difference in the groups with symptomatic and asymptomatic carotid stenosis.

Our use of the new SMI ultrasound technique demonstrated a statistically significant predominance of signs of plaque microvascularization on the ipsilateral stroke side. These results correlate with literature data and reflect the association of the presence of neovessels with potential plaque instability and risk of cerebral ischemic events [2]. Based on meta-analysis data from Zhou Y et al. it is possible to confirm the feasibility of using SMI to detect intra-plaque neovascularization [12]. When assessing the stiffness of the plaque from SWE data, we obtained significant differences in the observation groups. Our results showed a severe stiffness of plaques in patients with stroke compared to the non-stroke group, which corresponds to the literature [2, 8, 9, 13]. However, when assessing the stiffness of the symptomatic and asymptomatic plaque, significant differences were obtained only in the right carotid basin.

The absence of a statistically significant difference in the other carotid basin may be due to the systemic nature of the inflammatory process and the presence of soft carotid plaques in symptomatic patients on both sides, as well as a small number of observations.

A further prospect of our development is to combine a number of clinical data and the above-mentioned factors of unstable plaque into a prognostic model in order to stratify patients at risk of cerebral ischemic events.

CONCLUSIONS

1. Statistically significant differences in the characteristics of symptomatic and asymptomatic carotid plaques were found: maximum plaque thickness p=0,04, stenosis degree according to the NASCET protocol (p=0.04 in the right ICA), types of plaques echogenicity according to the Gray-Weale-Geroulakos classification (p=0,04 in the right ICA), the presence of microvascularization according to SMI data (p=0,02 i p=0,01 according to the right and left sides), the plaque stiffness indicator according to SWE data (p=0.001 in the right ICA).
2. The presence of microvascularization according to SMI data and the low stiffness of the plaque according to SWE data can characterize the potential instability of the AP. These criteria should be added to the traditional US assessment of carotid plaques.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Availability of rehabilitation for victims of mine-explosive injury in the conditions of territorial community

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ABSTRACT

Aim: The aim of the study was to determine the needs for long-term rehabilitation of persons with damage as a result of a mine-explosive trauma and the availability of rehabilitation for these persons in the territorial community.

Materials and Methods: Research materials included domestic and foreign scientific sources and normative legal acts on the topic. Research methods included the content analysis, bibliosemantic, data summarization, medical and statistical.

Results: The needs for long-term rehabilitation are determined by combined damage, among which damage to the limbs (34.78%-65.22%) [10], craniocerebral injuries (7.9%-12.7%) [11], the acoustic system (40.5%) [16], injuries of bones and soft tissues of the face (10.85%) [18]. **In** 2018, for the first time, 1.2 per 10,000 adult population of participants of the Anti-Terrorist Operation/Joint Forces Operation were recognized as persons with disabilities [7]. Permanent limitations of life activities were caused mainly by brain and limb injuries. In general, long-term rehabilitation is available to persons with injuries in the territorial community in accordance with European approaches. At the same time, the participation of the general practitioner-family doctor is limited by regulatory requirements only to refer the patient to rehabilitation specialists and other specialists.

Conclusions: High needs for long-term rehabilitation of persons brain and limb injuries as a result of mine-explosive trauma have been established. There is a need to expand the participation of general practitioners-family doctor in the organization and implementation of rehabilitation as a full-fledged member of a multidisciplinary rehabilitation team, which requires making appropriate changes to regulatory acts.

KEY WORDS: Long-term rehabilitation; head and limb injuries; regulatory support; general practitioners-family doctors

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INTRODUCTION

Starting from 1980-1990, mine-explosive weapons became widespread in numerous local wars and armed conflicts taking place in the world. The consequences of its use led to a significant increase in the frequency of mine-explosive injuries in the general structure of combat injuries [1].

In Ukraine, the frequency of mine and explosive injuries has increased significantly since 2014, when the military conflict began in the east of the country. The number of wounded people with mine-explosive injuries has increased significantly in the conditions of full-scale Russian aggression: servicemen who are directly on the front line, and the civilian population, especially residents of the front-line zones, suffer from it. This is due to numerous factors of damage due to the explosion: shock wave, mechanical trauma, high temperature, flame, toxic effect of gaseous products of the explosion [2].

A mine-explosive injury often leads to damage to several anatomical areas, which complicates the patient's condition and increases the amount of necessary medical care [3]. The consequences of mine-explosive injuries are various manifestations of post-traumatic stress: anxiety, asthenic, dysphoric, somatoform syndromes. They are found in 38.8% of servicemen who were injured [4].

Studies [5] show that the anatomical localization of lesions are most often wounds of the limbs (52.0%), head (16.8%), gunshot wounds of soft tissues of multiple body parts (14.8 %). Authors' analysis data [6] showed similar results: limb injuries make up 64.1%, head and neck – 16.0%, chest – 8.9%, abdomen – 6.9%, other injuries – 4.1%.

The consequences of combat wounds often become permanent limitations of life activities. Thus, in 2018, for the first time, 3,805 participants of the Anti-Terrorist Operation/Joint Forces Operation (ATO/JFO) were recognized as persons with disabilities, which was 1.2 per 10,000

adult population, of which 2,668 persons (70.1%) were recognized as having a disability of the 3rd group, of the 2nd group – 1057 people (27.8%), 80 people (2.1%) – of the 1st group [7]. Permanent limitations of life activities were caused mainly by brain and limb injuries.

Rehabilitation is an effective means of early restoration of functions of damaged organs and parts of the body, reduction of levels of disability and improvement of the quality of life of the injured. The need for rehabilitation is constantly increasing due to the continuation of large-scale external aggression in Ukraine. The appropriate response of direct providers of medical services to the needs of the injured is determined primarily by the availability of rehabilitation, especially in the long term, after discharge from the hospital, in the conditions of the territorial community [8].

The low availability and efficiency of the rehabilitation system in Ukraine was confirmed by the conclusions of the WHO evaluation mission in 2015 [9].

This was the reason for significant changes in the organization of rehabilitation in the field of health care in 2016-2022. However, these processes were not completed before a full-scale invasion. Therefore, there is a need for further regulation of access to rehabilitation, especially in the long-term period for victims with mine-explosive injuries of the limbs and head, which determines the relevance and timeliness of the study.

AIM

The aim of the study was to determine the needs for long-term rehabilitation of persons with head and limb injuries as a result of a mine-explosive injury and the availability of rehabilitation for these persons in the territorial community. The objectives of the study were to determine the frequency and main clinical characteristics of limb and head injuries as a result of mine-explosive trauma; to conduct an analysis of the regulatory support for the organization of rehabilitation of these persons in the territorial community and the participation of a general practitioner-family doctor in rehabilitation.

MATERIALS AND METHODS

Research materials included domestic and foreign scientific sources and normative legal acts on the topic. Research methods included the content analysis, bibliosemantic, data summarization, medical and statistical.

COMPLIANCE WITH ETHICAL STANDARDS

The principles of bioethics were observed during the preparation of the article in accordance with the requirements of the Declaration of Helsinki and the legislation of Ukraine, which was confirmed by the conclusion of the commission on bioethics dated 22.03.2024 (protocol No. 3) of State Institution of Science «Research and Practical Center of Preventive and Clinical Medicine» State Administrative Department.

RESULTS

It has been established that patients with explosive injuries most often receive complex, multisystemic injuries. The study of the frequency and nature of injuries due to mine and explosive injuries in Ukraine was conducted by scientists based on the experience of treating servicemen who took part in the ATO/JFO and who are repelling the enemy at the present time, in conditions of large-scale the invasion of Russian troops into Ukraine.

Damage to the limbs can be traumatic amputation, fractures, crushing, compartment syndrome, burns, cuts, lacerations, acute arterial occlusion, injuries caused by air embolism. As discovered by the authors [10], the lower limb is more often injured (62.22% of cases), the upper limb is injured in 37.79%. Simultaneous bilateral damage to the lower limbs accounted for 65.22%, upper – 34.78%. In the structure of limb amputations, lesions of the hip and lower leg (29.31% of cases each), and foot (15.52% of cases) occurred most often. Amputation of the hand was registered in 13.79%, at the level of the forearm – in 8.62%, of the shoulder – in 3.45% of cases.

Head lesions are most often manifested by closed and open mine-explosive craniocerebral trauma combined with extracranial injuries. The frequency of head injuries during ATO/JFO was 37.5%, of which gunshot and explosive injuries – 7.9%, closed craniocerebral injuries – 12.7% [11].

Common manifestations of craniocerebral injury, depending on the degree of severity, are general brain and focal symptoms, signs of intracranial hypertension, and impairment of vital functions. Violations of cognitive functions (decreased memory, attention, difficulty in thinking processes), emotional instability (irritability, conflict, aggressiveness, impulsivity) are observed with a mild course and in the remote period of the injury [12].

A specific feature of craniocerebral injury due to the action of a mine blast wave is its combination with damage to the auditory and vestibular apparatus, traumatic injuries of the middle and inner ear. Damage to the structures of the auditory system occurs as a result of akubarotrauma, which can lead to a rupture of the eardrum, destruction of the auditory ossicles, damage to the cochlear canal, development of sensorineural deafness or deafness. Tears in the auditory canal or along the tympanic membrane may occur in patients with temporal bone fractures. Aquabarotrauma accounted for 6.6% – 7.1% of the overall structure of com-

bat sanitary losses during ATO/JFO/ Mine-explosive injury was accompanied by aquabarotrauma in 40.5% of cases, according to military mobile hospitals [13, 14].

Damage to the facial part of the skull as a result of mine-explosive wounds directly on the battlefield is defined by experts as the most severe among combat injuries of the face in the conditions of modern war. Diagnosed large-scale destruction of soft tissue structures, in particular, the oral cavity and oropharynx, leading to impaired external breathing, and bone defects of various sizes in all civilians and 53.3% of military personnel wounded in this area [15]. Primary surgical treatment of maxillofacial wounds was performed in 10.85% of patients in dental offices of military mobile hospitals during ATO/JFO [16].

Thus, injuries to the limbs and head are the most frequent and severe injuries that occur as a result of a mine-explosive injury. Their consequences can be tragic and take a person's life in the event of a serious injury. In any case, victims need emergency medical care immediately after the injury and step-by-step provision of medical care and rehabilitation, depending on the severity of the clinical condition.

It was established that the requirements for the organization of rehabilitation of the population are regulated by general and special legislative and by-laws and departmental regulatory documents. These requirements apply to the organization of rehabilitation of persons with life-limiting injuries due to mine-explosive injuries in wartime conditions [17-22].

Actual changes were made to each regulator with the start of a full-scale invasion of Russian troops into Ukraine, in accordance with the risks of mass casualties to the population and military personnel.

According to the data of the content analysis, it is shown that, in general, the organization of the rehabilitation of victims should begin in the acute period of the injury and continue in the post-acute and long-term period, if necessary. Rehabilitation is carried out by multidisciplinary rehabilitation teams consisting of specialists of various specializations according to an individual rehabilitation plan. Each team necessarily includes a doctor of physical and rehabilitation medicine, a psychologist and other specialists, depending on the nature of the pathology and the features of the patient's limitations in life. Rehabilitation takes place according to a rehabilitation route, which sequentially passes through a hospital, an outpatient health care facility, home rehabilitation and/or rehabilitation in the territorial community.

In accordance with the objectives of the research, the legislative and regulatory requirements for the organization of rehabilitation in conditions close to the place of residence of persons with the consequences of mine-explosive injuries have been identified. This is important for patients' access to rehabilitation, especially in the long term. Long-term rehabilitation is provided with the consent of the patient and according to his needs in the territorial communities. The legislation of Ukraine assigns responsibility to territorial communities for ensuring the medical and social needs of the population living there.

Territorial communities create and maintain the appropriate infrastructure and provide it with rehabilitation specialists. The infrastructure may include rehabilitation facilities of various types: centers, departments, services, divisions, etc. The community can create conditions for the development of private rehabilitation institutions on its territory or provide rehabilitation of its citizens in neighboring communities on the basis of agreements.

The legislation of Ukraine provides for the independent activity of rehabilitation specialists in the community or their joint activity with specialists of health care institutions located on the territory of the community. These can be both outpatient multidisciplinary facilities and primary care facilities.

Such an organization of long-term rehabilitation involves the provision of rehabilitation assistance both in rehabilitation institutions and at home. In this way, the availability of rehabilitation is ensured for various contingents of the community's population with life-limiting activities: children and adults with disabilities due to congenital and chronic diseases; servicemen with the consequences of combat injuries; the civilian population, which suffered as a result of military aggression; participants in hostilities and others.

At the same time, general practitioners-family doctors have only the right to refer patients to a doctor of physical and rehabilitation medicine and rehabilitation specialists for the purpose of carrying out a rehabilitation examination, establishing a rehabilitation diagnosis and prescribing rehabilitation measures, provided that this was not done at the previous stages of rehabilitation.

It should be noted that the general practitioner-family doctor is the doctor of first contact with the attached patient and observes him for a long time. The patient can be a former military serviceman with rehabilitation needs, and an ordinary civilian who was injured during hostilities. According to the qualification characteristics, general practitioners-family doctors are obliged to perform dynamic monitoring of patients with chronic pathological conditions, which are, in particular, the consequences of injuries from mine-explosive injuries [23].

Knowledge and ability to conduct an examination of the ear, throat, nose, determine the acuity of hearing, identify clinical manifestations and draw up a patient route for acoustic ear injury, perforation of the tympanic membrane, carry out diagnostics, examination and assessment of the condition of patients with head and limb injuries, know and draw up a rehabilitation algorithm patients after surgical interventions at home and on an outpatient basis, to know

the indications for referral to specialists, to consult patients and their families on the prevention and treatment of health disorders from various organs and systems are among the competencies of a general practitioner-family doctor.

Therefore, a general practitioner-family doctor can be a full-fledged member of a multidisciplinary rehabilitation team, next to a doctor of physical and rehabilitation medicine, a physical therapist, an occupational therapist, a speech and language therapist, a psychologist, who provide rehabilitation assistance in the community to persons with the consequences of a mine-explosive injury.

Such activity requires strengthening the information and communication component in the work of a general practitioner-family doctor. It concerns the interaction with other members of the multidisciplinary rehabilitation team, social workers of the territorial community, public health specialists, specialist doctors of outpatient and inpatient facilities where rehabilitation assistance is provided, on issues of information exchange about the current state of the patient and implementation of an individual rehabilitation program.

Close contact should also be established with the patient in order to involve him directly in rehabilitation under the conditions of a full-fledged partnership, fostering loyalty to the optimization of the lifestyle and implementation of rehabilitation measures. It is important to work with the patient's family to provide support and help restore health.

DISCUSSION

According to the results of the study, it was found that in Ukraine, most often during the period of anti-terrorist operation and full-scale invasion of the aggressor country, military personnel and the civilian population receive injuries to the limbs and head as a result of mine and explosive injuries. This determines the high needs of the victims in rehabilitation. The obtained results are confirmed by the data of foreign researchers regarding the consequences of mine-explosive trauma of the specified body parts and generalize and supplement information about their frequency and localization during other large-scale and local military conflicts in the world, which is the originality of the conducted research [23-26].

The severity and combination of injuries require rehabilitation of victims in the acute, post-acute and long-term period. It was established that long-term rehabilitation is available to persons with injuries in the territorial community in accordance with European approaches. [27]. They envisage a variety of infrastructural components of rehabilitation in inpatient and outpatient settings, primary medical care and in the conditions of territorial communities and the provision of rehabilitation assistance by rehabilitation specialists.

However, the role of general practitioners-family doctors in Ukraine in the organization and implementation of rehabilitation is somewhat limited, as the regulations only allow them to refer patients to rehabilitation specialists and other specialists.

At the same time, a general practitioner-family doctor possesses a sufficient volume and range of competences, determined by qualification characteristics, in order to be a full-fledged member of a multidisciplinary rehabilitation team. His information and communication interaction with other members of the multidisciplinary rehabilitation team and the patient and his family needs strengthening. These recommendations can be enshrined in legal documents regulating the activity of a general practitioner-family doctor and the organization of long-term rehabilitation.

METHODOLOGICAL LIMITATIONS

The methodological limitations of this study should be considered its theoretical orientation, which does not allow to establish to what extent the regulatory requirements for the organization of long-term rehabilitation in the conditions of the territorial community are fulfilled.

The prospects are to conduct further research in the conditions of the territorial community, which will show the actual picture of the organization of long-term rehabilitation, in particular, of persons affected by mine-explosive injuries, and the use of recommendations for the improvement of regulatory requirements based on the topic and results of this study.

CONCLUSIONS

1. High needs for long-term rehabilitation of persons injured as a result of mine-explosive trauma have been established. The needs are determined by combined damage, among which damage to the limbs (34.78%-65.22% of cases), craniocerebral injuries (7.9%-12.7% of cases), damage to the acoustic system (40.5% of cases) occurs most often, injuries of bones and soft tissues of the face (10.85% of cases).
2. Ukraine has developed a powerful legislative framework and legal regulation of the availability of rehabilitation, in particular, for victims of mine-explosive trauma in the conditions of the territorial community. However, the participation of a general practitioner-family doctor in the organization and provision of rehabilitation is limited only to the right to refer a person for consultation to rehabilitation specialists and other outpatient and inpatient care specialists.
3. The spectrum and scope of competencies of a general practitioner allows him to be a full-fledged member of a multidisciplinary rehabilitation team, which requires making appropriate changes to regulatory acts.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Clinical implementation of partial splenic artery embolization for the prevention of recurrent bleeding from esophageal varices in portal hypertension

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ABSTRACT

Aim: To evaluate the effectiveness of PSAE for secondary prevention of VB episodes in patients with chronic liver disease (CLD) and CSPH.

Materials and Methods: One hundred twenty patients (from 2008 to 2020) were submitted of PSAE as secondary prevention treatment. The results of the treatment of 27 patients between 2008 and 2012 (first period) were compared with those of 93 patients treated with PSAE since 2013 (second period), as procedure and management protocol were modificated. VB recurrence rate and mortality (related and non-related to bleeding episodes) were defined as study end-points in both groups at 12-months follow-up.

Results: At 12-months follow-up, 11 (40,7 %) and 54 (58,1 %) patients in groups 1 and 2, respectively, were free from VBs (p=0,129). Overall mortality rate was significantly higher in group 1, as compared to group 2: 10 (37,0 %) versus 6 (6,4 %) patients, respectively (p<0,001), – due to higher frequency of fatal VB events (7 (26,0 %) vs. 3 (3,2 %) patients, respectively; p=0,001).

Conclusions: PSAE is an effective treatment for secondary prevention of VB in patients with CLD and CSPS. The management protocol modification resulted in the decrease in overall mortality rate and mortality related to recurrent VB episodes.

KEY WORDS: partial splenic artery embolization, chronic liver desease, liver cirrhosis, variceal bleeding, portal hypertension

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INTRODUCTION

Portal hypertension leads to a number of complications, including the development of portosystemic shunts and esophageal varices. Such complications can lead to bleeding from varicose veins in the esophagus and patient death. Currently, the leading role of visceral hemodynamics disturbances in the development of the portal hypertension syndrome has been proven [1].

To correct portal hypertension and prevent recurrences of esophageal bleeding in patients who have undergone an initial episode of variceal bleeding, non-selective beta-blockers are prescribed [2]. However, the effectiveness of pharmacological methods for preventing variceal bleeding is limited.

Another direction for the prevention of variceal bleeding in portal hypertension is surgical. This includes the creation of portosystemic shunts, including the minimally invasive version of this operation – the transjugular intrahepatic portosystemic shunt (TIPS). Such surgeries lead to a reduction in pressure in the portal system, a decrease in the frequency of bleeding recurrences, but result in a number of complications, among which is encephalopathy. Consequently, the use of such operations in clinical practice is limited [3].

Liver transplantation is considered the «gold standard» for the treatment of complicated portal hypertension. This surgery is one of the most complex and expensive in the field, which limits its application [3].

Under such circumstances, partial splenic artery embolization (PSAE) may become the treatment of choice for patients. At the same time, despite the long history of the method (since 1979), there is currently no universally recognized surgical technique or patient management protocol in the world [3].

From the literature, there are known cases of PSAE complications, including fever, abdominal pain, ascites, pleural effusion, splenic abscess, and peritonitis. Late period observations include cases of recanalization of the

Table 1. Clinical evaluation of result of PSAE application

Code	Result evaluation	Description
1	«Good»	No VB episodes during follow up 12 months
2	«Stable»	No more than 1 non-fatal VB episode
3	«Unstable»	Two or more non-fatal VB episodes
4	«Fatal», related to VB	Lethal result due to fatal VB episode
5	«Fatal», non related to VB	Lethal result not related to VB episode

Table 2. Baseline demographic, anthropometric and clinical characteristics of the enrolled patients from the studied groups

Parameters		PASE, n=120		p
		Group 1 (N=27)	Group 2 (N=93)	
Age, years		47,8±11,00	50,2±10,30	0,296
Gender, n (%)	Males	18 (66,7)	52 (55,9)	0,379
	Females	9 (33,3)	41 (44,1)	
BMI, kg/m^2		24,3±4,73	25,6±4,30	0,179
Esophageal varices grade, n (%)	2	18 (66,7)	64 (68,8)	0,819
	3	9 (33,3)	29 (31,2)	
MELD score		9,0±2,81	8,8±3,30	0,775

Notes: BMI – body mass index.

splenic artery [4-6], necessitating the optimization of the surgical technique and patient management protocol. This optimization aims to enhance the efficacy of partial splenic artery embolization and minimize the surgical risk.

AIM

The aim of the study was to optimize the technique for preventing variceal bleeding (VB) from the esophageal and gastric veins using PSAE, and to provide clinical justification for the effectiveness of the proposed method.

MATERIALS AND METHODS

From 2007 to 2020 one hundred twenty patients aged 27 to 72 years (mean [M] ± standard deviation [SD]: 49,5±10,46) years, who had previously experienced one or more episodes of bleeding from gastroesophageal varices GOV-1 and GOV-2 types, underwent PSAE to prevent subsequent VB episodes at Bogomolets National Medical University clinic. The severity of chronic liver disease was assessed by the Model for End-Stage Liver Disease (MELD) score. The grade of esophageal varices development was assessed using the NIEC classification (North Italian Endoscopic Club).

In all cases, the intervention involved combined PSAE with the injection of polyvinyl embolus into the splenic artery lumen, followed by the placement of spiral coils (Gianturco type). The effectiveness and safety of PSAE were evaluated in all 120 patients over a 12-month observation period (Table 1).

The study unfolded in two phases: the first was the initial stage of clinical implementation, which involved 27 patients between 2008 and 2012, referred to as group 1. The second phase was dedicated to applying the refined embolization method, enrolling 93 patients from 2013 to 2020, known as group 2.

During the second stage, a modified protocol was implemented, which included the usage of hydrophilic catheters and introducers of a smaller diameter, hydrophilic wires, innovative methods of embolization using short flexible coils with tight filling of the vessel lumen along the central axis, a smaller volume of contrast media, and a hydraulic method of pushing coils.

Nonselective beta-blockers were administered at a dose of 40-60 mg per day in all cases, in accordance with the AASLD/Baveno recommendations [2]. The effectiveness of PSAE was evaluated by closely monitoring the presence and number of recurrent variceal bleeding episodes during a 12-month follow-up period.

The patients gave their informed consent for the studies conducted in compliance with ethical principles of medical research involving human participation. These ethical principles include the Declaration of Helsinki (2008), the basic provisions of Good Medical Practice, and the Council of Europe Convention on Human Rights and Biomedicine (1997). The clinical study was carried out after obtaining a favorable opinion from the ethics commission and permission to conduct the study in accordance with current legislation in Ukraine and modern ethical norms and principles for conducting clinical studies.

Table 3. The results of clinical implementation of PSAE as secondary prevention option

Result coding	Result evaluation	PASE, n=120		p
		Group 1 (N=27)	Group 2 (N=93)	
[1+2]	«Satisfactory», n (%)	15 (55,5)	78 (83,9)	0,004
1	«Good», n (%)	11 (40,7)	54 (58,1)	0,129
2	«Stable», n (%)	4 (14,8)	24 (25,8)	0,306
[3+4+5]	«Unsatisfactory», n (%)	12 (44,5)	15 (16,1)	0,004
3	«Unstable», n (%)	2 (7,4)	9 (9,7)	1,000
4	«Fatal», related to VB, n (%)	7 (26,0)	3 (3,2)	0,001
5	«Fatal», non related to VB, n (%)	3 (11,1)	3 (3,2)	0,127

The data were analyzed by the use of EZR statistics software package [7]. Quantitaitve variables were presented as M ± SD, and qualitative – as absolute and relative (%) frequency. To compare the independent groups, we applied the Student's T-test (for quantitative variables) and Fisher's exact test (for qualitative data). The clinical effect size was assessed by odds ratio (with 95 % confidence interval [CI]). A 2-tailed p-value <0,05 was considered as statistically significant.

RESULTS

The enrolled patients from the studied groups were comparable by the certain baseline demographic, anthropometric and clinical characteristics (Table 2).

Before undergoing PSAE, 120 patients had a history of 391 episodes of varicose bleeding, with an average of 3,26 episodes per patient. However, during the 12 months of follow-up, only 43 episodes of VB in 49 patients were recorded, with an average of 0,36 episodes per patient. Of the 120 patients, 93 (77,5 %) showed satisfactory results (absence or no more than 1 episode), while 27 (22,5 %) had unsatisfactory outcomes, among them 16 (13,3 %), who died during the observation period. The satisfactory/unsatisfactory ratio was 3,44.

The results of clinical implementation of PSAE in patients from the studied groups are presented in Table 3.

In goup 1, satisfactory results were achieved in 15 patients (55,5 %), and in group 2 – in 78 (83,9 %). The result of 11 (9,2 %) patients of both groups, who survived two or more bleeding episodes during follow-up, was evaluated as «unstable». Among the «unsatisfactory» cases, 16 patients died. Seven patients in group 1 and three in group 2 died due to fatal bleeding episodes, while three patients in both groups died from acute liver failure.

Besides achieving a greater number of satisfactory outcomes, the mortality rate from fatal episodes in group 2 was markedly lower than in group 1 (3.2 % compared to 26.0 %, respectively). Furthermore, the likelihood of an unsatisfactory outcome in the second group was reduced by over four times (OR = 0,24 [95 % CI 0,09-0,61]).

The overall mortality rate was significantly higher in the first phase of PSAE clinical implementation, with 10 out of 27 patients (37,0 %) compared to group 2, where it was 6 out of 93 patients (6,4 %) (p<0,001). Thus, the mortality risk in group 2 was reduced by 8,33 times (OR = 0,12 [95 % CI 0,04-0,37]).

Severe post-procedure (within 30 days) complications, not related to recurrent bleeding episodes, were observed in 12 patients, including one case of total splenic abscess complicated by fatal fulminant sepsis. Other complications, such as acute pancreatitis, total portal vein thrombosis, left-sided pleural effusion, hematoma of the approach site (2 cases), and acute renal failure (3 cases), were successfully managed with appropriate therapy. Post-embolization syndrome was not considered as a severe post-procedural complication, as its manifestations were easily mitigated with drug treatment.

The total mortality rate was at 13,3 % (16 out of 120 patients), which was less than the rates observed with other secondary prevention methods such as endoscopic sclerotherapy and the use of non-selective beta-blockers, at 37,1 % and 28,4 %, respectively [8]. In our study this rate dropped to 6,4 % following enhancements in embolization technology

DISCUSSION

The main goal of our study was to determine perspective approaches to the prevention of recurrent bleeding from phlebectasies of the esophagus and stomach. According to the literature sourses, endoscopic and pharmacological methods are associated with a mortality rate ranging from 28 % to 32 % [9-11]. Among the existing methods, mini-invasive approaches are currently attracting special attention, the effectiveness of which is explained by the direct effect on the vessels of the splanchnic bed, where the main hemodynamic pathological changes that take part in the formation of portal hypertension occur [12].

We managed to prove the effectiveness of the use of PSAE as a method of secondary prevention of varicose bleeding against the background of diffuse liver diseases. In addi-

tion, the measures proposed by us for the comprehensive management of such patients contributed to an increase in the quality of life of patients and in long-term observation reliably demonstrated an increase in the life expectancy of patients and a decrease in the number of episodes of recurrent bleeding.

Literature data and our experience indicate that PSAE is an effective and safe procedure [3, 6, 13]. One of the effects of PSAE, which is corroborated by both our data and literature, is the correction of thrombocytopenia. This effect additionally contributes to the minimization of the risk of bleeding, including during long-term follow-up [14-15], which we have also observed in our study.

During the first stage of our work, PSAE was performed as an emergency intervention within the first 5-7 days following a bleeding episode. The short preparation period did not allow for a comprehensive examination, nor the preoperative correction of the patient`s clinical condition, which worsened the conditions for performing PSAE. The reasons for the unsuccessful outcomes were: the severity of the patient`s condition, insufficient examination and assessment of operational risks, lack of clear criteria for patient selection, and management of the postoperative period. The first stage of clinical implementation was accompanied by numerous technical complications due to technological shortcomings and the available means of embolization.

During the second stage, preoperative preparation was optimized, and the endovascular surgery was scheduled no earlier than 2-3 weeks after a bleeding episode to stabilize the patient`s condition. A comprehensive evaluation of portal hemodynamics was performed using ultrasound flowmetry, and CT-angiography of the abdominal organ vessels was carried out. The analysis of CT-angiography data facilitated the planning of the endovascular surgery, revealing individual anatomical features and anomalies of the abdominal organ vessels (splenic artery aneurysms, arteriovenous malformations, etc.).

Summarizing our experience and literature data, we can conclude that negative outcomes after technically successful PSAE may be associated with non-compliance on the part of the patient: refusal to take non-selective beta-blockers, alcohol consumption, ignoring recommendations on restrictions of physical activity in the first months after the intervention [16-18]. Our data indicate that serious complications after PSAE are rare and depend on the patient management tactics and adherence to them by the patient [19-21].

CONCLUSIONS

PSAE, employed as a secondary preventive measure, is recognized as safe and effective for managing clinically significant portal hypertension that is complicated by episodes of VB.

The results obtained at this stage allow for its recommendation in broad clinical practice beyond specialized centers. The refined protocol for the application of PSAE, by addressing technological shortcomings, has allowed unlocking the potential of this preventive method and improving treatment outcomes for patients with chronic liver disease and clinically significant portal hypertension.

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CONFLICT OF INTEREST

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ORIGINAL ARTICLE

CONTENTS

Interrelation of daily blood pressure profile with left ventricular myocardial hypertrophy in men of working age with hypertension

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ABSTRACT

Aim: To analyze the relationship between daily blood pressure biorhythms and left ventricular myocardial hypertrophy in working-age men with arterial hypertension.

Materials and Methods: Fifty-seven men with AH (mean age: 44.6±1.3 years) underwent Echo-CG and daily ABPM. Non-dipper and night-peaker patterns indicated BP biorhythm disturbances, while normal dipper and over-dipper patterns indicated undisturbed BP biorhythms. LVH was defined as LMMI > 115 g/m^2.

Results: About 60% of participants exhibited diurnal BP rhythm disorders, with a higher prevalence of LVH in this group compared to those with normal BP biorhythms (32% vs. 22%, p>0,05). Patients with normal daily BP biorhythms had significantly higher circadian indices of HR, systolic and diastolic BP, and double product compared to those with disturbed BP rhythms.

Conclusions: In young men with "non-dipper" and "night-peaker" patterns, LVH appears to be more pronounced than in those with normal daily BP biorhythms. This approach may optimize the timing of antihypertensive drug administration.

KEY WORDS: arterial hypertension, daily blood pressure profile, left ventricular hypertrophy

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INTRODUCTION

According to the WHO, the age-standardized mean prevalence of arterial hypertension (AH) among adults aged 30-79 years was 34% among men and 32% among women [1]. Hypertension increases the risk of cardiovascular complications, especially in young men, as they have a 99% higher risk of stroke compared to men with normal blood pressure, and a 10/5 mm Hg reduction in systolic and diastolic blood pressure, respectively, reduces the risk of cardiovascular events by 20% [2].

According to the results of the CARDIA subanalysis conducted in the United States, the presence of hypertension in young people increases the risk of cardiovascular disease by 8 times compared to people with normal blood pressure [3]. Daily blood pressure monitoring (DBP) in patients with arterial hypertension (AH) provides additional and important data, such as the state of nighttime BP reduction, the amount of morning rise, assess the circadian variability of BP and determine the daily BP profile. Identifying the relationship between the daily BP profile and target organ damage is important because each of the four markers of organ damage (left ventricular hypertrophy (LVH), microalbuminuria, increased pulse wave velocity, and carotid plaques) is an independent predictor of cardiovascular mortality [4].

ABPM has certain advantages over office BP measurement, namely, better reproducibility of average BP values over 24 hours, more accurate prediction of target organ damage, therapy outcomes, mortality, and the ability to identify white-coat hypertension (WCH) and masked hypertension. It is important for a doctor to identify patients with a disturbed daily blood pressure profile, namely non-dipper and night-peaker, which are considered pathological, because such patients are at a much higher risk of developing cardiovascular diseases and their complications.

AIM

The aim of the study was to identify and analyze the relationships between the parameters of daily blood

Table 1. The structure of the distribution of patients in groups without violations of daily blood pressure biorhythms and with violations of daily blood pressure biorhythms, depending on the presence of left ventricular hypertrophy

Total group, n=57			
Group without disturbances in the diurnal rhythm of blood pressure, n=23		**Group with disorders of the diurnal rhythm of blood pressure, n=34**	
Patients with left ventricular hypertrophy, n=5	Patients without left ventricular hypertrophy, n=18	Patients with left ventricular hypertrophy, n=11	Patients without left ventricular hypertrophy, n=23
8,8%	31,6%	19,3%	40,4%

Table 2. Proportion of patients with LVH in groups with normal and disturbed BP biorhythms

Group with normal daily BP biorhythms		Group with disturbed daily BP biorhythms	
Have a LVH – 21,7%	Do not have LVH – 78,3%	Have a LVH – 32,4%	Do not have LVH – 67,6%

pressure biorhythms and indicators of left ventricular myocardial hypertrophy in men of working age with hypertension who have different types of daily blood pressure profile.

MATERIALS AND METHODS

The subject of the study was 57 men of working age with arterial hypertension of I and II degree, the average age of which was 44.6 ± 1.3 years (M±m).

All patients underwent a general clinical examination, which included echocardiography and daily blood pressure monitoring. The blood pressure biorhythms were studied by means of daily ambulatory blood pressure monitoring, which was performed using blood pressure monitors VAT-41 (IMESK, Ukraine) and the ABP-Pro program. The following daily blood pressure patterns were considered to be disturbances of the daily blood pressure biorhythm: non-dipper and night-peaker. An undisturbed biorhythm was considered to be one that belonged to the categories of normal dipper and over-dipper. For heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP), and for the double product (HR*BP), their circadian indices (CI) were calculated as the ratio of the mean daytime to the mean nighttime value. Left ventricular myocardial hypertrophy (LVH) was assessed by the left ventricular myocardial mass index (LVMI), which was determined by echocardiography (Philips EPIQ Elite). The criterion for the presence of LVH was considered to be a value of LMMI > 115 g/m^2 [5].

Statistical processing of the data was performed using the SPSS-21.0 program. The mean group values (M) and their errors (m) were calculated. The analysis of the reliability of differences between the mean group values was performed using Student's T-test for independent samples. The reliability of differences between proportions within groups was assessed using Student's T-test (the reliability of differences between the mean values of binary variables in two groups was assessed) and Pearson's Chi-square test. To confirm the hypothesis about the difference in proportions, the level of reliability of the values of the criteria used was chosen at the level of $p<0.05$. Linear (Pearson's linear correlation coefficient, R) and rank correlation (Spearman's rank correlation coefficient, R_{sp}) were used to study the relationship between the indicators.

RESULTS

THE STRUCTURE OF THE DISTRIBUTION OF PERSONS IN GROUPS

To investigate the association between BP biorhythm disturbances and left ventricular myocardial hypertrophy (LVH), the total group was divided, according to the indicators of daily monitoring, on a binary basis, into those with BP biorhythm disturbances and those without them. After the first binary division, a second binary division was performed in each of the obtained subgroups (with unimpaired and impaired BP biorhythms) based on the presence or absence of LVH (according to echo-CG). The result of the division is shown in Table 1.

Individuals with diurnal BP rhythm disorders accounted for about 60% of the total sample, and those without diurnal BP rhythm disorders accounted for about 40%.

The next step in analyzing the internal structure of the groups was to determine the proportion of patients with left ventricular hypertrophy within each of the two groups, with normal and disturbed daily BP biorhythms (Table 2, Fig. 1, Fig. 2).

The proportion of patients with LVH in the group with disturbed diurnal BP rhythm was almost 1.5 times higher (32 vs. 22%) than in patients with normal BP biorhythm, however, these differences were not sig-

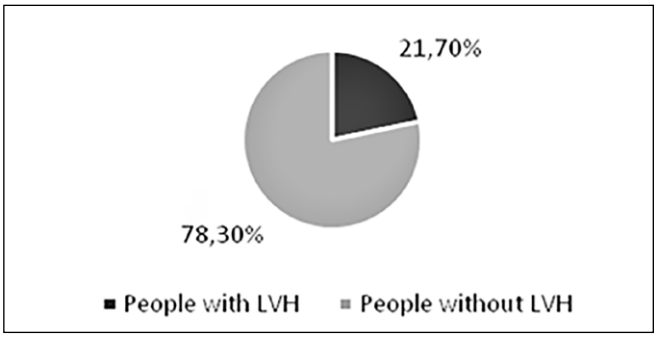

Fig. 1. Specific proportion of people with LVH in the group with preserved daily BP biorhythms.

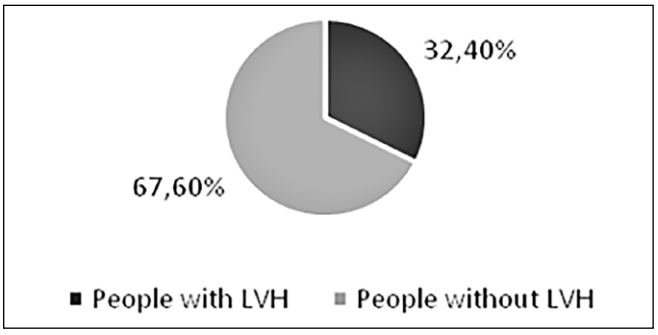

Fig. 2. Specific proportion of people with LVH in the group with disturbed daily BP biorhythms.

nificant (Student's t test = - 0.865; p = 0.391; Pearson's Chi-square test = 0.765; p = 0.382), which may indicate only a trend. Such a lack of distinct differences in the structure of the groups may be due to the fact that our study involved men of relatively young age, with a short history of hypertension, when LVH had not yet significantly formed. Thus, the observed tendency to increase the proportion of patients with LVH in the group with disturbed daily BP biorhythms is in favor of the negative impact of these BP rhythm disturbances on the development of structural heart disease.

AVERAGE GROUP INDICATORS

Analyzing the mean group values of anthropometry, daily blood pressure monitoring and echo-CG in groups of patients with normal and disturbed blood pressure biorhythms (Table 3), the following can be noted.

While heart rate, blood pressure, double product, area under the graph of both systolic and diastolic pressure, as well as the AASI vascular stiffness index, echocardiographic parameters did not differ significantly between the groups of patients with normal and disturbed daily blood pressure biorhythm, circadian indices, on the other hand, revealed significant differences. Thus, in patients with a normal daily BP biorhythm, circadian indices of heart rate, systolic and diastolic pressure, and double product were significantly higher than in the group of patients with a disturbed BP rhythm. In cardiology practice, at present, the indicators of cardiovascular functioning biorhythms in people with hypertension cover only circadian changes in systolic and diastolic blood pressure. At the same time, clinical classifications do not take into account the circadian fluctuations of heart rate and the calculated index – the double product, which is an approximate equivalent of the mechanical work of the heart [6]. It is interesting to note that in the group of individuals with disturbed daily biorhythms, calculated using circadian systolic and diastolic pressures, significantly lower values of circadian indices of heart rate and double product are additionally noted. This highlights the importance of taking into account in the clinical assessment of hypertension biorhythms not only the mechanical component of the heart, which is associated with overcoming vascular resistance and is expressed in blood pressure, but also the circadian biorhythm of the chronotropic function of the sinus node, assessed by the instantaneous heart rate.

The correlation analysis between age, daily blood pressure monitoring, anthropometry, and echo-CG revealed the following. In the group of patients with disturbed diurnal BP biorhythm and absence of LVH, a significant positive correlation between mean daily heart rate and LVMI was found ($R_{Sp.}$ = 0,417; p = 0,048). In the group of patients with disturbed diurnal blood pressure biorhythm and the presence of LVH several strong correlations were found. In particular, there was a negative relationship between age and left ventricular ejection fraction (R = -0,705; p = 0,015; $R_{Sp.}$ = -0,703; p = 0,016). A positive correlation of body mass index was noted simultaneously with several Echo-CG parameters characterizing LVH - with the left ventricular myocardial mass index (R = 0,686; p = 0,020), with the thickness of the interventricular septum ($R_{Sp.}$ = 0,690; p = 0,019), with the thickness of the left ventricular posterior wall ($R_{Sp.}$ = 0,636; p = 0,036). The circadian indices of systolic and diastolic pressure revealed strong significant negative correlations with the indicators characterizing left ventricular hypertrophy. Thus, the circadian index of systolic pressure was negatively correlated with the index of left ventricular myocardial mass ($R_{Sp.}$ =-0,673; p = 0,023). And the circadian diastolic pressure index had strong negative correlations with the thickness of the interventricular septum ($R_{Sp.}$ =-0,731; p = 0,011) and the thickness of the left ventricular posterior wall ($R_{Sp.}$ =-0,636; p = 0,036).

DISCUSSION

We found that, according to the data of daily blood pressure monitoring, 60% of men of working age with

Table 3. Average group values of indicators

Indicator	Persons with a normal blood pressure biorhythm	Persons with disturbed blood pressure biorhythm
Age, yrs.	42,1 ± 3,5	40,0 ± 2,1
Body mass index (BMI)	28,03 ± 1,12	29,80 ± 0,89
HR per 24h, /min	76,40 ± 1,91	78,96 ± 1,90
HR per day, /min	83,60 ± 2,07	84,26 ± 2,12
HR per night, /min	62,93 ± 2,11	68,87 ± 1,91
Circadian heart rate index	1,34 ± 0,04	1,23 ± 0,03 *
Systolic blood pressure per 24h, mmHg	127,9 ± 2,6	126,6 ± 2,8
Systolic blood pressure per day, mmHg	134,3 ± 2,8	129,2 ± 2,7
Systolic blood pressure per night, mmHg	115,7 ± 2,5	121,4 ± 2,9
Circadian index of systolic blood pressure	1,16 ± 0,01	1,07 ± 0,01 **
Diastolic blood pressure per 24h, mmHg	79,7 ± 2,3	78,2 ± 2,3
Diastolic blood pressure per day, mmHg	85,5 ± 2,4	81,3 ± 2,2
Diastolic blood pressure per night, mmHg	68,9 ± 2,0	72,4 ± 2,5
Circadian index of diastolic blood pressure	1,24 ± 0,02	1,13 ± 0,02 **
Double product per 24h	9801 ± 362	10015 ± 358
Double product per day	11263 ± 432	10880 ± 351
Double product per night	7296 ± 313	8424 ± 379
Circadian index of the double product	1,56 ± 0,05	1,31 ± 0,03 **
Systolic blood pressure area per day	5,81 ± 1,50	4,38 ± 1,44
Systolic blood pressure area per night	3,58 ± 1,22	7,13 ± 2,07
Diastolic blood pressure area per day	6,00 ± 1,28	4,33 ± 1,04
Diastolic blood pressure area per night	3,75 ± 1,09	7,23 ± 1,72
Systolic blood pressure area per 24h	5,05 ± 1,37	5,32 ± 1,64
Diastolic blood pressure area per 24h	5,23 ± 1,19	5,31 ± 1,24
AASI	0,36 ± 0,04	0,36 ± 0,03
Max daytime systolic blood pressure, mmHg	171,5 ± 6,3	161,9 ± 4,0
Max daytime diastolic blood pressure, mmHg	113,0 ± 3,5	109,5 ± 2,6
Max nighttime systolic blood pressure, mmHg	135,5 ± 3,2	148,2 ± 7,9
Max nighttime diastolic blood pressure, mmHg	85,3 ± 2,4	99,1 ± 8,4
left ventricular ejection fraction, %.	60,7 ± 1,4	60,7 ± 0,9
stroke volume, ml	68,1 ± 3,5	72,4 ± 1,8
minute volume, l/min	4,9 ± 0,5	5,4 ± 0,2
thickness of the interventricular septum, cm	1,23 ± 0,07	1,25 ± 0,03
left ventricular posterior wall thickness, cm	1,09 ± 0,04	1,12 ± 0,02
mass of the left ventricular myocardium, g	219,9 ± 16,5	228,4 ± 8,9
left ventricular myocardial mass index (LVMI), g/m^2	103,2 ± 6,4	104,5 ± 3,3

Notes: * – significance of differences in mean group values at the level of $p < 0.05$; ** – significance of differences in mean group values at the level of $p < 0,01$.

hypertension had pathological blood pressure profiles of the "non-dipper" and "night-peaker" types. The relationship between disturbed blood pressure biorhythms and myocardial hypertrophy revealed in the study was manifested in a 1.5-fold increase in the proportion of patients with LVH in the group with disturbed daily blood pressure biorhythms compared with the group with normal blood pressure biorhythms.

In addition, in the group of patients with a combined disorder of the daily blood pressure biorhythm with LVH, this relationship was manifested by a strong negative correlation of circadian blood pressure indices with indicators of left ventricular myocardial hypertrophy. In patients with concomitant disturbance of daily BP biorhythms with LVH, a negative correlation of age with LVEF is also noted, which may indirectly indicate

accelerated functional aging of the cardiovascular system. The presence of positive correlations of body mass index with LV wall thickness and LVMI may indicate its prognostic value in relation to the development of structural heart lesions in hypertension.

Based on our experimental data, there is reason to believe that circadian indices of heart rate, systolic and diastolic blood pressure, and the double product are sensitive markers of the prognosis of left ventricular myocardial hypertrophy. And this sensitivity is especially high in patients with a combination of disturbances in the daily BP biorhythm with LVH. Further studies are needed to clarify the prognostic significance of the above circadian hemodynamic indices in relation to the progression of LVH and the course of hypertension.

According to the results of scientific studies, the daily blood pressure profiles of "non-dipper" and "night-peaker" are associated with a significant number of negative factors, including damage to target organs – left ventricular hypertrophy, thickening of the intima-media complex, progressive decrease in renal function, cognitive impairment, and increased risk of all-cause and cardiovascular mortality [10]. And the detection of signs of LV remodeling and, in particular, LVH in patients with hypertension is associated with a higher incidence of angina pectoris, myocardial infarction (MI), ventricular arrhythmias, heart failure and a decrease in LVEF, aortic root dilatation, peripheral arterial disease, cerebrovascular and renal complications, cardiovascular and sudden cardiac death (SCD).

The increased risk of complications depends not only on the level of blood pressure (BP), but is associated with the degree of LV hypertrophy [7-10]. The correlation between LV mass and blood pressure, especially office blood pressure, is usually weak. The average daily pressure fluctuations are more correlated with LV mass (Rosei E., Muiesan M., 2017). The presence of LVH is one of the risk factors for resistant hypertension. In people with LVH, cardiovascular complications occur 2-4 times more often than in people without LVH, regardless of other risk factors [11, 12].

The analysis of the degree of heart damage in young and middle-aged men with hypertension performed in our study confirms the results of those studies that indicate the importance of changes in the circadian rhythm of blood pressure on the damage to target organs already at the initial stages of this disease.

CONCLUSIONS

Thus, young men with hypertension should be examined with ABPM to determine the daily BP profile. According to the results of the study, we have reason to believe that in young men with pathological daily BP profile ("non-dipper" and "night-peaker"), heart damage in the form of left ventricular myocardial hypertrophy tends to be more pronounced than in individuals with normal daily BP biorhythms. The proposed diagnostic approach, which takes into account the factor of the presence of disturbances in the daily rhythm of blood pressure and heart rate, allows to obtain additional information on the prognosis of the disease and to optimize the choice of the time schedule for the administration of antihypertensive drugs. The presence of LVH and pathological blood pressure profile are important criteria for a high risk of cardiovascular complications in patients with hypertension and indicate the feasibility of more aggressive treatment of such patients.

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ORIGINAL ARTICLE

CONTENTS

Assessment of socio-demographic characteristics and social status of patients with negative symptoms in schizophrenia at different stages of the disease

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ABSTRACT

Aim: To determine the features of socio-demographic characteristics of patients with negative symptoms of schizophrenia.

Materials and Methods: 252 patients with negative symptoms of schizophrenia took part in the study: 83 patients with the first episode of schizophrenia, 88 patients with schizophrenia in a state of exacerbation, and 81 patients with schizophrenia in a state of remission. During the research, a comprehensive approach was used, which consisted in the use of clinical-psychopathological, clinical-anamnestic and statistical research methods.

Results: Socio-demographic characteristics of patients with negative symptoms in schizophrenia were established. Among patients with the first episode of schizophrenia, the majority were of 20-29 years old, mostly with secondary education, unmarried, with a mental labor, with low and average levels of a material well-being, poor and satisfactory living conditions. Among patients with negative symptoms of schizophrenia in an exacerbation state, the majority was of persons of 30-49 years old, with a special secondary education, mostly divorced, with a disability, with a low and extremely low level of material well-being, with poor and very poor living conditions prevailed. Among patients with negative symptoms of schizophrenia in a state of remission, there was a predominance of persons of 30-39 and 50-60 years old, with a special secondary education, divorced, mainly with a physical labor, with a low and average level of material well-being and poor living conditions.

Conclusions: The obtained data can be used to establish diagnostic criteria for patients with negative symptoms in schizophrenia, depending on the dynamics of the disease.

KEY WORDS: socio-demographic characteristics, patients with schizophrenia, negative symptoms, first episode of schizophrenia, schizophrenia in a state of exacerbation, schizophrenia in a state of remission

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INTRODUCTION

Negative symptoms (NS) are an integral part of schizophrenia, which leads to disruption of social adaptation, interpersonal interaction and disability [1]. More than half of patients with chronic schizophrenia have at least one negative symptom, and the prevalence of persistent NS after the first psychotic episode is 11-37% [1, 2]. NS in schizophrenia include motivational (abulia, anhedonia, and social withdrawal) and social (alias and affective flattening) disorders [3]. NS worsen the quality of life and the level of social functioning of patients with schizophrenia [1].

In global psychiatric science and practice, there are still many questions about the typology of schizophrenia, the description of its clinical manifestations [4, 5]. Psychiatrists of different countries draw attention to the fact that these descriptions do not always coincide. And these contradictions, these different interpretations of the same, seemingly, manifestations of the disease, but in different countries, in different people, in people of different ages, different sexes, etc., lead to some confusion [6]. Therefore, modern strategies for the study of schizophrenia require interdisciplinary and multimodal approaches that allow a comprehensive assessment of the conditions of its occurrence, development, and course. Socio-demographic factors can be considered as factors affecting the prognosis of the course and outcome of the disease [1, 7]. In this regard, a comprehensive approach to the study of socio-demographic characteristics of patients with schizophrenia involves

Table 1. Gender distribution of patients with negative symptoms in schizophrenia

Sex	1st group (n = 83)		2nd group (n = 88)		3rd group (n = 81)	
	n	% ± m%	n	% ± m%	n	% ± m%
Men	38*	45.78± 4.11	40*	45.45± 3.86	25	30.86± 3.21
Women	45	54.22± 4.47	48	54.55±4.23	56*	69.14± 4.80

Notes: – n – number of persons in the distribution class; % – relative frequency; m% – average error of relative frequency; differences are statistically significant: * - at $p < 0.05$.

the study of the influence of social factors on the formation and course of schizophrenia and determines the relevance of this study.

AIM

The purpose of this study was to identify the features of determining the socio-demographic characteristics of patients with negative symptoms of schizophrenia.

MATERIALS AND METHODS

252 patients with negative symptoms in schizophrenia took part in the study: 83 patients with the first episode of schizophrenia (1st group), 88 patients with schizophrenia in a state of exacerbation (2nd group) and 81 patients with schizophrenia in a state of remission (3rd group). Patients were given full information about the study, in accordance with the principles of the Helsinki Declaration of Human Rights, the Council of Europe Convention on Human Rights and Biomedicine, relevant laws of Ukraine and international acts, and they were asked to sign an informed consent for participation in the study, which was approved by the ethics committee (protocol No. 26 dated Dec. 18th, 2023).

The following research methods were used: clinical-psychopathological, clinical-anamnestic and statistical. The clinical-psychopathological research method included a standardized interview and observation, with the help of which a primary diagnosis of negative symptoms in patients with schizophrenia was carried out in accordance with the diagnostic criteria of ICD-10. As a result of using the clinical-anamnestic method, socio-demographic data of the patients, information about the characteristics of their material and living conditions, family and professional status and level of education were obtained. Statistical analysis included the use of the following characteristics: relative frequency – P (%), representativeness error – m (mean relative frequency error – m_p (m%)), arithmetic mean (M). The average relative frequency error was determined by the formula:

$$m_p = \pm \sqrt{\frac{P \times q}{n}},$$

where: m_p is the average relative frequency error; q is the difference between the base of the relative frequency and the relative frequency itself (q = 100 - P); n is the number of persons in the distribution class. Fisher's exact test (p-value) was used to compare relative frequencies in two independent samples. For each gradation of the diagnostic criterion, its contribution to the diagnosis was determined: Kullback's measure of informativeness (MI) was calculated and diagnostic (prognostic) coefficients (DC) were calculated [8]. The critical value of the level of statistical significance (p) was taken as $p < 0.05$. The data obtained in the study were processed using Microsoft Excel 2019 MSO license program, serial number 00414-50000-00000-AA861.

RESULTS

Analysis of the distribution of patients with a predominance of negative symptoms by gender showed that the 1st group consisted of 38 men (45.78 ± 4.11) % and 45 women (54.22 ± 4.47) % (Table I). In the 2nd group there were 40 men (45.45 ± 3.86) % and 48 women (54.55 ± 4.23) %. The 3rd group consisted of 25 men (30.86 ± 3.21) % and 56 women (69.14 ± 4.80) %. It was found that there were more women than men in the total examined sample, but the statistical analysis of the results showed that there were more men in the 1st group (45.78 %, p = 0.018, DC = 1.71, MI = 0.13) and the 2nd group (45.45 %, p = 0.019, DC = 1.68, MI = 0.12), than in the 3rd group, in which women predominated (69.14 %, p = 0.019, DC = 1.03, MI = 0.08).

The distribution of patients by age is presented in Figure 1. In the 1st group, persons of age of 20-29 years old prevailed (67.47± 4.69) %, in the 2nd group the majority of patients were represented by the age group of 30-39 years (51.14± 4.11) % and 40-49 years old (36.36± 3.33) %, in the 3rd group most patients were of 30-39 years old (40.74± 3.92) % and a significant part of the patients was of 50-60 years old (25.93± 2.79) %.

It was established that there were more patients of age of 20-29 years old in the 1st group (67.47 %) than in the 2nd group (9.09 %, p = 0.0001, DC = 8.71, MI = 2.54) and the 3rd group (14.81 %, p = 0.0001, DC = 6.58, MI = 1.73). Patients of the 2nd group were distinguished by

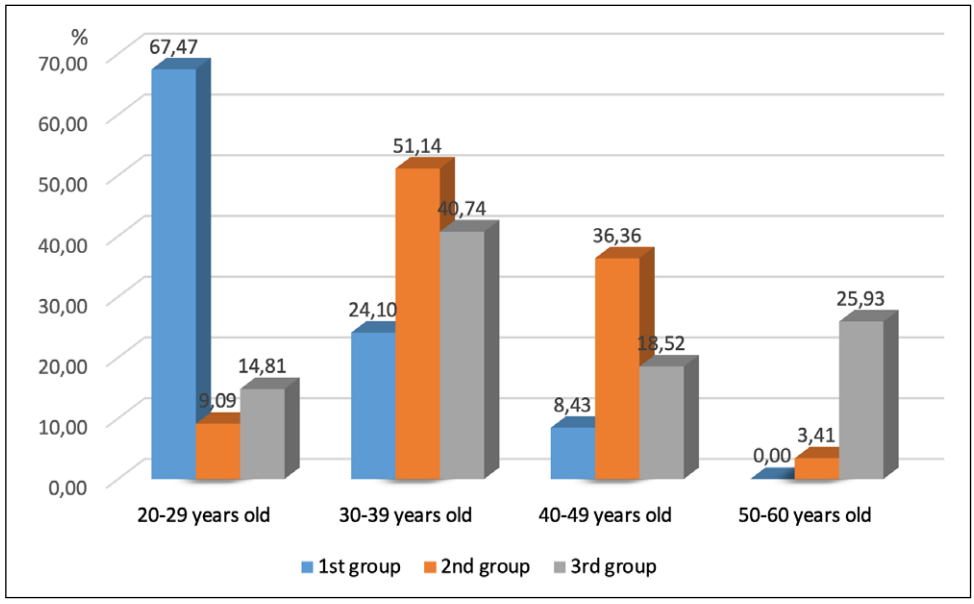

Fig. 1. Distribution of patients with negative symptoms in schizophrenia by age.

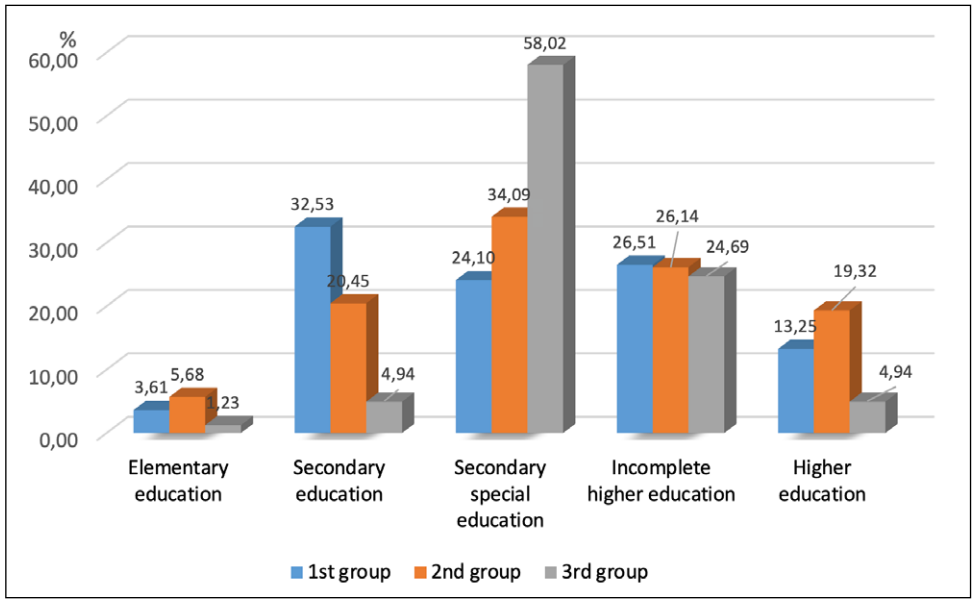

Fig. 2. Distribution of patients with negative symptoms in schizophrenia by level of education.

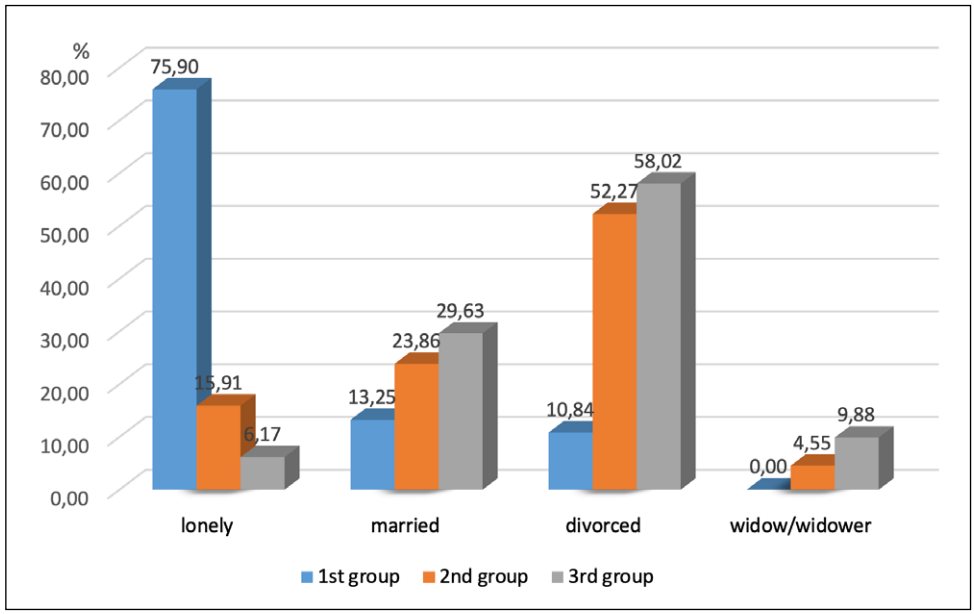

Fig. 3. Distribution of patients with negative symptoms in schizophrenia by family status.

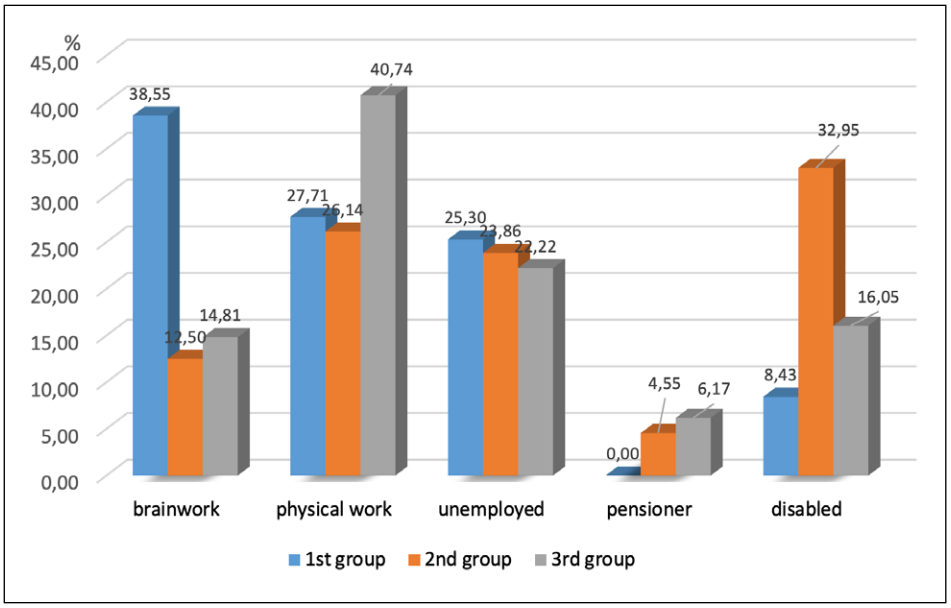

Fig. 4. Distribution of patients with negative symptoms in schizophrenia by kind of job.

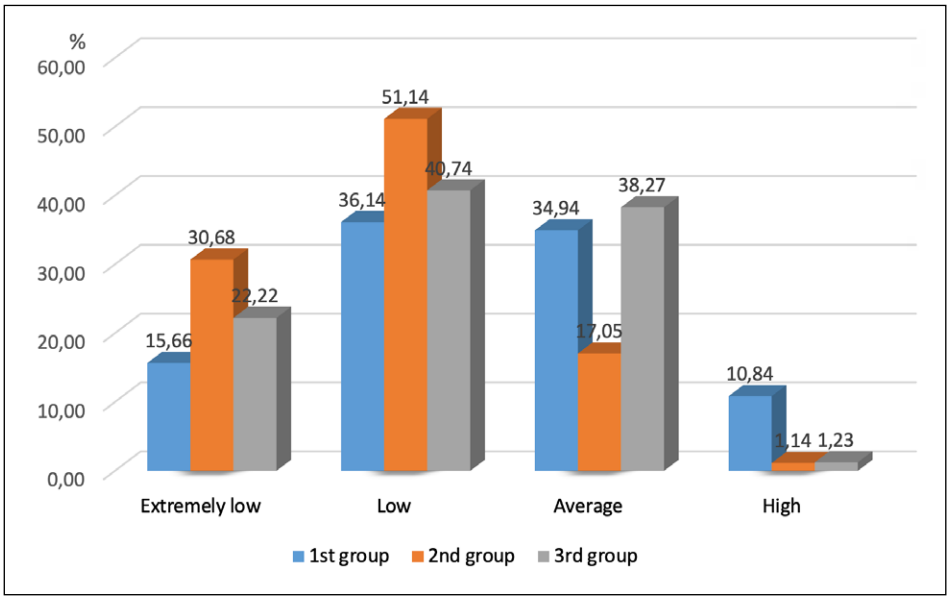

Fig. 5. Distribution of patients with negative symptoms in schizophrenia by level of material well-being.

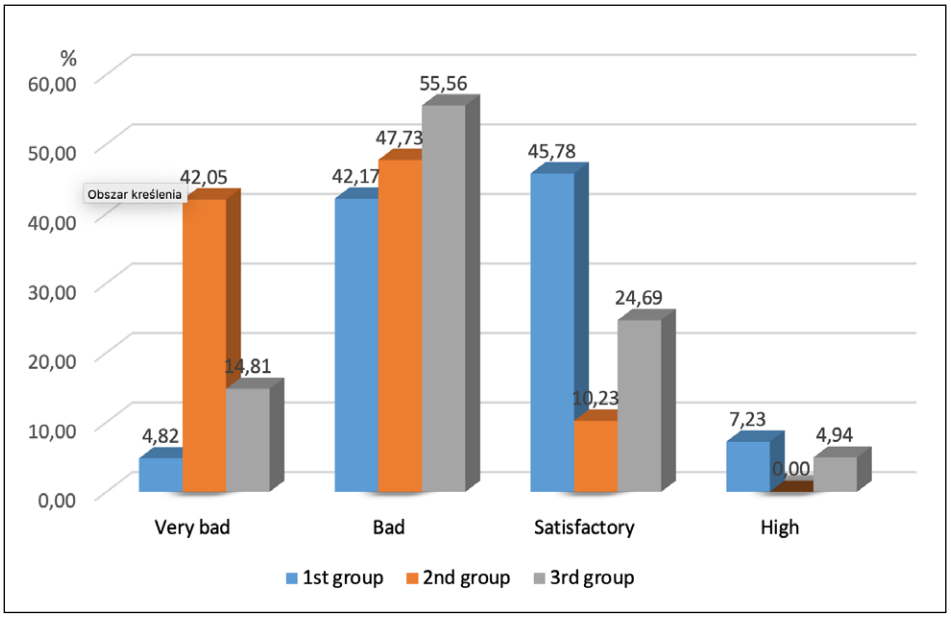

Fig. 6. Distribution of patients with negative symptoms in schizophrenia by level of housing conditions.

the predominance of the number of persons of age of 30-39 years (51.14 %) and 40-49 years (36.36 %) old in comparison with the 1st group (24.10 %, p = 0.0001, DC = 3.27, MI = 0.44 and 8.43 %, p = 0.0001, DC = 6.35, MI = 0.89, respectively) and the 3rd group (40.47 %, p = 0.049, DC = 0,99, MI = 0.05 and 18.52%, p = 0.004, DC = 2.93, MI = 0.26, respectively). Patients of the 3rd group were distinguished by the predominance of the number of people of age of 50-60 years old (25.93 %) in comparison with the 1st group (p = 0.0001) and the 2nd group (3.41 %, p = 0.0001, DC = 8,81, MI = 0.99).

Analysis of the distribution of the examined by level of education demonstrated that among patients of the 1st group there was a predominance of individuals with a secondary (32.53± 3.26) %, incomplete higher (26.51± 2.77) % and special secondary education (24.10± 2.56) % (Fig. 2). In the 2nd group, patients with a special secondary education (34.09± 3.18) %, incomplete higher education (26.14± 2.58) % and with secondary education (20.45± 2.10) % predominated. In the 3rd group, the vast majority of patients had a special secondary education (58.02± 4.70) %.

The analysis of differences made it possible to determine that there were more patients with secondary education in the 1st group (32.53 %) compared to the 2nd group (20.45 %, p = 0.028, DC = 2.01, MI = 0.12) and 3rd group (4.94 %, p = 0.0001, DC = 8.19, MI = 1.13), among which there were more people with secondary special education (34.09 %, p = 0.048, DC = 1,51, MI = 0.08 and 58.02 %, p = 0.0001, DC = 3.82, MI = 0.65, respectively).

The assessment of the marital status of the examinees made it possible to determine, that unmarried persons predominated in the 1st group (75.90± 4.51) %, and divorced persons in the 2nd (52.27± 4.15) % and the 3rd groups (58.02± 4.70) % (Fig. 3).

It was proved that the number of lonely persons was greater among patients of the 1st group (75.90 %) in comparison with the 2nd and 3rd groups 15.91 %, p = 0.0001, DC = 6.79, MI = 2.04 and 6.17%, p = 0.0001, DC = 10.90, MI = 3.80, respectively), and the number of divorced was greater among patients of the 2nd (52.27 %) and 3rd groups (58.02 %) in comparison with patients of the 1st group (10.84%, p = 0.0001, DC = 6.83, MI = 1.42 and p = 0.0001, DC = 7.28, MI = 1.72, respectively).

Distribution of patients by the kind of job demonstrated that the patients of the 1st group had more people with brainwork (including students) (38.55± 3.69) %, a significant part of patients were persons engaged in physical labor (27.71± 2.87) % and a quarter of patients were unemployed (25.30± 2.67) % (Fig. 4). In the 2nd group, 32.95 % of patients had a disability, a significant number of people engaged in physical labor (26.14± 2.58) %, and 23.86 % of patients did not have a job. In the 3rd group, most patients had physical labor (40.74± 3.92) % or did not have a job at all (22.22± 2.45) %.

Statistical analysis of the results allowed to confirm that the patients of the 1st group differed from the 2nd and 3rd groups by a greater number of patients with brainwork (38.55 %, p = 0.0001, DC = 4.89, MI = 0.64 and p = 0.0001, DC = 4.15, MI = 0.49, respectively). Patients of the 2nd group differed from the 1st and 3rd groups by a greater number of patients with disabilities (32.95 %, p = 0.0001, DC = 5.92, MI = 0.73 and p = 0.005, DC = 3.12, MI = 0.26 respectively). Patients of the 3rd group differed from the 1st and 2nd groups by a greater number of patients with a physical labor (40.74 %, p = 0.028, DC = 1.67, MI = 0.11 and p = 0.017, DC = 1.93, MI = 0.14 respectively).

Assessment of the distribution of patients with negative symptoms in schizophrenia by the level of material well-being demonstrated that among the patients of the 1st group there was a predominance of persons with a low (36.14± 3.52) % and average (34.94± 3.44) % level of material well-being, in the 2nd group – with low (51.14± 4.11) % and extremely low level (30.68± 2.94) %, in the 3rd group – with low (40.74± 3.92) % and average level (38.27± 3.76) % of material well-being (Fig. 5).

It was proved that extremely low and low levels of material well-being were more typical for patients of the 2nd group (30.68 % and 51.14 %) than for patients of the 1st group (15.66 %, p = 0.009, DC = 2.92, MI = 0.22 and 36.14 %, p = 0.017, DC = 1.51, MI = 0.11, respectively). The average level of material condition was more typical for patients of the 1st and 3rd groups (34.94 % and 38.27 %) than for patients of the 2nd group (17.05 %, p = 0.003, DC = 3.12, MI = 0,28 and p = 0.001, DC = 3.51, MI = 0.37, respectively).

Analysis living conditions among patients with negative symptoms in schizophrenia demonstrated that the majority of patients of the 1st group defined their own living conditions as "bad" (42.17± 3.91) % and "satisfactory" (45.78± 4.11) %, patients of the 2nd group – as "bad" (47.73± 3.97) % and "very bad" (42.05± 3.68) %, in the 3rd group, the majority of patients considered their own living conditions as "bad" (55.56± 4.63) % (Fig. 6).

Statistical analysis made it possible to establish that "very bad" living conditions prevailed among patients of the 2nd group (42.05 %) in comparison with the 1st group (4.82 %, p = 0.0001, DC = 9.41, MI = 1, 75) and the 3rd group (14.81%, p = 0.0001, DC = 4.52, MI = 0.62). "Satisfactory" living conditions prevailed among patients of the 1st group (45.78%) in comparison with the 2nd group (10.23 %, p = 0.0001, DC = 6.51, MI = 1.16) and the 3rd group (24.69 %, p = 0.0001, DC = 3.83,

MI = 0.28). Patients of the 3rd group were distinguished by a larger number of patients with poor living conditions (55.56 %) compared to patients of the 1st group (42.17%, p = 0.028, DC = 1.20, MI = 0.08).

DISCUSSION

Summarizing the presented results, it should be noted that the carried-out study made it possible to identify the socio-demographic characteristics of patients with negative symptoms in schizophrenia and to determine their features, which are important for assessing the severity and consequences of the mental process. Socio-demographic features of patients with NS in schizophrenia were established:

a) among patients with the first episode of schizophrenia (1st group) there was a predominance of persons of age of 20-29 years old (67.47 %, p = 0.0001), with secondary education (32.53 %, p = 0.028), unmarried (75.90 %, p = 0.0001), with mental labor (38.55 %, p = 0.0001), with low and medium levels of material well-being (36.14 % and 34.94 %, p = 0.003, respectively), poor and satisfactory living conditions (42.17 % and 45.78 %, p = 0.0001, respectively);

b) among patients with NS in schizophrenia in a state of exacerbation (2nd group) there was a predominance of individuals of 30-49 years old (87.50 %, p = 0.049), with special secondary education (34.09 %, p = 0.048), divorced (52.27 %, p = 0.0001), with the presence of disability (32.95 %, p = 0.0001), with a low and extremely low level of material well-being (51.14 %, p = 0.009 and 30.68 %, p = 0.017, respectively), with poor and very poor living conditions (47.73 % and 42.05 %, p = 0.0001, respectively);

c) among patients with NS in schizophrenia in a state of remission (3rd group) there was a predominance of individuals of age of 30-39 years (40.74 %) and 50-60 years old (25.93 %, p = 0.0001), with special secondary education (58.02 %, p = 0.0001), divorced (58.02 %, p = 0.0001) mainly with the physical labor (40.74 %, p = 0.028), with a low and medium level of material well-being (40.74 % and 38.27 %, p = 0.001, respectively) and poor living conditions (55.56%, p = 0.028).

The obtained data are consistent with the studies of K. Altynbekov, N. Raspopova, A. Abetova (2023), the results of which showed that among 1200 patients with paranoid schizophrenia, patients of average working age prevailed (31-50 years old – 55.59 %), a large part of whom, despite a fairly good level of education, were socially maladapted in family and household relations, more than 80 % of them had disabilities due to mental illnesses, which may indicate the severity of the main mental disorder [9]. Other researchers agree that demographic, clinical and treatment characteristics, as well as socioeconomic variables predict the course of schizophrenia [10]. It is also determined that marital status, professional skills, physical exercise and social support influenced the quality of life of patients with schizophrenia [11]. It has been proven that the onset of schizophrenia is associated with socio-demographic, clinical, genetic, and environmental characteristics [12].

Clinical and anamnestic correlations of socio-demographic characteristics of patients with schizophrenia with the severity of forms, type of course and manifestations of schizophrenia, duration and progression of the disease, number of relapses, hospitalizations and duration of episodes, analysis of premorbid features of development and the presence of leading symptom complexes in patients with schizophrenia require further clarification. It would also be appropriate to study the hereditary burden of schizophrenia in order to find out its possible influence on the prognosis of the development of negative disorders in the structure of schizophrenia.

CONCLUSIONS

As a result of the study, the socio-demographic characteristics of patients with negative symptoms in schizophrenia were identified and their typical characteristics were determined. These characteristics include demographic data and features of material and living conditions, family and professional status, and level of education. The obtained data should be used to improve the diagnosis of patients with negative symptoms in schizophrenia.

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The study was conducted in accordance with the principles of the Helsinki Declaration of the World Medical Association «Ethical principles of medical research involving a person as an object of research». The study protocol was approved by the local ethics committee (protocol № 26 dated 18.12.23). All study participants provided informed consent in writing to participate in the study.

The study was conducted as a fragment of the complex scientific project of the National Development Program: "To study factors predicting the formation, course and outcome of depressive disorders in order to develop effective means of therapy and rehabilitation" (registration number 0116U000016, subject code NAMN.DR.2P.16).

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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ORIGINAL ARTICLE

CONTENTS

Structural analysis of prognostic diagnostics of cardiovascular system adaptive capacity and assessment of psycho-physiological resistance to stressogenic cognitive loads

Ihor V. Kuzin, Sofia K. Chala, Svitlana I. Kalashchenko, Liudmyla M. Chernenko, Kyrylo A. Chalyy, Anatolii M. Hrynzovskyi

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ABSTRACT

Aim: To conduct a structural analysis of cardiological signs of adaptation to stressogenic cognitive loads by identifying factor features of correlations between heart rate variability (HRV) and coping-testing data indicators.

Materials and Methods: 43 people aged 19.7±1.8 years (23 boys and 20 girls) were monitored for their HRV. Methods included DC-06000 portable ECG recorder, 3X series "badge" type (single channel) and COPE Test. The study process includes four stages.

Results: As a result of further factor correlation analysis, it was revealed that Factor 1 "HRV Stress Indicators" has a negative correlation ($p<0.05$) of "moderate" strength $\rho s= -0.363$ with Factor 2 "Strategies to avoid problems and stresses" and a positive correlation of "weak" strength $\rho s=0.167$ with Factor 3 "Psychoemotional Indicators". If two factors correlate with each other, it indicates they are related and can interact, which is important for adequate interpretation of the results of factor analysis.

Conclusions: Structural analysis of the complex of cardiological signs of adaptivity to stressogenic cognitive loads and coping-testing data revealed the existence of three correlated factors: Factor 1 "HRV Stress Scores", Factor 2 "Strategies to avoid problems and stress", Factor 3 "Psychoemotional indicators". The revealed negative correlation of Factors 1 and 2 may indicate that in case the impact of Factor 2 "Strategies to avoid problems and stress" increases, the intensity of Factor 1 "HRV Stress Scores" (i.e., stress signs according to the indicators of heart rate variability) may decrease.

KEY WORDS: medicine, students, electrocardiography, heart rate, cognition

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INTRODUCTION

An assessment of a person's resilience to stress can be performed by analyzing coping strategies. Coping strategies are the ways people, consciously or unconsciously, choose to minimize the impact of stress and/or overcome it [1]. There are many various coping strategies, but they can be summarized in several groups such as: (a) problem-oriented strategies, which are aimed at solving the problems that caused stress, including planning, information searching, problem diagnosing and developing strategies to solve it; (b) emotionally-oriented strategies, which are aimed at reducing emotional tension resulted from stress, including relaxation, meditation, social support, and search of inner peace; (c) socially oriented strategies, which are aimed at maintaining and increasing social support in difficult life situations, including seeking help, support and participation in group activities; (d) preventive strategies that aim to prevent stress before it occurs, including a healthy lifestyle, healthy diet, physical activity, and other positive behavioral patterns (stereotyped actions).

To assess a person's resilience to stress, one can apply coping strategies study methods, which envisage conducting of coping-tests using different variations of questionnaires, e.g.:

1. Ways of Coping Questionnaire (WAYS) is 66-items standardized questionnaire on coping strategies that people use in different situations, it has been developed in 1988 by S. Folkman and R. Lazarus [2].
2. The Stress Questionnaire allows us to measure the level of stress experienced by a person.
3. The Singapore Women's Health Study questionnaire is used to determine the stress influence on women's health and can be used to compare the results with normative data.
4. The Perceived Stress Scale is a brief 10-items questionnaire allowing us to assess the level of stress perceived by a person [3].

The data from these questionnaires can be collected in the form of national and international databases that contain results of surveys of various population groups, in particular people who are getting education [4-7].

These data can be instrumental in assessment of the extent to the results of a particular survey differ from those that might be expected for the general population. In the process of comparing survey results with normative data, it is important to consider factors such as age, gender, ethnicity, cultural peculiarities and other factors that may affect the survey results.

Several methods can be used to assess a person's resilience to stress, based on the results of analysis of questionnaires on coping strategies:

1. Quantitative data analysis. Coping strategies questionnaire may contain questions allowing us to collect quantitative data that permit to determine which coping strategies a person uses in different situations. These data can be analyzed to investigate which coping strategies are associated with stress levels reduction and improving stress resilience.
2. Qualitative data analysis. The questionnaire may also contain questions allowing us to collect qualitative data on how a person perceives and reacts to stress.
3. Comparison of results. The results of the questionnaire can be compared with normative data to find out the extent a particular individual differs from the general population in terms of use of coping strategies use and stress resilience.
4. Interview and observation. In addition to the questionnaire, other methods such as interviews and observation can be used to collect additional information on how a person responds to stress and how he/she uses coping strategies. These methods can complement and extend the data obtained from the questionnaire.

AIM

To conduct a structural analysis of cardiological signs of adaptation to stressogenic cognitive loads by identifying factor features of correlations between heart rate variability (HRV) and coping-testing data indicators.

MATERIALS AND METHODS

In order to improve the existing methods of prognostic diagnostics of the cardiovascular system adaptability and evaluation of psycho-physiological resilience to stressogenic cognitive loads, 43 people aged (mean ± standard error) 19.7±1.8 years (23 boys and 20 girls) who are getting higher medical education were monitored for their HRV. Data were collected using a DC-06000 portable ECG recorder, 3X series "badge" type (single channel), before and after research application of immersive technology with stressogenic loads on visual-spatial cognitive functions and entered into a computer through "Harmony" specialized software for further streamlining and analysis. Coping-testing data were collected using the COPE Test (Coping Orientation to Problems Experienced Inventory) questionnaire.

The study group inclusion criteria were as follows: previous experience with immersive technologies, written consent to voluntary participation in the examination, absence of contraindications for the examination. Exclusion criteria comprised the following: presence of acute respiratory viral infections (ARVI), presence of significant psycho-physical stress during 8 hours before the study, refusal to be examined after the study start at any of its stages. Taking into account the current legislation requirements, all subjects gave their written consent to participate in the study and consent for personal data processing prior to the study.

The received data received statistical analysis by the licensed software IBM SPSS Statistics Base v.22; sublicense No138 issued on 04.08.2016, licentiate LTD "Prognostic decisions". Correlation analysis is required to establish the presence and determine the strength of linkage between the heart rhythm vegetative stability under stress and the results of measured stress resilience and stress response based on coping-testing indicators. To identify the indicators, that can jointly indicate prognostically significant stress response parameters, the matrix of Spearman's rank correlation ρs coefficient values, which refers to indicators of strength of relationship evaluation (dependence of feature variation). In this case, qualitative characteristic of the correlation is determined using the Chaddock scale (the strength of correlation) and Promax rotation factor correlations. Applicability of the data set for factor analysis has been tested and confirmed using the Kaiser-Meyer-Olkin test (KMO-test). KMO-test yielded a value of 0.612 for the Overall MSA (Measure of sampling adequacy), that is adequate for factor analysis. Additional verification was carried out using p-value Bartlett's test, with a result of $p<0.001$ indicating that factor analysis can be applied to reduce the number of variables to fewer factors explaining most of the variance in the available data.

The study was conducted in compliance with the standards of the Declaration of Helsinki and approved by the independent ethics committee at Bohomolets National Medical University (Kyiv, Ukraine). All students gave their written informed consent to participate in the study. All data from the students were anonymized prior to the analysis.

Institutional Review Board of SI "Public Health Center MoH of Ukraine" gave positive conclusion for bioethics examination #241 from 17 November 2022.

The study process includes four stages. The first stage involved 20 minutes psychological monitoring by means of the automated psychodiagnostic complex "Person Psychological Safety" [8, 9], using the COPE Test questionnaire.

In order to assess a person's resilience to stressful loads based on HRV data, HRV characteristics of a person under stress and in a state of relaxation can be compared. That was the reason why the second stage of the study involved monitoring of HRV indicators in students who were under stress and mobilized their functional reserve prior to conducting a research application of immersive technology with loads on visual-spatial cognitive function [10]. Recording of HRV indicators readings in pre-stress mobilization state was performed with a portable cardiograph (model DC-06000) [11], which recorded ECG indicators in three leads aVR, aVL, aVF (Einthoven triangle) using disposable silicone electrodes. This allowed the research team to reduce the time of an individual examination procedure to 10 minutes, including limb electrodes attaching, HRV indicators recording and electrodes removal, which meets the requirements of a short-term HRV monitoring [12].

Third stage of the study involved introduction of stressogenic load on visual-spatial cognitive function of the participants. Students wore VR glasses (Oculus Quest 2 128Gb model), took two motion controllers (sticks) and were immersed in virtual reality for 10 minutes, interacting with Sharecare You program (Sharecare Inc.) [14], which is used to study fundamental clinical disciplines, in particular human anatomy, with active involvement of immersive technologies. At the fourth stage of the study, having completed the loading process on participants' visual-spatial cognitive function, the students' HRV indicators were repeatedly recorded.

RESULTS

We done correlation analysis between HRV indicators and variables associated with COPE Test methodology. List of designation of variables associated with HRV indicators of study participants included Frequency of heart rate (FHR), Stress index (SI), Functional condition according to Baevsky, The degree of mental stress according to Mashin, Emotional state index (ESI), Psychoemotional index, low frequency/ high frequency (LF/HF), Vegetative balance index (VBI), standard deviation of adjacent RR intervals (SDNN), square root of the average sum of squares of the differences between the following RR-intervals (RMSSD).

Also, list of designation of variables associated with the study participants results of coping-testing applying COPE Test methodology included Positive reformulation and personal growth, Perceived avoidance of a problem, Concentration on emotions and their active expression, Use of instrumental social support, Active coping, Stressful event denial, Evaluation of a problematic situation as useful, Humor as a means of relieving stress and tension, Behavioral avoidance of a problem, Expecting more favorable environment to solve a problem, Use of emotional social support, Sedative drugs use.

Table 1 presents the correlation matrix of specific statistically significant links between variables of HRV indicators and coping strategy characteristics.

As a result of the correlation analysis, the list of specific HRV indicators and coping strategies with correlation links was revealed. In identified cases illustrated in Table 1, the strength of correlation measured with Cheddock scale was "moderate" ($0.3<|\rho s|<0.5$), statistically significant ($p<0.05$) and predominantly negative, i.e., increasing value of one study variable is associated with a decreasing value of the variable correlated with it.

In Table 1 attention should be paid to numerous negative correlations of the HRV indicators of "Vagosympathetic interaction index" LF/HF under pre-stress mobilization state with the following coping strategies: (a) "Perceived avoidance of a problem" ($\rho s=-0.343$); (b) "Concentration on emotions and their active expression" ($\rho s=-0.319$); (c) "Stressful event denial" ($\rho s=-0.356$); (d) "Behavioral avoidance of a problem" ($\rho s=-0.322$) and (e) "Use of emotional social support" ($\rho s=-0.321$). The revealed correlations can be interpreted as possible connection of the stress-induced increase of the value of the vagosympathetic interaction index of LF/HF HRV with relatively low indicators of certain coping strategies that fall into conditional "avoidance-denial" category.

It is under the influence of stressogenic cognitive load, which activates the sympathetic nervous system and consequently affects HRV, that we can expect a moderate increase of LF/HF index, indicating a predominance of sympathetic activation over a parasympathetic one [14]. In our study, the value of LF/HF index in pre-stress mobilization state turned out to be 20 % higher (VBI – vegetative balance index) than LF/HF in the relaxation state. However, the relevant confidence interval (95 % CI) for VBI has a value ranging from -1 to 69 and contains "0" on the left margin, which requires additional clarification of the statistical reliability of the identified difference between LF/HF in the mobilization and relaxation states. LF/HF index is one of numerous HRV indicators [15], it does not fully reflect individual features of cardiovascular system regulation during stress. However, in some cases, an increase of LF/HF index may indicate the effective mobilization of the body resources to overcome stress, which suggests high stress resilience.

Table 1. Correlation matrix of statistically significant links between variables of HRV indicators and coping strategies characteristics

Coping strategies	HRV indicators					
	Frequency of heart rate (FHR)	Stress index (SI)	The degree of mental stress according to Mashin	Emotional state index (ESI)	LF/HF	Vegetative balance index (VBI)
Perceived avoidance of a problem	-	-	-	-	-0,343*	-
Concentration on emotions and their active expression	-	-	-	-	-0,319*	-
Active coping	0,337*	-	0,307*	-	-	-
Stressful event denial	-	-	-	-	-0,356*	-
Evaluation of a problematic situation as useful	-	-	-	-0,302*	-	-
Behavioral avoidance of a problem	-0,329*	-0,327*	-	-	-0,322*	-0,302*
Use of emotional social support	-	-	-	-	-0,321*	-

Note: * – the difference is significant in comparison with the original data ($p<0,05$).

Table 2. Factor loadings Matrix for HRV indicators and coping strategies

Variable	Factor 1	Factor 2	Factor 3
RMSSD	-0.921	-	-
SDNN	-0.910	-	-
Vegetative balance index (VBI)	0.832	-	-
Stress index (SI)	0.812	-	-
Frequency of heart rate (FHR)	0.590	-	-
Perceived avoidance of a problem	-	0.661	-
Behavioral avoidance of a problem	-	0.622	-
Concentration on emotions and their active expression	-	0.582	-
Use of emotional social support	-	0.564	-
Stressful event denial	-	0.499	-
Expecting more favorable environment to solve a problem	-	0.435	-
Emotional state index (ESI)	-	-	0.965
Psychoemotional index	-	-	0.912

To determine the relationships structure of HRV indicators and coping test data in the context of the resilience analysis and adaptive capacity to stressogenic cognitive loads, it is sensible to apply factor analysis, which allows us to find hidden dependencies between the observed variables, conduct reduction of data dimensionality and identify the main factors associated with common properties of aggregated groups of variables, which are significant for predictive evaluation of stress resilience in further research.

Based on the conducted research factor analysis using Promax rotation of combinations of 25 variables, the factor loadings matrix has been formed. Factor loadings matrix presented in Table 2 reflecting the significance of each variable in each of the three determined, but not yet interpreted, factors.

The factor loadings matrix was formed by three factors, which, after data reduction, included 13 most important components amongst the initial 25 variables. Factor 1 has the highest eigenvalue of 4.185 among all factors and explains the highest variance proportion of 27.9 % in the overall variability of all data. Factor 2 has an eigenvalue of 2.131 and explains 14.2 % of the variance in the total variability of the data. Factor 3 has an eigenvalue of 1.640 and explains 10.9 % of the variance in the overall data variability.

Factor Loadings are key factor characteristics that show the correlation degree between each of the vari-

ables and the corresponding factor. Factor Loadings with a value higher than 0.3 is considered sufficiently strong, and a value higher than 0.5 is considered very strong.

Factor 1 is loaded by (i.e., the factor structure contains) the following HRV indicators (in decreasing order of FL and, accordingly, significance of the indicator): RMSSD (FL=-0.921); SDNN (FL=-0.910); Vegetative balance index – VBI (FL=0.832); tension index – TI (FL=0.812) and frequency of heart rate – HR (FL=0.590), which determines the choice to name the Factor 1 – "HRV Stress Scores" (HRVSS). The variable coping strategy "Frequency of heart rate" correlates with the rest of the variables ($p<0.05$) with a "significant" strength of relationship ($0.5<|\rho s|<0.7$ according to the Cheddock scale). Other variables Stress index, Vegetative balance index, SDNN, RMSSD correlate between each other ($p<0.05$) with "high" ($0.7<|\rho s|<0.9$) or "very high" ($0.9<|\rho s|< 0.99$) strength of relationship.

Factor 2 is loaded by (i.e., the factor structure contains) the following coping strategies (in decreasing order of FL): "Perceived avoidance of a problem" (FL=0.661), "Behavioral avoidance of a problem" (FL=0.622), "Concentration on emotions and their active expression" (FL=0.582), "Use of emotional social support" (FL=0.564), "Denial of a stressful event" (FL=0.499), "Waiting for more favorable conditions to solve a problem" (FL= 0.435), which determines the choice of the name for Factor 2 – "Strategies to avoid problems and stress" (APSS).

It should be noted that coping strategy "Perceived avoidance of a problem" with maximum of FL=0.661 is the only one, which moderately correlates with nearly all other variables (except coping strategy "Denial of a stressful event") which load Factor 1, namely: (a) Spearman correlation coefficient with coping strategy "Concentration on emotions and their active expression" $\rho s=0.323$ ($p=0.035$); (b) with coping strategy "Behavioral avoidance of a problem" $\rho s= 0.421$ ($p=0.005$); (c) with coping strategy "Waiting for more favorable conditions to solve a problem" $\rho s= 0.302$ ($p=0.049$) and (d) with coping strategy "Use of emotional social support" $\rho s= 0.361$ ($p=0.018$).

Factor 3 is loaded by the following indicators that are indirectly related to HRV (in decreasing order of FL): emotional state index – ESI (FL=0.965), psychoemotional index (FL=0.912), which determines the choice to name Factor 3 – "Psychoemotional indicators" (PEI).

As a result of further factor correlation analysis, it was revealed that Factor 1 "HRV Stress Indicators" has a negative correlation ($p<0.05$) of "moderate" strength $\rho s= -0.363$ with Factor 2 "Strategies to avoid problems and stresses" and a positive correlation of "weak" strength $\rho s=0.167$ with Factor 3 "Psychoemotional Indicators". If two factors correlate with each other, it indicates they are related and can interact, which is important for adequate interpretation of the results of factor analysis. Factor 2 APSS and Factor 3 PEI have no statistically significant correlation with each other. Negative correlation of Factor 1 and Factor 2 may indicate that in case of increased impact of Factor 2 "Strategies to avoid problems and stress", the intensity of Factor 1 "HRV stress indicators" (i.e., signs of stress by heart rate variability indicators) may decrease.

Based on the results of factor analysis of correlations between the heart rate variability indicators under stressogenic cognitive loads and coping-testing data, the main factors were defined, namely: Factor 1 "HRV stress indicators", Factor 2 "Strategies to avoid problems and stresses", Factor 3 "Psychoemotional indicators" and the relationship between them was described. These outputs may be instrumental for understanding the interaction between physiological and psychological processes and improving the existing methods for prognostic diagnostics of the cardiovascular system adaptivity and evaluation of psychophysiological resilience to stressogenic cognitive loads.

DISCUSSION

HRV indicators and coping testing can be interrelated due to their respective relationship with the functioning of the autonomic nervous system and the specificity of psychophysiological reactions to stressors, which are partially determined by individual preferences regarding coping strategies. The verification of this hypothesis involved the use of correlation matrices and factor analysis by the authors [16] with further interpretation and validity of the obtained results. Our research in practice showed the validity of this hypothesis, by revealing a negative correlation of Factor 1 and Factor 2, and, accordingly, a reduction in signs of stress according to HRV indicators.

A decrease in HRV may be associated with a poor functioning of the autonomic nervous system, which may cause an increase in stress levels and a decrease in stress resistance. Studies have shown that a higher level of stress resistance of a person can be associated with a higher level of HRV [17]. In addition, effective coping with stress can reduce stress levels and improve the functioning of the autonomic nervous system, which in turn can increase HRV.

However, during the analysis of the obtained data, we found that effective coping strategies do not always correspond to positive coping strategies. Thus, Factor 2, which corresponds to coping "Strategy to

avoid problems and stresses", refers to distress and is a manifestation of maladaptation.

Numerous scientific publications investigate various aspects of cognitive loads and their impact on human productivity and health, and also discuss the mechanisms underlying the relationship between cognitive loads and stress [18, 19].

In view of the data published in other sources, we received confirmation that the training and further professional activity of specialists whose functions are related to making quick decisions in conditions of increased responsibility requires an analysis of the potential stressogenic effect of cognitive loads and an analysis of the cardiological signs of adaptation to such stress-induced states. Thus, it is important to improve and optimize tools for diagnosing the adaptive capacity of the cardiovascular system and assessing psycho-physiological resistance to stressful mental and emotional loads.

CONCLUSIONS

1. As a result of the conducted analysis of the data of monitoring of heart rate variability readings and coping testing data in the age category of 19.7±1.8 years, a relevant structure of factor correlations was revealed, and prognostically significant cardiological signs and coping strategies for adaptation to stressogenic cognitive loads were substantiated.
2. Structural analysis of the complex of cardiological signs of adaptivity to stressogenic cognitive loads and coping-testing data revealed the existence of three correlated factors: Factor 1 "HRV Stress Scores", Factor 2 "Strategies to avoid problems and stress", Factor 3 "Psychoemotional indicators".
3. The revealed negative correlation of Factors 1 and 2 may indicate that in case the impact of Factor 2 "Strategies to avoid problems and stress" increases, the intensity of Factor 1 "HRV Stress Scores" (i.e., stress signs according to the indicators of heart rate variability) may decrease. Justification of this correlation provides the prerequisites for improving the prognostic diagnosis of a person's adaptive potential to the impact of stressogenic cognitive loads.
4. In the context of further improvement of techniques applied to evaluate cardiological signs of individual stress resilience, it seems relevant and important to expand the subpopulation of persons who can be involved in the study of the structure of indicators' correlation between heart rate variability and coping testing in the context of immersive technology with loads on visual-spatial cognitive function.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Holter ECG monitoring and platelets characteristics in patients with coronary artery disease and atrial fibrillation

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ABSTRACT

Aim: To check the relationships between platelet characteristics and Holter ECG monitoring results in patients with atrial fibrillation (AF) and coronary artery disease (CAD).

Materials and Methods: 300 investigated patients were separated into three groups: I (CAD) – 149 patients with CAD without arrhythmias, II (CAD and AF) – 124 patients with CAD and AF paroxysm, and the control group (CG) – 27 patients without CAD and arrhythmias.

Results: In the II group was detected an increase in mean platelet volume (MPV) (9.30%) and platelet-to-leucocyte ratio (PLR) (41.12%) and a decrease in platelet count (PC) (12.20%) in comparison with the I group, $P<0.05$. Also, in the II group was found an increase in platelet leucine (12.63%), isoleucine (10.73%), and a decrease in serine (5.06%), threonine (23.05%), valine (30.83%), glycine (32.21%) levels in comparison with the I group, $P<0.05$. PC, MPV, and PLR ratios were correlated with supraventricular extrasystoles per hour ($r=-0.352$, $r=0.308$, and $r=0.359$, consequently), $P<0.05$. Platelets distribution width (PDW) was correlated with ST-segment changes ($r=0.371$), $P<0.05$. Platelet threonine, serine, glycine, alanine, and valine levels were correlated with total supraventricular extrasystoles ($r=-0.374$, $r=-0.358$, $r=-0.402$, $r=-0.307$, $r=-0.312$, consequently) and supraventricular extrasystoles per hour ($r=-0.374$, $r=-0.358$, $r=-0.402$, $r=-0.307$, $r=-0.312$, consequently), $P<0.05$. Platelet lysine, taurine, cysteine, and phenylalanine levels were correlated with ST-segment changes ($r=-0.319$, $r=-0.344$, $r=-0.376$, and $r=0.317$, consequently), $P<0.05$.

Conclusions: Platelet features (PC, MPV, PDW, PLR, and amino acid spectrum) are significantly correlated with supraventricular arrhythmias and ST-segment episodes, which shows their role in AF and CAD pathogenesis.

KEY WORDS: coronary artery disease, atrial fibrillation, electrocardiography, platelets, amino acids

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INTRODUCTION

There is no doubt that pathogenetically atrial fibrillation (AF) and coronary artery disease (CAD) are characterized by prothrombotic state and platelet activation. Adequate anticoagulation is the first step and the main basis in the management of AF paroxysms [1, 2]. Platelet conditions represent hemostatic balance and can directly affect the prothrombotic state, which plays a major role in the supraventricular arrhythmia development. Increased mean platelet volume (MPV) is the known marker of platelet activation. Also, AF is significantly associated with reduced platelets count (PC), which can be explained by their overuse and synthesis decrease. The rise of platelets distribution width (PDW) also is common for cardiovascular pathology and some metabolic states, like diabetes mellitus [3]. Platelets also can represent prothrombotic potential and atherosclerotic plaque composition. Platelet activation in CAD patients is connected with increased integrin αIIbβ3 levels [4], which also can be promoted by circulatory branched-chain amino acids (AA) [5, 6].

Holter ECG monitoring is indicated for patients with AF paroxysms for the determination of the best treatment strategy or heart rate control management. For stable CAD patients, it is only reasonable in case of ischemia cardiac clinical features [7]. So, connections between Holter ECG monitoring findings: rhythm abnormalities, ST-segment changes, QTs-interval differences, and platelets morphological and biochemical characteristics are still unexplored.

AIM

The aim of this study was to investigate the relationships between Holter ECG monitoring findings and platelet characteristics in patients with atrial fibrillation paroxysm and coronary artery disease.

MATERIALS AND METHODS

300 patients were separated into three groups: I (CAD) – 149 patients with CAD without arrhythmias, II (CAD and

Table 1. Baseline characteristics of the study groups, mean ± standard error

Characteristic /group	I group	II group	CG
Age (years)	67.71±3.90	67.96±0.94	56.25±2.18
Men (%)	48.99	47.97	48.15
Smoking (%)	51.01	41.46	40.74
History of myocardial infarction (%)	30.87+	26.02#	0
History of stroke (%)	8.72+	8.13#	0
Diabetes mellitus (%)	18.12+	14.63#	0
Obesity (%)	8.84+	12.0#	0
BMI (kg/m^2)	27.02±0.33	26.93±0.43	27.12±2.10
Total bilirubin (mmol/l)	11.3±0,09	12.4±0,08	11.7±0.11
Uric acid (mmol/l)	380.5±28.16+	404.9±36.11#	310.2±29.12
GFR (ml/min)	62.03±2.31+	67.73±1.98#	84.01±5.48
TC (mmol/l)	5.73±0.37+	6.18±0.31#	4.32±0.21

Notes: +-p<0.05 I group – CG; #-p<0.05 II group – CG

AF) – 124 patients with AF paroxysm and CAD, and the control group (CG) – 27 patients without arrhythmias and CAD. Investigated patients were hospitalized and observed in the cardiological and therapeutic departments in the Kyiv City Clinical Hospital No. 12 in 2018-2023 years. Diagnosis CAD was based on the history of coronary artery stenotic changes during invasive coronary angiography. Diagnosis of AF paroxysm was based on 12 leads electrocardiography at rest. These diagnoses were matched the resent ESC guidelines [1, 2]. Heart failure in stage B or C was found in the I and II group of patients [8]. Exclusion criteria included heart failure Class III to IV (by New York Heart Association), ejection fraction <40%, valvular AF, thyroid pathology, chronic kidney disease (Glomerular Filtration Rate, GFR <60 mL/min), reported malignancies, pregnancy, inflammatory bowel disease and irritable bowel syndrome, probiotics or antibiotics usage for a month before the study, vegetarians. Informed consent was signed by the all subjects according to the Declaration of Helsinki. The study was performed at the base and got approval of the Kyiv City Clinical Hospital No. 12 ethical commission (protocol # 8 from 22/08/2018).

Holter ECG monitoring (Cardiosens_K, Kharkiv, 2014) in V1, aVF, and V5 leads during 24 hours was performed for the patients with AF within 24 hours after sinus rhythm restoration, and for the patients without AF on the first day of observation. PC, MPV, PDW, and platelets-to-leucocytes ratio (PLR) were obtained from the common blood count. Platelet AA level was detected by the method of ion exchange liquid column chromatography. Patients' blood sampling was made from the cubital vein fasted before treatment on the first day of hospitalization.

Results have been introduced as mean ± standard error for continuous variables or [95% confidence interval (CI)] as a number for categorical variables. Normality distribution was checked by the Pearson criterion. Data comparison was performed by Wilcoxon signed-rank test or Student t-test with two critical regions depending on the distribution type. Correlation analysis was done by the Spearman's coefficient [9]. All calculations were done in MATLAB R2014a (License number 271828, MathWorks, Inc., USA).

RESULTS

In investigated groups, significant differences in age and gender, total bilirubin, body mass index (BMI), and smoking history were not checked. In the I and II groups uric acid (by 22.66% and 30.53% respectively) and total cholesterol (TC) (by 32.64% and 43.06% respectively) levels were significantly higher and glomerular filtration rate (GFR) (by 26.16% and 19.38% respectively) were lower versus CG, P<0.05. Also, CG patients did not have obesity, stroke, diabetes mellitus, or myocardial infarction history, as the I and II groups patients. Data are presented in Table 1.

The average Holter monitoring lasted for 22,13±0.22 hours in average. The I and II groups were characterized by significant decrease in minimum heart rate (HR) (13.82% and 11.36%, consequently) and average (9.38% and 14.14%, consequently) versus the CG, P<0.05. In the II group had a significant rise in supraventricular ectopic beats (SVEs) per hour, total SVEs, single SVEs, pair SVEs, ventricular ectopic beats (VEs) per hour, total VEs, single VEs, and pair VEs, AF paroxysm, and its duration versus the I group, P<0.05. ST -segment deviations were not found in the CG. It was no significant difference in ST-segment changes between I and II groups, P<0.05. The data are presented in Table 2.

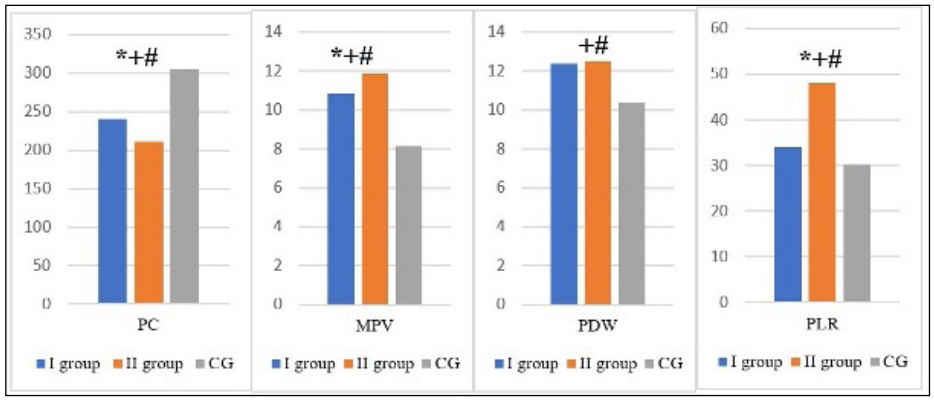

Fig. 1. Platelet morphological characteristics in investigated patients.
Notes: *-P<0.05 I-II groups; +-P<0.05 I group – CG; #-P<0.05 II group – CG.

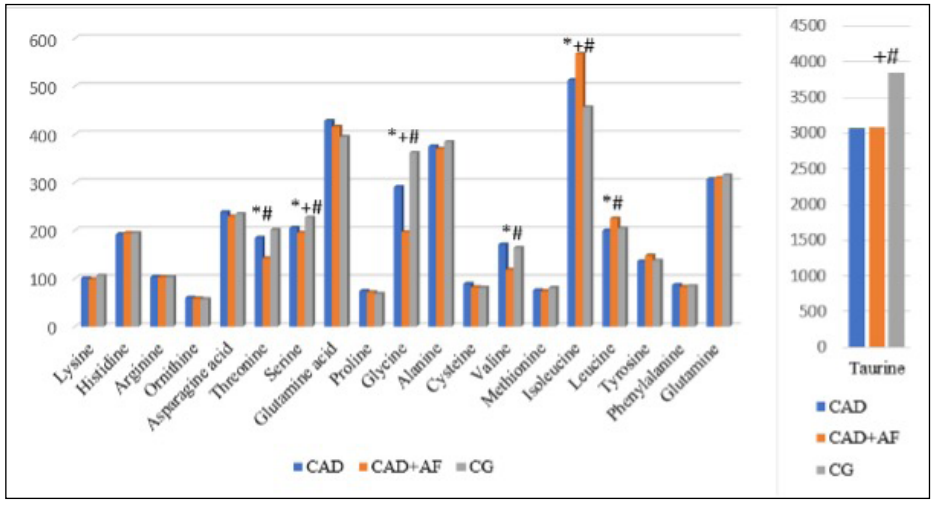

Fig. 2. Platelets amino acids profile in investigated patients, μmol/l.
Notes: *-P<0.05 I-II groups; +-P<0.05 I group – CG; #-P<0.05 II group – CG.

In the II group, a significant depletion in PC (12.20%) and a rise in MPV (9.30%) and PLR (41.12%) was revealed versus the I group, P <0.05. In the I group, a significant decline in PC (21.25%) and a growth in MPV (33.58%), PDW (20.31%), and PLR (12.37%) was detected versus the CG, P <0.05. In the II group, a significant decrease in PC (30.85%) and a rise in PDW (20.31%), MPV (46.00%), and PLR (58.58%) was observed versus the CG, P <0.05. The data are shown in Fig. 1.

In the II group, a significant rise in isoleucine (10.73%), and leucine (12.63%) and a decline in serine (5.06%), threonine (23.05%), valine (30.83%), glycine (32.21%) levels were found versus the I group, P <0.05. In the I group was found a significant growth in isoleucine (12.41%) and a decline in serine (9.31%), glycine (19.73%), and taurine (20.26%), levels versus the CG, P <0.05. In the II group, a significant increase in leucine (10.20%), isoleucine (24.47%), and a fall in serine (13.90%), taurine (19.84%), valine (27.87%), threonine (29.37%), and glycine (45.59%) levels were obtained versus the CG, P <0.05. The data are presented in Fig. 2.

The correlation analysis between platelets morphological characteristics, amino acids spectrum, and Holter ECG monitoring indexes is shown in Table 3 and Table 4.

DISCUSSION

Holter ECG monitoring is a significant part of the investigation in patients with AF paroxysms and CAD [7]. In our study, we selected patients with CAD and without arrhythmias and CG using Holter ECG monitoring. That's why, these groups had significantly lower levels of supraventricular and ventricular rhythm abnormalities, and CG had no ST episodes. According to our data patients with AF and CAD are characterized by a rise in MPV and PLR and a decrease in PC. These results were expected according to the literature data [4, 5]. Platelet characteristics are deeply connected with inflammation, myocardial fibrosis, and remodeling [10]. Also, PC, MPV, and PLR significantly correlated with supraventricular arrhythmias. According to the literature data, an increase in PLR can be an independent indicator of ventricular repolarization and depolarization heterogeneity [11]. The rise of MPV is associated with platelet activation, which is characterized by intracellular calcium exchange disturbances and can lead to electrolyte disbalance [12]. In animal experiments, platelet activation is connected with cellular hypoxia [13], which is also important in arrhythmia pathogenesis [1]. At the same time, PDW is mostly correlated with ST-segment changes. According to some data, PDW

Table 2. Holter ECG monitoring indexes in investigated groups, mean ± standard error or mean [95% CI]

Characteristic /group	I group	II group	CG
Maximum HR, bpm	110.20±2.48	106.6±3.89	109.8±3.97
Minimum HR, bpm	45.6±1.68	46.9±1.66 #	52.91±1.30 +
Average HR, bpm	66.98±0.99 *	63.46±1.24 #	73.91±2.20 +
SVEs total	36 [95% CI 24-43] *	729 [95% CI 331-982] #	7 [95% CI 0-15] +
SVEs single	32 [95% CI 24-43] *	502 [95% CI 307-766] #	7 [95% CI 0-15] +
SVEs pair	0 [95% CI 0-3] *	27 [95% CI 8-42] #	0 +
SVEs group	0 [95% CI 0-1]	5 [95% CI 0-9] #	0 +
SVT	0 [95% CI 0-1]	0 [95% CI 0-1] #	0 +
Longest SVT, sec.	0 [95% CI 0-16]	0 [95% CI 0-42] #	0 +
SVEs per hour	8 [95% CI 3-17] *	38 [95% CI 11-112] #	0 [95% CI 0-2] +
AF paroxysm	0 *	0 [95% CI 0-1] #	0
Longest AF paroxysm, sec.	0 *	0 [95% CI 0-44] #	0
VEs total	0 [95% CI 0-3] *	3 [95% CI 0-15] #	0 [95% CI 0-1] +
VEs single	0 [95% CI 0-3] *	3 [95% CI 0-15] #	0+
VEs pair	0 [95% CI 0-2] *	3 [95% CI 0-15] #	0+
VEs group	0 [95% CI 0-1]	0 [95% CI 0-2] #	0+
VT	0	0	0
Longest VT, sec.	0	0	0
VE's per hour	14 [95% CI 5-19] *	32 [95% CI 17-41] #	0 [95% CI 0-1] +
Pauses more than 3 sec	0	0	0
Longest pauses, sec.	0	0	0
Changes ST segment, quantity episodes	0 [95% CI 0-3]	0 [95% CI 0-6] #	0 +
Maximum ST depression, μV	0 [95% CI 0-118]	0 [95% CI 0-124] #	0 +
Maximum ST elevation, μV	0 [95% CI 0-133]	0 [95% CI 0-112] #	0 +
Maximum ST episode duration, minutes	2 [95% CI 1-5]	2 [95% CI 1-5.5] #	0 +

Notes: +-p<0.05 I group – CG; #-p<0.05 II group – CG; *-p<0.05 I-II groups; HR – heart rate; AF – atrial fibrillation; SVE – supraventricular ectopic beats; VE - ventricular ectopic beats; SVT – supraventricular tachycardia, VT – ventricular tachycardia.

is directly connected with GPIIb/IIIa receptor activity [14], which is associated with increased risks of MI [15].

Besides, patients with AF and CAD had a significant increase in platelet isoleucine, and leucine and a significant decrease in threonine, serine, glycine, and valine levels in our study. Platelet glycine, alanine, serine, threonine, valine, and leucine levels are mostly correlated with arrhythmias due to obtained data. According to the previous data, an increase in circulating levels of leucine and tyrosine and a decrease in glycine, serine, and alanine levels are associated with cardiovascular diseases. Serine is a precursor of glycine synthesis. Glycine has antihypertensive, antioxidative, anti-inflammatory, and metabolic effects [6]. According to some data, glycine can counteract angiotensin II, which prevents left ventricular hypertrophy and stimulates growth factor β and endothelin-1, which prevents myocardial fibrosis [16]. Moreover, activation of myocardial glycine receptors provides ischemic conditioning in experiments [17]. Also, alanine, serine, threonine, and their exchange violations regulate Ca2+ dependent kinase 2 activity and myocardial sarco/endoplasmic reticulum (SR) Ca^{2+} ATPase pump, which changes Ca2+ handling proteins exchange, reduce Ca2+ uptake, and prevent O-GlcNAcylation induced increase in Ca^{2+} leak [18, 19]. Leucine participates in electrical remodeling processes by modulation of L-type Ca2+ channels and excitation-contraction activity [20]. Valine is responsible for fatty acid oxidation in cardiomyocytes, which leads to antioxidative properties, but on the other hand, sometimes it can suppress glucose oxidation in cardiac tissue [21].

Table 3. Correlation matrices between Holter ECG monitoring indexes and platelet morphological characteristics

Holter ECG monitoring indexes / Platelet morphological characteristics	PC	MPV	PDW	PLR
Maximum HR	0,196	-0,050	0,145	0,153
Minimum HR	0,347*	-0,188	-0,214	0,116
Average HR	0,377*	-0,360*	-0,012	0,382*
SVE total	-0,377*	0,374*	0,272	-0,119
SVE single	-0,399*	0,374*	0,247	-0,154
SVE pair	-0,301*	0,366*	0,130	-0,014
SVE group	-0,047	0,363*	0,196	0,002
SVT	0,043	0,197	0,008	0,326*
Longest SVT	0,052	0,194	0,008	0,329*
SVEs per hour	-0,352*	0,308*	0,211	0,359*
AF paroxysm	-0,164	0,451*	0,163	0,357*
Longest AF paroxysm	-0,155	0,456*	0,178	0,341*
VE total	-0,323*	0,420*	0,172	-0,203
VE single	-0,364*	0,434*	0,270	-0,131
VE pair	0,047	0,050	0,136	0,115
VE group	0,041	0,020	0,075	0,041
VE's per hour	-0,123	0,159	0,035	-0,221
Changes ST segment	0,028	0,101	0,371*	-0,096
Maximum ST depression	0,053	0,098	0,385*	-0,08
Maximum ST elevation	0,070	0,084	0,271	-0,08
Maximum ST episode duration	0,041	0,092	0,308*	-0,08

Notes: *- correlations with moderate or strong force (r>0.3 or r<-0.3), P<0.05. HR – heart rate; AF – atrial fibrillation; SVE – supraventricular ectopic beats; VE - ventricular ectopic beats; SVT – supraventricular tachycardia, VT – ventricular tachycardia.

We established that platelet lysine, taurine, cysteine, and phenylalanine levels correlated with ST-segment episodes. Cysteine is a precursor of taurine, they are sulfur contains amino acids. As reported, taurine and cysteine have strong anti-ischemic properties. Taurine is a trigger for osmotic preconditioning, by its antioxidant properties. Cysteine inhibits vascular endothelial growth factor and hypoxia-inducible factor 1-alpha [22, 23]. Also, according to the latest data in experiments lysine can prevent cardiac fibrosis and apoptosis by influencing cardiomyocytes mitochondria, sarcolemma, and architecture [24]. In animal models, an increase in circulated phenylalanine is closely associated with cardiac aging: fibrosis, ectopic activity, and inflammation [25].

So, the role of platelets' morphological and biochemical features in arrhythmia pathogenesis in CAD patients is important and needs further investigation.

CONCLUSIONS

The features of platelet characteristics, Holter ECG monitoring indexes, and their correlations in patients with coronary artery disease and atrial fibrillation were described in our study:

1. Patients vwith atrial fibrillation paroxysm and coronary artery disease characterized by a significant increase in mean platelet volume (9.30%) and platelet-to-leucocyte ratio (41.12%) and a significant decrease in platelets count (12.20%), P<0.05;
2. Patients with atrial fibrillation paroxysm and coronary artery disease characterized by a significant increase in platelet isoleucine (10.73%), leucine (12.63%), and a significant decrease in serine (5.06%), threonine (23.05%), valine (30.83%) and glycine (32.21%) levels in comparison with coronary artery disease patients without atrial fibrillation, P<0.05;
3. Platelets count, mean platelet volume, and platelet-to-leucocyte ratio correlated with supraventricular extrasystoles per hour (r=-0.352, r=0.308, and r=0.359, consequently), P<0.05;
4. Platelet distribution width correlated with ST-segment changes (r=0.371), P<0.05;
5. Platelet threonine, serine, glycine, alanine, and valine levels negatively correlated with supraventricular arrhythmias: total supraventricular extrasystoles (r=-0.374, r=-0.358, r=-0.402, r=-0.307, r=-0.312, respectively) and supraventricular extrasystoles per hour (r=-0.374, r=-0.358, r=-0.402, r=-0.307, r=-0.312, respectively), P<0.05;

Table 4. Correlation matrices between Holter ECG monitoring indexes and platelets morphological characteristics, P<0.05

Holter ECG monitoring indexes / Platelet amino acids	Maximum ST episode duration	Maximum ST elevation	Maximum ST depression	Changes ST segment	VE's per hour	VE group	VE pair	VE single	VE total	Longest AF paroxysm	AF paroxysm	SVEs per hour	Longest SVT	SVT	SVE group	SVE pair	SVE single	SVE total	Average HR	Minimum HR	Maximum HR
Lysine	**-0,320***	**-0,307***	**-0,326***	**-0,319***	0,071	0,089	0,074	0,187	0,189	-0,102	-0,111	-0,135	-0,073	-0,065	-0,213	-0,165	-0,107	-0,115	0,098	-0,008	**-0,329***
Histidine	-0,128	-0,109	-0,118	-0,134	-0,022	0,128	0,009	0,024	0,027	0,068	0,066	-0,109	0,028	0,030	0,056	0,060	-0,096	-0,097	-0,153	-0,054	-0,030
Arginine	-0,18	-0,120	-0,183	-0,177	-0,030	0,015	-0,099	-0,038	-0,037	0,038	0,012	0,020	0,186	0,168	0,015	-0,011	0,009	0,009	0,020	0,042	-0,110
Ornithine	-0,18	-0,089	-0,179	-0,175	-0,162	-0,028	-0,015	-0,142	-0,142	0,214	0,232	0,075	-0,016	-0,036	0,023	-0,042	-0,001	0,024	0,109	0,008	-0,079
Taurine	**-0,356***	-0,296	**-0,343***	**-0,344***	-0,078	0,045	-0,115	-0,252	-0,253	-0,043	-0,031	-0,180	-0,052	-0,071	-0,035	-0,102	**-0,324***	-0,186	**0,488***	0,114	0,027
Asparagine acid	-0,016	-0,055	-0,028	-0,013	0,009	0,069	-0,024	-0,176	-0,175	-0,094	-0,104	-0,133	-0,077	-0,074	-0,206	-0,211	-0,192	-0,172	-0,022	-0,001	0,007
Threonine	-0,111	-0,132	-0,127	-0,125	-0,153	0,050	-0,050	-0,205	-0,207	-0,223	**-0,328***	**-0,374***	-0,116	-0,115	**-0,357***	**-0,382***	**-0,333***	**-0,358***	0,083	0,046	0,075
Serine	-0,034	-0,085	-0,032	-0,033	-0,024	-0,061	0,034	**-0,234***	-0,23	-0,298	-0,318	**-0,358***	-0,163	-0,175	-0,145	-0,176	-0,211	**-0,318***	0,126	0,067	0,107
Glutamine acid	-0,052	-0,124	-0,072	-0,063	-0,020	0,022	0,022	0,124	0,124	-0,018	-0,033	-0,091	0,131	0,148	-0,039	-0,095	-0,074	-0,091	-0,136	0,075	-0,086
Proline	0,070	0,079	0,070	0,066	-0,097	0,006	-0,019	-0,182	-0,178	0,002	0,022	0,065	0,085	0,084	0,161	0,111	0,056	0,065	-0,060	**-0,384***	0,113
Glycine	0,048	0,104	0,046	0,045	-0,102	0,017	0,019	**-0,406***	**-0,403***	-0,4	**-0,494***	**-0,402***	**-0,338***	**-0,344***	**-0,316***	**-0,376***	**-0,484***	**-0,479***	**0,394***	-0,066	0,098
Alanine	-0,171	-0,192	-0,187	-0,178	0,048	0,024	0,035	-0,045	-0,046	-0,149	-0,139	**-0,307***	**-0,331***	**-0,323***	**-0,325***	**-0,375***	-0,191	**-0,312***	**0,357***	0,154	0,085
Cysteine	**-0,386***	0,281	**-0,379***	**-0,376***	0,013	-0,076	0,035	-0,068	-0,065	-0,009	0,004	0,295	0,104	0,104	0,131	0,119	0,213	0,215	-0,140	**0,302***	-0,058
Valine	0,067	0,020	0,072	0,068	-0,078	0,087	0,015	-0,238	-0,235	**-0,376***	**-0,341***	**-0,312***	**-0,311***	**-0,328***	**-0,319***	**-0,375***	**-0,308***	**-0,389***	0,090	-0,134	-0,050
Methionine	0,118	0,095	0,104	0,118	-0,065	-0,049	-0,006	0,025	0,022	-0,017	-0,011	-0,140	-0,038	-0,042	0,001	-0,106	-0,186	-0,192	0,120	-0,054	0,057
Isoleucine	-0,064	-0,117	-0,069	-0,061	0,019	0,013	0,041	0,152	0,150	0,049	0,034	-0,038	0,060	0,073	-0,005	-0,053	-0,015	-0,032	-0,033	0,073	0,059
Leucine	0,078	0,144	0,078	0,074	0,134	0,028	0,119	0,291	0,292	0,117	0,123	0,048	**0,308***	**0,395***	0,152	0,196	0,163	0,150	-0,018	0,162	0,007
Tyrosine	-0,059	-0,048	-0,075	-0,067	0,071	0,086	-0,047	0,124	0,123	-0,096	-0,109	-0,077	0,012	0,018	-0,197	-0,151	0,002	-0,013	0,047	0,113	0,084
Phenylalanine	**0,321***	0,279	**0,319***	**0,317***	0,015	0,061	0,060	0,011	0,018	-0,02	-0,020	-0,106	-0,173	-0,167	-0,013	-0,148	-0,118	-0,108	-0,033	-0,215	0,082
Glutamine	-0,191	-0,145	-0,198	-0,201	-0,114	0,056	0,087	0,009	0,013	0,064	0,052	-0,230	-0,109	-0,109	-0,177	-0,160	-0,210	-0,207	0,096	0,161	0,012

Notes: *- correlations with moderate or strong force (r>0.3 or r<-0.3), P<0.05.

6. Platelet lysine, taurine, cysteine, and phenylalanine levels correlated with ST-segment changes (r=-0.319, r=-0.344, r=-0.376, and r=0.317, consequently), P<0.05.

The role of platelet amino acids spectrum abnormalities should be deeply investigated in further studies and possible approaches to their correction.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Trauma-informed training as a means of stabilizing the negative impact of stressful and destructive factors of war on the inner world of future specialists

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ABSTRACT

Aim: To determine the conditions for the implementation of trauma-informed training as a means of stabilizing the negative impact of stressful and destructive factors of war on the inner world of future specialists.

Materials and Methods: 1,100 students studying in the conditions of martial law took part in the experimental work.

Results: As a result of the negative impact of the stressful and destructive factors of the war on the inner world, the future specialists the following manifestations of the deterioration of the health were established: depression (99%), sudden change of mood (92%), worsening of well-being during sudden changes in the weather (66%), irritability (52%), aggressiveness (11%), anger (7%). It was found that future specialists wanted to postpone completing the educational task until later, as they perceived it as very difficult (79%).

Conclusions: The conditions for the implementation of trauma-informed studying were formulated as a means of stabilizing the negative impact of stressful and destructive factors of war on the inner world of future specialists. 1. During the organization of learning, teachers take into account the fact that psycho-traumas, which are caused by stressful and destructive factors of war, disturb students until they experience them. 2. Teachers take into account the traumatic experience of future specialists. 3. The teachers' actions aim to restore future professionals' sense of security, reestablish contact with other study participants, and regain control over their own lives and studies.

KEY WORDS: experiences, traumatic experiences, medical complaints, stabilization during studies at a higher education institution

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INTRODUCTION

The solution to various problems in the conditions of military actions on Ukraine's territory, including the war's impact on the life of Ukrainians and the organization of education for the adult and younger generations, is widely presented in scientific articles. We focused only on the research results that will prove our research's relevance in terms of medical and pedagogical emphasis.

After the first year of the Russian invasion, an increased prevalence of stress, anxiety, and post-traumatic stress disorder symptoms among Ukrainians was recorded; in particular, it was established that the most vulnerable group was refugees, who felt much worse than displaced persons [1].

In other articles, various categories of displaced persons negatively affected by war's stressful and destructive factors were identified as research objects. The results of these studies are:

1. Identification of three groups of factors that negatively affect the subjective well-being of students of grades 1-10 in the conditions of the introduction of martial law on the territory of Ukraine. These are [2]: 1) factors associated with external influences on the organization of student education (shelling, air raids, problems in the family (regarding students of grades 1-10); training in bomb shelters, training as an electronic student (regarding students of grades 1-4)); 2) factors related to the emotional and physiological states of the teacher (states of depression or nervousness of the teacher (regarding students of grades 1-10); illness of the teacher (regarding students of grades 1-4)); 3) factors related to cognitive processes, emotional and physiological states of students (dissatisfaction of physiological needs (I want to eat, sleep), safety needs (I feel anxious), negative emotional manifestations, a decrease in cognitive activity and cognitive independence (regarding students 1-10 classes)).

2. Identification of seven groups of influencing factors on the process of organizing distance learning in the conditions of military operations, including subjective factors of negative impact on the personality and results of distance learning (self-limitation; focus on the learning result; avoidance of tasks; pessimistic behavior; low general level of self-esteem; low level of involvement in educational work) [3].
3. Generalization of data on the primary actions of teachers during the education of students during the period of martial law in Ukraine [4]: 1) during direct interaction, teachers, first of all, paid attention to the psychological state of students (if necessary, provided psychological support; provided exercises for psychological relief; used techniques for regulating the emotional state; allocated more time for collective performance of exercises and tasks; balanced informed students that an "air alarm" signal had been announced, reminded them how to act in this case).
4. Generalization of data on stressors. It was established that during the introduction of martial law on the territory of Ukraine, students were most worried when, due to the conduct of military operations in the territory of their residence, constant air raids, and lack of electricity supply and communication, they could not join synchronous e-learning and directly interact with the electronic teacher and electronic students. Significantly, 96 % of student respondents constantly felt the need to study educational material by interacting with an electronic teacher and students. 78 % of student respondents noted that interaction during study helped them overcome anxiety caused by military actions, maintain the pace of study, learn new educational material faster and more effectively, and experience positive emotions. All student respondents said they dream of live communication with the teacher and fellow students [5].
5. It has been established that most students studying during the war in Ukraine have an average and low vitality level. A direct connection of vitality with a solid and mobile nervous system, as well as hyperthymic and demonstrative accentuations of character, has been revealed. The inverse relationship is associated with the vitality of pedantic, unbalanced, dysthymic, and exalted accentuations of character, all personality disorders [6].

AIM

To determine the conditions for the implementation of trauma-informed training as a

means of stabilizing the negative impact of stressful and destructive factors of war on the inner world of future specialists, in particular, future teachers and future public health specialists.

MATERIALS AND METHODS

A total of 1,100 people took part in the study. These are future teachers (in particular, future teachers of primary classes, future teachers of preschool education institutions, and future managers of the primary education quality system) and future public health specialists who studied for two years in higher education institutions in Ukraine (Borys Grinchenko Kyiv University, O.O. Bogomolets National Medical University). The study participants for the period of its conduct belonged to the category of persons who were negatively affected by the stressful and destructive factors of the war.

The work uses a set of research methods: general scientific (analysis, synthesis, comparison, systematization, generalization) and empirical (observation, individual interviews, anonymous testing, and testing to identify a tendency to loneliness as typical behavior of a future specialist).

Anonymous testing included the following questions [7]:

1. What group of people do you identify with? (List of groups to be selected: a) with the 1st group, that is, those who are injured as a result of the negative impact of stressful and destructive factors of war and feel the need for treatment (respiratory and immune systems, abnormalities in the work of the gastrointestinal tract) because it has significantly worsened their state of health; b) with the 2nd group, i.e., with those who are injured as a result of the negative impact of stressful and destructive factors of the war, feeling the deterioration of their health, engage in self-medication; c) with the 3rd group, i.e., those who are traumatized as a result of the negative impact of stressful and destructive factors of war, experience a deterioration in their health, in particular, increased irritability, aggressiveness, short-term outbursts of anger, a sharp change in mood, depression, worsening of well-being during sudden changes the weather; d) with the 1st and 2nd groups; e) with the 1st and 3rd groups; e) with the 2nd and 3rd groups; g) with the 1st, 2nd and 3rd groups.
2. If you identified yourself with the first group, choose the direction of treatment that you needed. (List of treatment directions for selection: a) treatment of the respiratory system; b) treatment of the immune system; c) treatment of the respiratory and immune systems; d) treatment of the gastrointestinal tract; e) your answer option).
3. If you identified with the 2nd group, write down the means you use for self-medication.
4. If you identified yourself with the 3rd group, choose the dominant manifestation or dominant manifestations of the deterioration of your health. (List of states to choose from a) increased irritability; b) aggressiveness; c) brief outbursts of anger; d) a sudden change in mood; e) depression; f) deterioration of well-being during sudden changes in the weather).

5. What desires did you most often feel during training, which takes place in the conditions of military operations on the territory of Ukraine? (Wish list for selection: a) desire to retire; b) the desire not to perform the educational task because it is perceived as too tricky; c) your option as desired).

The loneliness test was carried out to distinguish cases of loneliness as a result of the negative impact of stressful and destructive war factors on the inner world of future specialists (future teachers and public health specialists) from loneliness as a typical behavior of a future specialist.

The test to determine the tendency to loneliness consisted of 12 questions (1. After classes, can you go for a walk around the city alone? 2. Do you consider it a catastrophic situation when you have no one to go on vacation with (no company)? 3. In two hours, you have an exciting meeting. Can you do something to occupy yourself at this time? 4. Do you like to look at the flames of a fire? 5. When doing something important, do phone calls annoy you? 6. Do you like to walk? 7. Can you meet New Year alone and remain in a good mood? 8. How many guests do you invite to your birthday? 9. Do you feel free in the company of four strangers? 10. What will you do if you are in a foreign city and need help finding the right street? (Answer options: a) ask a passerby; b) turn to Google for help; c) try to find it yourself). 11. Do you like gifts? 13. Did you dream of becoming an actor?).

Processing of results: 1) 1 point each for the answer "yes" to questions No. 1, 3, 4, 5, 6, 7, 10b, 12. 2) 1 point each for the answer "no" to questions No. 2, 8, 9, 11. 3) 2 points for answering "yes" to question No. 10c.

Analysis of the results: More than 8 points – the respondent is prone to loneliness and likes to think and analyze different situations. 4-8 points – the respondent is moderately sociable and sometimes seeks to be alone to organize thoughts and feelings. But after spending a short time alone, you enjoy talking to people. Less than 4 points – the respondent is very sociable.

The coefficient (Kz) was used – the ratio of the sum of positive answers to the total number of questions. The Kz coefficient was calculated according to the formula:

$$K = \frac{X_P \cdot 100\%}{P},$$

where:

X_p – the number of negative answers ("no") of all respondents;

P – the maximum possible number of positive answers ("yes") in the group;

P = (number of respondents) x (number of questions).

The researchers followed all protocols and procedures required by the Biomedical research Ethics Committee and conform to the directive of the Ukrainian Legislation on health care, Helsinki Declaration 2000 and European Society Directive 86/609 on human participation in biomedical research to ensure adherence to all standards for adequate protection and well-being of participants.

RESULTS

According to the results of an anonymous questionnaire, the respondents identified themselves with the group of people who were injured as a result of the negative impact of stressful and destructive factors of war and sought medical treatment (96 % of cases) because they felt a significant deterioration in the state of the respiratory system (74 % of cases), respiratory system and gastrointestinal tract (22 % of cases) (Fig. 1).

Also, respondents (78 % of cases) identified themselves with the group of people who resorted to self-medication (took pills advised by friends or close relatives; drank herbal teas). Most respondents (69 % of cases) initially engaged in self-medication and only then turned to a doctor (Fig. 2).

All respondents identified themselves with the group of people who experienced a deterioration in their health as a result of the negative impact of the stressful and destructive factors of the war. After analyzing the complaints of the respondents, we found the following dominant manifestations of health deterioration: depression (99 % of cases), sudden change in mood (92 % of cases), worsening of well-being during sudden changes in the weather (66 % of cases), increased irritability (52 % of cases), aggressiveness (11% of cases), outbursts of anger (7 % of cases).

After analyzing the respondents' complaints, we found manifestations of deterioration of well-being, which lecturers should take into account when organizing training (Fig. 3).

Most often, the respondents felt the desire to sleep (97 % of cases), to postpone the completion of the educational task for later because it was perceived by them as very difficult (79 % of cases), to be alone (56 % of cases), to be near relatives, to be constantly on the phone with them (12 % of cases), to rest in nature (5 % of cases).

As a result of comparing the results of the anonymous testing with the test results to determine the tendency to loneliness, it was established that loneliness is typical behavior only for a small part of the respondents (3% of cases). Regarding a significant part of the respondents (53 % of cases), the manifestation of the desire to be alone was caused by the negative impact of the stressful and destructive factors of the war on their inner world. The same influence caused an inadequate perception of the complexity of the educational task and delay in its completion, the obsessive desire to contact loved ones, and the constant feeling of them next to you.

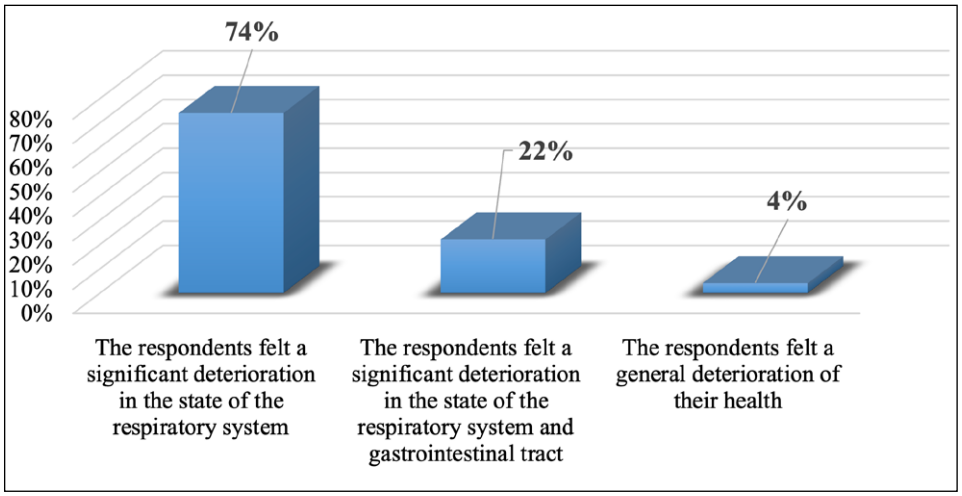

Fig. 1. The respondents sought medical treatment.

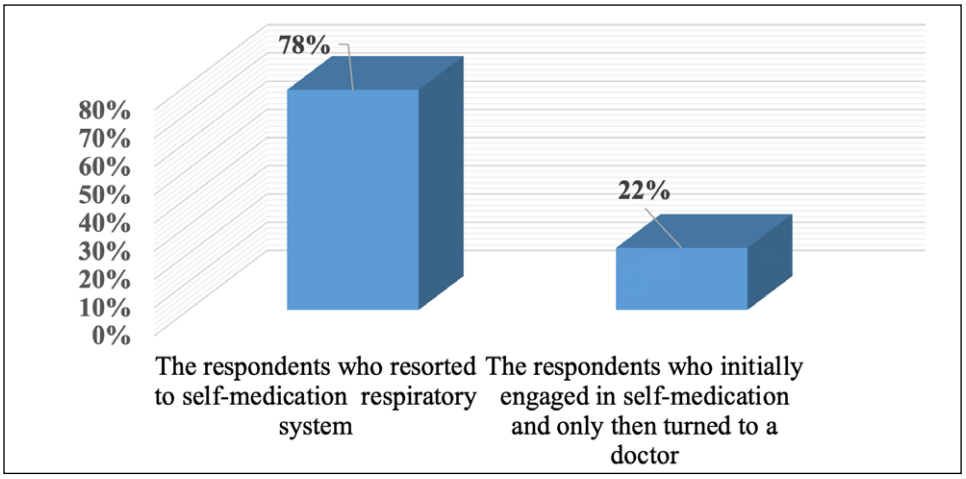

Fig. 2. The respondents resorted to self-medication.

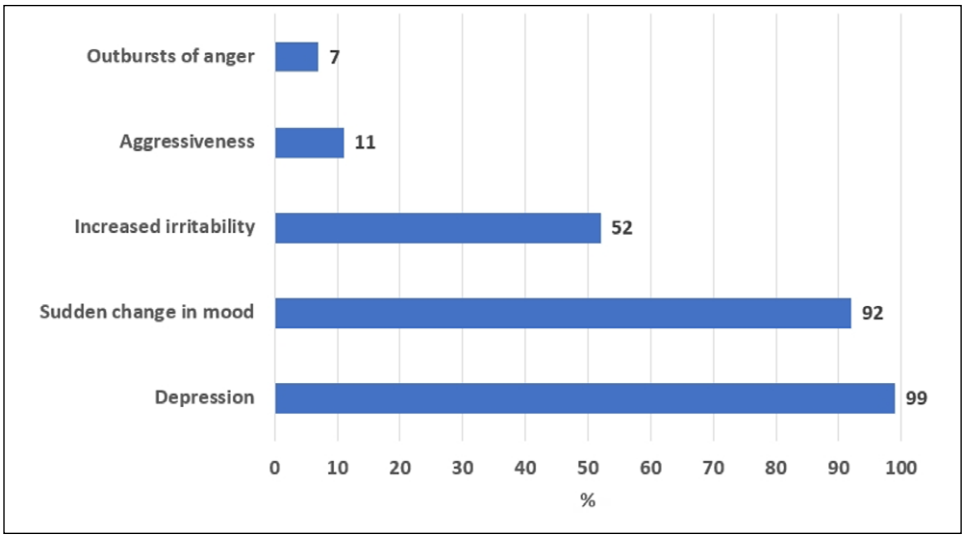

Fig. 3. The complaints of the respondents, which lecturers should take into account when organizing training.

DISCUSSION

Experimental data indicate that the negative impact of the stressful and destructive factors of the war on the inner world of future specialists after the two-year Russian invasion of Ukraine caused an increase in the level of morbidity among future specialists. For comparison, we used data from articles in which the results of research by scientists in the pre-war period were made public. These are the conclusions of scientists. 1. Almost half of the students who participated in the study feel the influence of a factor (anxiety) that increases the likelihood of emotional burnout. Up to 50 % of respondents are in the first phase of emotional burnout or have already passed it [8]. 2. A significant decrease in the functional reserves of the student's body was the result of intense and long-term performance of educational activities

with the simultaneous experience of "negatively" colored actual emotional states generated by events during educational activities or events that occurred before that in professional activities or family relationships [5].

According to generalized data covering the pre-war period and the annual period of hostilities on the territory of Ukraine [1], the prevalence of stress among Ukrainians in 2012 was 45 %; in 2016 – 50%; in March 2022 – 53 %, after the end of the war year – 80 %. According to the results of our research, at the end of the second year of the war, the spread of stress reached a mark of 96 %. However, we must emphasize the limitations of our study. This is the coverage of the experiment only by persons who received higher education during the full-scale military invasion of the territory of Ukraine. Our study did not include other reports of Ukrainians.

As a result of individual interviews, information was obtained about the traumatic experience acquired by future teachers and future public health specialists. In this study, we did not focus on the entire palette of types of traumatic experiences but singled out only those traumatic experiences that were typical for all respondents without exception. These are 1) fear of shelling; 2) anxiety in anticipation of night and morning shelling; 3) concern about the condition and life of relatives, friends, acquaintances, and soldiers; 4) increased sensitivity to sounds in the environment; 5) experiences during sleepless nights; 6) loss of self-control during training in the warehouse, constant distractions to information about the state of events during the "air alarm" signal.

A person's inner world is a structure open to influences and changes. The person himself is involved in the processes of influence and change. S. Maksymenko structures the processes that take place in the inner world of a person according to the direction of actions [9]. First, a person changes, structures, and develops his inner world with the help of psychological means.

Over time, the inner world becomes a means of self-management for a person.

The change in the form, structure, and integrity of value-meaning formations in the inner world of a person is caused by his experiences. The appearance of changes as a result of experiences is necessary to prioritize meanings and values and build cause-and-effect relationships in the value-meaning formations of his inner world.

Scientists explain the essence of the experience process in different ways. In the context of the implementation of trauma-informed training for future teachers and future public health specialists, we use the scientific work of S. Maksymenko [9, 12] and M. Papuchi [10, 11], which explain:

1. The essence of experience (Experience is a representation to oneself of what is happening in the surrounding world, the human body, in the middle of the individual).
2. The essence of the process of experiencing (Experience arises from an impression. The process of experiencing is the process of "transferring" something that is not yours into your own).
3. Functional purpose of the process of experiencing (The process of experiencing is a bridge connecting conscious and unconscious processes; what contributes to a person's awareness of this or that state; what structures a person's inner world; something that becomes a mechanism for starting a structure-creating interaction in the inner world of a person).

Therefore, the basis of the implementation of trauma-informed training is the presence of the impact of psycho-trauma on the inner world of future specialists. In particular, we took into account the fact that psycho-traumas caused by stressful and destructive factors of war have an impact on the inner world of future teachers and future public health specialists. First, psycho-traumas significantly slowed down or even stopped the process of structuring and restructuring the inner world of future professionals. Secondly, what was not covered by structuring in the inner world is perceived by future specialists as alien to them and something that constantly confuses and traumatizes them. Thirdly, impressions, sensations, and emotions not experienced by future specialists remain alien to them, unmastered by their inner world, and pass into the unconscious, forming a structure that does not correspond to the inner world. Fourth, the direct or indirect activation of this structure during training causes negative states and high emotional tension, which, in turn, causes several negative changes in the health of future specialists.

CONCLUSIONS

The implementation of trauma-informed training contributes to the stabilization of the negative impact of stressful and destructive factors of war on the inner world of future specialists if three conditions are met. 1. During the organization of training, teachers take into account the fact that psycho-traumas, which are caused by stressful and destructive factors of war, disturb students until they experience them. 2. During the organization of training, teachers take into account the traumatic experiences of future specialists. 3. The teachers' actions aim to restore future professionals' sense of security and their own ability, reestablish contact with other study participants, and regain control over their own lives and studies.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Algorithm of management actions for the formation and implementation of a resilient health care quality system

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ABSTRACT

Aim: Development of an algorithm of management actions for the formation of a resilient system of quality of medical care in health care institutions of obstetric and gynecological profile and formalization of its closed structural and logical scheme.

Materials and Methods: A set of theoretical approaches of social medicine and methods of business process reengineering is used, taking into account the dominant ones: systemic and integrated approach and alarm and process approaches; the concept of resilience; quality of medical care; reproductive health care using business ecosystem methods.

Results: The algorithm of management actions for the formation of a resilient system of quality of medical care in obstetric and gynecological health care institutions, which is formalized in nine stages: analysis of needs and identification of problems; substantiation of performance requirements; development of a health care quality strategy; involvement of stakeholders; formation of a system of relative indicators; development of an action plan; implementation of a set of measures; monitoring and evaluation; improving the quality of health care.

Conclusions: The results made it possible: construction of a closed structural and logical scheme of management actions, taking into account the combination of factors of influence, harmonized with the main functions of the resilient system, which determine the peculiarities of its functioning; justification of the boundaries of managerial and social responsibility of management entities according to the binary components of the medical and social justification of the process of improving the quality of medical care.

KEY WORDS: quality management, algorithm of management actions, resilient quality system of obstetric and gynecological care, health care facilities

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INTRODUCTION

In the context of solving the problem of improving the quality of medical care in obstetric and gynecological health care facilities and its modernization, the key basis for reconstruction processes is the development of its structural and functional resilient model, because this type of model solution allows to ensure 1) integration of resources and processes [1, 2] in obstetric and gynecological health care facilities through the integration of various resources and processes that ensure the quality of medical care, including human resources, technologies, procedures and management systems; 2) adaptability of the medical and management system to changes, as it will be built on the principles of resilience and flexibility[3, 4]; 3) improving quality management processes by integrating management actions to control and improve the system [5]; 4) improving interaction with patients and employees by tightening logistics and information and communication links, taking into account needs and expectations; 5) stability and sustainability of the functioning of the *obstetric and gynecological health care institution* (OGHCI), taking into account the principles of resilience in the context of stabilizing the system in conditions of uncertainty and crisis situations [5-7]. Achieving clarity of tasks and objectivity of the format of the resilient health care quality system will necessarily require formalization of the structural and logical scheme of implementation of the algorithm of management actions in practice in the context of its phased development.

AIM

Development and substantiation of the algorithm of managerial actions for the formation and implementation of a resilient system of quality of medical care in health care institutions of obstetric and gynecological profile and formalization of a closed structural and logical scheme for the implementation of tasks with detailing and determining the managerial and social responsibility of management entities.

MATERIALS AND METHODS

A set of methodological and theoretical approaches of social medicine and a number of multidisciplinary provisions of business process reengineering were used to develop and substantiate an algorithm of management actions for the formation and implementation of a resilient system of quality of medical care in OGHCIs: a) systemic and integrated approach [1], which allowed to consider and describe a resilient health care quality system as a holistic unity with structural multidimensional relationships, in which each element interacts with others to achieve common goals; b) alarm and process approach [2, 3] in substantiating the algorithm of management actions for the formation of a resilient system of quality of medical care in obstetric and gynecological *health care facilities* (HCF) with the identification of key risks, challenges and dangers that arise in the provision of medical care and management of HCF. At the same time, taking into account the provisions of the alarm and process approach allows to establish the composition of procedures for: identifying risks and hazards (to analyse the state of affairs and identify potential threats to the quality of medical care in obstetric and gynecological health care facilities); assessment of possible consequences on a scope of probability (determination of the importance and probability of risk/hazard occurrence, assessment of potential consequences); development of risk management strategies (specific measures to prevent, identify and minimize risks and hazards); implementation of action plans and monitoring of their effectiveness; analysis and improvement of the resilient system (evaluation of results, analysis of the causes of risks and hazards, and making necessary changes to improve the system). The following dominants are taken into account: a) the concept of resilience [4, 5], which is the basis of a closed algorithm, providing the quality system with signs of stability and recovery; b) quality of medical care [6] (accessibility, effectiveness, safety, patient orientation etc.); c) empirical data and results of studies in the field of reproductive health care and quality management [7-10] on the use of management methods and tools [11, 12], which allowed to optimize management actions for the formation and implementation of a resilient system of quality of medical care in OGHCI; d) continuity of process improvement [13] to focus management actions on improvement and adaptation to change by incorporating organizational, medical and social feedback mechanisms into the algorithm with monitoring the effectiveness of the implementation of the *resilient health care quality system (RHCQS)* to ensure its effectiveness and adaptability to the specific needs and conditions of the functioning of OGHCIs.

The design of the study did not provide for the observance and consideration of the principles of bioethics, since in the scientific and applied development an exploratory analysis of the sequence of implementation of management actions was carried out to form and introduce into practice an effective system of quality of medical care, the development of which was carried out taking into account theoretical and methodological developments in ensuring the quality of medical care in health care institutions of the obstetric and gynecological profile.

RESULTS

Defining the current task as the formation of a resilient system of quality of medical care in the OGHCI, we confirm that the algorithm of managerial actions for the formation and implementation of RHCQS should take into account the dominant WHO guidelines [6] and the methodological experience of structural and informational redesign of obstetric and gynecological service [14, 16, 17]. Therefore, we formalized the management algorithm (Table 1) with a clear nine-step process. We emphasize that [15, 18]: a) the above algorithm of management actions has a closed nature, so its structural and logical scheme (Fig.1) is built on a closed cycle of implementation of management and organizational actions, which will allow RHCQS to remain relevant and effective in the face of constant changes and growing demands of the reproductive health care market); b) since RHCQS was developed taking into account the dominant systemic and integrated approach and alarm and process concepts, management and organizational actions are divided into two areas, respectively (see Table 1). The proposed closed algorithm (see Fig.1) provides a general action plan for the development (formation) of RHCQS in HCFs [19], and organizational, medical and social processes will require cooperation of all stakeholders and systematic monitoring and improvement to achieve the best results.

The presented managerial, organizational and economic actions (see Table 1 – steps II, V and IX) will help to substantiate clear requirements for the effectiveness of RHCQS and ensure its effective implementation and operation. Step "V" "Formation of a multi-level system of relative indicators for assessing and forecasting the quality of medical care" is of particular importance – it can be used both for assessing and monitoring and managing the quality of obstetric and gynecological care).

The substantiation of a multilevel system of indicators should be performed using scientific and applied econometric approaches [19-21] to the formation of

Table 1. Closed algorithm of management actions for the formation of a resilient system of quality of medical services in obstetric and gynecological health care institutions *

No.	Step by algorithm	Content of management and organizational actions	
		By systemic and integrated concept	By alarm and process concept
I	Analysis of needs and identification of problems, threats and risks	Analyse the current state of the health care delivery system in obstetric and gynecological facilities. Identify the main problems and shortcomings that need to be addressed, as well as threats and risks to the sustainable functioning of the health care facility.	Analysis of the current situation and identification of potential threats to the quality of medical care. Identification of risks and vulnerabilities in the health care facility. Assessment of possible consequences on the scope of probability of risk or danger, assessment of consequences.
II	Justification of the requirements for the effectiveness of RHCQS in OGHCIs	- Analysis of the state of the healthcare quality system, identification of strengths and weaknesses and opportunities for improvement. - Determination of key indicators that reflect the effectiveness of the quality system (share of complications, patient satisfaction, level of professional competence of medical staff, etc.) - Establishing the goal and objectives to be achieved through the implementation of the quality system (e.g., reducing complications/increasing patient satisfaction). - Take into account the requirements of quality standards and regulatory requirements related to medical care in the field of obstetrics and gynecology, and include them in the performance requirements. - Involvement of stakeholders in the process of justifying performance requirements, including representatives of medical staff, administration, patients, and regulatory authorities. - Formulation of requirements for the quality system performance to be achieved within a set period of time (should be specific, measurable, achievable, realistic and within a set timeframe). - Evaluation and monitoring of the results of fulfilment of the existing performance requirements, making necessary adjustments and improvements if required.	
III	Determination and development/ improvement of the medical care quality strategy	Develop a strategy for building RHCQS based on the problems, threats and risks (of different nature) identified in the previous steps and achieving the goals. To determine the main priorities and areas of activity based on the results of the implementation of RHCQS.	Development of risk management strategies in HCFs, identification of measures to prevent, identify and minimize risks and hazards. Planning and development of measures to counteract critical situations and respond to them.
IV	Involvement of stakeholders	Involve all stakeholders, including medical staff, facility administrators, patient representatives and other interested groups, in the process of building a resilient quality system and in decision-making in this area.	
V	Formation of a multi-level system of relative indicators for assessing and forecasting the quality of medical care	- Analysis of needs and targeting of indicators: based on the results of the analysis of the current state of the health care quality system and identification of key aspects that need to be measured and evaluated (based on the ten components of RHCQS). Setting goals and strategies to improve the quality of healthcare services. - Selection of indicators: based on the analysis, determine a set of key indicators that will reflect the level of quality of medical care. They can be either structural (availability of equipment and resources), procedural (waiting time for an appointment) or performance (level of complications after procedures). - Formation of a multi-level assessment system, including the main levels (structural, process, performance) and sub-levels (quality indicators for different procedures or services). Each level should have an appropriate set of indicators and methods of their measurement with the possibility of their formalization according to a single criterion in the form of a relative indicator. - Development of a measurement and data collection system: justification of a system for collecting, processing and analysing data on quality of care indicators: this will include the creation of databases, implementation of data collection procedures and training of medical staff on their use. - Determination of criteria for evaluation and comparison: determination of a single criterion for evaluating and comparing health care quality indicators at different levels. This will help to identify trends, problem areas, and make management decisions to improve the quality of care. - Continuous updating and improvement: It is urgent to ensure continuous updating and improvement of the system of relative indicators based on new requirements, scientific research and best practices in the field of reproductive medicine. We need to clarify and change the indicators as needed, and modernize the models for their calculation so that they reflect the most up-to-date standards of quality of care in OGHCI.	

Continuation of Table 1

No.	Step by algorithm	Content of management and organizational actions	
		By systemic and integrated concept	By alarm and process concept
VI	Development of an action plan	To develop a specific action plan identifying the main and specific tasks, responsible persons, deadlines and resources needed to complete each step to build a resilient healthcare quality system in OGHCI in a short time frame, even with resource constraints and a constant increase in threats and risks.	Improvement of procedures for informing and communicating with patients, ensuring access to information about treatment procedures and processes. Development/improvement of feedback mechanisms. Implementation of risk management strategies and monitoring of their effectiveness.
VII	Implementation of a set of measures	Implement the recommended measures, including updating procedures and protocols, training and professional development of medical staff, and implementing quality monitoring and control systems based on a multi-level system of relative indicators.	Tests and simulations: conducting training and simulation exercises with medical staff to test the effectiveness of action plans and respond to unforeseen circumstances.
VIII	Monitoring and evaluation	To conduct ongoing monitoring and evaluation of the effectiveness of the implemented measures. Determine the level of achievement of the set goals and make adjustments to the strategy for implementing a resilient healthcare quality system, if necessary.	Development and implementation of a system for monitoring and tracking quality indicators, controlling the effectiveness of measures and timely response to negative trends and risks.
IX	Provision and continuous improvement of the resilient quality system and the quality strategy of medical care	Ensure a closed-loop system of continuous improvement, including responding to new requirements and standards, implementing innovations and best practices. The latter includes not only finding and eliminating deficiencies, but also actively improving the structure, functions, tasks and processes of the system itself. It is important to continue developing and adapting RHCQS based on the data, feedback and identified needs. - Improvement of the structure: analyse the effectiveness of the current structure of the quality system and make the necessary changes to improve the organization and management. - Clarify the functions and tasks of RHCQS, clarify the tasks it should perform in light of changing requirements and needs. - Process updates: review and optimize quality management-related processes in the healthcare facility to ensure greater efficiency and effectiveness. - Training and development of quality staff. - Responding to changes: be prepared to respond to changes and transformations in the external environment, take into account regulatory requirements and new quality standards by adapting and improving OGHCI.	Professional development of staff in crisis response: organization of educational programs and trainings for medical staff of OGHCI on the effectiveness and adequacy of emergency response. Development and implementation of an automated notification and crisis response system for prompt notification and coordination of employees and patients during emergencies. Fulfilment of tasks to ensure the stability and efficiency of the work of OGHCI in conditions of uncertainty, which will help maintain a high level of quality of medical care. Improvement of the quality system (based on the results of the analysis): evaluation of the results, analysis of the causes of risks and hazards, introduction of necessary changes to improve RHCQS.

Source* Determined and substantiated by the author, as detailed in [18].

absolute, integral, generalized integral, aggregate and composite performance indicators. Given the certainty of the nine steps in the formation of RHCQS, we need to determine for each step the responsible OGHCI and the timing of the implementation of the relevant functions for the introduction into medical practice (Table 2).

It should be noted that the responsibility for each of the nine steps of the closed-loop algorithm for the formation of RHCQS may be distributed between different levels of management in the healthcare facility and between different stakeholders. Moreover, the above division of responsibilities (see Table 2) will help ensure that each step in the process of forming and putting this system into operation is effectively implemented. We should pay attention to the expediency of addressing the issue of medical and social justification of the

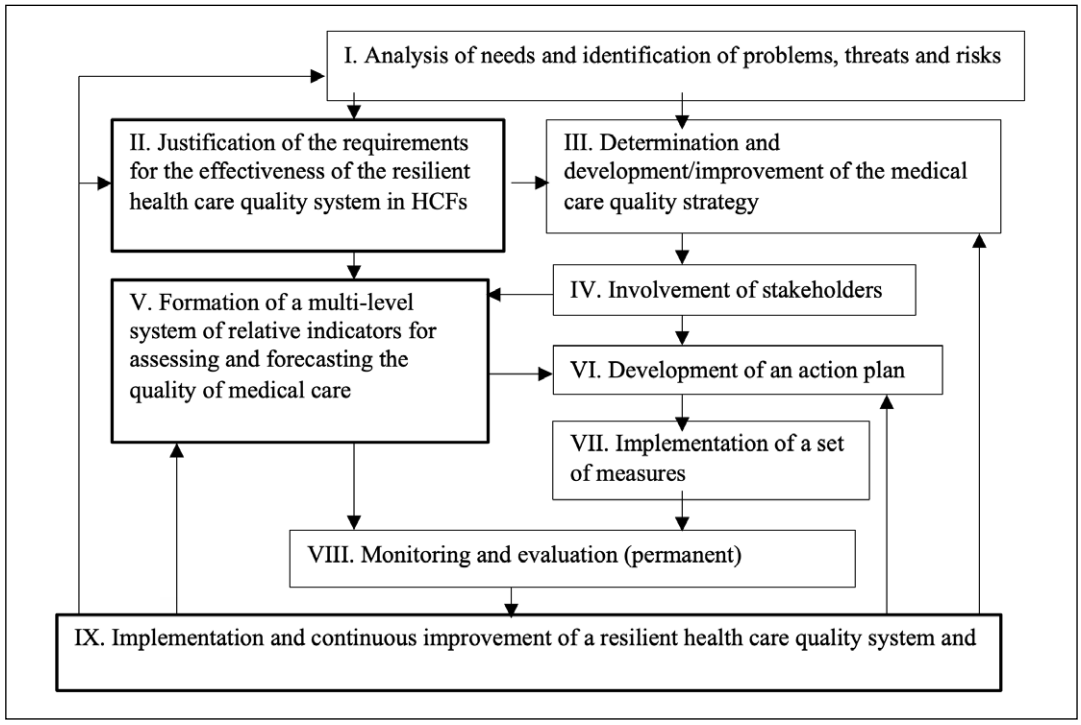

Fig. 1. Closed structural and logical scheme for the implementation of management actions for the formation and implementation of a resilient health care system in the obstetric and gynecological health care institutions (author's development – detailed in [18]).

process of improving the modern (resilient) quality system of medical care in HCFs in the context of the implementation of social responsibility functions by management entities, which aim to prove the need and benefits of such changes for the medical institution, society, patients and other stakeholders. Therefore, using our experience [18], we propose to utilize a binary set of measures and medical and statistical procedures to intensify the processes of modernization of the quality system. It is mandatory to maintain, define and calculate the main medical and statistical components according to the formalization – Table 3. The main components of the medical and social substantiation of the processes of improvement (modernization) of RHCQS in OGHCI also include the medical and social responsibility of management entities to employees and staff of the medical institution [22, 23], therefore, such responsibility is considered by the author from two perspectives.

The binary components of the medical and social substantiation of the process of improving RHCQS in OGHCI should help to create and generate systemic conditions for its implementation in obstetric and gynecological practice while ensuring the fulfilment of social responsibility functions by management entities. Recognition of the need to develop an algorithm of management actions for the formation and implementation of RHCQS in OGHCI in conditions of uncertainty can be formulated as follows: in the current conditions, when the health care system is facing significant challenges, the development and implementation of RHCQS is an extremely important and urgent task. The uncertainty that accompanies modern medical practice requires flexibility, adaptability, and the ability to respond quickly. Therefore, the development of a management action algorithm is becoming a key element of the strategy for improving the health care quality system, as the implementation of RHCQS will help health care facilities adapt to changing conditions and the impact of uncertainty, which will determine the creation of a flexible structure that will allow for a quick response to emergencies and ensure the stability of medical care. The development of a management action algorithm will provide a clear methodology for the formation and implementation of new approaches to quality management that: a) is the basis for organizing systematic work in the area of finding and solving problems in the field of reproductive medicine; b) ensure effective control over the processes and results of health care quality management; c) will help to achieve a high level of safety and quality of medical care for patients and staff; d) increase the level of efficiency of healthcare facilities; e) ensure public trust in the healthcare system.

DISCUSSION

The conducted scientific and applied research has shown the relevance of the problem of developing a closed algorithm of management actions for the for-

Table 2. Managerial responsibility of the management entities of obstetric and gynecological health care institutions for the implementation of the resilient health care system *

Step	Name	Responsible	Terms
I	Analysis of needs and identification of problems, threats and risks	Medical Care Quality Department and/or Analytics/Economic Department.	1-2 months
II	Justification of the requirements for the effectiveness of the functioning of the resilient system of quality of medical care in obstetric and gynecological HCFs	Medical Director and/or Head of the Medical Care Quality Department.	1 month
III	Determination and development/ improvement of the medical care quality strategy	The management of the institution with the support of the Medical Care Quality Department.	2 months
IV	Involvement of stakeholders	The management of the institution with the support of the departments of medical care quality and external relations.	1-2 months
V	Formation of a multi-level system of relative indicators for assessing and forecasting the quality of medical care	Medical care quality department with the involvement of heads of departments of HCFs and the monitoring/information and methodological support department.	2-3 months
VI	Development of an action plan	Temporary team and/or project office, under the leadership of the medical director.	1 month
VII	Implementation of a set of measures	The Medical Care Quality Department together with the HR and Infrastructure departments.	3-6 months
VIII	Monitoring and evaluation (permanent)	Medical care quality department, internal audit department and monitoring department (information and methodological support).	Ongoing, with regular periodic evaluations
IX	Implementation and continuous improvement of RHCQS and the relevant type of strategy in OGHCI	Management of the facility and the medical care quality department.	Ongoing, as a permanent process of improvement

Source* Compiled and systematized by the author.

mation of a resilient system of quality of medical care, based on the principles of flexibility, adaptability and continuous improvement using systemic and complex and alarm-process approaches to the modernization of the activities of OGHCI. Therefore, the author supports the statements presented in [10, 14, 16, 17, 23] that it is necessary to analyse the current state of the health care system (including obstetrics and gynecology) in advance, taking into account the characteristics and requirements of a particular industry in order to identify specific and complex measures to implement an improved quality system. Therefore, this will require: a) development of new standards and protocols, improvement of quality control procedures, training of medical personnel on the implementation of the concept of resistance, etc.; b) development and use of mechanisms for monitoring and evaluating the effectiveness of the set of measures to ensure continuous improvement of the resilient quality system; c) involvement of all stakeholders in the process of developing and implementing the management action algorithm, including medical staff, patients, administration, and public organizations and stakeholders. It is extremely important to ensure the resilience and readiness of the reproductive health facility to changing conditions and uncertainty, ensuring a high level of quality of care and meeting the needs of patients at all times.

In addition to the above, we believe that the urgent task should be the priority formation of applied marketing tools in the context of the activation of the reconstructive transformation of the resilient system of managing the quality of medical care in obstetric and gynecological health care institutions. Its formalization can be carried out in the case of using digital and cognitive information technologies to modernize monitoring systems and communication links with patients of obstetric and gynecological health care institutions.

CONCLUSIONS

Based on the results of the study, an algorithm of managerial actions for the formation and implementation of RHCQS in OGHCI was built, which was formalized by nine structurally and logically interrelated steps of implementing measures: I) analysis of needs and identification of problems, threats and risks; II) substantiation of the requirements for the effectiveness of the resilient health care quality

Table 3. Binary components of the medical and social substantiation of the process of improving the quality of medical care in OGHCI*

Components of medical and social justification	Content of medical and statistical, organizational and managerial measures to modernize the quality of medical care in HCFs
In relation to patients of the obstetrics and gynaecological healthcare facilities	
Definitive epidemiological and health and social data	Presentation of statistical data on the prevention and treatment of diseases in the field of obstetrics and gynecology, in particular, maternal and newborn mortality, the importance of regular visits to a gynecologist to prevent various diseases, such as cervical cancer or acute and chronic gynecological diseases. Determination of the effectiveness of the existing health care quality system and its comparison with the projected values of its level in case of introduction of a resilient system in the health care facility (by a composite indicator to be calculated on the basis of the developed and substantiated original multi-level system of relative indicators for evaluation and forecasting).
Economic costs and benefits	Estimation of costs and socioeconomic consequences in case of insufficient quality of medical care in obstetrics and gynecology. Comparison of the costs of implementing a new resilient health care quality system with the expected benefits of this restructuring and the benefits of reducing complications and improving reproductive health.
Determination of the scope of social impacts	Analysis of the social consequences associated with the shortcomings and accumulation of risks in obstetrics and gynecology care for women, their families and society as a whole, including disability, psychological discomfort, reproductive health risks, etc.
Improving the availability and quality of medical services	Definitions, justifications and calculations related to the results of improving the health care quality system, as well as how the introduction of a resilient health care quality system in health care facilities will increase accessibility and improve the quality of services for all segments of the population, including vulnerable groups.
Consideration of ethical and moral aspects	Addressing the ethical principles and moral responsibilities of healthcare professionals and reproductive healthcare institutions to provide quality medical care, especially in the field of obstetrics and gynecology, where the health and lives of women and, accordingly, newborns are at risk.
Regarding employees and staff of OGHCI	
Enhancement of employee safety and health	Management entities must ensure proper working conditions for medical staff, including the provision of the necessary equipment, protective equipment, training on safety and health in the workplace, and its digitalization. This should be in line with their high social responsibility to the HCF employees.
Creating a favourable working environment	The directorate and management of the health care facility should take into account the needs and interests of employees in the process of developing and implementing a new quality system. The transformation and modernization of the existing quality system may indirectly cause certain prejudices among the HCF employees and reluctance to change. It is necessary to take into account their opinions and suggestions, providing opportunities for professional and personal development, as well as maintaining work balance in the healthcare facility by intensifying the process of converting various information in all its forms (text, audio, graphic) into a digital format that should be understandable to employees using modern gadgets and software.
Improvement of the quality of medical care	Improvement of the healthcare quality system, including in the field of obstetrics and gynecology, will lead to better working conditions and performance of medical staff, which in turn will have a positive impact on their health and job satisfaction.
Increasing ethical requirements and strengthening relationships	Management entities of HCFs must adhere to ethical principles in their interaction with employees, avoid discrimination and ensure fair remuneration. They are obliged to create conditions for the development of positive interpersonal relations in the HCF employees.

Source* Compiled and substantiated by the author, taking into account [15, 19-22].

system in health care facilities; III) determination and development/improvement of the medical care quality strategy; IV) involvement of stakeholders; V) formation of a multi-level system of relative indicators for assessing and forecasting the quality of medical care; VI) development of an action plan; VII) implementation of a set of measures; VIII) monitoring and evaluation; IX) ensuring and continuous improvement of the resilient healthcare quality system and the corresponding type of strategy in healthcare facilities. This made it possible to build a closed structural and logical scheme of the algorithm of management actions, taking into account the combination of influence factors, harmonized with the main functions of the resilient system, which determine the direction and features of its functioning, taking into account the resource constraints in the OGHCI and the possible increase in the scale of various threats and risks to the sustainable development of a medical institution. The methodological substantiation of the boundaries of managerial and social responsibility of management entities according to the binary components of the medical and social substantiation of the

process of improving the modern system of quality of medical care in OGHCI is provided. The obtained and substantiated experience is the basis for the development of a structural and functional model of a resilient system of quality of medical care in obstetric and gynecological health care facilities, the formalization of which will improve the quality of care and safety, increase patient satisfaction and management efficiency.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Forecasting the need for palliative and hospice care using the creeping trend method with segment smoothing

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ABSTRACT

Aim: To determine the limits of refinement of the forecast of the need for palliative and hospice care (PHC) among adults and children, made by the methods of linear, logarithmic and exponential trends, using the improved forecasting method.

Materials and Methods: Based on the calculated demand for 2018-2020, a demand forecast was made using the linear trend method for 2021 and 2022, which was verified by comparing it with the calculation based on available statistical data for 2022. To improve the forecasting result, the creeping trend method with a smoothing segment was used.

Results: The estimated need for PHC by the linear trend method for 2022 was 87,254 adults and 46,122 children. The predicted need for this year by the linear trend method was 172,303 for adults and 45,517 for children. The prediction using the sliding trend method with segment smoothing was found to be 4.7 times more accurate and reliable for adults and all age groups combined, but was less accurate and not reliable for children. It was found out that in order to achieve a reliable forecast, it is necessary to clarify the data of medical statistics regarding of malignant neoplasms and congenital malformations, as well as demographic statistics.

Conclusions: The method of a creeping trend gave more accurate results and made it possible to determine the reliability of the forecast, allowed to take into account the simultaneous influence of various input parameters.

KEY WORDS: demographic statistics, improved forecasting methods, congenital malformations, malignant neoplasms in children, temporarily occupied territories

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INTRODUCTION

The Quality of Death Index of Ukraine in October 2015 was 25.5, which ranked the country 69th out of 70 countries that participated in the rating that year [1]. In the 2021 rating, in which 81 countries have already participated, Ukraine remained in the 69th place, but already with an indicator of 53.7 [2]. In part, this change in the number of points is associated with a change in the calculation method developed in 2010 [3, 4], partly with the improvement of the palliative and hospice care financing system [5]. But it should be noted that there are a number of unsolved problems in the PHC system of the country, including insufficient integration of the PHC system into the general system of medical care; permanent shortage of personnel (lack of doctors and nurses) in hospices, palliative departments and wards; lack of adequate analgesia for the vast majority of palliative patients with chronic pain; imperfection of training programs on palliative care in medical education institutions; low awareness of the population and medical professionals about many PHC problems; insignificant influence of non-government organizations on PHC policy in the country; lack of euthanasia system for palliative patients with chronic pain; lack of a state-recognized methodology for determining the need for PHC (both calculation based on available data and forecasting) [6, 7].

AIM

To determine the limits of refinement of the forecast of the need for palliative and hospice care among adults and children, made by the methods of linear, logarithmic and exponential trends, in accordance with the list of palliative diagnoses recommended by the WHO, using the improved forecasting method.

MATERIALS AND METHODS

The list of palliative diseases of adults and children, included in the forecast, corresponds to the recommendation of the WHO and the "best practices" of countries with a developed PHC system, fully integrated into national health care systems in countries of group *4b* according to the classification of Lynch T., Wright M., and Clark D. [8] (Table 1). The given list was followed by the researchers of the Ukrainian Center for Public Data, who developed a methodology for calculating the need for PHC for Ukraine in 2018 [9]. We used this methodology to determine the need for PHC for Ukraine for 2019 and 2020 [10]. Based on this calculation, a forecast of the need for PHC for 2021 and 2022 was also made [11], which was verified in 2023.

The verification of the forecast by comparison with the result of the calculation based on the available data showed a significant discrepancy with the forecast of the need for PHC for 2021 and 2022 [11]. An important factor that had an impact on the collection of medical statistics data was the full-scale war in Ukraine that began in 2022. In 2022, the official medical statistics data for 2021 were not made public, so we considered the estimated data to be equal to the projected linear trend method. In 2023, data from official medical statistics were released, which led to the search for a more accurate forecasting method.

ICD-10 – International Statistical Classification of Diseases and Related Health Problems 10th Revision [12].

HIV/AIDS – human immunodeficiency virus/acquired immunodeficiency syndrome.

The search for literature sources to compare the obtained results with the data of other researchers was conducted in the PubMed, Google Scholar and Scopus databases retrospectively up to the year 2000 inclusive. Processing of digital results was carried out in Excel (Microsoft, USA). Statistical data obtained from open databases of official statistics ec.europa.eu/eurostat; ukrstat.gov.ua; medstat.gov.ua; tbc.gov.ua; ncru.inf.ua; WHO [13]. The study was approved by the Bioethics Commission of the Kharkiv National Medical University (Protocol No.10 on September 12, 2023).

RESULTS

The choice of the linear trend method (mathematically corresponds to the regularity of $y=ax+b$) for forecasting the need for PHC for 2021 and 2022 was associated with a steady tendency to decrease the determined need during 2018-2020. We attributed this decline to a number of objective and subjective factors. Among the first were the phenomena of the growing demographic crisis, among the second – the deterioration of the quality of data collection of medical statistics. Checking the results of forecasting by the linear trend method using the calculation of the need for PHC according to the available statistical data showed a discrepancy of 76.74% among adult palliative patients and 1.86% among children (Table 2).

The accuracy of the forecast by the creeping trend method with a constant smoothing segment is higher due to the built-in multifactor dispersion load [14, p. 57-60; 15, p. 76], the physical meaning of which is the mutual influence of variances and standard errors of various calculated factors. In our case, it was the number of available population and the number of patients with palliative diagnoses who were discharged from medical institutions at the end of the year. The forecasting took into account the variance of samples and patients with palliative diagnoses, and checked for reliability according to the Student's test and adjusted to 95% CI. The prognosis for children was outside the 95% CI for some of the palliative diagnoses, among which the group of congenital malformations (Q00-Q99 according to ICD-10) was noted to have the most statistically significant standard error. For each diagnosis, the forecast for 2022 was also calculated using the methods of logarithmic (mathematically corresponding to the pattern $y=R\times ln(x)+b$) and exponential (mathematically corresponding to the pattern $y=ge^{hx}$) trends. All values within the 95% CI did not fall outside the "linear trend– logarithmic trend" or "linear trend – exponential trend" intervals. For adult palliative patients, the forecast using the creeping trend method turned out to be 4.7 times more accurate compared to the forecast using the linear trend method. The "smoothing" effect shows an exception to the 2021 forecast, for which Ukraine did not release data in early 2022 due to the outbreak of a full-scale war. At the same time, the forecast for adults and in total for all age categories was reliable.

Thus, it was the statistics regarding children with palliative diagnoses that needed correction. In our opinion, the collection of statistical information regarding this category of palliative patients was influenced by the following factors: the reform of the genetic service of Ukraine on the eve of the war; significant migration of children during full-scale war (both overseas and internal displacement). Verification of the data by methods of standardization of samples of children with palliative diagnoses according to the number of available population in the regions with temporarily occupied territories that were liberated already in 2022 (Zhytomyr, Kyiv, Chernihiv, Sumy, Kharkiv regions) showed a decrease in the standard error of the average samples to the levels of variance 0.70-0.84 (for diagnoses of groups Q00-Q99 and C00-C97 with weighting coefficients in the total population of children requiring PHC, 0.1648 and 0.1348, respectively), which allows us to consider the adjustment sufficient to match the result adjusted by the creeping trend method forecast in 95% CI. That is, in order to obtain a reliable forecast for children who need PHC, in the next forecast for 2024, it is enough to specify data on 1/3 of palliative patients of this profile with diagnoses of malignant neoplasms and congenital malformations.

Table 1. Palliative diseases of adults and children according to WHO recommendations

Palliative diagnoses of adults		Palliative diagnoses of children	
Group of diseases, nosology	ICD-10 code	Group of diseases, nosology	ICD-10 code
Malignant neoplasms * ***	C00-C97, D00-D48	Malignant neoplasms **	C00-C97
Cardiovascular diseases *	I00-I99	Cardiovascular diseases **	I00-I99
Tuberculosis * **	A15-A19	Tuberculosis **	A15-A19
Diabetes * **	E10-E14	Diabetes **	E10-E14
HIV/AIDS *	B20-B24	HIV/AIDS **	B20-B24
Dementia **	F00-F03	Mental retardation (heavy and deep) **	F72-F79
Fibrosis and liver cirrhosis *	K74	Chronic hepatitis **	K73, K75.2, K75.3
Rheumatoid arthritis **	M05-M06	Congenital malformations **	Q00-Q99
Chronic obstructive lung diseases *	J43-J47	Perinatal conditions **	P05-P96
Kidney disease *	N00-N15, N20-N23	Children's cerebral palsy **	G80
Notes: categories of patients taken into account when calculating the need		Inflammatory diseases of the central nervous system **	G00, G03, G04, G06, G08, G09
** – dead persons;*		E70.0	
*** – discharged from a medical institution with a corresponding diagnosis at the end of the year;*		E84	
**** – registered for the first time.*			
Phenylketonuria **		E76	
Cystic fibrosis **			
Mucopolysaccharidoses **			

Notes: data of national medical statistics, if they are collected for the specified diagnoses, are multiplied by coefficients determined by an expert (they are multiples of such parts of the total population of patients as 1/10, 1/5, 1/4, 1/3 and 1/2). The categories of patients listed as discharged at the end of the year receive treatment on an outpatient basis or in an inpatient basis, and for children with palliative diagnoses, in most cases, they are associated with a disability due to a palliative diagnosis. For adult palliative patients with tuberculosis, one of the categories of patients is counted in the presence of a multiresistant form of the disease.

Table 2. Calculation and forecast of the need for palliative and hospice care in Ukraine among adults and children in 2019, 2020 and 2022

Method calculation or forecasting	Year	Adults		Children	
		Number of patients	Certainty [+/0/–] and (deviation [±%])	Number of patients	Certainty [+/0/–] and (deviation [±%])
Calculation according to available data	2019	245,070	+	53,133	+
	2020	213,739	+	49,000	+
	2022	87,254	–	46,122	–
Linear trend	2022	172,303	0 (+97.47%)	45,517	0 (–1.31%)
Creeping trend	2022	105,341	+ (+20.73%)	44,660	– (–3.17%)

Notes: the credibility score is defined for calculation based on available statistical data as high (+) or low (–), for prediction – as sufficient (+) within the 95% confidence interval (CI), insufficient (–), or not estimated (0). The deviations of the predicted values for 2022 using the linear trend and creeping trend methods are calculated as a percentage of the value for 2022 calculated from available statistical data. It should also be noted that the calculation based on the available data was carried out without taking into account the temporarily occupied territories of Ukraine: in 2019 and 2020 – 2 regions and the Autonomous Republic of Crimea, in 2022 – 9 regions and the Autonomous Republic of Crimea.

DISCUSSION

The situation regarding inaccurate forecasting in Ukraine since the beginning of a full-scale war is not unique. During the last 20 years, more than 10 countries that were in a state of war, natural disasters or migration crises faced similar problems, and at the same time worked on improving national PHC systems [16]. Political support and minor additional efforts can allow Ukraine to collect the necessary medical statistics data to obtain a reliable result necessary for the calculation of PHC funding for health guarantee programs.

According to its developers, the methodology for calculating the need for PHC at the national level proposed by the Ukrainian Center for Public Data can be improved and revised. Therefore, when calculating the need for PHC for 2019 and 2020 [10], we previously excluded adult dementia and severe

and profound mental retardation in children from the list of palliative diagnoses due to the fact that Ukraine stopped collecting statistical data on these categories of patients. At the next stage of the research, we resumed the calculation of these palliative diagnoses, listing them based on indirect data, and made a forecast for 2021 and 2022, taking into account the incidence [11]. When performing the forecast, another category raised doubts about the reliability of the result: the number of patients with chronic obstructive pulmonary disease in 2019 and 2020 increased significantly due to the COVID-19 pandemic. But according to the method of calculating patients with coronavirus infection, it was necessary to calculate them separately. The problem of inaccurate forecasting disappeared after the end of the pandemic.

Another difficult category for clarifying the prognosis was a large group of children with severe perinatal conditions. According to the UN Sustainable Development Goals, child mortality by 2030 should be reduced to 12 per 1,000 live births among children under 1 month of age, and to 25 per 1,000 live births among children under 5 years of age. In the WHO European Region, both indicators were the lowest for 19 years (2000-2019). In 2019, the last year analyzed in the WHO Global Levels of Disease and Health Report 2023, the under-5 mortality rate in the WHO European Region was 7-8 per 1,000 live births. However, global under-5 mortality still remains high, with 1.1 million deaths, with the highest relative rates in the African region. According to forecasts, 54 countries in the world will not reach the goals regarding the levels of maternal and child mortality [13, p. 6, 110]. The mortality of children under 5 years of age in the world is primarily related to infectious diseases (acute respiratory infections, diarrhea, and malaria) [17]. But in the European Region of the WHO, among the factors causing the death of children, along with respiratory infections, neonatal sepsis, meningitis (corresponding to the categories of palliatively ill children with inflammatory diseases of the central nervous system), the consequences of premature birth, asphyxia during childbirth, birth trauma and congenital malformations are important. That is, child disability and mortality are closely related to the condition of pregnant women, the course of childbirth and the level of maternal mortality.

Regarding the three groups of children with palliative diagnoses (I00-I99, A15-A19 and F72-F79), the relative weight of which in the overall prognosis was 0.37%, 1.05% and 5.23% (or 166, 469 and 2 338 out of 44,660 of all children with palliative diagnoses in the one-year forecast), it should be noted that adjusting the forecast by balancing the variances and standard errors was not effective in increasing the reliability of the forecast.

CONCLUSIONS

The choice of the creeping trend method with a segment of constant smoothing turned out to be justified: it made it possible to determine the reliability of the forecast, was more accurate compared to the linear trend method, supplemented by the methods of logarithmic and exponential trends, made it possible to reduce the forecasting error associated with the lack of official medical statistics data in Ukraine for 2021. The forecast for 2022 for Ukraine using the creeping trend method allowed to obtain a reliable (within 95% confidence interval) for adults and for palliative patients of all age groups, but did not allow to obtain a reliable result for children with palliative diagnoses. It was determined that in order to achieve a reliable result, it is necessary to improve the collection of medical statistical data on children with palliative diagnoses of groups of malignant neoplasms and congenital malformations, as well as demographic statistical data on children in temporarily occupied territories after their liberation.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

The essence of students' vitality in the context of its reflexive determination

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ABSTRACT

Aim: Theoretical analysis of the problem of the individual's vitality in the context of its reflective determination, an empirical study of the formation of its components, and the proof of correlations with various types of reflection.

Materials and Methods: The following psychodiagnostic methods were used in the empirical study: "Methodology of vitality diagnosis" by S. Maddi in an adaptation by D. Leontiev; test for determining the reflection of interpersonal interaction T. Pushkar in the modification of N. Senchyna; the method of research of reflexivity of thinking (T. Pashukova, A. Dopira, G. Dyakonov); the technique "Determining the level of reflection" (O. Anisimov); method "Determining the level of reflexivity" (A. Karpov, V. Ponomaryova).

Results: It was established that the majority of students in both the first and fourth years have an average and low level of vitality. Vitality is directly connected to intellectual, personal, and situational reflection on a temporal basis; that is, the specified types of reflection are the leading determinants of vitality, which is statistically proven.

Conclusions: The study showed the high importance of resilience for the full functioning of student youth in modern complex life conditions and its determination by the level of development of various types of reflection.

KEY WORDS: vitality, reflection, types of reflection, reflexive determination

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INTRODUCTION

The problem of the viability of the individual has become extremely urgent in the transgressiveness and fluidity of modern society in martial law conditions in Ukraine. Essential features of Ukrainian society have become danger, various risks and threats (being in the zone of military operations and storage facilities, forced displacement), and the psychological state of the population, in particular, Ukrainian youth – frustration, deprivation, anxiety, fear, general neuroticism, depression. These destructive factors objectively determined negative deviations from the usual way of life, changes in priorities, and accents. They reinforced the need to develop and strengthen such a core personality construct as resilience.

The origins of "sustainability" are related to existential psychology. According to its well-known representatives (S. Maddi, S. Kobeis, P. Tillich), all life events result from decision-making, regardless of whether they are significant or insignificant, conscious or unconscious [1]. S. Kobeis and S. Maddi introduced the concept of viability into scientific circulation [2]. At the same time, S. Maddi interprets sustainability as a particular system and develops a model within which he considers sustainability as an essential internal resource (setting) that a person can understand and change to support his physical, mental, and social health [3]. That is, S. Maddi interprets the phenomenon of resilience as a unique structure of attitudes and skills, which makes it possible to turn changes into opportunities, reflecting a person's psychological vitality and enhanced effectiveness associated with his motivation to overcome stressful life situations [4].

In modern science, a variety of interpretations of resilience appears, namely: as the leading resource for overcoming life's difficulties, as a person's ability to

control life events and manage them, to perceive difficulties as a valuable experience and successfully cope with them, using them as an opportunity for personal growth [5, 6]; as an integral quality of a person, which is based on active life attitudes, is accompanied by the ability to achieve a goal, ensures self-determination and internal balance, contributes to the disclosure of resource potential and becomes a leading condition for full-fledged development [7, 8]; as the ability to effectively exist despite life's obstacles and difficulties, a person's ability to maintain a balance between adaptation to new requirements and the desire to live harmoniously and fully [9, 10]. So, resilience is a particular personality resource that provides control, overcoming life's difficulties, and the desire to live fully in crises thanks to internal balance, self-regulation, and self-determination.

Based on the analysis of the works of the founders of the sustainability problem (S. Maddi, S. Kobeis), as well as modern researchers (T. Larina, V. Predko, T. Tytarenko, O. Chykhantsova, etc.), we single out such characteristics as value-meaning regulation, developed willpower, social competence, development of cognitive structures, adequate self-esteem, resistance to frustration, ability to maintain life balance and harmony.

Sharing the position of S. Kobeis and S. Maddi [11], in the structure of sustainability, we single out *involvement* (commitment), which synthesizes a valuable and meaningful attitude to oneself and the surrounding world, to interaction with "others", which motivates a person to self-realization, leadership and full-fledged life in stressful crisis conditions; *control,* which involves activity in the search for ways to influence and get out of crisis life situations, control over circumstances as opposed to anxiety, a state of helplessness and passivity; *acceptance of risk* (challenge), which is based on the idea of development through overcoming risks, on the individual's perception of life events and problems as a challenge and test.

It is worth paying attention to the aspect of the study related to various determinants and correlates of viability. There are scientific hypotheses regarding correlations of vitality, namely: 1) with properties of the nervous system and individual psychological characteristics of the personality (T. Vasheka, O. Lych, B. Palamar, S. Palamar, V. Zhelanova, T. Safir, N. Kurdil) [12]; 2) with personal values (O. Chikhantsova) [13]; 3) on the emotionality of the individual (T. Ulyanova) [14]; 4) with somatic diseases (L. Serdyuk, O. Kupreeva) [15].

The presented study emphasizes the reflexive determination of sustainability and states that the structure of sustainability proposed by S. Kobeis and S. Maddi has obvious reflexive origins.

Concentrating on the reflective aspects of sustainability, we note that we interpret the phenomenon of reflection as a complex, multifunctional, interdisciplinary construct, which is an individual's appeal to himself (to his consciousness, thinking, results of activities, to the perception of himself through the eyes of other people), which appears in the context of reflective consciousness, reflective thinking, reflective activity, reflective communication as a synthetic reality, which is a process, property, and state [16].

At the same time, reflection contains a cognitive component – self-understanding; an affective component an attitude towards oneself; behavioral – self-regulation of individual behavior; and socio-perceptive – a basis for adequate perception and understanding of others. Therefore, reflection performs the functions of understanding, self-knowledge, a form of theoretical activity, a principle of thinking, a category of consciousness, and the basis of communication and perception.

Reflexive determination of involvement as a component of sustainability is related to awareness of one's hierarchy of values, its dynamics, and reorientation in difficult life conditions, with an analysis of one's behavior in crisis conditions. These reflective processes are provided through personal, retrospective, and situational reflection. This component of vitality, which reflects a valuable attitude towards other people, is realized in communicative and situational reflection, which allows one to understand another and form the need to empathize with him. Setting up for a full-fledged life in crisis conditions is associated with personal, intellectual, and perspective reflection. Since the installation is characterized by stability and orientation towards the future. Control, as an aspect of sustainability, is associated with personal, intellectual, situational, and perspective reflection, which leads to awareness of one's activity in the search for ways out of a crisis; knowledge about the inner world of another person, knowledge about awareness of the attitude of others towards oneself (communicative reflection); knowledge about the organization and positions of group interaction participants (cooperative reflection). Acceptance of risk is based on types of reflection aimed at "self" (intellectual, personal) and on perspective reflection associated with reflexive-anticipatory processes.

AIM

The purpose of the study was to carry out a theoretical analysis of the phenomena of sustainability and reflection, as well as substantiation and experimental verification of the reflexive determination of sustainability. To achieve the goal and the hypothesis of a direct

Table 1. Distribution of respondents by the level of sustainability components, in %

Levels / Components	1st year						4th year					
	High		Average		Low		High		Average		Low	
	%	Absol.	%	Absol.	%	Absol.	%	Absol.	%	Absol.	%	Absol.
Vitality	12,12	8	51,52	34	36,36	24	19,35	12	58,07	36	22,58	14
Involvement	10,61	7	54,54	36	34,85	23	19,35	12	50,00	31	30,65	19
Control	12,12	8	51,52	34	36,36	24	16,13	10	58,06	36	25,81	16
Acceptance of risk	30,30	20	48,49	32	21,21	14	35,48	22	43,55	27	20,97	13

Table 2. Distribution of respondents by levels of reflection types, in %

Level	Scale		Intellectual	Cooperative	Personal	Communicative
Low	1st year	%	33,33	6,06	10,60	15,15
		Absol.	22	4	7	10
	4th year	%	20,97	1,61	3,23	9,68
		Absol.	13	1	2	6
Below average	1st year	%	-	33,33	21,21	-
		Absol.	-	22	14	-
	4th year	%	-	11,29	14,52	-
		Absol.	-	7	9	-
Average	1st year	%	56,06	34,85	62,12	54,55
		Absol.	37	23	41	36
	4th year	%	54,84	53,23	40,32	45,16
		Absol.	34	33	25	28
Above average	1st year	%	-	9,09	1,52	-
		Absol.	-	6	1	-
	4th year	%	-	12,90	19,35	-
		Absol.	-	8	12	-
High	1st year	%	10,61	16,67	4,55	30,30
		Absol.	7	11	3	20
	4th year	%	24,19	20,97	22,58	45,16
		Absol.	15	13	14	28

Table 3. Significant correlations of vitality with types of reflection in students

	Viability	Involvement	Control	Risk Acceptance
Methodology for the study of reflexivity of thinking (T. Pashukova)				
Intellectual reflection	0,621**	0,252*	0,548**	0,457**
Method "Determining the level of reflection" (O. Anisimov)				
Personal reflection	0,534**	0,465**	0,453**	0,221*
Cooperative reflection	0,271*	-	0,343**	-
Test for determining the reflection of interpersonal interaction T. Pushkar in the modification of N. G. Senchyna				
Communicative reflection	0,381**	0,222*	0,342**	-
Methodology "Determining the level of reflexivity" (A. Karpov, V. Ponomareva)				
Retrospective reflection	0,226*	0,365**	-	-
Situational reflection	0,514**	0,476**	0,481**	-
Perspective reflection	0,426**	-	0,463**	0,232*

Notes: * – correlation is significant at p <0,05

** – correlation is significant at p <0,01.

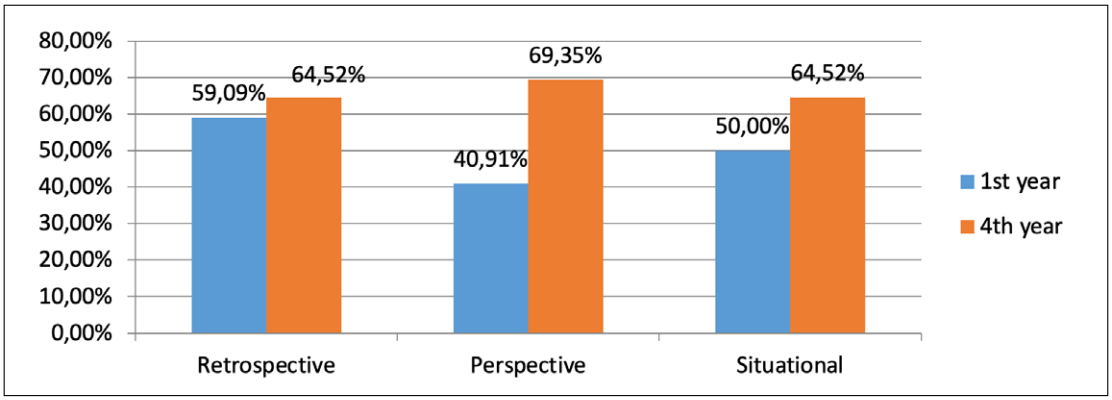

Fig. 1. Histogram of the distribution of the formation of types of reflection by time among first- and fourth-year students, in %.

connection between the types of reflection and the levels of resilience, the following research tasks were identified: to diagnose the level of resilience and its components among students during the war; diagnose the level of formation of various types of reflection and establish their correlations with vitality.

MATERIALS AND METHODS

The peculiarity of our sample lies in the fact that it consists of students of the first (bachelor) level of higher education under the educational programs 012.00.01 "Preschool Education" and 013.00.01 "Primary Education" of Borys Grinchenko Kyiv University and Luhansk National University named after Taras Shevchenko, located in Lubny, Poltavska Oblast.

The study was conducted over six months (from September 2023 to February 2024). The sample consisted of 128 students in the 1st and 4th years, with an average age of 19.5 years; 1st year – 66 people, 4th year – 62 people. These were students traumatized by rocket fire and forced displacement, as well as education in between air raids or in a bomb shelter. Such objective circumstances of modern life require a certain balance of internal resources and vitality and artificially created danger.

The following diagnostic toolkit was used in the research: "Methodology of vitality diagnosis" by S. Maddi in the adaptation of D. Leontiev (to study the level of vitality and the development of certain of its components); the test for determining the reflection of interpersonal interaction by T. Pushkar in the modification of N. Senchyna (to research communicative reflection); the method of research of reflexivity of thinking (T. Pashukova, A. Dopira, G. Dyakonov) (to determine intellectual reflection); the method "Determining the level of reflection" (O. Anisimov) (the goal is diagnosis of personal and cooperative types of reflection); the method "Determining the level of reflexivity" (A. Karpov, V. Ponomaryova) (the purpose of determining retrospective, situational and perspective reflection).

In order to analyze the data obtained, we distributed the respondents by the levels of formation of the studied indicators (in %), using MS Excel for calculation. To establish the correlation between resilience and reflexivity of the respondents, we used correlation analysis, namely Pearson's parametric correlation coefficient, which was calculated using the SPSS Statistics 27 statistical software package. Statistical analysis allowed us to identify relationships between indicators at the significance level of 0.05 and 0.01 (at $p<.01$ and $p<.05$).

The researchers followed all protocols and procedures required by the Biomedical research Ethics Committee and conform to the directive of the Ukrainian Legislation on health care, Helsinki Declaration 2000 and European Society Directive 86/609 on human participation in biomedical research to ensure adherence to all standards for adequate protection and well-being of participants.

RESULTS

According to the results of the vitality diagnosis of first- and fourth-year students (Table 1), only 12.12% of first-year students and 19.35% of fourth-year students have a high level of vitality. 51.52% of first-year and 58.07% of fourth-year students have an average level. A low level was diagnosed in 36.36% of first-year students and 22.58% of fourth-year students.

Regarding specific components of vitality, the following results were obtained: a high level of involvement is observed in 10.61% of first-year students and 19.35% of fourth-year students, an average level – in 54.54% of first-year students and 50.00% of fourth-year students, a low level - 34.85% of first-year students and 30.65% of fourth-year students. Control at a high level was found in 12.12% of first-year students and 16.13% of fourth-year students, at an average level - in 51.52% of first-year students and 58.06% of fourth-year students, and a low level was observed in 36.36% of first-year students and 25.81% of the fourth.

The analysis of the obtained data allows us to conclude that among the students, the most pronounced component of resilience was diagnosed as "risk-taking": 30.30% of first-year students and 35.48% of fourth-

year students were diagnosed with a high level, while 48.49% of first-year students had an average level, and 43.55% of the fourth year, and low - in 21.21% of first-year students and 20.97% of fourth-year students.

The results of the distribution of respondents by levels of reflection types are shown in Table 2.

According to the scale of *intellectual reflection,* the following data were obtained: a low level was found in 33.33% of first-year students and 20.97% of fourth-year students, an average level was diagnosed in 56.06% of first-year students and 54.84% of fourth-year students, and a high level was observed in 10.61% of first-year students and 24.19% of fourth-year students. The average level of intellectual reflection prevails among students, but the indicators are somewhat higher among students in the fourth year.

The data obtained according to the scale of cooperative reflection show that 6.06% of first-year students and 1.61% of fourth-year students have a low level of cooperative reflection, and 33.33% of first-year students and 11.29% of fourth-year students have a below-average level, 34.85% of first-year students and 53.23% of fourth-year students were diagnosed with an average level of development of cooperative reflection, an above-average level was found in 9,09% of first-year students and 12.90% of fourth-year students. A high formation of cooperative reflection is observed in 16.67% of first-year students and 20.97% of fourth-year students. So, in the group of fourth-year students, the indicators of cooperative reflection exceed those of first-year students. So, the average and below-average levels prevail among first-year students, and the average level tends to increase among fourth-year students.

The analysis of the results of the *personal reflection* study allows us to draw the following conclusions: a low level is observed in 10.60% of first-year students and 3.23% of fourth-year students, a below-average level was found in 21.21% of first-year students and 14.52% of the fourth year, an average level of development of personal reflection was diagnosed in 62.12% of first-year students and 40.32% of fourth-year students, an above-average level was found in 1.52% of first-year students and 19.35% of fourth-year students, a high level of development of personal reflection was found 4.55% of first-year students and 22.58% of fourth-year students. Therefore, the average level of personal reflection with a downward trend prevails among first-year students, while the average level with an upward trend prevails among fourth-year students.

Among first-year students, a low level of communicative reflection is observed in 15.15%, among representatives of the fourth year in 9.68%, in 54.55% of first-year respondents and 45.16% of fourth-year respondents, an average level of communicative reflection development was diagnosed, a high level was found 30.30% of first-year students and 45.16% of fourth-year students. Thus, among students of both the first and fourth years, the lowest results are observed on the scale of intellectual reflection. However, the level of philosophical reflection formation is higher among the representatives of the fourth year than among the students of the first year. According to other scales, there is also a difference between the courses; the results of the fourth-year students slightly exaggerate the results of the first-year students.

The results of the distribution of the formation of types of reflexivity by time, namely retrospective, situational and prospective, are graphically shown in Fig. 1.

The given data indicate that retrospective reflection is manifested in 59.09% of first-year students and 64.52% of fourth-year students; perspective reflection – in 40.91% of first-year students and 69.35% of fourth-year students; and situational reflection – in 50.00% of first-year students and 64.52% of fourth-year students. Thus, we can state that retrospective reflection is a priority for first-year students, while prospective reflection prevails among representatives of the fourth year; that is, reflection is responsible for analyzing their future activities.

The results of the correlation analysis shown in Table 3 indicate the presence of a close connection between intellectual reflection and vitality ($r = 0.621$ at $p < 0.01$), involvement ($r = 0.252$ at $p < 0.05$), control ($r = 0.548$ at $p < 0.01$) and risk-taking ($r = 0.457$ at $p < 0.01$). Thus, the higher the indicators of intellectual reflection, the higher the vitality indicators.

It was established the presence of a direct relationship at a high level of statistical relationship of personal reflection with vitality ($r = 0.534$ at $p < 0.01$), involvement ($r = 0.465$ at $p < 0.01$), control ($r = 0.453$ at $p < 0.01$) and moderate risk taking ($r = 0.221$ at $p < 0.05$) at a reliable level. Cooperative reflection is related to control ($r = 0.343$ at $p < 0.01$) and vitality ($r = 0.271$ at $p < 0.05$); that is, a direct relationship was found at a high and reliable level, so knowledge about the organization and the positions of participants in group interaction affects the increase in the level of vitality, in its control component.

It should be noted that there is a direct relationship at a high level of significance of communicative reflection with vitality ($r = 0.381$ at $p < 0.01$), control ($r = 0.342$ at $p < 0.01$), and at a reliable level of significance with involvement ($r = 0.222$ at $p < 0.05$). Therefore, knowledge about awareness of the attitude of others towards oneself and valuable attitude towards other people in the process of communicative reflection, which allows one to understand another and form the need to empathize with him, affects the increase in the level of involvement, control, and vitality in general.

Regarding reflection in the time dimension, we can see the following results: a direct relationship between retrospective reflection and vitality ($r = 0.226$ at $p < 0.05$) and involvement ($r = 0.365$ at $p < 0.01$) was found. Situational reflection is directly correlated with resilience ($r = 0.514$ at $p < 0.01$), involvement ($r = 0.476$ at $p < 0.01$), and control ($r = 0.481$ at $p < 0.01$). Prospective reflection with resilience ($r = 0.426$ at $p < 0.01$), control ($r = 0.463$ at $p < 0.01$) and risk taking ($r = 0.232$ at $p < 0.01$). That is, the presence of prospective reflection among the respondents affects the increase in the level of such a component of sustainability as "Risk Acceptance". In students with pronounced situational reflection, the components "Involvement" and "Control" prevail, while the dominance of retrospective reflection is associated with increased involvement.

DISCUSSION

Each of the components of the sustainability model [9], based on which our research was conducted, demonstrates the variability of manifestations due to the expansion of experience in responding and interacting with others and the environment, which can have both positive and negative effects. Since a person is naturally vulnerable, the mechanisms of vitality can act as a buffer, reducing the impact of negative factors on the individual [9].

Among such survival mechanisms, the most valuable is the search for social support, especially in the context of terrorist attacks [13]. However, social support did not reduce the relationship between a stressful event and coping [14]; it is defined as information that makes the subject believe that he is cared for, loved, respected, and is a member of a network of mutual obligations [14]. In our study, the scale "seeking social support" directly correlates with the component "involvement". Evidence that supportive interpersonal interactions protect against the health effects of life stress is reviewed [15].

These facts testify in favor of the correct actions of the Ukrainian government regarding the organization of social awareness of the behavior of adults and children in the event of danger (for example, about the location of bomb shelters, safe places in the house, about places of humanitarian and medical aid, about centers of "invincibility", about places with, first aid courses, etc.) through mass media, chatbots, SMS messages, even when the Internet is not working, which in the complex can be called elements of the "culture of survival". The importance of such a culture, in conditions of limited time for cognitive processing of information for making the right decisions, prevents the effect of "freezing" [16].

We consider resilience as a personal characteristic, the foundation of whose strength is connected with the peculiarities of the nervous system, the ability to respond constructively to difficult life circumstances using appropriate coping strategies, which confirm the results of the correlation analysis. The constancy of resilience as a personality trait that exists regardless of time and types of adversity has been proven in studies involving student youth.

CONCLUSIONS

Thus, the most pronounced component of vitality was diagnosed as "aspiration to risk"; involvement and control were formed at the average level. Reflection turned out to be a significant determinant of students' vitality. The leading factors of high vitality of students are the formation of various types of reflection: by direction (intellectual and personal; cooperative and communicative) and by time (situational, retrospective, and prospective). Considering the interpretation of the correlation coefficients, we can conclude that a high positive relationship was found between resilience and intellectual reflection, personal reflection, and situational reflection; the specified types of reflection are the leading determinants of resilience, which is statistically proven.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Systemic inflammation and quality of life in patients with coronavirus disease: interrelation features

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ABSTRACT

Aim: To characterize the features of the interrelation of systemic inflammation with the quality of life of patients with coronary virus disease.

Materials and Methods: 30 patients were examined 1 month after inpatient treatment for COVID-19. Quality of life (QoL) of patients was determined according to the questionnaire Medical Outcomes Study – 36-item Short Form (SF-36). The glucose level, circulating immune complexes (CICs), concentration of immunoglobulin (Ig) A, interleukin (IL)-8 and IL-33 levels were determined in the blood serum of patients.

Results: QoL of patients after coronavirus disease is significantly deteriorated: patients note a significant limitation in physical functioning, pain perception, vitality, role-physical and social functioning and mental health. The increase in glycemia and glycated hemoglobin levels in post-COVID-19 patients was significantly associated with the deterioration of patients` general health (GH) ($r = -0,228$; ($p=0,040$) and ($r = -0,280$; ($p=0,014$), respectively). The IL-33 concentration in such patients correlated directly with role-physical functioning (RP) ($r = 0,385$; $p=0,029$). The CICs level decline was associated with deterioration of RP ($r = 0,227$; $p=0,042$) and GH ($r = 0,227$; $p=0,041$).

Conclusions: The study of clinical-functional, biochemical, immunological and psychological indicators, quality of life, and their mutual influences should be included in the development of the program for the diagnosis, treatment, and rehabilitation of patients after the transfer of COVID-19 at the outpatient stage of treatment by doctors of general practice-family medicine.

KEY WORDS: systemic inflammation, quality of life, coronavirus disease, interrelation features

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INTRODUCTION

COVID-19 is an acute respiratory infection caused by the acute respiratory syndrome virus SARS-CoV-2. The severity of this condition is determined by such risk factors as age, male gender, concomitant chronic diseases and aberrant metabolic status [1, 2].

Numerous randomized studies and meta-analyses have shown [1, 2] a long-term inflammation with profound synthesis of cytokines (interleukins IL-1β, IL-6) at COVID-19, which is a prognostic factor for type 2 diabetes mellitus development [3, 4]. Chronic mild inflammation leads to the progression of atherosclerosis through tumor necrosis factor-alpha (TNF-α) and interleukin-10 (IL-10) [4].

Chronic mild inflammation leads to the progression of atherosclerosis through interleukin-10 (IL-10) and tumor necrosis factor-alpha (TNF-α) [4]. C. Huang et al. [5] and N. Lelapi et al. [6] reported that COVID-19-associated coagulopathy culminates in deep vein thrombosis, pulmonary embolism, and stroke, which increases the risk of adverse cardiovascular events.

S. Gando and T. Wada [7] demonstrated three main pathophysiological mechanisms of COVID-19-associated coagulopathy: angiotensin (Ang)-II-induced coagulopathy, hyperfibrinolysis due to coagulation factor XII (FXII) and kallikrein/kinin system (KKS) activation, and disseminated intravascular coagulation (DIC) syndrome, provoking systemic inflammation, coagulation and fibrinolysis activation associated with organ dysfunction, bleeding and poor prognosis. Thrombin, plasmin, and inflammation control is a major goal in ameliorating COVID-19-associated coagulopathy [7]. But at the same time, S. Gando and T. Wada [7] emphasized that the expediency of fibrinolytic and antifibrinolytic therapy for COVID-19 is still unknown. Based on the study of well-defined molecular mechanisms of COVID-19-associated coagulopathy, further research is needed to create reliable strategies for its prevention and treatment [7].

A new promising strategy for COVID-19 treatment is the combination of anticoagulants and antidepressants (selective serotonin reuptake inhibitors – SSRIs) [1].

In the treatment of SARS-CoV-2, SSRIs are used, which leads to a decrease in the release of cytokines [8]. M. Szilveszter et al. [1] reported that inflammation/infection-triggered cytokine storm, vasculopathy, obesity, hyperglycemia and advanced age are significant risk factors for COVID-19 severe complications and the cause of reduced quality of life (QoL) for these patients.

AIM

To evaluate the features of the interrelation of systemic inflammation with the quality of life of patients with coronary virus disease.

MATERIALS AND METHODS

30 patients were examined 1 month after inpatient treatment for COVID-19 based on the Municipal Non-Profit Enterprises "Primary Medical and Sanitary Care Center" No. 1 and No. 3 of Sviatoshyn district of Kyiv. We diagnose COVID-19 based on the Order of the Ministry of Health of Ukraine No. 762 dated April 2, 2020 «Protocol of providing medical assistance in the treatment of coronavirus disease (COVID-19)» [9], the clinical guideline "Clinical management of COVID-19" [10], Order of the Ministry of Health of Ukraine No. 771 dated 04.20.2021 "Protocol of providing rehabilitation assistance for patients with coronavirus disease (COVID-19) and convalescents [11]. In our study, ethical principles were applied, taking into account GIP-SH and the Declaration of Helsinki [12]. The written informed consent of all participants was obtained, and all bioethical conditions were met and agreed with the ethics committee.

Thirty patients aged (mean ± standard error [M ± m]) 57,17±1,33 years, 22 men and 8 women, were examined. The enrolled patients were examined by the Order of the Ministry of Health of Ukraine dated April 20, 2021, No. 771 «Protocol for the provision of rehabilitation care for patients with coronavirus disease (COVID-19) and convalescents» [11]. QoL of patients was determined according to the Medical Outcomes Study – 36-item Short Form (SF-36) [13] during a visit to a family doctor. We studied general (GH) and mental health (MH); physical (PF); role-physical (RP), role-emotional (RE) and social (SF) functioning; pain (BP), and viability (VT).

The blood glucose level of patients was measured by the enzymatic colorimetric method. The glycated hemoglobin concentration was measured by the ion exchange chromatography on immunoenzymatic photometer [14]. The level of circulating immune complexes (CIC) (mainly C1q-binding immunoglobulins G) was measured by the precipitation methodology on an immunoenzymatic photometer. The concentration of immunoglobulin A (IgA) was determined by the methodology of solid-phase immunoenzyme assay on an immunoenzymatic photometer [15]. The interleukin (IL)-8 and IL-33 levels were determined by the «sandwich» methodology of indirect non-competitive heterogeneous enzyme immunoassay [16].

Mathematical statistics methods were used for the mathematical processing of study results [17]. We used the computer program «Statistica 7.0 for Windows». The studied indicators had a distribution close to normal. Average values of indicators (M), and their errors (m) were calculated. A correlation analysis with the measurement of Pearson`s correlation coefficient (r) was performed. The critical level of statistical significance was $p<0,05$.

RESULTS

In previous studies, we reported a significant decrease in patients` QoL after coronavirus disease: severe limitation of physical functioning, pain perception, vitality, role-physical and social functioning, and mental health. Even a month after treatment, patients noted significant fatigue, memory disorders and dizziness, shortness of breath and cough, sleep and heart rhythm disturbances, and vascular thrombosis. Almost a third of the examined patients noted significant limitations in physical activity due to pain and deterioration of well-being without its improvement in self-assessment, and about half had psychological problems, and noted hyper-anxiety or depression [18].

O.-Z. Akácsos-Szász et al. [19] hypothesized that COVID-19-induced coagulopathy in the presence of metabolic syndrome and type 2 diabetes mellitus. Thus COVID-19 is characterized by coagulopathy and hemostatic imbalance [19].

Despite that the glucose level in the examined patients was at the upper limit of reference, it was correlated inversely with GH ($r= -0,228$; $p=0,040$) (Fig. 1A). In addition, we revealed an inverse correlation of glycated hemoglobin with GH ($r= -0,280$; $p=0,014$) (Fig. 1B).

R. Ker et al. [20] found that cytokines disturb normal hemostasis in humans and are probably one of the key factors in the thrombotic potential of SARS-CoV-19, contributing to an imbalance in prothrombotic and intrinsic anticoagulant pathways, such as loss tissue factor pathway inhibitor activity, downregulation of thrombomodulin expression on endothelial cells, and decreased antithrombin III levels in blood serum [21].

Cytokine IL-6 is a mediator of inflammation and a stimulus of the acute phase response. The role of IL-6

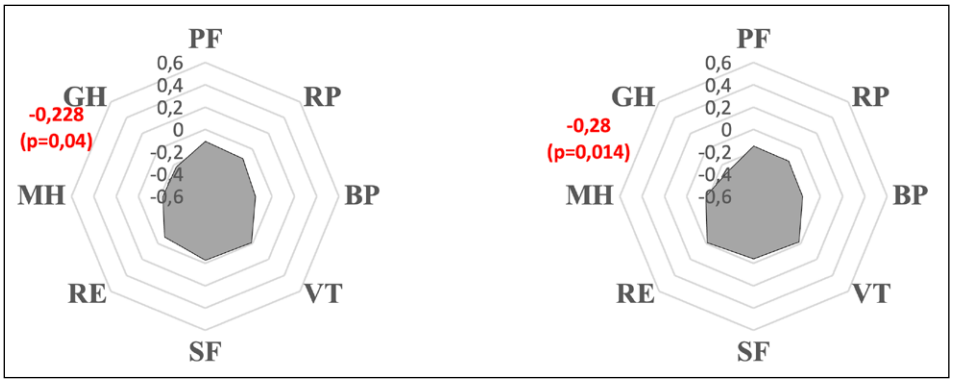

Fig. 1. The correlations of glucose (A) and glycated hemoglobin (B) levels with QoL parameters (n=30).

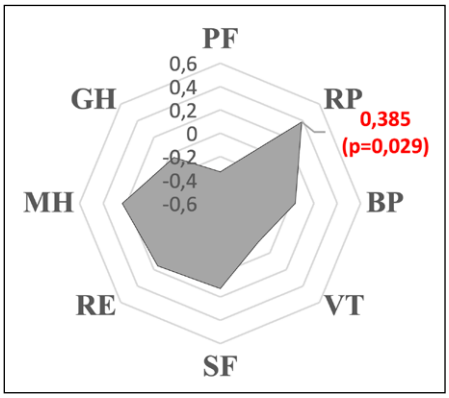

Fig. 2. The correlations of IL-33 level with QoL parameters (n=30).

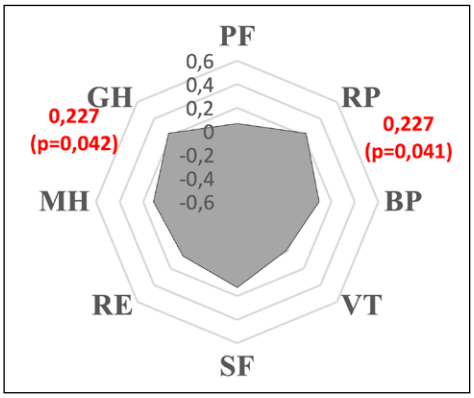

Fig. 3. The correlations of CIC level with QoL parameters (n=30).

in the pathological inflammatory response that causes severe COVID-19 is important. IL-10 is one of the most important regulatory cytokines that largely determine the direction of the immune response: under IL-10 activity the cellular response (regulated by Th1) is suppressed and the humoral response (Th2) is stimulated. It belongs to anti-inflammatory cytokines [22]. In our previous studies, IL-6 and IL-10 levels in patients after coronavirus disease were (median, interquartile range [Me, IQR]) 4,3 (2,4-5,8) pg/ml and 3,0 (0,9-3,9) pg/ml, respectively [23].

We did not observe any significant correlations of IL-8 with QoL parameters. At the same time, IL-33 in post-COVID patients related to RP (r=0,385; p=0,029) (Fig. 2).

A great important has synergism between IgA and mechanisms of nonspecific defense – complement, lysozyme, phagocytosed cells and their enzymes. This contributes to the implementation of antibacterial protection, increasing its overall effectiveness. In examined COVID-19 patients the level of IgA was (Me [IQR]) 1,6 (1,3-1,95) pg/ml [23].

One of the most important biological functions of immunoglobulins is the antigen-binding and the formation of circulating immune complexes (CIC), which is a physiological process that is aimed at maintaining the stability of its internal environment. The CIC formation is one of the components of the physiological immune response. The most important function of CIC is the ability to activate the complement system, which determines its role in the inflammation process and regulation of the immune system's functional activity. All patients with COVID-19 had a CIC of (Me [IQR]) 0,037 (0,025-0,047) IU/ml [23].

The level of CIC was associated with RP (r=0,227; p=0,041) and GH (r=0,227; p=0,042) (Fig. 3). On the contrary, we did not reveal any significant correlations of IgA level concentration and QoL parameters.

Thus, the increase in both glycemia and glycated hemoglobin levels in COVID-19 patients was significantly associated with the deterioration of patients` GH. Moreover, the IL-33 level was directly correlated with RP. Finally, a decline in CICs level was associated with the deterioration of RP and GH.

DISCUSSION

S. Gando and T. Wada [7] emphasize that thromboplasmatic coagulopathy in COVID-19 consists of Ang II-induced coagulopathy, activated FXIIa and KKS-enhanced fibrinolysis, and DIC syndrome. All of these conditions induce systemic inflammation via each pathomechanism-developed production of inflammatory cytokines. Coronavirus disease upregulates angiotensin-converting enzyme and leads to increase of Ang II levels. Ang II-induced coagulopathy affects platelet activation, thrombin generation, expression

of plasminogen activator inhibitor-1, and endothelial damage and thrombosis 1 [7].

L. Giubelan et al. [24] found differences in inflammatory biomarkers in patients with moderate or severe COVID-19: patients with obesity or diabetes mellitus had significantly higher levels of leukocytes, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), D-dimers and serum glucose concentrations. A. Mureşan et al. [25] showed that elevated inflammatory markers are independent predictors of adverse prognosis for all patients with SARS-CoV-2.

D. Sun et al. [26] demonstrated that some cytokines (IL-6, IL-2, IFN-γ, TNF-α, MIP (macrophage inflammatory protein), and MCP-1 (monocyte chemoattractant protein 1) present in critically ill patients. Angiotensin II (AngII) triggers the nuclear factor kappa-B (NF-κB) activation, resulting in hyperinflammation, mainly via enhanced synthesis of IL-1β and IL-6. With a severe course of COVID-19, these interleukins increase significantly [27].

J. Gómez-Mesa et al. [28] determined that IL-6 and IL-1α play an important role in inflammatory response and blood coagulation system conjunction; at inflammation macrophages release tissue factor in response to IL-6. IL-6 is also involved in the production of fibrinogen and factor VIII. In addition, IL-6 acts on the endothelium, enhancing the vascular endothelial growth factor synthesis, and resulting in vascular hyperpermeability and hypotension [29]. Conversely, TNF-α and IL-1 are the most important mediators of endogenous coagulation cascade inhibition [28], which is crucial in the development of COVID-19 complications and essentially worsens the QoL in such patients.

Even a month after COVID treatment, patients complained of shortness of breath and cough, arrhythmia, vascular thrombosis, memory disorders, muscle disorders, fatigue, hair loss [23]. Our findings are comparable to a meta-analysis of 12 studies, including 4,828 patients with persistent symptoms six months after infection [30]. Impaired QoL on the visual analog scale (EQ-VAS) reached 59 % in the complete sample; and with severe coronavirus disease and complaints of fatigue during examination, QoL indicators deteriorate even more [30]. R. Meys et al. [31] showed that the QoL value in such patients is lower than the average population data even three months after treatment, which is consistent with our data.

CONCLUSIONS

1. The QoL of patients after coronavirus disease has significantly deteriorated: patients note a significant limitation in physical functioning, pain perception, vitality, role-physical and social functioning, and mental health. Almost a third of the surveyed needs indicate significant problems with physical and emotional activity, social and role functioning; about half have psychological problems and report increased anxiety or depression.
2. The increase in glycemia and glycated hemoglobin levels in post-COVID-19 patients were significantly associated with the deterioration of patients` GH. The IL-33 concentration in such patients correlated directly with RP. The CICs level decline was associated with the deterioration of RP and GH.
3. The study of clinical-functional, biochemical, immunological and psychological indicators, quality of life, and their mutual influences should be included in the program of diagnosis and rehabilitation of patients after the COVID-19 at the outpatient stage of treatment by doctors of general practice-family medicine.

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CONFLICT OF INTEREST
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ORIGINAL ARTICLE

CONTENTS

Dynamic muscular endurance as an indicator of functional readiness of cyber-athletes

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ABSTRACT

Aim: To study the dynamic muscular endurance of hand movement according to the tapping test in connection with the manifestations of cognitive qualities of cyber-athletes and students involved in computer games as a hobby.

Materials and Methods: Dynamic muscular endurance of the right and left hands of the examined subjects was studied (using the tapping test method), as well as the reaction to a moving object using the diagnostic complex "Diagnost-1". Correction tables (Landolt rings) were used to study voluntary attention. 45 students of the National University of Ukraine on Physical Education and Sport of both sexes, aged 17-26, took part in the study, among whom 10 are cyber-athletes (sports experience of 1-10 years), 15 amateurs (involved in computer games as a hobby) and 20 students who do not play computer games (control group).

Results: In cyber-athletes and students involved in computer games, the dynamic muscular endurance of the movement of the hand of the subdominant hand was greater than in students who did not engage in computer games. A higher level of dynamic muscular endurance for the subdominant hand and less functional asymmetry according to the tapping test scores in cyber-athletes were associated with a more successful performance of the attention test.

Conclusions: A higher level of dynamic muscular endurance for the subdominant arm and a smaller functional asymmetry according to the tapping test indicators in e-athletes can be considered as an indicator of functional readiness.

KEY WORDS: e-sports, tapping test, cognitive qualities

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INTRODUCTION

At the current stage of sports development, eSports acts as a social phenomenon in a broad sense, as it contains common features inherent in other types of sports [1, 2]. Cybersports, or competitive computer games, is a form of competitive activity in which participants (gamers) use their physical and mental abilities to compete in various games in a virtual electronic environment [3]. As is known, the psychophysiological state of athletes is a component of the general functional state [4-6]. The state of psychophysiological functions of athletes in any sports affects the effectiveness of sports activities [7]. Other authors believe that the main factor of successful competitive activity should be considered functional readiness, which indicates the athlete's physical ability to perform specific actions that determine the meaning of his sport [8]. Agreeing with the authors and relying on the provisions of the theory of functional systems and adaptation, it can be assumed that the functional readiness of an e-athlete includes psychophysiological and cognitive components [9].

One of the indicators of the functional state of the body, which characterizes the ability of all links of the motor analyzer for speed and endurance, that is, dynamic muscular endurance (DME), is the maximum pace of hand movement according to the tapping test method [10]. The tapping test technique is widely used in the research of domestic scientists in the modern psychophysiology of sports [10]. At the current stage, considerable attention is paid to the study and development of methodical approaches, which at a high level make it possible to assess the psychological state and functional state of the central nervous system (CNS) of athletes [11]. For now, the study of the dynamic muscular endurance of the movement of the hand using the tapping test method can become the factor that will significantly increase the effectiveness of the training process in eSports.

AIM

The aim of the research is to study the dynamic muscular endurance of hand movement according to the

tapping test in connection with the manifestations of cognitive qualities of cyber-athletes and students involved in computer games as a hobby.

MATERIALS AND METHODS

The work was performed at the Research Institute of the National University of Ukraine on Physical Education and Sport. 45 students of NUUPES of both sexes, aged 17-26, took part in the study, including 10 cyber-athletes (1-10 years of sports experience), 15 amateur students (involved in computer games as a hobby) and 20 students who do not play computer games (control group). In most of the examined, the right hand was dominant. Students were tested during intersessional training. In accordance with the purpose of the work, the dynamic muscular endurance of the right and left hands of the athletes was studied (using the tapping test method). The indicator of functional asymmetry was determined as the ratio of the tapping test indicators for the dominant and subdominant hand (DME1 and DME2, respectively). To determine the maximum pace of movement of the hand, the diagnostic complex «Diagnost-1» (M. V. Makarenko, V. S. Lyzogub) was used.

Correction tables (Landolt rings) were used to study voluntary attention and to assess the pace of psychomotor work, work capacity and resistance to monotonous work that requires constant attention. The results of the test were evaluated by the number of viewed and missed signs with a completion time of 5 minutes. The method allows to determine the level of concentration of attention [12]. The «Three Words» technique was used to investigate the peculiarities of the creative imagination of the examinees [13].

Statistical data processing was carried out using non-parametric statistics methods. Medians and interquartile range (Me [25%; 75%]) were used to describe the sampling distribution. The Mann-Whitney test was used to compare independent samples. Correlation analysis was performed according to Spearman's test.

When conducting research with the participation of students, the legislation of Ukraine on health care and the Declaration of Helsinki of 2000, the directive of the European Society 86/609 on the participation of people in medical and biological research [14].

RESULTS

The examinees were divided into two groups: Group I – cyber sportsmen (n=10) and Group II – amateur students (n=15). The peculiarities of dynamic muscular endurance were studied according to the maximum rate of movement of the hand during 60 s separately for the dominant and subdominant hand in e-athletes and amateur students involved in computer games as a hobby (Table 1).

According to the results of the correlation analysis of the obtained data, DME and functional asymmetry between the dominant and subdominant hand were not related to the age and sports experience of the subjects. In both groups, the DME for the dominant hand was greater than for the subdominant hand ($p<0.01$). However, no differences were found between the selected groups in terms of DME and functional asymmetry (Table 1).

Therefore, the next step was to compare the united group of students involved in computer games (e-sport athletes and amateur students) with the control group (students who do not play computer games) – i.e., III and IV groups (Table 2).

According to the results of the correlation analysis of the obtained data, DME and functional asymmetry between the dominant and subdominant hand were not related to the age and sports experience of the examined groups III and IV. In both of these groups, the DME for the dominant hand was greater than for the subdominant hand ($p<0.01$). A significant difference was found between the III and IV groups of students according to the DME indicator for the subdominant hand and the functional asymmetry indicator (Table 2). In e-athletes and students involved in computer games, the DME of movement of the subdominant hand was greater than in students who did not play computer games. Accordingly, the functional asymmetry between the dominant and subdominant hand in e-athletes and amateur students was smaller than in the control group. No differences were found between the III and IV groups according to the DME index for the dominant hand (Table 2). The obtained data are consistent with the results of previous studies when testing qualified female athletes of game sports: for the subdominant hand, the DME of hand movement was significantly greater in female athletes of the older age group. The asymmetry of the tapping test indicators between the right and left hands in athletes of the older age group was smaller than in athletes of the younger age group [15]. It should be noted that, according to the literature, a decrease in functional asymmetry in experienced athletes indicates optimal training tactics [16], and in cyber-athletes it may indicate a state of functional readiness.

Correlation analysis of the obtained data in the group of e-athletes showed the existence of relationships between the measured indicators of the tapping test and the cognitive indicators of the «Rings of Landolt» and «Creative imagination» tests (Table 3).

Table 1. Tapping test indicators, age and experience of sports training of e-athletes (n=10) and amateur students (n=15), Me [25%, 75%]

Indexes	I group, eSportsmen, n=10	II group, amateur students, n=15
Indicator of dynamic muscular endurance of the movement of the dominant hand, the number of clicks	394,50 [381,00; 404,00]#	399,00 [378,00; 438,00]#
Indicator of dynamic muscular endurance of movement of the subdominant hand, number of clicks	361,00 [341,00; 375,00]	371,00 [349,00; 390,00]
Indicator of functional asymmetry	1,12 [1,03; 1,15]	1,08 [1,04; 1,12]
Age, years	19,00 [18,00; 22,00]	19,00 [18,00; 19,00]
Sports experience (eSports), years	7,00 [2,00; 8,00]	7,00 [6,00; 10,00]
Total sports experience, years	12,00 [8,00; 13,00]	12,00 [8,00; 14,00]

Note: # $p<0.01$ – significant difference between the indicators for the dominant and subdominant hand according to the Mann-Whitney test.

Table 2. Tapping test indicators, age and experience of sports training of e-athletes and amateur students (n=25) compared to the control group (n=20), Me [25%, 75%]

Indexes	III group, cyber sportsmen and amateur students, n=25	IV group, students who do not play computer games, n=20
Indicator of dynamic muscular endurance of the movement of the dominant hand, the number of clicks	399,00 [380,00; 424,00]#	397,50 [375,00; 424,00]#
Indicator of dynamic muscular endurance of movement of the subdominant hand, number of clicks	370,00 [348,00; 389,00]*	355,50 [306,00; 368,00]
Indicator of functional asymmetry	1,09 [1,04; 1,15]*	1,14 [1,09; 1,25]
Age, years	19,00 [18,00; 19,00]	19,50 [18,00; 20,00]
Sports experience (eSports), years	7,00 [5,00; 8,00]	–
Total sports experience, years	12,00 [8,00; 13,00]	12,25 [9,00; 15,00]

Notes: # $p<0.001$ – significant difference between the indicators for the dominant and subdominant hand according to the Mann-Whitney test; * $p<0.05$ – significant difference between III and IV groups according to the Mann-Whitney test.

However, no such correlations were found in the group of amateur students.

The analysis of the research results became the basis for the development of evaluation criteria for the tapping test indicators for cyber athletes (Table 4).

DISCUSSION

The evaluation criteria of indicators can become the basis for creating an express diagnosis of dynamic muscular endurance of hand movement, the functional state of the neuromuscular system of cyber-athletes, and thus allow for a differentiated assessment and management of the training process in this sport.

In our opinion, in the context of eSports competitions, it is important to note that hand movements of the athletes play a key role in the execution of game commands and strategies. Agility and precision of movements can determine the speed and efficiency of an eSports player in the gameplay. This becomes an especially important aspect for those who exhibit a pronounced kinesthetic sensitivity and agility. Their high agility allows them to quickly and accurately react to changes in the game, perform complex combinations of movements and ensure a high level of accuracy when conducting battles or performing other tasks.

Attention appears as an important factor in this context, and it can have different characteristics such as concentration, persistence, volume, distribution, switching, etc. These characteristics of attention are widely studied in various fields of sports psychology [17].

A higher level of DME for the subdominant hand and a smaller functional asymmetry according to the tapping test indicators in e-athletes were associated with a more successful performance of the attention test (respectively, $r = 0.70$, $p<0.05$; $r = –0.69$, $p<0,05$). Also, a tendency was revealed: a greater number of clicks in the tapping test for both hands corresponded to a greater speed of information processing according to the «Landolt Rings» test (Table 3). This fact can be a professionally determined result for cyber-athletes and amateur students, because their subdominant hand works on the keyboard and responds to strategic and tactical tasks, and the dominant hand works with the mouse.

According to the results of research by domestic specialists in the field of physical culture and sports, the tapping test can be used to diagnose the functional state of athletes, as well as specific features of adaptation to stressful situations [18, 19, 20]. DMV of hand movement according to the taping test was related to sports experience in game sports, the state

Table 3. Correlations of the tapping test indicators and cognitive indicators according to the Landolt Rings, Creative Imagination tests in e-athletes (n = 10), r^s

Indexes	Correlations, r^s					
	CL1	CL2	CL3	CL4	CL5	TU
DME 1, number of clicks	–	–	–	0,55	0,61	–
DME 2, number of clicks	**0,82****	**0,67***	**0,70***	0,62	0,62	–
FA, DME 1/ DME 2	**-0,67***	**-0,72***	**-0,69***	–	–	-0,57

Notes: DME 1 – an indicator of dynamic muscular endurance of the movement of the dominant hand; DME 2 – an indicator of dynamic muscular endurance of the movement of the subdominant hand; FA is an indicator of functional asymmetry; CL 1 – the number of symbols viewed in 5 minutes, the «Landolt Rings» test; CL2 – the number of missed symbols in 5 minutes, the Landolt Rings test; CL 3 – success rate, Landolt Rings test, points; CL 4 – an indicator of the speed of information processing, um. unit; CL 5 – information processing speed indicator, points; TU – indicator according to the «Creative imagination» test, points; *statistical significance of correlation coefficient $p<0.05$; **$p<0.01$.

Table 4. Evaluation criteria of tapping test indicators for e-athletes

Indexes	High level	Average level	Low level
Indicator of dynamic muscular endurance of the movement of the dominant hand, the number of clicks	> 404,00	381,00 – 404,00	< 381,00
Indicator of dynamic muscular endurance of the movement of the subdominant hand, number of clicks	> 389,00	348,00 – 389,00	< 348,00
Indicator of functional asymmetry	< 1,03	1,03 – 1,15	> 1,15

of psychophysiological functions of athletes [21], and the level of sports qualification among representatives of speed-endurance sports [22].

For e-athletes engaged in «non-muscular» sports, it is important to consider the role of motor activity in maintaining optimal physical and mental qualities [23]. Despite the lack of physical activity, the presence of sufficient motor activity can affect metabolic processes in the body, contributing to the stimulation of the psychophysical and intellectual capabilities of the individual [23-25].

CONCLUSIONS

1. Based on the analysis of the scientific and methodological literature and the generalization of the practical results of the studies of experts in the psychophysiology of sports and our own research, it was found that dynamic muscular endurance (DME) according to the indicators of the tapping test (the maximum rate of movement of the dominant and subdominant hand) can be used as a model characteristic for monitoring and forecasting the functional state of athletes.
2. A higher level of DME for the subdominant hand and less functional asymmetry according to the tapping test indicators in e-athletes were associated with a more successful performance of the attention test (respectively, $r = 0.70$, $p<0.05$; $r = –0.69$, $p <0.05$). Also, a trend was revealed: a greater number of clicks in the tapping test for both hands corresponded to a higher speed of processing information according to the Landolt Rings test.

PROSPECTS FOR FURTHER RESEARCH

It is interesting to conduct a further study with a correlation analysis between the studied psychophysiological indicators and the results of the competitive activity of cyber-athletes.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Ultrasound assessment of the risk of venous thromboembolic complications in thrombosis of varicose transformed tributaries of the great saphenous vein

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ABSTRACT

Aim: To evaluate the ultrasound criteria for venous thromboembolic complications in patients with thrombosis of varicose veins of the tributaries of the great saphenous vein (GSV).

Materials and Methods: The results of ultrasound examination of 52 patients with thrombosis of varicose veins of the tributaries of GSV were analyzed. The indicators of venous hemodynamics were compared with the control group (CG) (n=32).

Results: Varicose transformation of GSV and failure of its valvular apparatus were detected in 44 (84.6%) patients, in 8 (15.4%) patients the superficial venous highway was intact. Vertical reflux was diagnosed in varicose ectasia of GSV: local reflux in 14 (31.8%), widespread reflux in 14 (31.8%), and total reflux in 16 (36.4%) patients. The diameter of GSV in tributary varicothrombophlebitis was 8.9±0.27 mm ($p<0.05$ vs. CG) and 11.2±0.25 mm ($p<0.05$ vs. CG) in the horizontal and vertical positions, respectively. The proximal and distal borders of thrombosis exceeded the clinical ones by 15.26±1.21 cm ($p<0.05$) and 7.94±1.32 cm ($p<0.05$), respectively. The spread of tributary thrombophlebitis to the superficial venous highway was detected in 14 (26.9%) patients, among whom 12 (85.7%) patients had unfixed apices of thrombotic masses.

Conclusions: The results obtained convincingly demonstrate the need for early ultrasound examination of patients with tributary thrombophlebitis, which allows to identify the real limits of the thrombotic process, timely diagnose the transition of the thrombotic process to superficial and deep venous lines, effectively predict the risk of venous thromboembolic complications and choose the optimal surgical tactics.

KEY WORDS: superficial vein thrombosis, venous thromboembolic complications, varicose transformation, great saphenous vein

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INTRODUCTION

Thrombosis of superficial veins in 59-90% of cases is a complication of varicose veins [1-3]. According to the STEPH and SEMERGEN studies, the thrombotic process occurs in 50 – 80% of cases in the great saphenous vein (GSV), in 30-40% – in the tributaries of the great saphenous vein, and in 11-20% – in the small saphenous vein [1-3]. When it occurs in the tributaries of GSV and, with the progression of the disease, thrombosis quickly spreads to the superficial and deep venous main veins [4]. This is facilitated by common risk factors for superficial and deep vein thrombosis [2, 5-7]. Thus, the incidence of deep vein thrombosis and pulmonary embolism in patients with superficial vein thrombosis is 2.6 – 24.6% and 0.5 – 13.0% of patients, respectively [1, 2, 4, 5, 8-10].

Despite this, most researchers do not pay the necessary attention to superficial vein thrombosis, considering it a mild and minor disease [2, 5, 6, 11], although the clinical diagnosis of this pathology is not difficult and the diagnosis is made at the outpatient stage [1, 2, 5]. At the same time, the clinical diagnosis is not accurate, it does not allow to identify the nature, localization and boundaries of thrombotic masses, to exclude the presence of transfascial thrombosis [4, 5, 11]. Ultrasound examination is indicated for all patients with suspected superficial vein thrombosis without exception [5, 8, 12, 13], but ultrasound monitoring is not required after the diagnosis is made [14].

According to a retrospective cohort study conducted in Spain, which included 1166 patients with isolated superficial vein thrombosis of the lower extremities, 24.4% of patients already had a history of venous thromboembolic events [9]. Within 6 months from the time of detection of superficial vein thrombosis, venous thromboembolic complications were detected in 8.9%, of whom 1.4% died [9]. At the same time, ultrasound examination was performed in only 60.3% of patients, and anticoagulant therapy was prescribed for 22 days in 77% of patients [9]. A number of other randomized trials recommend prescribing anticoagulant therapy only in case of ultrasound evidence of thrombotic masses

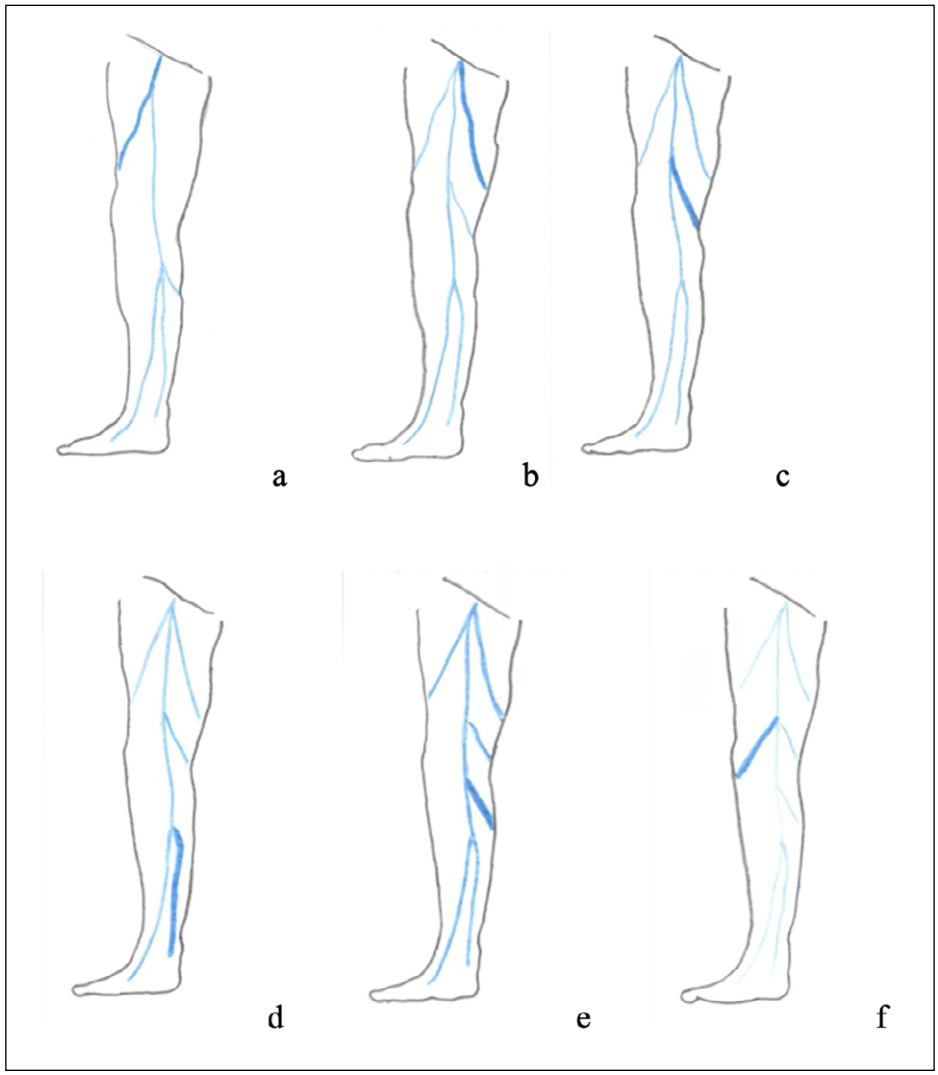

Fig. 1. Localization of thrombosis in varicose transformation of the tributaries of GSV: a) lateral accessory branch; b) medial accessory branch; c) medial intersaphenous vein of the thigh; d) Leonardo's vein; e) medial intersaphenous vein on the lower leg; f) anterior popliteal tributary of the GSV.

spreading to the sapheno-femoral and saphenopopliteal mouths, in other cases, researchers recommend the administration of low-molecular-weight heparins in prophylactic doses, non-steroidal anti-inflammatory drugs and compression garments [2, 5, 8].

Thus, ultrasound criteria for the risk of venous thromboembolic complications in thrombosis of superficial varicose veins play an important role in the choice of surgical tactics.

AIM

To evaluate the ultrasound criteria for venous thromboembolic complications in patients with varicose vein thrombosis of the transforming tributaries of GSV.

MATERIALS AND METHODS

The paper analyzes the results of ultrasound examination of 52 patients with thrombosis of varicose transformed tributaries of GSV treated from May 2020 to December 2023. The age of patients ranged from 23 to 67 years and averaged age was (mean ± standard error) 34±1.7 years. The gender distribution was 38 (73.1%) women and 14 (26.9%) men. The algorithm of outpatient examination of patients included general blood and urine tests, blood sugar, blood biochemical parameters, coagulogram, ultrasound examination of the veins of the lower extremities (Philips CX-50, Philips Ultrasound Inc., USA). Indicators of venous hemodynamics during ultrasound examination were compared with the control group (n=32).

Ultrasound methods of examination of the lower extremity veins are the gold standard for the diagnosis of varicose veins. Ultrasound examination was performed consistently to assess the condition of the superficial and deep venous systems, as well as the penetrating veins of the lower extremity. The examination was completed with an ultrasound examination of the contralateral limb. The examination was performed in a vertical and horizontal position. Vein patency, diameter (in mm), presence of varicose transformation, capacity

Table 1. Venous hemodynamics in tributary varicothrombophlebitis

Ultrasonography of the main line	Varicose transformation GSV			Valves failure GSV		Reflux GSV				GSV barrel diameter (mm) on Valsalva sample			
										main group		control group (n=32)	
Localization of the thrombotic process	local	diffuse	no	yes	no	local	widespread	total	no	vetically	horizontally	vetically	horizontally
medial additional branch (n=11)	3	5	3	8	3	3	3	2	3	8,3±0,21*	9,5±0,25*	2,3±0,12	3,4±0,19
lateral additional (n=5)	1	4	-	5	-	1	3	1	-	8,6±0,22*	10,1±0,23*	2,6±0,17	3,2±0,12
external vena cava vein (n=2)	1	-	1	1	1	1	-	-	1	8; 11	10; 12	2,7±0,32	2,9±0,41
superficial peritoneal vein (n=1)	1	-	-	1	-	1	-	-	-	7	10	2,6±0,24	3,1±0,42
internal superficial enveloping vein of the thigh (n=3)	1	1	1	2	1	1	-	1	1	6; 9; 10	7; 10; 11	2,9±0,23	3,2±0,27
anterior popliteal tributary (n=2)	-	2	-	2	-	-	-	2	-	7; 10	10; 12	3,1±0,72	3,3±0,56
Leonardo's vein (n=21)	5	14	2	19	2	5	5	9	2	10,2±0,25*	11,3±0,31*	3,2±0,26	3,5±0,21
anterior arch vein of the shin (n=7)	2	4	1	6	1	2	3	1	1	9,3±0,22*	10,7±0,24*	2,9±0,34	2,9±0,42
Total (n=52)	14	30	8	44	8	14	14	16	8	8,9±0,27*	11,2±0,25*	3.8±0.31	4.8±0.27

Comment.: * – $p<0,05$ (vs. control group).

of the valve apparatus, presence of venous reflux and failed penetrating veins were assessed. Special attention was paid to the examination of the deep venous system to exclude thrombotic occlusion or post-thrombotic changes.

The study was conducted in accordance with the provisions of the Helsinki Declaration of the World Medical Association «Ethical Principles for Medical Research Involving Human Subjects» (revision 2008) and approved by the Bioethics Committee of the School of Medicine of Uzhhorod National University. All patients signed an informed consent to participate in the research work.

Statistical processing of the research results was carried out by the use of Microsoft Excel 2010 and Statistica (version 5.0) for Windows software. Quantitative features were presented as mean ± standard error. The significance of difference between two independent groups was analyzed by the use of Mann-Whitney U-test, and between dependent samples of data – by the Wilcoxon T-test. The level of significance was $p<0.05$.

RESULTS

On the basis of clinical and ultrasound data, the following localization of thrombosis in varicose transformation of the tributaries of GSV was found (n=52):

– medial accessory branch of the GSV – 11 (21.2%);
– lateral accessory branch of the GSV – 5 (9.6%);
– external vena cava – 2 (3.8%);
– superficial superior mesenteric vein – 1 (1.9%);
– internal superficial femoral vein – 3 (5.8%);
– anterior popliteal tributary of the GSV – 2 (3.8%);
– posterior arch vein (Leonardo's vein) – 21 (40.4%);
– anterior arch vein of the lower leg – 7 (13.5%) patients (Fig. 1).

Ultrasonography revealed varicose transformation of GSV and failure of its valvular apparatus in 44 (84.6%) patients with tributary thrombophlebitis, and in 8 (15.4%) patients the superficial venous highway was intact. Among the examined patients, local varicose transformation with segmental valvular insufficiency of GSV was detected in 14 (31.8%), and diffuse varicose transformation with widespread valvular insufficiency – in 30 (68.2%) cases. In the presence of variceal ectasia

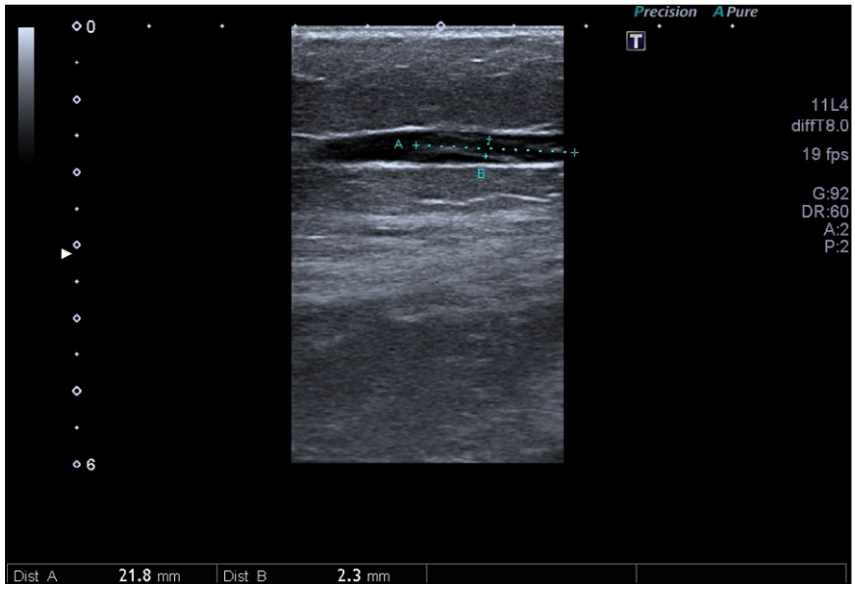

Fig. 2. Thrombotic occlusion of the medial accessory branch on the thigh.

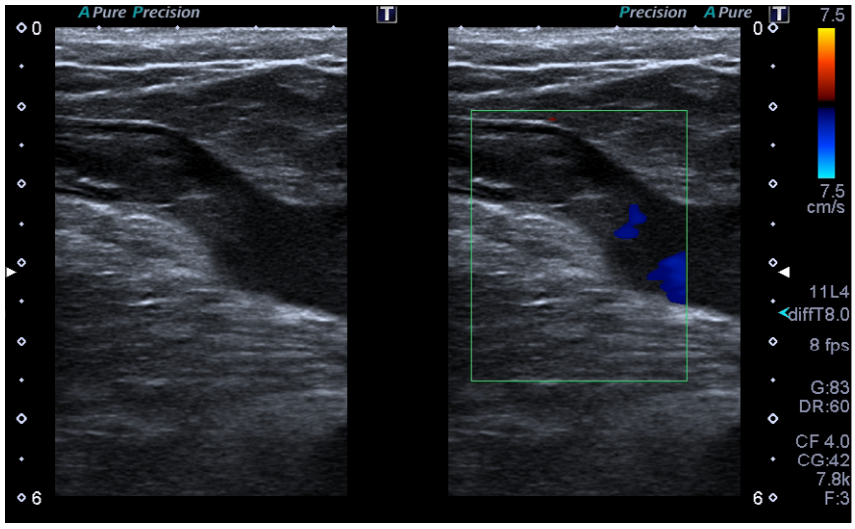

Fig. 3. Thrombosis of the saphenofemoral spigot.

of the trunk of GSV and failure of the valve apparatus of the latter, vertical reflux was diagnosed in all patients: local – in 14 (31.8%), widespread – in 14 (31.8%) and total – in 16 (36.4%) patients. The diameter of the trunk of GSV in the Valsalva test in inflow varicothrombophlebitis was on average 8.9±0.27 mm and 11.2±0.25 mm in horizontal and vertical provisions, respectively, being higer as compared to indicators in the control group: 3.8±0.31 mm ($p<0.05$) and 4.8±0.27 mm ($p<0.05$) in horizontal and vertical provisions, respectively (Table 1).

In case of thrombotic lesions of the varicose vein inflow, during the ultrasound examination, it is necessary to clearly define the boundaries of the thrombotic process (Fig. 2), to exclude or confirm the spread of thrombosis to the superficial venous main and/or deep venous system. Particular importance in assessing the spread of the thrombotic process was given to the examination of the saphenofemoral coexistence (Fig. 3) and the penetrating veins (Figs. 4, 5).

The ultrasound and clinical boundaries of the thrombotic process differed in all cases. In particular, during the ultrasound examination, the proximal and distal boundaries of superficial vein thrombosis exceeded the clinical ones by 15.26±1.21 cm ($p<0.05$) and 7.94±1.32 cm ($p<0.05$), respectively. Conducting control ultrasound examinations within the first week from the moment of diagnosis confirmation in patients with tributary thrombophlebitis who were prescribed anticoagulant therapy revealed a tendency to spread the thrombotic process in the proximal (in 12 (23.1%) cases) and distal (in 5 (9.6%) cases) directions. Particular importance during the ultrasound control study was given to the detection of the transition of the thrombotic process to the superficial venous highway. The spread of tributary thrombophlebitis to the superficial venous highway, despite anticoagulant therapy, was detected in 14 (26.9%) patients, among whom varicose transformation of the superficial high-

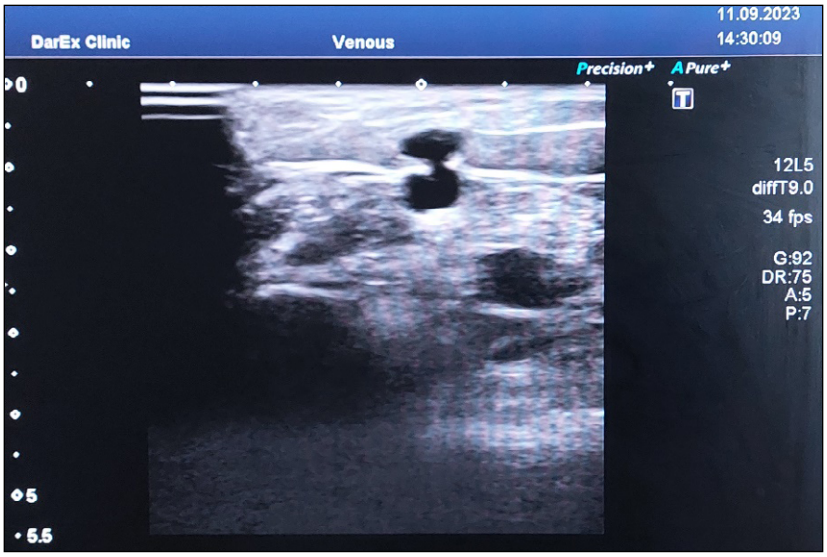

Fig. 4. Failed penetrating vein (cufflink symptom).

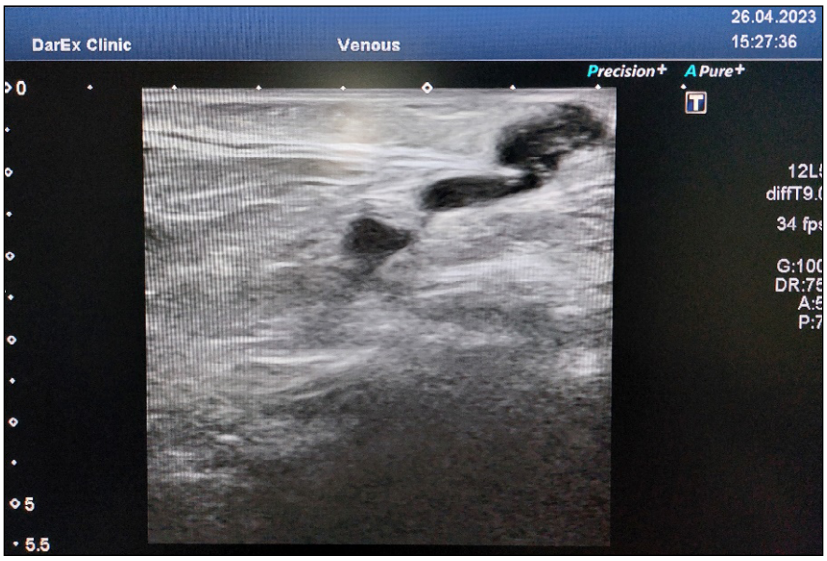

Fig. 5. Thrombotic occlusion of the failed penetrating vein.

way was detected in 9 (64.3%) patients. At the same time, in 12 (85.7%) of 14 patients with the spread of tributary thrombophlebitis to the superficial venous highway, the presence of an unfixed top of thrombotic masses was observed. Flotation of the thrombotic tip along with valve failure and venous reflux in the venous main line contributes to the progression of thrombosis, creates obstacles to the fixation of the thrombotic tip and its detachment with subsequent thromboembolism. The forces that contribute to the fragmentation of the floating tip are directed along the length of the thrombus and directly depend on the severity of venous reflux. Thrombus detachment is usually preceded by a sudden increase in venous pressure.

The incidence of venous thromboembolic complications also depends on the nature of the thrombotic masses and the duration of the pathological process. Ultrasound evaluation of the echostructure of thrombotic masses allowed us to distinguish the following types of thrombi:

– «fresh» (disorganized) – in 15 (28.9%)
– partially organized – in 23 (44.2%);
– organized – in 14 (26.9%) patients.

Disorganized and partially organized thrombotic masses that were not fixed or only partially fixed to the venous wall were considered the most embolism-prone, with the duration of the pathological process in varicose veins not exceeding 7-10 days. This was evidenced by the progression of thrombotic lesions in 17 (44.7%) of 38 patients with disorganized thrombi.

Thus, the results obtained convincingly demonstrate the need for early ultrasound examination of patients with tributary thrombophlebitis, which allows to identify the real limits of the thrombotic process, timely diagnose the transition of the thrombotic process to superficial and deep venous lines, effectively predict the risk of venous thromboembolic complications and choose the optimal surgical tactics.

DISCUSSION

The German registry of treatment of patients with superficial vein thrombosis shows considerable variability in conservative methods of treatment of this pathology, with significant differences in treatment regimens, indications for anticoagulant prescription, and duration of administration [7]. At the same time, current recommendations for anticoagulant therapy are followed only in two-thirds of cases, and one-third of patients do not receive anticoagulants at all [7]. However, even with anticoagulant therapy, the percentage of deep vein thrombosis, pulmonary embolism, or their recurrence over the next 3 months does not decrease [7], which is confirmed by the results of early repeated ultrasound examinations [15]. A retrospective analysis of ultrasound examination methods of 11739 patients revealed a recurrence of superficial vein thrombosis during the year in 27.2-31.4% of cases [16]. Multidisciplinary guidelines provide clear guidelines for ultrasound diagnosis of deep vein thrombosis, but do not determine the risk of venous thromboembolic complications in lower extremity superficial vein thrombosis [17]. However, 25% of patients with initial manifestations of superficial venous thrombosis, even without varicose ectasia, have asymptomatic pulmonary embolism [7].

A single-center retrospective study, which was based on ultrasound monitoring of 316 patients with superficial vein thrombosis, revealed that within 3 months from the onset of the disease, despite conservative treatment, thrombotic events occur in 29.2% of patients, in particular: in 19.2% of patients, progressive course of superficial vein thrombosis, in 9.8% – recurrence of superficial vein thrombosis, in 5.7% – deep vein thrombosis occurs, and in 1.0% – pulmonary embolism was observed [18]. In this case, 82% of all venous thromboembolic events occurred in patients who received anticoagulant therapy from the moment of seeking medical help [18]. At the same time, in international and national recommendations, there are few indications regarding ultrasound imaging of superficial vein thrombosis [19].

The question of ultrasound assessment of the risk of venous thromboembolic complications in superficial thrombophlebitis remains open.

CONCLUSIONS

1. The ultrasound and clinical limits of the thrombotic process always differ, in particular, the proximal and distal limits of superficial vein thrombosis exceed the clinical ones by an average of 15.26±1.21 cm ($p<0.05$) and 7.94±1.32 cm ($p<0.05$), respectively.
2. During the first week from the moment of diagnosis confirmation, despite anticoagulant therapy, there was a tendency to spread the thrombotic process to the proximal and distal directions in 23.1% and 9.6% of patients, respectively.
3. The spread of tributary thrombophlebitis to the superficial venous highway, despite anticoagulant therapy, was detected in 26.9% of patients, of whom 64.3% had varicose transformation of the superficial highway and 85.7% of patients had an unfixed apex of thrombotic masses.
4. In all patients with progression of the thrombotic process, thrombotic masses were disorganized.

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ORIGINAL ARTICLE

CONTENTS

Benefits of a combined surgical technique for patients with secondary neovascular glaucoma

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ABSTRACT

Aim: To assess the effectiveness and safety of the proposed surgical technique for treating secondary neovascular glaucoma.

Materials and Methods: We examined 28 eyes of 28 patients (16 women and 12 men), aged 46±7,2 years, with secondary neovascular glaucoma. All patients underwent a comprehensive ophthalmological examination before and during treatment. Two-stage treatment was applied to all patients. At the first stage – performed an advanced technique of non-penetrating deep sclerectomy while administering anti-VEGF (anti-vascular endothelial growth factor) intravitreal or intracameral injections. At the second – we performed externalization of Schlemm's canal followed by YAG laser trabeculectomy. Statistical analysis of the results was used the SPSS v. 11.0, MedStat v.15.1 software package for medical and biological research.

Results: The proposed surgical technique, leads to a gradual decrease in intraocular pressure (IOP) and regression of the iris and anterior chamber angle neovascularization. The postoperative course was uneventful for all the patients. In the early postoperative period, the IOP was observed to be normalized in all the eyes. The IOP ranged from 12 to 16 mm Hg. The neovascularization regression occurred (in 100 % of cases) within 5-7 days.

Conclusions: Gradual reduction of IOP reduces intraoperative complications. Intravitreal or intracameral injections of anti-proliferative agents contribute to the regression of neovascularization and further gradual reduction of IOP. Performing a laser trabeculectomy in the area where a non-penetrating deep sclerectomy was previously performed creates new pathways for the outflow of intraocular fluid from the anterior chamber and reduces the risks of reintervention.

KEY WORDS: surgery for neovascular glaucoma, neovascularization, anti-VEGF therapy, inflammatory process, ultrasound, cavitation

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INTRODUCTION

Over the past decades, there has been a rise in vascular diseases worldwide. One of the most severe manifestations and complications of vascular ophthalmological pathology, causing a rapid visual deterioration and subsequent blindness, is secondary neovascular glaucoma.

Ischemic central retinal vein thrombosis and branch retinal vein thrombosis are underlying factors for the disease in 30-40 % of cases. In recent years, the trend has been toward an increase in the number of working-age individuals affected by the disease [1, 2].

The inner retinal layers hypoxia, resulting in the production of vascular endothelial growth factors (VEGF), is basic to the development of secondary neovascular glaucoma.

The new vessels have incomplete endothelial coverage, and therefore, they have thin serous membranes that are prone to bleed. Iris neovascularization and vessel extension into the structures of the anterior chamber angle cause gradual blockage, which results in the angle closure and intraocular pressure (IOP) decompensation [1]. Moreover, this localization of neovascularization entails the high risk of intraoperative hemorrhagic complications, and as a consequence, it leads to IOP fluctuation, significantly reducing a desirable surgical hypotensive effect.

Existing neovascular glaucoma fistulizing surgery is usually highly traumatic and followed by intra- and postoperative hemorrhagic complications, which reach up to 50-55 % of cases [3-5].

The speed and extent of neovascularization are influenced by the concentration of angiogenic factors in the vitreous body and the aqueous humor of the anterior chamber.

To reduce intra- and postoperative hemorrhagic complications and achieve the regression of neovascularization there are used intravitreal and intracameral VEGF inhibitor injections [6, 7].

As an independent treatment, intravitreal anti-VEGF injections lead to a slight decrease in IOP when the angle

Table 1. Demographics and clinical features of patients with secondary neovascular glaucoma according to the stages of neovascularization and the state of the anterior chamber angle (N=28)

Index		n/N (%±m%)
Glaucoma Stage	II	9 (32±7.1)
	III	19 (68±7.2)
Neovascularization (stage)	II	12 (43±8.2)
	III	16 (57±7.5)
Gonioscopy: open angle /partially open angle	open	10 (36±7.9)
	partially open	18 (64±7.1)

Note: m% – percentage error.

of the anterior chamber is open due to neovascularization regression in this area.

However, the achieved clinical lowering of IOP is not long-lasting, so glaucoma surgery becomes necessary to drain fluid from the anterior chamber.

To stop progressive vision loss caused by neovascular glaucoma, it is necessary to influence the process of neovascularization and compensate IOP.

Searching new pathogenesis-based methods of surgical treatment for secondary neovascular glaucoma and preventing intra- and postoperative hemorrhagic complications are of importance for modern ophthalmology [8-10].

In our opinion, using anti-VEGF therapy in conjunction with lowering IOP in the treatment of neovascular glaucoma may produce a synergistic effect and be more effective than conventional glaucoma surgery with the prior administration of anti-VEGF injections [11].

AIM

To assess the effectiveness of the proposed surgical technique for treating secondary neovascular glaucoma, which involves a stepwise reduction of IOP used in combination with anti-VEGF therapy, as well as to evaluate its safety.

MATERIALS AND METHODS

We have developed a surgical technique for treating patients with secondary neovascular glaucoma, which involves performing a non-penetrating deep sclerectomy while administering anti-VEGF intravitreal or intracameral injections [12].

At the second stage we conducted the externalization of Schlemm's canal, then performed YAG laser trabeculectomy in combination with a non-penetrating deep sclerectomy.

We examined 28 eyes of 28 patients (16 women and 12 men), aged (mean [M] ± standard deviation [SD]) 46 ± 7,2 years, with secondary neovascular glaucoma.

In 10 patients, the neovascular glaucoma developed as a result of central retinal vein thrombosis, and in 18 patients, it occurred due to branch retinal vein thrombosis. The disease duration ranged from 6 to 8 months. All the patients (28 eyes) were treated by the proposed technique: a non-penetrating deep sclerectomy used in combination with administering anti-VEGF intravitreal injections for 16 patients and administering anti-VEGF intracameral injections for 12 patients.

Most patients had severe comorbidities: 71.4% of patients suffered from stage II/III hypertension, and 42.8% of patients had severe cerebral and coronary artery atherosclerosis.

The patients underwent standard examinations, which included visual acuity assessment, perimetry, tonometry, gonioscopy, biomicroscopy, and the optical coherence tomography of the optic nerve head.

Against the background of ocular hypotensive therapy (2-3 medications), the IOP ranged from 28 to 42 mm Hg and averaged out (M±SD) 34.2 ± 1.2 mm Hg. The optic nerve changes in 9 eyes (32.1%) were indicative of stage 2 glaucoma and those in 19 eyes (67.9%) corresponded to stage 3 glaucoma. The iris and anterior chamber angle neovascularization corresponded to grade 2 and grade 3 as per Weiss classification. The anterior chamber angle was open in 10 eyes, and it was partially open in 18 eyes (Table 1). The majority of patients had changes in the optic nerve, respectively, stage 3 glaucoma and neovascularization of the angle of the anterior chamber of grade 3 (Table 1).

Non-penetrating deep sclerectomy was performed for the open angle of the anterior chamber [11, 12]. During the postoperative period, the patients received instillations of antibacterial, steroid, and non-steroidal anti-inflammatory drugs.

Upon achieving regression of the iris and anterior chamber angle neovascularization, to create new pathways for the outflow of intraocular fluid from the anterior chamber, within 2-4 weeks we undertook the YAG laser trabeculectomy in the area where the non-penetrating deep sclerectomy was previously performed [12].

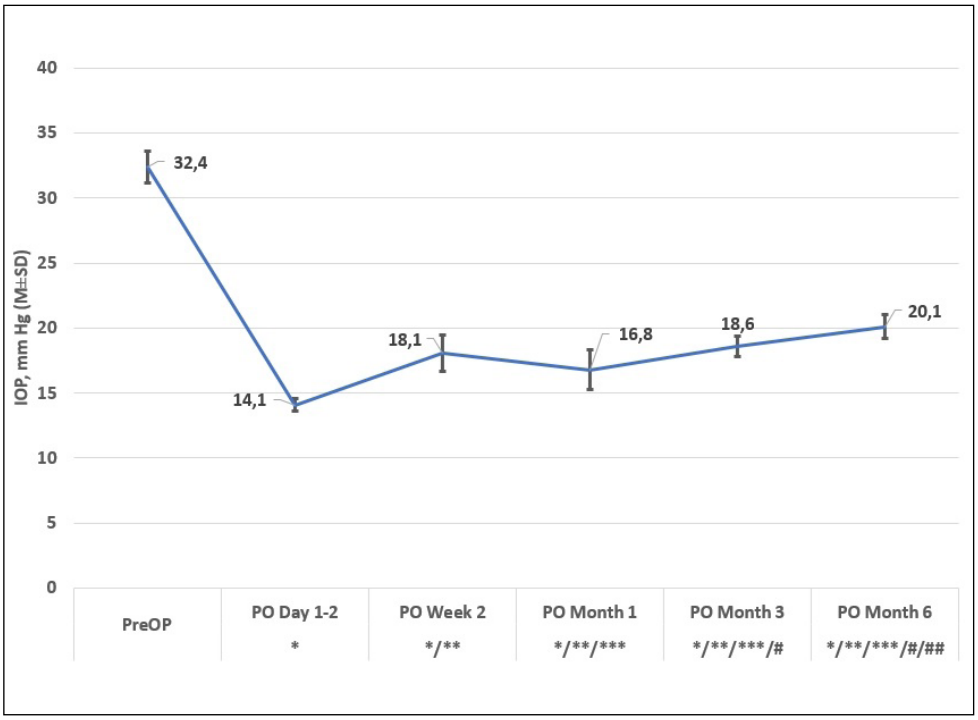

Fig. 1. Preoperative (PreOP) value and postoperative (PO) IOP dynamics. across the observation time series (mm Hg). * – p<0.05 vs. preOP; ** – p<0.05 vs. PO day 1-2; *** – p<0.05 vs. PO week 2; # – p<0.05 vs. PO month 1; ## – p<0.05 vs. PO month 3.

We assessed the outcomes 1, 2 weeks, and 1, 3, 6 months following surgery.

The researchers followed all protocols and procedures required by the Biomedical Research Ethics Committee and conform to the directive of the Ukrainian Legislation on health care, Helsinki Declaration 2000 and European Society Directive 86/609 on human participation in biomedical research to ensure adherence to all standards for adequate protection and well-being of participants. Informed consent was received from all respondents who took part in this research.

Statistical analysis of the results was performed using the SPSS v. 11.0, MedStat v. 5.2, MedCalc v.15.1 software package (MedCalc Software bvba) for medical and biological research. The quantitative variables were presented as M ± SD, qualitative – as absolute and relative (%) frequency (with percentage error [±m%]). The significance of difference in IOP between different postoperative follow-up periods was assessed by means of the Friedman test, with post hoc comparisons by the use of the Wilcoxon signed-rank test. The statistical difference was considered as $p<0.05$ (considering the Bonferroni correction).

RESULTS

The research has shown that the proposed surgical technique, which includes performing a standard non-penetrating deep sclerectomy while administering intravitreal or intracameral injections of antiproliferative agents for secondary neovascular glaucoma, leads to a gradual decrease in IOP and regression of the iris and anterior chamber angle neovascularization.

The analysis of the proposed combined technique and the postoperative results has shown that performing a non-penetrating deep sclerectomy (Stage I) reduces IOP. Moreover, lowering pressure by means of a non-penetrating deep sclerectomy compensates for a potential elevation in the IOP in response to administering anti-VEGF intravitreal or intracameral injections.

Having achieved the regression of neovascularization, we could perform the YAG laser trabeculectomy (Stage II) to create new pathways for the outflow of intraocular fluid from the anterior chamber. 28 patients (28 eyes) with secondary neovascular glaucoma underwent the surgical procedures.

The proposed combined technique included the following stages:

– retrobulbar anesthesia;
– the limbus-based incision of the conjunctiva and Tenon's capsule (it lasts from 11 to 13 hours).
– fashioning the superficial limbus-based scleral flap (3 × 4 mm; 1/3 scleral thickness), and then dissecting the scleral flap 1.5 mm into the clear cornea.
– excising the middle scleral flap with underlying Schlemm's canal exterior wall and corneal stroma behind the Descemet's membrane.
– juxtacanalicular trabecular tissue removal;
– excising the deep scleral flap behind the ciliary body, measuring 2 x 1 mm and 3-4 mm near the limbus;
– administering aflibercept 2 mg/0.05 mL anti-VEGF injections into the vitreous cavity or anterior chamber using a standard technique;

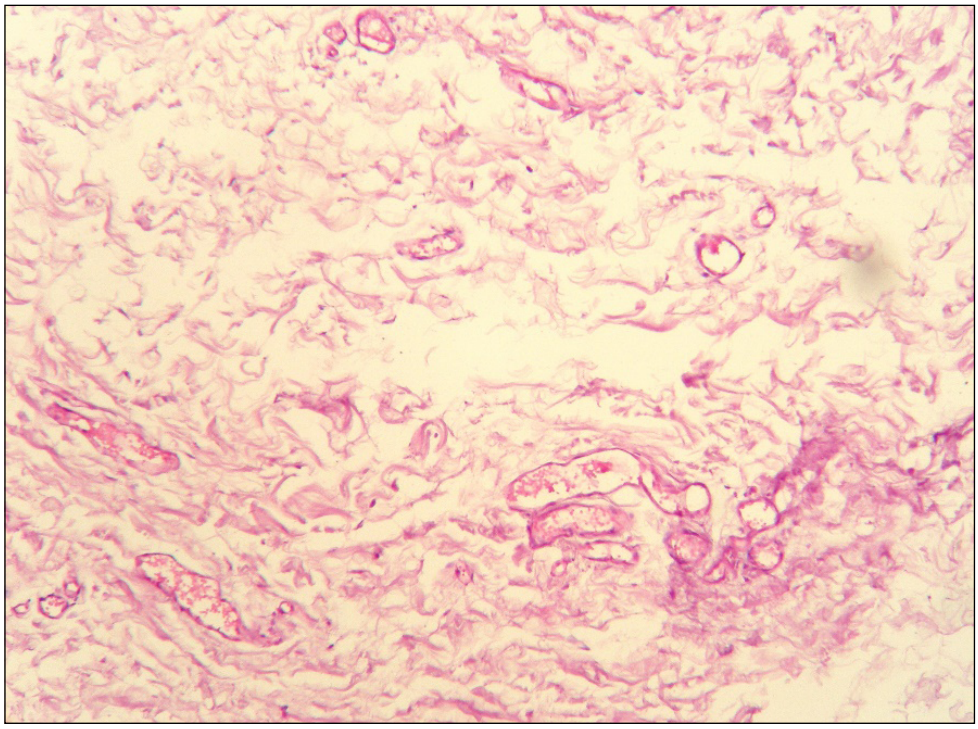

Fig. 2. Scleral flaps. Histological preparation.
Section stained with H&E, x400.

– closing the conjunctiva with two interrupted sutures; no sutures were inserted into the scleral flap;
– applying an aseptic dressing.

Hemorrhagic complications (minor hyphema) were observed in 3 eyes (10.7%). The hyphema resolved on its own within 4-5 days, no additional interventions were required.

The postoperative course was uneventful for all the patients. In the early postoperative period, the IOP was observed to be normalized in all the eyes that was accompanied by an evident filtering bleb. The IOP ranged from 12 to 16 mm Hg. The neovascularization regression occurred (in 100 % of cases) within 5-7 days.

To create new pathways for the outflow of intraocular fluid from the anterior chamber, within 2-4 weeks we undertook the YAG laser trabeculectomy in the area where the non-penetrating deep sclerectomy was previously performed.

Once the trabeculectomy was done we noted the filtering bleb enlargement. The IOP ranged from 16 to 18 mm Hg (with an average of 16.8±1.5 mm Hg), antihypertensive medications were not used. We did not observe any difference in the neovascularization regression at administering anti-VEGF intravitreal and intracameral injections.

The first 3 months monitoring has found that the IOP stayed within normal limits in 24 patients (86%), while in 4 patients (14%) it was normal in response to the antihypertensive treatment (Fig. 1).

The first 6 months monitoring has found that the IOP stayed within normal limits in 20 patients (71 %), while in 8 patients (29 %) it was normal in response to the antihypertensive treatment. There was no vision impairment (visual acuity and visual field decrease) during the monitoring period.

The normalized IOP made it possible to preserve visual functions in patients with secondary neovascular glaucoma.

Minor response to the surgical trauma, absent acute-phase response following surgery, few minor intraoperative complications (partial hyphema was in 10.7 % of cases), a sustained reduction of elevated IOP (71 %), feasible surgical techniques were reported.

In addition, this method of combined surgical treatment is appropriate, since our previous studies have shown that in glaucoma, in the area where anti-glaucoma intervention is usually performed, processes peculiar to chronic progressive inflammation occur.

This is evidenced by the results of histological examination of tissue (parts of scleral flaps) removed during anti-glaucoma surgery. When conducting microscopy, thickening of all layers of the sclera, the signs of neovascularization with endotheliocytes proliferation were determined in our study group (28 patients); it may point to chronic inflammatory process occurrence. The slightly changed cell nuclei of fibrous tissue (increased in size and more intensely colored, are located alone or form unstructured clusters) were established to indicate alteration in the examined tissue cells, and therefore, they may affect the postoperative scarring (Fig. 2).

The significant swelling of the surrounding tissue, which pathologically changed the structure of the

tissue itself was also observed that could lead to an increase in outflow resistance and IOP (Fig. 2).

Therefore, the additional administration of anti-VEGF injections during surgery in patients with secondary neovascular glaucoma is pathogenetically justified.

DISCUSSION

Treating patients with secondary neovascular glaucoma is an unsolvable problem in modern ophthalmology. Despite the advances in the development of the improved diagnostic and treatment technologies for eye diseases, there is no consistent treatment approach to this pathology. Long-term efforts aimed at improving secondary neovascular glaucoma management have not reduced the urgency of the problem [1, 3, 13].

Due to the drug therapeutic failure, surgical treatment is a focus area for normalizing IOP and stabilizing visual functions in patients with secondary neovascular glaucoma, in particular after central retinal vein occlusion [3, 13].

The spectrum of surgical modalities used in patients with secondary neovascular glaucoma is rather wide: it includes as traditional filtering procedures for glaucoma so cryosurgical, drainage, and laser techniques [3, 6, 14].

The literature review analysis focused on surgery for secondary neovascular glaucoma has shown that this problem remains to be done as of today [8, 9]. Pathogenetic surgical approaches to secondary neovascular glaucoma have always been of ophthalmologists' particular emphasis. They are based on the understanding of the pathogenesis of intraocular fluid outflow disorder onset and development [10, 13]. In the case of secondary neovascular glaucoma, the intraocular fluid outflow disorder is localized in the filtration angle: trabeculae, Schlemm's canal, the anterior chamber angle [1, 2].

The majority of researchers agree that the main cause of outflow disorder is the anterior chamber angle and trabeculae areas. The cause of neovascular glaucoma is known to be a pathological neoplasm of blood vessels in the iris and the anterior chamber angle. The trigger for progressive neovascularization of the anterior vascular tract is ischemia of the retina, caused by its circulation disorder [6, 14].

Neovascular proliferation is induced by angiogenic factors (VEGF, etc.), which are produced by the inner layers of the retina in a state of hypoxia. The neovascularization factor is defined as a substance that provokes the uncontrollable growth of newly formed pathological vessels; their conglomerates lead to various hemorrhages with subsequent tissue destruction [4, 5]. The speed and spread of neovascularization are influenced by the concentration of angiogenic factors in the vitreous body and the aqueous humour of the anterior chamber [4, 5].

In its further development a newly formed fibrovascular tissue tends to retraction, which results in goniosynechiae formation. The process spreading over the perimeter of the anterior chamber angle leads to its closure. The oversaturation of intraocular tissues with newly formed vessels, their close location to the filtration area block the outflow of intraocular fluid, which impedes IOP normalization, increases the risk of intraocular hemorrhages [6-8]. Our evidence suggests that the inflammatory processes occur not only in the anterior chamber angle, which subsequently worsen the hydrodynamics of the intraocular fluid. The chronic inflammatory process occurs both in the Tenon's capsule and in the scleral capsule, that affects anti-glaucoma surgery outcomes.

Recently, secondary neovascular glaucoma surgery tends to combined interventions which influence various components of the disease pathogenesis, but an optimal treatment strategy is still absent.

Most of the existing surgical interventions are associated with a high risk of hemorrhagic intra- and postoperative complications, which is a consequence of both high IOP and the presence of newly formed vessels of the iris and the anterior chamber angle. Hemorrhagic complications and increased proliferation of connective tissue in the area of surgery reduce the hypotensive effect of surgery and limit their use in secondary neovascular glaucoma. Non-penetrating surgery, which is so widely used in the treatment of primary glaucoma, is characterized by the least number of complications, in secondary neovascular glaucoma it has a restricted effect due to the rapid scarring of the bleb [5, 7, 13].

There are few effective methods for treating progressive rubeosis iridis. The argon-laser coagulation of ischemic areas of the retina, newly formed vessels of the iris and the anterior chamber angle are widely used. The disadvantages of this method are the short-term occlusion of newly formed vessels, reactive hypertension, and a high risk of inflammatory complications [3].

The existing interventional trials of such glaucoma, both by means of antimetabolites and without them, have no expected hypotensive effect. Using a variety of drainage and valve systems provides somewhat greater efficiency, but also has great deal of surgical implications [3].

Recently, intravitreal and intracameral VEGF-injections have been used as a step in treating neovascular glaucoma to achieve regression of newly formed vessels of the iris and the anterior chamber angle as well as to reduce the frequency of surgical and postsurgical hemorrhagic complications [3-5, 14].

As an independent treatment, anti-VEGF therapy facilitates the regression of the newly formed vessels of the iris and the anterior chamber angle, reduces vascular permeability, and partially decreases IOP. But the achieved hypotensive result is not long-lasting (4-6 weeks), so glaucoma surgery is necessary to create a filtration fistula [4, 6].

However, neither the isolated use of anti-VEGF drugs, nor the use of their combination with traditional surgical interventions gives the expected result. In addition, even the combined interventions cannot influence all pathogenetic components of the secondary neovascular glaucoma development [3, 4].

The treatment of such a significant abnormality requires a treatment landscape aimed at reducing IOP, reducing neovascularization, as well as affecting the foci of retinal ischemia and VEGF production [3, 4, 6, 14].

Today, the phenomenon of ultrasonic cavitation, which occurs when high-intensity ultrasonic vibrations are introduced into a liquid, is widely used in technology [15]. In addition to other possibilities, ultrasonic cavitation provides high-quality removal of contaminants from surfaces and disinfection. It should be noted that one of the most used bioeffects of ultrasound for therapeutic purposes is cavitation. The phenomenon of the formation of bubbles from gases that exist in living tissue is used. Irradiation of a liquid containing a gas bubble with an acoustic field can lead to the transformation of a low-energy density of acoustic waves into a high-energy pulsating bubble. When a bubble is located near a rigid boundary, a liquid jet is formed in the final stage of bubble collapse. The jet stream concentrates a large amount of the bubble's energy in a small area, quite far from the initial location of the bubble. The pressure created by the jet shock generated by the collapse of the bubble near the border can lead to the fragmentation of fragile objects such as kidney stones, etc., [15] and, in our opinion, to restore the elasticity of the trabecular meshwork, the main component of the drainage system of the human eye.

The treatment of such a serious pathology requires a complex of methods aimed at reducing IOP, reducing neovascularization, as well as affecting the foci of retinal ischemia and VEGF production [3, 4].

Thus, the proposed combined surgical technique for secondary neovascular glaucoma includes performing a non-penetrating deep sclerectomy while administering intravitreal or intracameral injections of angiogenesis inhibitors, reducing IOP gradually through performing a YAG-laser trabeculectomy, that makes it possible to effectively lower IOP and minimize intra- and postoperative complications, thereby it ensures a sustained normalization of IOP.

Due to the mentioned characteristics this technique can be used as the surgery of choice for secondary neovascular glaucoma. The results obtained in the course of this experimental research are the basis for a more detailed study of the problem of glaucoma treatment.

CONCLUSIONS

1. Applying the surgical technique for treating neovascular glaucoma is instrumental for a gradual decrease in IOP, that thereby reduces intraoperative complications.
2. The iris and anterior chamber angle neovascularization regression achieved through administering the intravitreal or intracameral injections of anti-proliferative agents leads to a further gradual lowering of IOP. Performing the YAG laser trabeculectomy in the area where the non-penetrating deep sclerectomy was previously performed creates new pathways for the outflow of intraocular fluid from the anterior chamber.
3. This combined technique lowers the risks of reintervention and emotional stress for the patients.
4. The further study of the neovascular glaucoma pathogenesis may make the treatment more effective and reduce the frequency and severity of surgical complications.

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CONFLICT OF INTEREST

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ORIGINAL ARTICLE

CONTENTS

Prognostication of the development of septic complications in children with burn injuries

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ABSTRACT

Aim: To determine the prognostic criteria for the development of septic complications in children with thermal injury.

Materials and Methods: A single-center retrospective-prospective cohort study included a retrospective analysis of 98 medical histories of children of different ages with severe burns who were treated from 2007 to 2017. A prospective study was conducted among children (n=63) from 1 to 5 years old, who received various degrees severity burn injury, according to an open comparative method in the period from 2018 to 2021.

Results: Indicators of a high risk of developing sepsis were burns by flames of any etiology, damage severity index ≥75 units, total burn surface ≥25 %, deep burn area ≥ 5%. The threshold value of procalcitonin (PCT) ≥ 0.86 ng/ml on the 1st-3rd day and PCT > 0.51 ng/ml on the 7th day of burn disease, had a prognostic value for assessing the probability of sepsis. On the 1st day of hospitalization, the development of sepsis was predicted if the C-reactive protein (CRP) value was higher than 6.98 ng/ml, on the 3rd – the CRP level was above 7.43 ng/ml, on the 7th day – above 7.28 ng/ml.

Conclusions: Based on the obtained data, we selected the criteria with the best prognostic characteristics, which allows us to predict and prevent the development of sepsis in the early stages of burn disease in children.

KEY WORDS: burn disease, prognostic criteria, biological markers for diagnosis and prediction of sepsis

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INTRODUCTION

Sepsis is considered as a life-threatening organ dysfunction, which is caused by a dysregulation of the patient's body's response to infection, which leads to an increase in hospital mortality [1].

Factors in the development of sepsis include patients with various disorders of the integrity of the skin – wounds, burns, skin infections, etc. To date, the proven risk factors for the development of sepsis in children with burns are the total burn surface (TBS), the deep burn area (DBA), thermo-inhalation lesions and the presence of invasive devices in them [2].

In burn patients, especially in children with a hyperreactive reaction to trauma, sepsis is characterized by a sudden onset and a rapid course. All patients with burns need careful attention to the possibility of developing sepsis until the wound is completely closed. The risk group for the development of burn sepsis includes injured children with early (first day after injury) manifestations of systemic inflammatory response syndrome (SIRS) [3].

The leukocytosis or leukopenia with an increase in the number of neutrophils and the appearance of immature cells in the general blood test are the simplest and fastest markers in the diagnosis of sepsis [4].

Hyperlactatemia in patients with a severe burn injury leads to an increase in septic complications and multiple organ dysfunction syndrome (MODS). Hyperlactatemia is considered a lactate level up to 4 mmol/l, and severe – more than 4 mmol/l [5]. C-reactive protein (CRP) levels are considered predictors of severe infection and/or sepsis in the general population. In patients with severe burn injury, the level of CRP is a marker of homeostasis disturbance and a criterion of SIRS. Long-term signs of SIRS (more than 3 days) in patients with severe burn injury (BI) indicate a high risk of developing MODS and probable high mortality [6].

Thus, it is relevant to determine the prognostic criteria of the course of burn disease at different degrees of thermal damage in different age categories of children and the effectiveness of preventing the development of burn sepsis with the possibility of identifying its early prognostic diagnostic markers.

AIM

To determine the prognostic criteria and diagnosis of the development of septic complications of burn disease by studying the dynamics of SIRS, MODS and biological markers for the identification of sepsis.

MATERIALS AND METHODS

A retrospective and prospective study was conducted to realize the purpose of the work and to solve the tasks.

A retrospective analysis of 716 medical records of children affected by burn injury (BI), who were treated in the Department of Anesthesiology and Intensive Care of Municipal Non-Profit Enterprise "Odesa Regional Clinical Medical Center" of the Odesa Regional Council, Odesa, Ukraine between 2007 and 2017, was carried out. For further analysis of the development of the course of burn disease were selected 98 medical records of children of different age categories with severe and extremely severe burn injuries, which were divided into 4 groups depending on age: 1 group (P1) (n=13) children aged 6 months – 1 year, 2nd group (P2) (n=61) aged 1-5 years, 3rd group (P3) (n=12) aged 5-11 years, 4th group (P4) (n=12) aged 11-18 years.

The prospective study included 63 children aged 1 to 5 years who received a BI of varying degrees of severity and met the criteria for inclusion in the study using an open comparative method in the period from 2018 to 2021.

The conducted research met the requirements of the Declaration of Helsinki and other international and national documents relating to bioethical principles of scientific research. All patients and their parents were informed about the nature of the clinical study, and gave written informed consent for the processing of informational data.

The stratification criteria in the prospective study of children with burns were the age of the children and the degree of severity of the thermal damage according to the damage severity index (DSI). The 1st group (P1) included children (n=29) from DSI 10-30 units, the 2nd group (P2) (n=20) DSI comprised 31-60 units, the 3rd group (P3) (n=14) DSI more than 61 units.

The stages of the study were the 1st day – upon admission, the 3rd day, the 7th day, the 14th and the 21st day of stay in the intensive care unit.

The calculation of TBS was performed using the Lund-Browder score, which includes age-related features of body proportions [7]. In order to determine the severity of thermal injury in all patients, an assessment of DSI, unit, TBS, %, DBA, %, respiratory tract burn, victim's age (months, years) was performed.

All patients were monitored and hourly assessment of the main indicators of vital functions and their correction, assessment of clinical laboratory and biochemical indicators of blood and urine. The study determined the dynamics of CRP, procalcitonin (PCT) and serum lactate levels. Diagnosis of sepsis was carried out in accordance with international recommendations for the treatment of septic shock and sepsis-related organ dysfunction in children [8], taking into account the age characteristics of vital signs of patients.

Descriptive methods were used to describe the primary data set statistics. For quantitative data of the hypothesis of the normal distribution law random variable was checked by the Shapiro-Wilk test (when $n < 50$) or Kolmogorov-Smirnov with Lilliefors correction (when $n \geq 50$).

If continuous variables had a normal distribution, they were presented as means ± standard deviations or as medians with interquartile ranges (IQRs). Categorical data were described with an indication absolute values and percentages. To compare the statistical characteristics of the central tendency of the t-test was used for normally distributed independent samples Student, in the absence of signs of normal distribution of data or in small samples – Mann-Whitney U-test; for dependent samples was used appropriate Student (T) or Wilcoxon (W) criteria. Multiple comparison indicators in all 3 groups of the prospective study were conducted by the non-parametric Kruskal – Wallis (H) test and further using Dunn's a posteriori test. Comparison of categorical data was carried out using Pearson's $\chi 2$ or two-sided exact Fisher's test (TFT).

To assess the relationship between the features, a correlation analysis was performed with by calculating Spearman's rank correlation coefficients (rs) and coefficients canonical correlation (Rc). Determination of predictors of burn injury (age, sex, etiological factor), the development of septic complications, MODS and death the outcome in patients with burn disease was performed using ROC analysis with calculation of the area under the ROC curve with error (AUC±SE) and 95 % confidence interval (CI), determination of the cut-off point and standard operating hours characteristics (sensitivity (Sen), specificity (Sp), diagnostic accuracy [DA]); univariate and multivariate logistic regression analysis with calculation of odds ratios (OR) with 95 % CI. The results of null hypothesis testing for all types of analysis were considered statistically significant at $p < 0.05$.

Statistical processing and analysis of the obtained data was carried out using STATISTICA v.6.1 program packages (StatSoft Inc., serial No. AGAR909E415822FA),

Table 1. General characteristics of children with severe and extremely severe burns (according to the data of a retrospective study), Me (IQRs)

Indicator	R1 group (n=13)	R2 group (n=61)	R3 group (n=12)	R4 group (n=12)	Intergroup differences (P_{KW-H})
Age, years	0,75 * (0,67; 0,83)	2,5 * (1,6; 3,0)	8,0 * (5,8; 9,0)	14,5 * (13,5; 15,5)	<0,001
DSI, units	86,0 (70,0; 100,0)	85,0 (70,0; 110,0)	91,5 (65,0; 182,5)	118,5 (66,0; 147,0)	0,698
TBS, %	40,0 (35,0; 43,0)	40,0 (30,0; 50,0)	40,0 (27,5; 75,0)	56,0 (35,0; 67,5)	0,333
DBA, %	15,0 (8,0; 20,0)	12,0 (7,0; 20,0)	15,0 (12,5; 45,0)	15,0 (8,5; 18,5)	0,427

Notes: Indicators are presented in the form of Me (IQRs); pKW-H – the level of statistical significance of the differences in indicators between the 4 groups as a whole (according to the Kruskal-Wallis test); * – p <0.001 (** – p =0.013) between the respective groups (according to Dunn's test).

Table 2. Demographic and etiological factors associated with the sepsis development in patients of the retrospective group with burn injury, n (%)

Indicator		Sepsis		Intergroup differences (p)	Spearman's correlation coefficient (rs, p)
		Positive (n=70)	Negative (n=28)		
Gender	boys, n (%)	39 (55,7)	20 (71,4)	0,151	rs= 0,145; p = 0,154
	girls, n (%)	31 (44,3)	8 (28,6)		
Age, years	from 6 month to 1 year	8 (11,4)	5 (17,9)	0,397	rs= 0,178; p = 0,080
	1-5 years	42 (60,0)	19 (67,8)	0,469	
	5-11 years	8 (11,4)	4 (14,3)	0,697	
	12 years and elder	12 (17,2)	0 (0)	0,017*	
Etiological factor	boiling water	45 (64,3)	24 (85,7)	0,036	rs= -0,212; p = 0,036
	flames of any etiology, including:	22 (31,4)	3 (10,7)	0,034	rs= 0,215; p = 0,034
	- open flame	13 (18,6)	2 (7,1)	0,156	rs= 0,143; p = 0,159
	- the flame of the voltaic arc	9 (12,9)	1 (3,6)	0,170	rs= 0,139; p = 0,174
	steam	1 (1,4)	0 (0)	1,00*	rs= 0,064; p = 0,53
	hot food	2 (2,9)	0 (0)	1,00*	rs= 0,091; p = 0,371
	boiling water + steam	0 (0)	1 (3,6)	0,286*	rs= -0,161; p = 0,114

Note. Intergroup differences were assessed by Pearson's $\chi 2$ test or TFT (*).

StatTech v. 2.5.9 (developer – "Stattech" LLC; registration No. 2020615715; registration date 05/29/2020) and the MedCalc Statistical package Software trial v.20.218 (MedCalc Software Ltd, Ostend, Belgium), which is in open access on the website https://www.medcalc. org; 2023.

RESULTS

Patients of all retrospective study groups were statistically comparable ($p > 0.05$) by gender of patients ($p = 0.559$), indicators of TBS ($p = 0.333$), DBA ($p = 0.427$) and DSI ($p = 0.698$) (Table 1).

Sepsis was diagnosed in 70 (71.4 %) children of the retrospective group and despite the high vulnerability of the age category of children under 5 years of age (11.4 % of patients with sepsis are children from 6 months to 1 year and 60,0 % of patients from 1 to 5 years), the frequency of sepsis increased with the age of the patients. In particular, sepsis was diagnosed in all children older than 12 years (n = 12). According to the results of the ROC analysis, the threshold value of the age of a child with a high probability of developing sepsis was more than 2.6 years. The area under the ROC curve was 0.659 ± 0.06 with 95 % CI: 0.557 – 0.752 at p = 0.008. The Sen and Sp of the criterion are 60.0 % and 67.9 %, respectively. Under such

Table 3. General characteristics of children with burn disease in the age group from 1 year to 5 years (according to the data of a prospective study), Me (IQRs)

Indicator	P1 group (n=29)	P2 group (n=20)	P3 group (n=14)	Intergroup differences (p)
DSI, units	21,0 (18,0; 24,0)	34,0 (32,0; 37,0)	69,5 (62,5; 82,5)	p_{KW-H}<0,001 p_{1-2} <0,001 p_{2-3} <0,001 p_{1-3} <0,001
TBS, %	8,0 (7,0; 10,0)	12,0 (10,0; 15,0)	25,0 (18,0; 27,0)	p_{KW-H}<0,001 p_{1-2} =0,003 p_{2-3} =0,006 p_{1-3} <0,001
DBA, %	0 (0; 1,0)	0 (0; 3,5)	15,0 (3,0; 20,0)	p_{KW-H}=0,003 p_{1-2} = 1,0 p_{2-3} =0,003 p_{1-3} <0,001

Notes: Indicators are presented in the form of Me (IQRs), pKW-H – the level of statistical significance of the differences in indicators between the 3 groups as a whole (according to the Kruskal-Wallis test); p – is the level of statistical significance of the differences in indicators between the respective groups (according to Dunn's criterion).

Table 4. Prognostic criteria for the development of sepsis in children aged 1 to 5 years with burn injury

Indicator		Threshold value	AUC (95 % CI)	Sen/Sp/DA (%)	p
Flame of any etiology		Availability	0,604 (0,50-0,701)	31,4/ 89,3/ 47,9	0,011
Boiling water + steam		Availability	0,741 (0,615-0,843)	50,0/ 98,3/ 93,7	0,032
DSI		>75,0 units	0,963 (0,883-0,995)	83,3/ 100,0/ 98,4	<0,001
Indicator		Threshold value	AUC (95 % CI)	Sen/Sp/DA (%)	*p*
TBS		≥ 25,0 %	0,95 (0,864-0,989)	83,3/ 94,7/ 93,7	<0,001
DBA		≥ 5,0 %.	0,822 (0,732-0,892)	88,6/ 71,4/ 83,7	<0,001
PCT	1 day	≥ 0,86 ng/ml	0,792 (0,618-0,911)	83,3/ 71,4/ 73,5	0,013
	3 day	≥ 0,86 ng/ml	0,759 (0,582-0,888)	83,3/ 71,4/ 73,5	0,044
	7 day	>0,52 ng/ml	0,836 (0,670-0,940	100/ 64,3/ 70,6	<0,001
CRP	1 day	> 6,98 ng/ml	0,786 (0,612-0,907)	66,7/ 92,9/ 88,3	0,050
	3 day	> 7,43 ng/ml	0,801 (0,628-0,917)	83,3/ 78,6/ 79,4	0,021
	7 day	>7,28 ng/ml	0,807 (0,635-0,921)	83,3/ 82,1/ 82,3	0,002
Rod nuclear neutrophils (3 day)		>10 %	0,827 (0,711-0,911)	66,7/ 91,2/ 88,9	< 0,001
Lymphocytes (1 day)		≤ 20,0 %	0,871 (0,763-0,942)	100,0/ 71,9/ 74,6	< 0,001

Notes: TV is the threshold value of the indicator (cut-off point); AUC (95 % CI) is the area under the ROC curve with a 95 % confidence interval; p – level of prognostic significance of AUC; Sen/Sp/DA – indicators of sensitivity / specificity / diagnostic accuracy.

conditions, the risk (chances) of developing sepsis in BI increase by 3.17 times compared to children younger than 2.7 years – the OR = 3.17; 95 % CI (1.25 – 7.99), p = 0.015. The analysis of etiological factors of burn injury in children with sepsis showed that the leading factor of them was scald – 45 (64.3 %) cases (Table 2).

In a third of victims with burn sepsis, the cause of BI was a flame of any etiology (in case of fire, ignition, from the action of an electric arc, etc.), while among patients without septic complications, such cases were three times less – 31.4 % (n =22) versus 10.7 % (n=3), respectively, at p = 0.034. That is, exposure to flame increases the risk of developing sepsis by 3.82 times – OR =3.82; 95 %, CI (1.04-14.01) at p = 0.043.

Patients of prospective research groups P1, P2 and P3 were statistically comparable (p >0.05) in terms of gender (p =0.609) and age of children (p =0.976), but probably differed in terms of DSI (p <0.001), TBS (p < 0.001) and DBA (p = 0.003) (Table 3).

Sepsis was diagnosed in 6 (9.5 %) patients of the prospective group on day 7.0 of the BD, which was probably more often noted in patients who received burns with boiling water in combination with steam (rs= 0.581; p < 0.001) and was closely correlated with severity BI according to DSI (rs = 0.417, p < 0.001) and percentage of vocational training (rs = 0.461, p < 0.001).

The analysis of data from retrospective and prospective studies of the development of purulent-septic complications in children with moderate, severe, and extremely severe BD made it possible to identify a number of predictors of the development of sepsis with the best prognostic characteristics (Table 4).

As presented in Table 4, indicators of the severity of BI – DSI (AUC= 0.963 (0.883-0.995), p < 0.001) and TBS (AUC = 0.95 (0.864-0.989), p < 0.001) with high indicators of sensitivity, specificity and, accordingly, prognostication accuracy at threshold values of DSI indicators >75.0 units (Sen = 83.3 %, Sp = 100%, DA = 98.4 %) and TBS ≥ 25% (Sen = 83.3 %, Sp = 94.7%, DA = 93.7 %).

PCT indicators from the 1st to the 7th day of BD had a prognostic value in the development of sepsis, which was confirmed by the results of comparative ROC analysis. According to the data of ROC analysis, it was established that the PCT threshold value of 0.86 ng/ml and higher on the 1st or 3rd day of BD had a prognostic value for assessing the probability of sepsis. On the 7th day of BD, the development of sepsis was predicted if the PCT value was higher than 0.51 ng/ml. At the same time, the sensitivity of the method of predicting the development of sepsis based on the level of PCT in the blood of patients increased and amounted to 100 %, while the specificity decreased to 64.3 % (Table 4).

According to the ROC analysis, it was established that CRP values at all studied stages of the acute period of BD have a good prognostic value for assessing the probability of sepsis (AUC in the range of 0.7-0.8) without statistically significant differences (p < 0.05). On the 1st day of hospitalization, the development of sepsis was predicted if the CRP value was higher than 6.98 ng/ml, on the 3rd – the CRP level was above 7.43 ng/ml, on the 7th day – above 7.28 ng/ml. At the same time, the sensitivity of the method for predicting the development of sepsis based on the CRP level was higher on the 3rd and 7th day (83.3 %), and the specificity was higher on the 1st day (Table 4).

According to the obtained data, the indicators of lymphocytes and rod-nuclear neutrophils in the peripheral blood should also be taken into account when predicting the development of sepsis in children with BD.

DISCUSSION

Burn injury in children leads to a massive release of inflammatory mediators into the bloodstream and the development of a complex systemic activation of the immune system with a damaging effect on all vital organs [9]. A burn of more than 15 % of total body surface area leads to the development of hypovolemic shock and, as a result, causes SIRS with the release of cytokines into the bloodstream with their subsequent dissemination to distant organs and tissues [10].

An increase in the level of lactate in the blood serum is an indicator of the duration of hypoxia and hypoperfusion, and is observed at the beginning of a burn injury as a reflection of its severity [11]. In the study of Gulhan et al. it was demonstrated that the level of CRP more than 6 ng/mL is a risk factor for the development of sepsis in children with severe burns [12]. An increase in the level of PCT at the beginning of a burn disease indicates the severity of the injury and an unfavorable prognosis for life [13].

As a result of the study, it is substantiated that quick recognition of sepsis using standardized screening and identification of patients at risk of developing sepsis should be an important component of programs to improve the quality of prevention and treatment of sepsis in children with BD. Therefore, in order to ensure the timely diagnosis of early burn sepsis in children with BI and improve the quality of the prognosis, we selected the most significant indicators of thermal damage (DSI, TBS, DBA) and laboratory blood markers associated with sepsis in the relevant observation periods.

It was determined that the indicators of CRP and PCT from the 1st to the 7th day of BD had a prognostic value in the development of sepsis, which was confirmed by the results of comparative, canonical and ROC analysis.

CONCLUSIONS

The article presents the definition of risk factors that probably influenced the development of sepsis and mortality, the assessment of their prognostic value taking into account the age, gender of patients, the etiological factor of burn injury, the severity of the lesion, the timing of the development of complications, MODS and the determination of the dynamics of changes in biological markers for the identification of sepsis, their of prognostic value for preventing the development of sepsis and MODS in children of different age groups with BD.

1. It has been proven that the etiological factor of BI and indicators of TBS, DBA predict the probability of developing septic complications in children with severe and extremely severe BI.
2. PCT and CRP indicators on the 1st day of BD are closely related to DSI and demonstrate the severity of the injury and the intensity of SIRS. From the 7th day of illness, the level of PCT and CRP reflect the development of sepsis in children with severe BI, which allows timely adjustment of antibacterial and intensive therapy in patients. The amount of lactate characterizes the presence of a violation of tissue perfusion, which is associated with the severity of the received burn injury from the 1st day of BD.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Evaluation of clinical and demographical finding in patients with oral lichen planus: A retrospective cross sectional study

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ABSTRACT

Aim: To learn more about Oral Lichen Planus Iraqi patients, including their background information, symptoms, and prognosis.

Materials and Methods: From the Oral and Maxillofacial Pathology Department, College of Dentistry, Baghdad University, we retrospectively reviewed the medical records of 68 patients with a histologically confirmed clinical diagnosis of oral lichen planus and subsequently contacted the patients by phone to evaluate their prognosis.

Results: Females were more likely than males to experience severe pain; the reticular form of Oral Lichen Planus was the most prevalent at 38.2%, but the erosive type was more prevalent among females. Only 53 of 68 patients responded to phone calls. More than 37% of those respondents reported involvement at a second location intra-orally following the first oral manifestation, and 20% had extraoral Lichen Planus, and approximately 22.6% of them observed changes in the morphology and behavior of the lesion after a brief period of time, while 26.4% experienced complete remission.

Conclusions: Females were more likely to have oral lichen planus. Females and elderly persons were more likely to have severe pain than other. The lesion must be monitored for symptomatic flare-ups over time.

KEY WORDS: epidemiology, lichen planus, oral lichen planus, retrospective study

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INTRODUCTION

Oral lichen planus (OLP) is a common inflammatory mucocutaneous condition that affects the oral mucosa [1, 2]. An important involvement for the immune system is suspected, however the exact reason is yet unclear, while there are several therapy options, the disease has a protracted clinical course [3, 4]. The incidence of OLP in the general population ranges from 1% to 2% [5]. Typically, it affects middle-aged and elderly people with a female/male ratio of 2:1 [6] and the age of onset is generally between the fourth and sixth decades of life [7]. Intraoral, buccal mucosa, tongue, and gingiva are most commonly involved while other areas like mucosa of the palate and floor of the mouth are rarely affected [8]. Approximately 20% and 15% of OLP are linked to genital and cutaneous lichen planus, respectively [9]. Although OLP may cause a wide variety of oral mucosal symptoms, the most common ones are bilateral and/or numerous symmetric lesions, often accompanied by other clinical patterns [10]. It has been found that aggravation and remission occur in cycles [11]. It is common for lichen planus to appear as OLP, either alone or in association with other lesions [12], according to Shah JS et al. [13] traditionally classified into six forms: reticular, plaque-like, popular, atrophic, erosive, and bullous. The most prevalent form of lichen planus is reticular, whereas the second most common type is erosive, which causes painful symptoms and has been linked to a probable malignant transformation of lichen planus [14, 15].

One of the most serious outcomes of OLP is oral squamous cell carcinoma (OSCC), with rates of malignant transformation ranging from 0.5% to 7%. [16, 17], As a result, the World Health Organization (WHO) designated OLP as a potentially malignant disease [18]. Therefore, it is crucial that patients with OLP be evaluated by a team of specialists, since there may be extraoral site involvement and increased risk of oral cancer. Dense infiltration of lymphocytes into the subepithelial space, lymphocyte penetration of the epithelium, and hydropic degeneration of the basal keratinocytes are histopathological hallmarks of OLP [19]. The therapy issue is complicated. The severity of the disease, the predominant clinical form of lesions, and the patient's symptoms should all be taken into account while planning a course of treatment. Asymptomatic reticular lesions often don't need treatment and may be monitored for progression [20]. The primary goals of

therapy are the resolution of symptoms and the healing of atrophic and ulcerative lesions.

AIM

The purpose of this investigation was to examine the demographic and clinical data of 68 OLP patients in Iraq.

MATERIALS AND METHODS

The current research, according to design was an observational retrospective, and was initiated in December 2022 and continued through May 2023 at the University of Baghdad's College of Dentistry's Department of Oral and Maxillofacial Pathology. Before beginning the research, permission was granted by the Ethics Committee at the University of Baghdad's College of Dentistry (project No. 695722, December 2022). For this study, the authors accessed the medical records of all patients diagnosed with oral Lichen Planus (LP) from the oral pathological laboratory between January 2017 and May 2023. These records included information such as the patients' ages, genders, diagnosis years, types of LP, oral manifestations, and biopsy, the authors were given permission to contact the LP patients via the phone numbers provided in the reports. The primary objective of this communication was to assess the disease prognosis and record any change in the morphology or behavior of the lesion. Additional questions were asked about extra oral LP lesions, including the time of lesion onset, the type of medication being taken, and the patient's family and medical history. The interview was conducted entirely in the native language. Each participant's replies and permission were gathered after an explanation of the study's goals was provided.

STATISTICAL ANALYSIS

SPSS (version 11.5) was used to analyze the data; descriptive statistics included the usage of frequency, percentage, mean, and standard deviation. Pain, oral clinical presentation, location, and type of OLP served as independent factors studied using the chi-square test for correlation with dependent variables (sex and age), a significant level was set at $p<0.05$.

RESULTS

In total, the medical records of 68 patients with a clinically and histopathologically confirmed diagnosis of OLP were studied (Table 1). The sample population was composed of 43 (63.2%) females and 25 (36.8%) males (ratio F:M = 2:1). The mean age at diagnosis was 49.25 ± 14.88 (46.36 ± 16.28 years for males) and (50.34 ± 14.36 years for females), and the peak of age-frequency distribution was the fifth decade (32.35%) of life (Fig.1).

Over 70% of the oral OLP had lesions in multiple oral cavity regions. The buccal mucosa was most commonly affected, followed by the tongue and gingiva, and the floor of the mouth was least affected (Fig.2), the most prevalent form of OLP was the reticular type (Fig.3).

Patients with reticular OLP accounted for 38.23% of all cases, erosive type for 29.41%, pigmented type for 4.4%, while patients with bullous OLP and atrophic OLP each accounted for 2.9% of all cases.

Buccal mucosa was the most prevalent place (69.1%), followed by tongue (17.6%) and gingiva (10.3%), and OLP lesions were lowest on the mouth floor (2.9%). The erosive, pigmented, bullous, and atrophic types were also documented. Predominantly males exhibited the reticular form (n=15) and while the erosive type was predominantly observed in females (n=20). Pain perception was shown to vary significantly across the sexes statistically. Patients with oral LP who were older than 40 years old reported significantly higher pain levels than their younger counterparts. There were no statistically significant differences between sexes or age groups in terms of clinical presentation, implicated locations, or OLP categories (Table 2).

Dysplastic alterations were seen on histology in 13 (19.1%) of the samples. There were five reticular samples and eight erosive instances. No correlations were found between dysplastic alterations and demographic factors such as age, gender, location, or OLP type. Only 53 patients could be reached by phone, according to the author in charge of communication (Table III) including 31 women and 22 males, with an average age of 49.64 ± 15.66 years and the average of the age of onset was 47.59 ± 14.38, most of them were non-smoker 33 (62.26%) and non-drinker 52 (98.11%), and about 11 (20.8%) of them have family history of OLP and while 21 (39.6%) have medical history of systemic disease. Lesion involved another site intraorally in 20 (37.73%) of patients after period of time, and another involved extraoral LP in 25 (47.2%) after diagnosed the lesion orally. After re-call, 12 (22.64%) of them have a change in morphology and behavior of lesion, with 14 (26.41%) of the having total remission of lesion. No malignant transformation was documented. Corticosteroids and analgesic were the drugs prescribed for 22 (38.59%) of them, while 31 (58.49%) of patients don't used any medication (Table 3).

DISCUSSION

Oral lichen planus is a chronic inflammatory mucucatenous disease that has the potential to become malignant

Table 1. The demographic and clinical characteristics of oral lichen planus (OLP) patients

Parameter	Patients	
	Abs.	%
Sex		
Male	25	36.8%
Female	43	63.2%
Male: female	1:2	
Age (years) Mean ± SD	49.25±14.88–	
Min–max	13–76	
Site of oral biopsy		
Cheek	47	69.1%
Tongue	12	17.6%
Gingiva	7	10.2%
Type of OLP		
White type	37	54.4%
Red type	31	45.5%
Pain		
Symptomatic	40	58.8%
Asymptomatic	28	41.1%

Table 2. Correlation between age and gender and other socioeconomic variables

Parameter	Male n,%	Female n,%	Age (years) <40 n,%	≥40 n,%
Pain				
Symptomatic	6, 8.8	34, 50.0	6, 15.0	34, 85.0
Asymptomatic	19, 27.9	9, 13.2	12, 42.8	16, 57.1
p–value*	0.001		0.01	
Site				
Buccal mucosa	15, 31.9	32, 68.08	14, 51.9	13, 48.1
Tongue	5, 41.66	7, 58.33	10, 62.5	6, 37.5
Gingiva	4, 57.1	3, 42.85	2, 50.0	2, 50.0
Floor of the mouth	1, 50.0	1, 50.0	12, 57.1	9, 42.9
p–value*	0.8		0.3	
Type of OLP				
White type	16, 43.2	21, 56.75	12, 52.2	11, 47.8
Red type	9, 29.0	22 ,70.96	3, 50.0	3, 50.0
p–value*	0.4		0.5	

*Bold font indicates significance at $p < 0.05$ by Chi-square test.

[21]. The primary conclusions of the present observational research were that the main age was 43 years and that women were more impacted than men. In the majority of instances, the oral cavity was where the initial OLP lesions appeared. Aging and the gender (female) were linked to the pain becoming worse. In all, only 53 people answered the phone, and after receiving corticosteroids and analgesics, 14 of them claimed complete remission. According to our research, OLP is more common among women than in men, that is in consistent with the results of prior international epidemiological investigations [22-24]. It is probable that estrogen has a substantial role in the increased occurrence of OLP in women, since estrogen has been proven to promote immunological reactivity [25]. However, some researchers have presented the opposite, showing a greater rate of OLP in men than females [26]. In this sample of patients, OLP often first appeared in the fifth decades of age. Comparable findings have been reported from other surveys in other nations [27-29], however, other

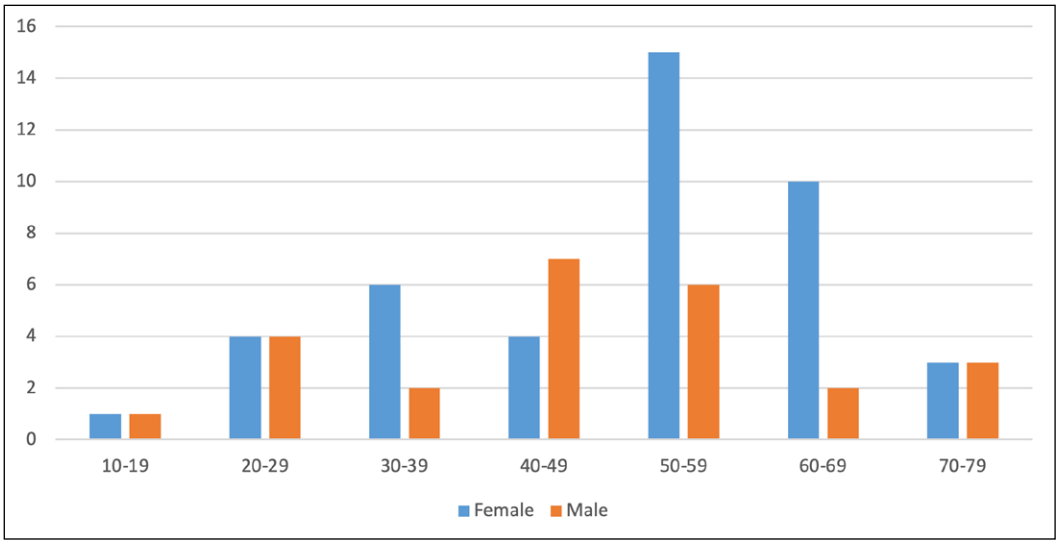

Fig. 1. Distribution of gender according to different groups of age.

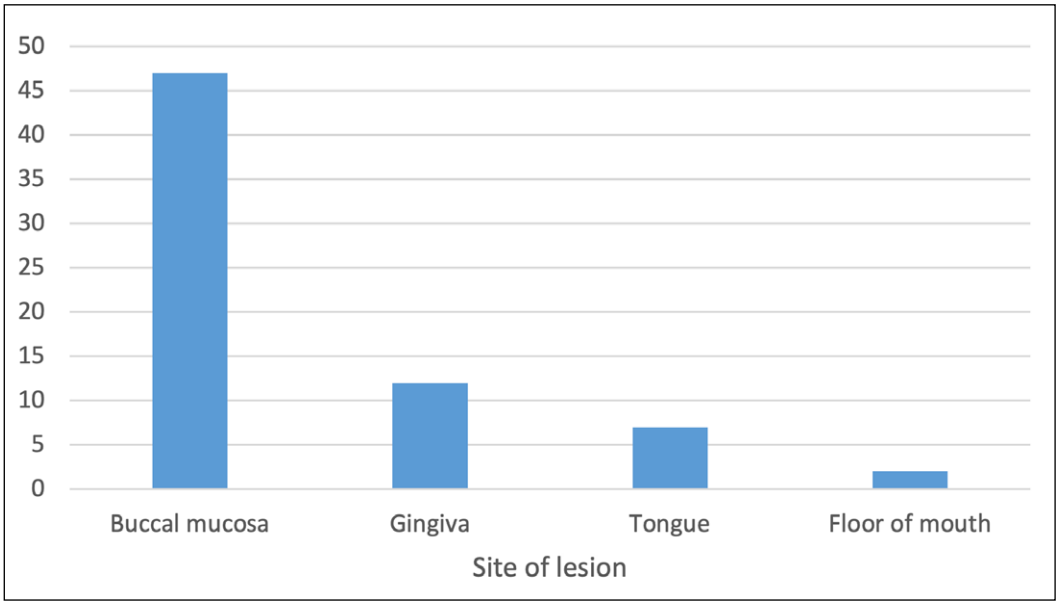

Fig. 2. OLP lesions' locations in patients.

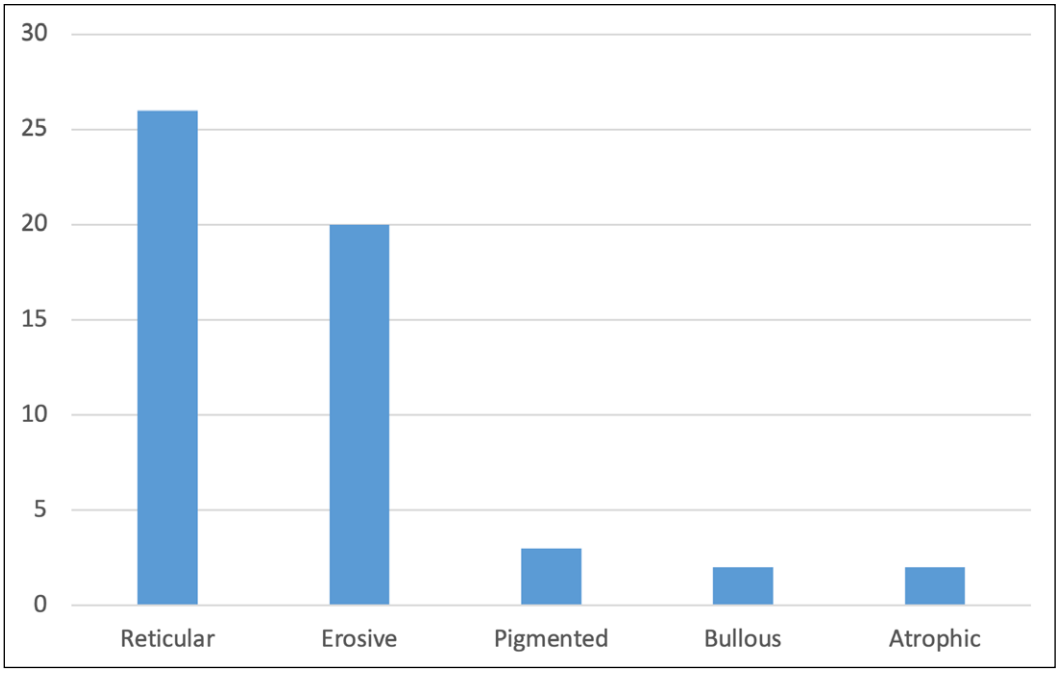

Fig. 3. Distribution of patients based on OLP type at the time of diagnosis.

Table 3. Variables based on the demographic and clinical characteristics of patients with oral lichen planus

Parameter	Patients	
	No.	%
Sex		
Male	22	41.50%
Female	31	58.49%
Age (years) Mean ± SD	49.64 ± 15.66	
Medical history of systemic disease		
Yes	21	39.6%
No	32	60,3%
Family history of OLP		
Yes	8	15%
No	45	84%
Another site involved later intraorally		
Yes	20	37.7%
No	33	62.2%
Another site involved later extraorally		
Yes	11	20.7%
Skin	7	63.6%
Genital area	3	27.2%
Nail	1	9.0%
No	42	79.2%
Healing		
Total remission of lesion	14	26.41%
No change in morphology and behavior of lesion	25	47.16%
Change in morphology and behavior of lesion	12	22.64%
Medication		
Don't administrate any medication	31	58.49%
Administrate medication	22	38.59%
Topical medication	14	63.63%
Systemic medication	8	36.36%

research has shown that the average age of OLP is in the fourth decade of life [30]. These variations in findings may have several causes, the most prominent of which are sample size, genetic predisposition, and other confounding variables. Oral manifestations of LP lesions include reticular lesions in 38.23% and erosions in 29.41% of cases. These trends mirrored those seen by Gotmare et al. [31], who reported that reticular and erosive OLP were the most prevalent types. Lesions caused by oral lichen planus (OLP) may appear anywhere in the mouth, however the buccal mucosa is the most usually affected region [32, 33] which also was the pattern observed in the present study. Patients' primary complaint in this study was severe pain. Consistent with earlier research, this study confirmed that pain is a common symptom of OLP [34]. A cluster of cytotoxic (CD8) T cells very near to the surface of the epithelium, leading to an exaggerated reaction to environmental triggers [35]. In addition, the pain experienced by women was much more intense than that experienced by men. It has been argued in the past that men have a greater pain tolerance or threshold than females [36]. There is currently no agreed-upon explanation for the observed disparity in pain perception between the sexes. However, it is possible that greater sensitivity to pain as we age contributes to the gradual decline in estrogen levels in women [37, 38]. Of the 68 OLP patients that were called, only 53 (77.94%) answered. There might be a variety of factors preventing contact with non-responding patients, including a change in contact information, relocation to another country, or even death. According to the responding patients, eight patients have a positive family history

of OLP. This result was consistent with findings from previous studies indicating that lichen planus patients have a positive family history. A higher frequency of human leukocyte antigen B7 (HLA-B7) has been identified in affected families [39]. Since OLP patients may be carriers of a disease with systemic consequences, a multidisciplinary team may be necessary for their management [40]. Twenty-one individuals with systemic diseases (such as hypertension, diabetes, or thyroid disease) were included in our research. OLP is a chronic inflammatory disorder that may be a precursor to cancer [16]. Inflammation has been shown to be a significant risk factor for the development of cancer in a number of studies. Oral and pharyngeal mucosal diseases that may progress to cancer are strongly linked to cigarette smoking [41], we tracked 20 smokers throughout the course of our study and found that some of them observed a progression from one lesion type to another. It's important to highlight that a patient with oral lichen planus may also have lichen planus lesions in other places of his body, according to a previous study [32]. Approximately 20% of patients contacted had further oral lesions from OLP after the original lesion appeared and 11% of patients had extraoral lesions 1-2 years after the initial oral presentation. In addition, we identified fourteen patients whose OLP spontaneously remitted, contrary to a previously reported finding that spontaneous remission of OLP is exceedingly uncommon [42, 43]. The development of oral cancer is the most serious consequence of OLP, although this was not seen in our study. The reported rate of malignant transformation of OLP is 0 to 10% [44], giving our patient group one of the lowest incidences of malignant transformation. As the etiology of OLP remains obscure, no etiological treatment is currently available [45]. The goal of therapy is to reduce the disease's functional effect and relieve symptoms. The majority of patients with asymptomatic reticular lesions do not require any form of treatment. In contrast, the majority of erosive lesions are extremely excruciating, necessitating treatment in these patients. Corticosteroids are typically the treatment of choice for OLP. The key limitations of this research are the absence of a clinical evaluation and the need of a bigger sample size. The prognosis was also determined through telephone conversation rather than via a physical examination. Furthermore, higher-level clinical studies establish causality, whereas observational research data just show correlation. Caution is warranted until further research confirms the conclusions of the present study, which provided results of illnesses linked to a recurrence rate and malignant transformation.

CONCLUSIONS

Results indicated that OLP was more prevalent among female Iraqis. Severe pain in OLP patients is strongly associated with females and older age groups; clinically, the disease undergoes remission and exacerbation, and all patients must be carefully monitored. All OLP patients should be followed up on a periodic basis. The correct diagnosis of any pathology is crucial for producing effective treatment and minimizing iatrogenic harm.

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The research received ethical clearance from the Institutional Review Committee (IRC) of the University of Baghdad's faculty of dentistry (project NO.6957722, Dec. 2022).

CONFLICT OF INTEREST

The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Crisis-ready educational skills of life support in newborns and adults' scenarios: the impact of simulation-based training on student proficiency

Mariia O. Yartseva, Olena V. Khomiak, Iryna V. Avramenko
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ABSTRACT

Aim: To assess the impact of multidisciplinary simulation training on the educational outcomes of medical students in the emergency care of adults and newborns and implement changes in the curriculum to master simulation scenarios more.

Materials and Methods: To assess the differences in learning outcomes between medical students who study the same curriculum without simulation interventions and those who undergo multidisciplinary emergency care simulation training. A quasi-experimental approach was used to assign students to the Intervention Group or the Control Group.

Results: According to individual criteria, the lowest scores in both groups were obtained for the stages that required the greatest accuracy and correct technique. After the appropriate cycle of initiation, the results in both groups improved significantly, but the results of students from the first group were significantly higher than those of students from the second group.

Despite the absence of a significant difference in the average overall score for the skills, students in the first group significantly improved the accuracy and correctness of the criteria that assess the technical aspects of performance, while students in the second group mainly improved the quality of the descriptive and communicative parts of the practical skill.

Conclusions: We believe that reallocating curricular time to additional hours dedicated to simulation scenarios will better prepare aspiring healthcare professionals for the demanding and dynamic nature of their career, as we continue to increase our understanding of the potential of simulation-based education.

KEY WORDS: simulation training, medical education, emergency care, multidisciplinary training, clinical skills acquisition

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INTRODUCTION

Simulation training is not new to medical education, despite its recent surge in popularity. Medical education has been using simulation training for a long time to combat the rise in mortality resulting from medical errors [1, 2]. It allows learners to acquire clinical skills without exposing patients to unnecessary risk [3].

One of the important scenarios nowadays is to model medical care in epidemics, wartime realities and natural disasters. Unforeseen situations that can happen at any time and in any place, make all medical staff to be ready to perform clearly and consistently [4]. Simulation helps to train for essential clinical and leadership competencies using experiential learning supporting the quadruple aim [5].

AIM

The study was aimed to robustly assess the impact of multidisciplinary simulation training on the educational outcomes of medical students in the emergency care of adults and newborns through careful execution and analysis, the study could provide valuable insights into the efficacy of simulation-based learning in medical education and the potential for changes in the curriculum and additional hours devoted to mastering simulation scenarios.

MATERIALS AND METHODS

To compare the educational outcomes of medical students who receive multidisciplinary simulation training in emergency care with those who study the same curriculum without simulation interventions.

Medical students were enrolled in a study after obtaining informed consent to participate in the study. Maintain confidentiality and data privacy.

Students were assigned to either the Intervention Group (Group 1, n = 41) or the control group (Group 2, n = 39) based on a quasi-experimental design.

Table 1. Evaluation of the practical skill "Resuscitation of a newborn" according to the main criteria

Resuscitation of a newborn	group 1 (n=41)		group 2 (n=39)	
	baseline, points	follow-up, points	baseline, points	follow-up, points
Criterion 1: Personal protection measures	0,42	0,48	0,40	0,46
Criterion 2: Assessing of the child's general condition	0,34	0,44	0,34	0,43
Criterion 3: Checking of the child's position	0,27	0,44*	0,28	0,39
Criterion 4: Demonstration of indirect heart massage	0,40	0,48	0,38	0,38
Criterion 5: Demonstration of the vital functions' assessment according to the ABCDE algorithm: Assessment A – Airway	0,35	0,47	0,34	0,47
Criterion 6: Assessment B – Breathing	0,39	0,49*	0,40	0,45
Criterion 7: Assessment C – Circulation	0,35	0,48*	0,35	0,40
Criterion 8: Assessment D – Disability	0,39	0,47	0,38	0,47
Criterion 9: Assessment E – Exposure	0,38	0,46	0,37	0,44
Criterion 10: Action comments	0,29	0,48	0,29	0,38
The total points on the completion of the station (max 5)	3,58	4,67*	3,54	4,26*

Note: * ($p<0,05$).

Matching to balance known confounders like previous academic performance, age, and gender between groups was done. In group 1 in addition to traditional instruction methods students participated in a multidisciplinary simulation program designed to cover key aspects of emergency care, including clinical decision-making, procedural skills, and teamwork in emergency scenarios. In group 2 they received traditional instruction methods for emergency care, such as lectures, readings, and non-simulation-based practical exercises only. The intervention and control conditions run concurrently over the same timeframe, within a single academic year to minimize temporal variations in curriculum and instructor influence.

Knowledge acquisition was assessed through standardized Objective Structured Clinical Examinations (OSCEs) checklists and their teamwork, communication skills and student satisfaction and self-efficacy were measured through validated assessment tools such as the TeamSTEPPS Teamwork Perceptions Questionnaire (T-TPQ) administered post-intervention.

Pre- and Post-Tests (Baseline and Follow-up results) with direct observation and assessment were obtained to measure knowledge and skills acquisition.

For the statistical evaluation of the data obtained, non-parametric statistics were used, based on the results of the Shapiro-Wilk test (more than 90% of the data had a non-normal distribution). Statistical processing of the results was performed using Microsoft Excel (Office Home Business 2KB4Y-6H9DB-BM47K-749PV-PG3KT) with the AtteStat add-in and STATISTICA 6.1 software (StatSoft Inc., serial No. AGAR909E415822FA).

The main statistical characteristics used in the work include: number of observations (n), relative values (P), level of statistical significance (p). Quantitative variables were presented as median (Me) with interquartile range (IQR). The Wilcoxon W-test was used to compare the central tendencies of two dependent samples. The critical p-value was considered as <0,05.

Limitations and Mitigation Strategies. The lack of randomization may introduce selection bias. Mitigation through careful matching and consideration of confounders was done.

RESULTS

In accordance with the study design, two independent assessments of three practical skills included in the OSCE exam's list of required practical skills were conducted.

In the preliminary assessment of the first practical skill "Resuscitation of a newborn", the results of both groups were comparable and amounted to 3.58 and 3.54 points for the first and second groups, respectively (Table 1).

According to individual criteria, the lowest scores in both groups were obtained for the stages that required the greatest accuracy and correct technique. After the appropriate cycle of initiation, the results in both groups improved significantly, but it should be noted that the results of students from the first group were significantly higher than those of students from the second group.

Furthermore, it is noteworthy that the primary factor contributing to the enhancement of the overall score was a notable progression in the proficiency and precision of abilities (criteria 3, 5, 6, 7), while the technical practical performance of the participants of the second group remained without significant changes. In addi-

Table 2. Evaluation of the practical skill "Registration of a standard ECG" according to the main criteria

Registration of a standard ECG	group 1 (n=41)		group 2 (n=39)	
	baseline, points	follow-up, points	baseline, points	follow-up, points
Criterion 1: Assessment of the situation – the safety of the surrounding environment	0,42	0,47	0,43	0,49
Criterion 2: Establishing communication with the patient, explaining the investigation to the patient	0,31	0,47*	0,30	0,49*
Criterion 3: Preparing the patient for the procedure	0,26	0,38	0,29	0,39
Criterion 4: Apply a layer of contact conductive gel to the electrodes	0,36	0,46	0,35	0,40
Criterion 5: Place 4 reusable limb electrodes (clothespins) and 6 chest electrodes	0,35	0,48	0,33	0,37
Criterion 6: Prepare the electrocardiograph for recording, calibrate the electrocardiograph gain, and record the calibration millivolt	0,29	0,48*	0,28	0,34
Criterion 7: Set the ECG recording speed. Check the quality of electrode placement by observing the ECG, check for need to turn on the "Filter"	0,31	0,43	0,28	0,30
Criterion 8: Record of an ECG	0,39	0,40	0,37	0,37
Criterion 9: Inform the patient about the end of the study, sign the ECG	0,32	0,46*	0,31	0,47
Criterion 10: Turn off the electrocardiograph, disconnect the electrodes, offer the patient a tissue to remove the ECG gel from the skin surface, ask to get dressed	0,29	0,47*	0,32	0,42
The total points and a mark on the completion of the station (max 5)	3,30	4,49	3,26	4,05

Note: * ($p<0,05$).

tion, students of the first group increased the speed of performing the key stages of the skill by 25.7% ($p<0,05$) and reduced the number of self-corrections of errors in the performance of the skill by 37.21% ($p<0,05$).

The results of the pre-assessment of the practical skill "CPR of adult" (Fig. 1.) also did not have a significant difference between students of both groups and amounted to 3.61 and 3.69 points, respectively. After completing additional training, students in the first and second groups improved their scores to 4.41 and 4.38 respectively.

However, despite the absence of a significant difference in the average overall score for the skill, students in the first group significantly improved the accuracy and correctness of the criteria that assess the technical aspects of performance, while students in the second group mainly improved the quality of the descriptive and communicative parts of the practical skill.

In the practical skill "Registration of a standard ECG", both groups have the lowest comparable results at the initial assessment – 3.3 and 3.26 points respectively. The most common problems in performing this skill for both groups were low speed of skill performance and technical errors with sufficient quality of the theoretical component. The second stage of assessment revealed a significant increase in the overall score of students of group 1 (4.49 vs. 4.05 ($p<0,05$), as well as the quality of technical criteria for the skill in students of the first group (Table 2). The assessment of students of group 2 was mainly based on the improvement of theoretical and communicative parts of the skill.

The speed of skill performance in group 1 students increased by 41.3%, while in the second group it remained unchanged.

We used TeamStepp 2.0 to assess teamwork and the degree of satisfaction with participation in an interdisciplinary simulation. The assessment of individual reflection was modified and brought closer to the possibilities of student worldview. The team performance observation tool included: team structure (assembles the team, assigns or defines roles and responsibilities of team members, holds team members accountable, includes patients and their families in the team), communication (provides short, clear, specific, and timely information, seeks information from all available sources, uses back checks to verify the information communicated, uses SBAR, challenge, back checks and handoffs to communicate effectively with team members), I A DESC script was used to constructively manage conflict situations within the team.

Constructive Approach to Conflict Management and Resolution (D – Describe a specific situation or behavior; provide specific details. E – Express how you feel about the situation/what you are concerned about. S – Suggest other alternatives and seek agreement. C – The consequences should be stated in terms of the impact on the team's goals; strive for consensus). Possible barriers included: inconsistent team membership, lack

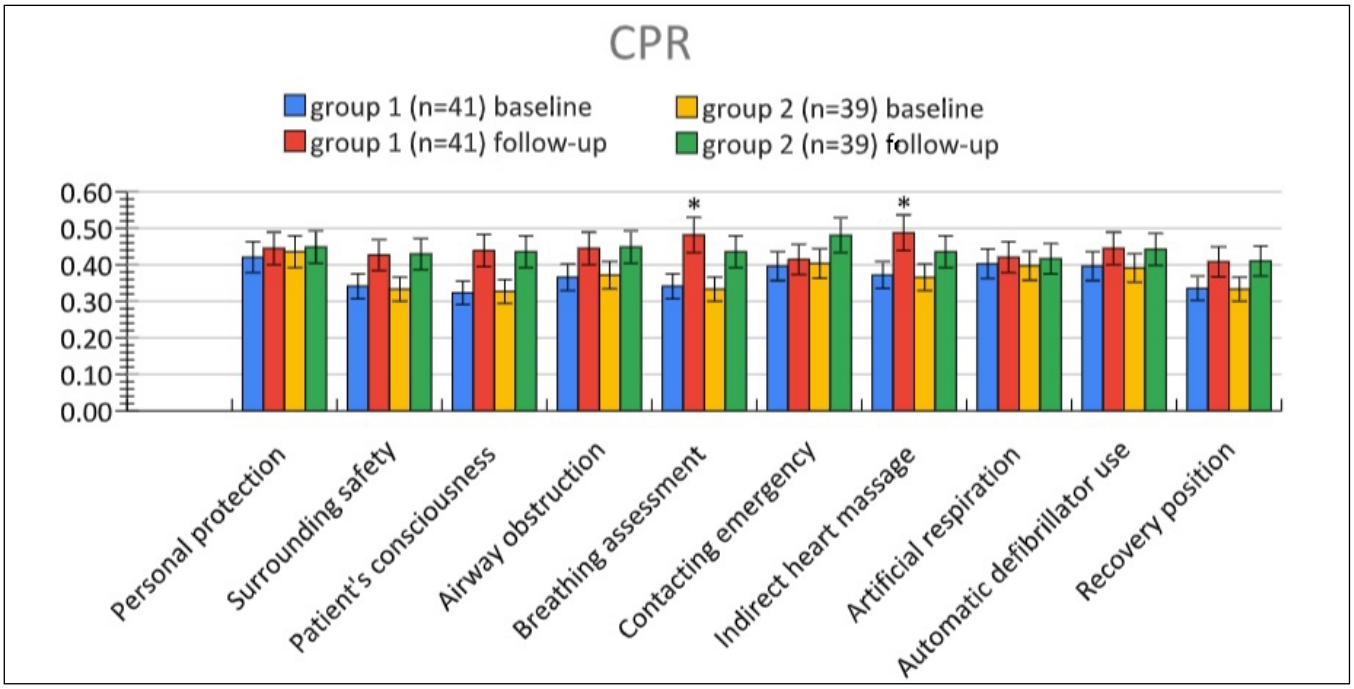

Fig. 1. Evaluation of the practical skill "CPR of adult" according to the main criteria (Me [IQR]).
Note: * ($p<0,05$).

of time for one simulation scenario, lack of information sharing within the team, hierarchy or vertical model of information transfer regarding the patient, defensiveness or personal protection, traditional thinking, complacency, and overconfidence, different communication styles and different types of information perception, conflict (explicit and latent), lack of coordination and control with colleagues, distractions, fatigue, stress (mental and physical), misinterpretation of signals, including from colleagues and the patient, lack of clarity in roles. The expected results were: a common mental model, increased adaptability, team orientation to one model of behavior in each scenario, mutual trust within the team, team productivity, and patient safety.

When evaluating the results of participation in the simulation, the participants of the first group were overwhelmingly satisfied with the results of the simulation (90.2%), 9.8% defined the degree of satisfaction as "average". Among the participants of the comparison group, 74.4% of students expressed satisfaction with their actions after participating in the OSCE. When assessing their overall self-confidence and subjective response to the practical skills included in the OSCE, students who participated in regular simulation training noted a faster reaction and understanding of the algorithm of actions to help the patient. Participants in the comparison group spent more time on organizational issues, preparing for the skills demonstration, and chose the wrong sequence of actions. Analyzing the block of questions about the team structure, the largest number of respondents identified the following two points as important: "The skills of the participants overlap sufficiently to allow for work sharing when necessary" and "Employees are held accountable for their actions." The exchange of necessary information on changes in patient vital signs during the simulation was delayed due to insufficient understanding of staff of their roles and responsibilities (61%). Half of the surveyed participants in Group 1 did not have clearly defined goals, and 43.9% of students did not believe that their unit was working at a high level of efficiency. When assessing leadership within the interdisciplinary team, 75.6% of participants said that the chosen team leader does not take into account the opinions of staff when making decisions about patient care, does not always successfully model appropriate team behavior (48.8%), and does not provide an opportunity to discuss the work of the unit after the event (29.3%). However, the overwhelming majority noted that the chosen leader successfully resolves conflicts during the simulation (82.9%). The set of questions on monitoring the situation showed significant differences of opinion within the interdisciplinary team depending on the change of roles. Students who played the role of doctors spent more time making decisions and performing practical skills, while students who played the role of nurses or patients paid more attention to the examination, physical examination of patients and changes in vital signs during monitoring. Almost all students chose the item "Staff share information about potential complications" as one of the top priorities,

while the items "Staff effectively anticipate each other's needs" and "Staff monitor each other's work" were rated by only 5 participants in regular simulation scenarios. The item "Staff corrects each other's mistakes to ensure that procedures are followed properly" was selected only in 26.8% of cases, because the leader did not provide for the possibility of correcting participants' mistakes within the simulation. Mutual support was rated at a fairly high level by all respondents. 82.9% chose a "high level" of mutual support during the training. The most frequently mentioned positions were: "Participants help colleagues during high workload" and "Participants ask for help from colleagues when they feel overwhelmed". 95.1% of respondents chose the answer "Staff members warn each other about potentially dangerous situations" as the one that affected their overall satisfaction with participation in the interdisciplinary simulation.

DISCUSSION

Even though it's well-known that simulation-based learning is beneficial in medical education [6-10], conducting a study to compare the educational outcomes of medical students receiving multidisciplinary simulation training in emergency care versus those who do not can still add substantial value to the field. In our paper, we want to focus on some potentially important beneficial aspects: focus on multidisciplinary education, student engagement and individual learning types, preparation for real-world practice, psychological impact, long-term retention of skills, adaptability and response to future challenges [11-15].

The analysis of communication between medical staff and patients and their families showed that the training participants mostly use common terminology when communicating with each other, which is primarily due to the use of the same language and the training of students in accordance with international emergency care standards. However, more than half of the participants in the scenario (61%) did not verify the information received from each other orally, which in some cases influenced the choice of patient management tactics.

The issue of searching for information from all available sources was also controversial, because during the simulation, students were provided with information through only one channel, which did not correspond to real situations in the work of doctors and slowed down decision-making. Thus, evaluating the emotional component and the degree of satisfaction from participating in simulation training, there is an overwhelmingly positive response to the proposed type of training. Students were more motivated and emotionally satisfied to participate in compulsory practical training if they could not work with a real patient during medical school.

Thus, this study would not only reinforce the existing understanding of the utility of simulation in medical education but also deepen the knowledge on its specific benefits, challenges, and opportunities. It would contribute to a more nuanced and evidence-based approach to incorporating simulation into medical training programs, ultimately aiming to enhance the quality of healthcare delivery.

CONCLUSIONS

This study has thoroughly examined the multifaceted impact of multidisciplinary simulation-based learning on medical student learning outcomes in the context of adult and neonatal emergency care. The findings highlight the significant benefits of simulation-based learning, particularly in promoting better knowledge acquisition, clinical skills and teamwork among medical students compared to traditional teaching methods. In addition, the study opens up new avenues for future research, highlighting the importance of studying the long-term impact of simulation on skill retention, psychological preparedness and adaptation to new healthcare challenges, especially during crises, wars and emergencies. By expanding our understanding of the potential of simulation-based education, we believe that reallocating curriculum time to more hours devoted to simulation scenarios will improve the preparedness of future healthcare professionals for the demanding and dynamic nature of their profession.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Efficacy and safety of a combination anti-tumor against breast cancer in the central and south of Iraq

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ABSTRACT

Aim: To explore efficacy and safety of combined anti-tumor treatments against breast cancer to help health professionals and decision-makers take strategies to slow the spread of breast cancer and improve women's health**.**

Material and Methods: A cross-sectional study was used by various Iraqi governments. The survey was conducted between July 1, 2022 and April 30, 2023. The study depended on describing studying of 100 patients in detail and with long-term follow-up who go to hospitals and take anti-cancer medications from different provinces of central and south Iraq. The questionnaire form contains 17 fields divided into three sections. The diagnosis tumor before and after treatment parameters: histopathology, CT-scan, tumor marker (Nuclear protein Ki67, Cancer antigen 153 (CA 153), human epidermal growth factor receptor 2, and carcinoembryonic antigen), renal function tests, liver function tests, and Complete Blood Count.

Results: The use of anti-tumor medications was coupled with markedly decreased tumor cell proliferation via reduced biomarker levels of cancer (CA-15-3), HER-2, and Ki-67 levels, and decreased the mammary ductal epithelium's thickness.

Conclusions: The study showed efficiency of combination medications to prevent breast cancer cell development by preventing cell growth.

KEY WORDS: breast cancer, anti-tumor treatments, histopathology, human epidermal growth factor

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INTRODUCTION

Cancer is a highly widespread ailment globally, ranking as the second leading cause of mortality, surpassed only by cardiovascular disease. Breast cancer (BC) stands as the most widespread kind of cancer globally, particularly among women residing in the United States and the second greatest cause of death for women between the ages of 45 and 55. Every year, this illness affects around a million people globally; of them, 320,000 people reside in Europe and 200,000 in America, which together account for more than half of all sufferers [1]. Based on empirical evidence, it has been observed that the incidence of breast cancer in Iraq exhibited an upward trend, increasing from 26.6 cases per 100,000 individuals in the year 2000 to 31.5 cases per 100,000 individuals in the year 2009 [2]. Breast cancer accounted for about 33% of all cancer cases reported in the country in the year 2019 [3]. Furthermore, a comparative analysis revealed that Iraq had a greater age-related incidence rate in comparison to Turkey, Iran, Saudi Arabia, and Bahrain, yet a lower rate when compared to Jordan and Kuwait [4]. Various factors contribute to the increased risk of breast cancer in women. These include age, parity, family history of breast cancer, especially in first-degree relatives, exposure to radiation, smoking, and genetic variables such as defects in the BRCA1 and BRCA2 genes [5]. According to estimates, modifiable risk factors like alcohol consumption, obesity, and physical inactivity account for about 20% of all breast cancer cases worldwide, which means enhancing healthy behaviours may lessen the burden of the illness [6].

The identification and recognition of early indicators have a vital role in reducing the likelihood of developing breast cancer. According to the guidelines for breast cancer prevention and early diagnosis set forth by the American Cancer Society, it is recommended that women who have a moderate-to-high risk of developing breast cancer undergo regular screening mammography starting at the age of 45 [7, 8]. Since that time, referral centres and specialised clinics for the early detection of breast cancer have been established at the major hospitals across the Iraqi governorates. The

goal of early detection and downstaging is to reduce the mortality rate from breast cancer by moving away from late stage (third and fourth) diagnoses and toward early stage (first and second), where recovery prospects are better and treatment costs are lower. It is a comprehensive program that offers high quality primary and secondary health services as well as early detection and examinations for all women aged 20 and over. One of the most crucial tasks for disease prevention and health care planning is to track cancer trends over time [9]. Breast cancer treatment must be clinically effective. A well selected combination of therapy modalities can reduce recurrence, resistance, and adverse effects and promote a healthy quality of life for patients [10].

THE AIM

The study aims to explore the efficacy and safety of combined antitumor treatments against breast cancer to help health professionals and decision makers put in place strategies to control the spread of breast cancer and improve women's health.

MATERIALS AND METHODS

A cross section study was used in various Iraqi governments. The survey was conducted between July 1, 2022 and April 30, 2023. The study depended on describing the study of participants, and we selected 130 participants (excluded 30 patients due to the inability to follow up with them for different causes, and the study was completed on 100 patients in detail and with long-term follow-up) who go to hospitals and take anti-cancer medications from different provinces of central and south Iraq (Al-Muthanna, Babylon, Karbala, Al Najaf, and Diwaniya). The survey was written in English. The questionnaire form contains 17 fields divided into three sections. The first section contains social information such as age and educational level. The second part consists of diagnosing the presence of a tumours before and after treatment parameters (histopathology, CT-scan, tumour marker: human epidermal growth factor receptor 2 (Her-2), the nuclear protein Ki-67, cancer antigen 15-3 (CA 15-3), and carcinoembryonic antigen (CEA), renal function tests, liver function tests, and complete blood count (CBC). The third part includes treatments and the duration of treatment. After that, we collected the obtained data in Microsoft Excel program tables and then statistically analyzed it as shown in the results using IBM SPSS Statistics version 26.

STATISTICAL ANALYSIS

The data were analysed using the statistical software for social sciences (SPSS® version 26, IBM Inc., Chicago, IL, USA). The standard deviation was used to express the numerical variables. When the Kolmogorov-Smirnov test failed to reveal a normal distribution, the variables were examined using the nonparametric Kruskal-Wallis's test to evaluate the mean differences between groups. Bivariate correlation study was conducted to assess the association between markers. Statistics were deemed significant at $P < 0.05$.

RESULTS

SOCIAL STATUS AND PRE-TESTAMENT ASSESSMENTS

In our study, which enrolled one hundred females, there were significant differences $p<0.05$ between participants depending on age; 73 (73%) of them were more than 50 years old, while most of them were 71 (71%) illiterates. A significant difference $p<0.05$ in histopathology and CT studied; however, 88 (88%) of females who assessed the disease via histopathology study had positive results (found a tumor), whereas 12 (12%) had negative results. On the other hand, according to the cancer markers, there is an insignificant difference $p>0.05$ in the HER-2 test between increased and normal in the investigated breast cancer, while for the Ki-67 and CEA markers, there is a significant difference $p<0.005$ between increased, decreased, and normal but uncorrelated with the results of histopathological and CT studies. Our results show that CA-15-3 was the most confirmed test of the two above; however, we found that there is a significant difference $p<0.005$ between increased and normal, and it correlated with the results of histopathological and CT studies (Table 1).

CORRELATION BETWEEN COMBINATION DRUGS AND DURATION OF TREATMENT WITH POST-TREATMENT ASSESSMENTS

Our results showed a negative correlation between combination of drug use and duration of treatments (r=-0.393) and also with both post-treatment histopath and CT studies (r=-0.030 and -0.161; repetitively). We found a negative correlation between the combination of drugs used and all post-treatment cancer markers HER-2, Ki-67, CA-15-3, and CEA (r=-0.041, -0.372, 0.262, and -0.140, repetitively) (Table II). We found a negative correlation between duration of treatment and both posttreatment histopath and CT studies (r=-.023 and -.023; repetitively) and also a negative correlation between combination of drug used and all post-treatment cancer markers HER-2, Ki-67, CA-15-3, and CEA (r=- 0.125, 0.539, 0.211, and -0.072, repetitively) (Table 2, Fig.1).

Table 1. Socio-types of participants

Variant	Sub-variant	Frequency	Percent	Sig. (2-tailed)	95% Confidence Interval of the Difference	
					Lower	Upper
Age	30-39	7	7.0	0.000	4.5396	4.7804
	40-49	20	20.0			
	>50	73	73.0			
	Total	100	100.0			
Education	Illiteracy	71	71.0	0.000	1.4546	1.9254
	Primary	8	8.0			
	Secondary	2	2.0			
	University	19	19.0			
	Total	100	100.0			
No. of drugs	One drug	15	15.0	0.000	2.6397	3.0803
	Two drugs	24	24.0			
	Three drugs	21	21.0			
	Four drugs	40	40.0			
	Total	100	100.0			
Duration of treatment	12 weeks	4	4.0	0.000	2.5394	2.7606
	36 weeks	27	27.0			
	> 50 weeks	69	69.0			
	Total	100	100.0			
Pre-treatment histopath	Found tumor	88	88.0	0.000	1.0552	1.1848
	Not found	12	12.0			
	Total	100	100.0			
Pre-treatment CT scan	Found tumor	100	100.0			
Pre-treatment HER-2	Increased	38	51%	0.543	1.7398	2.2062
	Normal	36	49%			
	Total	74	100%			
Pre-treatment Ki-67	Increased	13	50%	0.000	1.4461	2.1693
	Decreased	5	19%			
	Normal	8	31%			
	Total	26	100%			
Pre-treatment CA-15-3	Increased	67	73%	0.000	1.3582	1.7287
	Normal	25	27%			
	Total	92	100%			
Pre-treatment CEA	Increased	31	39%	0.000	1.9835	2.4165
	Decreased	2	3%			
	Normal	47	59%			
	Total	80	100%			

The effects of combination drugs on liver function and post-treatment assessment are presented in Table 3. The results of our study revealed a lack of significant correlation (P-value = 0.000) between the combined use of drugs and the levels of liver function enzymes (ALP, AST, and ALP). This indicates that there was no significant increase or decrease in the activity of these enzymes in the serum. Specifically, 84% of the participants had normal levels of these enzymes, while the remaining participants showed only minor changes (Table 3).

The impact of the combined medications and the renal toxicities are shown in table 4, and at follow-up assessments, we observed no statistically significant

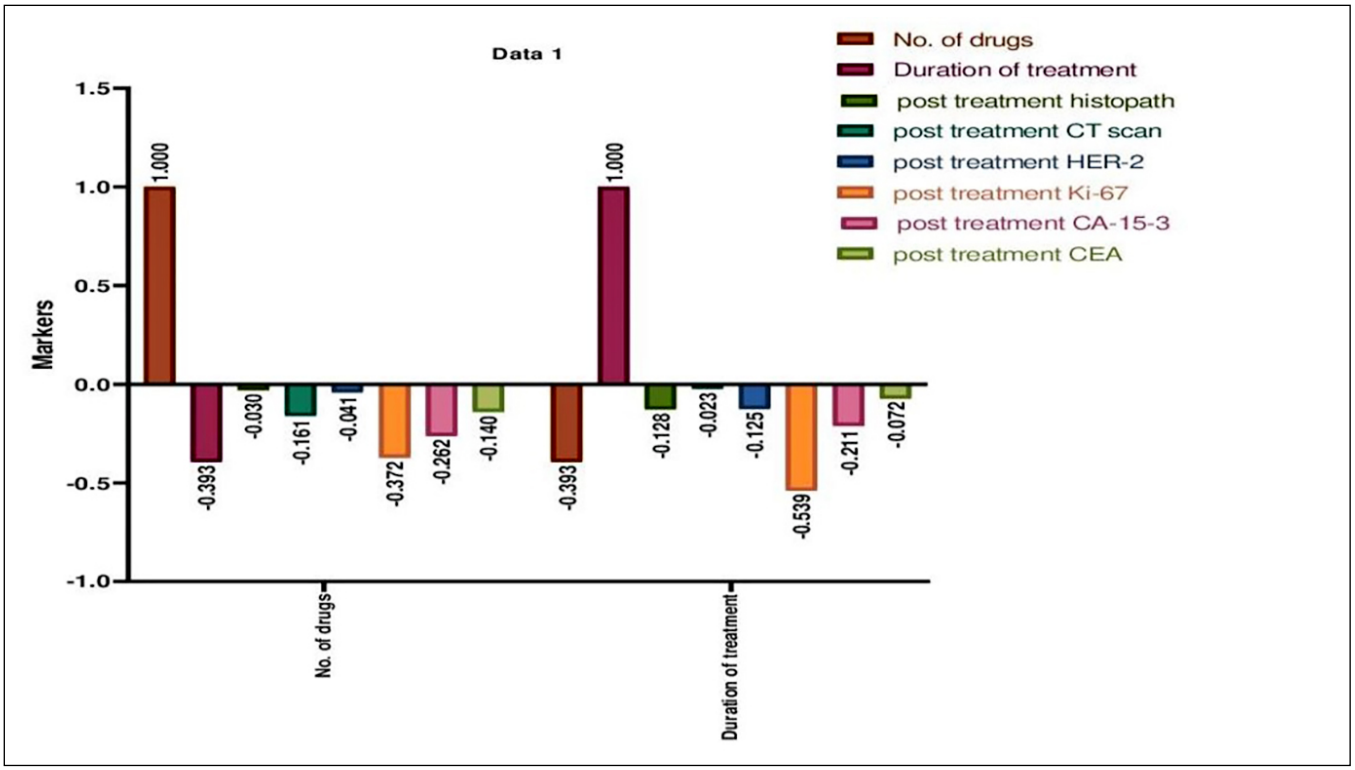

Fig. 1. Correlation between combination drugs and duration of treatment with post-treatment assessments

correlation (P value = 0.000) between the combined use of drugs and kidney function tests (specifically, serum levels of urea and creatinine). This indicates that the drugs did not have a significant impact on the levels of urea and creatinine in the serum. It is worth noting that 95% and 84% of the participants maintained normal levels of serum urea and creatinine, respectively.

DISCUSSION

According to our study, women over 50 are more likely to develop breast cancer. We propose that this is so because sedentary or overweight lifestyles, prolonged aberrant hormone shifts, and bad lifestyle choices are more likely to affect our cells. According to some research, it might just be that our lifestyle has had more time to catch up with us. Breast cancer risk is influenced by factors like smoking, excessive alcohol consumption, and age, especially after menopause [11, 12]. Seventy-nine percent of those who have breast cancer showed high health knowledge, as opposed to 21% showing low health education, and had a lower propensity to use the Internet to find healthcare information. The same research showed that a lower level of health awareness was linked to a lower secondary education level. The biggest correlation between the coordination of cancer care and quality of life was seen in breast cancer patients who had less health knowledge, according to a recent American study. A third US study examined the applicability of a multidimensional framework for examining factors (such as cultural attitudes, beliefs, and practice, as well as facilitators and barriers to cancer literacy), and discovered that the framework improved understanding of those elements that affect how different people approach problems for the detection and prevention of cancer. Additionally, Sinicrope et al. developed a home-based intervention program for Navajo-American women diagnosed with breast cancer, highlighting the importance of tailoring training materials to align with participants' cultural and linguistic backgrounds, while also emphasizing the advantages of a robust support network [13]. There has been an observed rise in the prevalence of breast cancer among women in the menopausal stage because of the woman's increased lifetime exposure to estrogen and progesterone due to her more frequent menstruation cycles [14]. Breast cancer screening with yearly mammography can begin at age 40 for women with an average risk [15]. According to their doctor's recommendations, some women with a higher-than-normal risk of developing breast cancer may begin tests early. When older ladies should cease varies depending on the rules. You can monitor your breast health with a number of other tests [16]. Ki-67 [17], CA15-3 levels [18], HER2 [19], and CEA [17] as cancer biomarkers that persist over time can be a sign that the therapy is ineffective. Cancer is still progressing. Lowering levels or levels that revert to normal may show that the treatment is effective when cancer is reoccurring.

Table 2. Correlation between combination drugs and duration of treatment with post-treatment assessments

		No. Of drugs	Duration of treatment	Post treatment histopath	Post treatment CT scan	Post treatment HER-2	Post treatment Ki-67	Post treatment CA-15-3	Post treatment CEA
No. of drugs	Pearson Correlation	1	-.39[3]**	-.030	-.161	-.041	-.372	-.262*	-.140
	Sig. (2-tailed)		.000	.770	.109	.733	.061	.012	.214
	N	100	100	100	100	72	26	92	80
Duration of treatment	Pearson Correlation	.393**	1	-.128	-.023	-.125	.539**	.211*	.072
	Sig. (2-tailed)	.000		.203	.821	.294	.004	.043	.524
	N	100	100	100	100	72	26	92	80

*. Correlation is significant at the 0.05 level (2-tailed)
**. Correlation is significant at the 0.01 level (2-tailed

Table 3. Effect of the combinations on the liver toxicities

		No. of drugs	N / [%]	Increased	Decreased	Normal	Total	P value
Live Function tests	Post treatment AST	One drug	n	2	0	13	15	0.000
			%	2.0%	0.0%	13.0%	15.0%	
		Two drugs	n	4	0	20	24	
			%	4.0%	0.0%	20.0%	24.0%	
		Three drugs	n	2	3	16	21	
			%	2.0%	3.0%	16.0%	21.0%	
		Four drugs	n	5	0	35	40	
			%	5.0%	0.0%	35.0%	40.0%	
		Total	n	13	3	84	100	
			% of Total	13.0%	3.0%	84.0%	100.0%	
	Post treatment ALT	One drug	n	4	2	9	15	0.000
			%	4.0%	2.0%	9.0%	15.0%	
		Two drugs	n	5	1	18	24	
			%	5.0%	1.0%	18.0%	24.0%	
		Three drugs	n	4	5	12	21	
			%	4.0%	5.0%	12.0%	21.0%	
		Four drugs	n	2	0	38	40	
			%	2.0%	0.0%	38.0%	40.0%	
		Total	n	15	8	77	100	
			% of Total	15.0%	8.0%	77.0%	100.0%	
	Post treatment ALP	One drug	n	2	0	13	15	0.000
			%	2.0%	0.0%	13.0%	15.0%	
		Two drugs	n	2	0	22	24	
			%	2.0%	0.0%	22.0%	24.0%	
		Three drugs	n	0	5	16	21	
			%	0.0%	5.0%	16.0%	21.0%	
		Four drugs	n	3	1	36	40	
			%	3.0%	1.0%	36.0%	40.0%	
		Total	n	7	6	87	100	
			% of Total	7.0%	6.0%	87.0%	100.0%	

Table 4. Effect of the combinations on the kidney toxicities

		No. of drugs	N / [%]	Increased	Decreased	Normal	Total
Renal function tests	Post treatment urea	one drug	n	0	1	14	15
			%	0.0%	1.0%	14.0%	15.0%
		two drugs	n	1	0	23	24
			%	1.0%	0.0%	23.0%	24.0%
		three drugs	n	0	0	21	21
			%	0.0%	0.0%	21.0%	21.0%
		four drugs	n	0	3	37	40
			%	0.0%	3.0%	37.0%	40.0%
		Total	n	1	4	95	100
			%of Total	1.0%	4.0%	95.0%	100.0%
	Post treatment creatinine	one drug	n	4	-	11	15
			%	4.0%	-	11.0%	15.0%
		two drugs	n	4	-	20	24
			%	4.0%	-	20.0%	24.0%
		three drugs	n	2	-	19	21
			%	2.0%	-	19.0%	21.0%
		four drugs	n	6	-	34	40
			%	6.0%	-	34.0%	40.0%
		Total	n	16	-	84	100
			%of Total	16.0%	-	84.0%	100.0%

Our results found pre-treatment biomarkers increased HER-2 (51%), Ki-6750%, CA-15-3 (73%), and CEA (37% of patients), which indicated an increase in cancer cells. Our results showed the number of combinations of drugs used increased as the duration of treatments decreased (r=-.393). On the other hand, the number of combination drugs increased as cancer biomarker levels decreased post-treatment (HER-2, Ki-67, CA-15-3, and CEA) (r=-0.041, -0.372, 0.262 and -0.140, repetitively) (Table 2), as well as histopath and CT studies (r=-.030 and -.161; repetitively). The significance of the Ki-67 proliferation index, which exhibits a notably greater magnitude in malignant breast cancers compared to benign tumours, has been the focal point of numerous investigations [20]. In our experiment, we saw a significant reduction in the percentage of cases during follow-up when administering a combination treatment of annonacin and nanodiamonds. Additionally, the anti-cancer effects were greatly increased, as seen by a significantly lower percentage of cells expressing Ki-67. We looked at the level of CA-15-3 expression in the patient's serum. The MUC1 gene produces the antigen Cancer antigen 15-3 (CA-15-3) is a widely recognized biomarker expressed on the surface of both benign and malignant epithelial cells. In the context of monitoring metastases in breast cancer patients, the serum concentration of CA-15-3 is utilized as an indicator [21, 22]. In our investigation, the serum level of CA153 rose in breast cancer patients and fell noticeably after treatment with antitumor drugs. This finding can be used as preliminary information to research the possible role of antitumor therapy in avoiding the spread of breast cancer [23]. Finally, we examined the effects of the combinations on renal and liver toxicities. Administration of combined antitumors did not significantly increase serum liver enzyme activity and also did not increase serum levels of urea and creatinine (Fig.3). A recent study agrees with our results [24].

CONCLUSIONS

Overall, this research highlights the innovative potential of combining anti-tumor treatments in breast cancer treatment. Future combining drugs had reduced the duration of treatment as well as no significant toxic effects.

RECOMMENDATION

Circulating tumor cell (CTC) counts should be used to confirm a breast cancer diagnosis or to guide therapy choices for breast cancer patients. Similarly, utilizing the combined antitumors reduces the duration of therapy as well as the high dose of a single agent and toxicity, in addition to resistance.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Coxarthrosis as a clinical and social problem. Analysis following hip arthroplasty

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ABSTRACT

Aim: The aim of this study was to determine how hip arthroplasty contributed to improvements in the clinical condition and quality of life of patients after the procedure.

Materials and Methods: The study included 30 patients who underwent surgery due to hip osteoarthritis at the Department of Endoprostheses of the Healthcare Center Regional Hospital in Busko-Zdrój. The subjective and objective condition of the patients was assessed before and after their arthroplasty procedure.

Results: Study patients reported the elimination of pain and showed an increased range of hip mobility. Their physical fitness was considerably improved.

Conclusions: 1. Coxarthrosis is a difficult clinical problem. 2. Hip arthroplasty resulted in the elimination of pain or its radical reduction. 3. After the procedure, study patients showed a considerably better level of physical fitness as compared to baseline and were able to walk a longer distance without pain. 4. The patients are happy and satisfied with the effects of hip arthroplasty.

KEY WORDS: coxarthrosis, treatment, arthroplasty

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INTRODUCTION

Hip osteoarthritis is a chronic condition developing in adults and affecting approximately 7.5% of the population. The World Health Organisation considers this condition to be one of the most serious problems related to the development of civilisation and lists it as the most common cause of disability. Hip osteoarthritis is characterised by joint cartilage destruction accompanied by the development of bony growths where the bone meets the cartilage, leading to joint space narrowing. The causes of this condition can be primary or secondary. Life requires very good motor function. Unfortunately, a joint affected by osteoarthritis is an obstacle to the efficient performance of everyday activities. Patients with hip osteoarthritis have to overcome challenging barriers every day. They experience pain, which also has psychological consequences such as low mood, reluctance to perform activities and limiting oneself to only performing necessary activities that are required to survive. Walking with a cane or crutches is not only difficult for hip osteoarthritis patients on a motor level; it also has social consequences as such patients require the help of another person. As a result, it contributes to the feeling of social dependency [1-12].

Treatment of hip osteoarthritis should be tailored individually to the needs of each patient, pain intensity and location as well as to how advanced the changes are. The management of this disorder is based on conservative treatment. Advanced degenerative changes and ineffective pharmacotherapy require surgical treatment in the form of arthroplasty. The main goal of replacing an affected joint with an endoprosthesis is to free the patient from pain and allow them to deal with the difficulties of daily living [8-19]. Rehabilitation following hip arthroplasty is a long-term process. The recovery of a patient after arthroplasty is associated with multiple limitations and the patient has to work on improving hip joint function and restoring an appropriate range of motion and muscle strength [19-30]. It is important to adjust the living conditions and adapt the building the patient lives in to their needs. It is also advised to adapt the surroundings by using non-slip mats, adapted beds and chairs, and bathroom handles. The patient also requires appropriate shoes that make walking easier and safer. Hip arthroplasty allows patients to resume their physical activity and thus helps them enjoy being professionally and socially active. Figure 1 and Figure 2 show radiographic images obtained before and after arthroplasty.

Fig. 1. Before arthroplasty

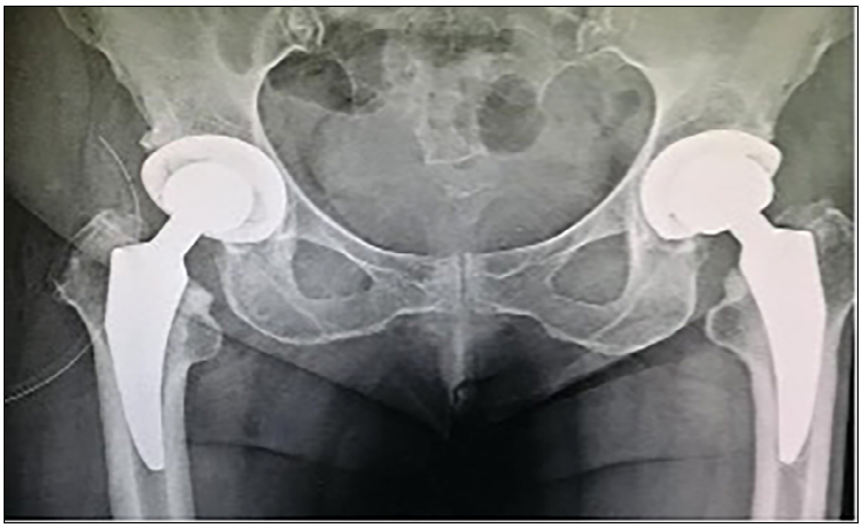

Fig. 2. After arthroplasty

THE AIM

The aim of the study was to find answers to the following question: how did hip arthroplasty contribute to improvements in the patients' clinical condition and quality of life after the procedure?

MATERIALS AND METHODS

The study included 30 patients who underwent surgery due to hip osteoarthritis at the Department of Endoprostheses of the Healthcare Center Regional Hospital in Busko-Zdrój. The study group consisted of 19 women and 11 men. All study patients experienced disruptive pain during walking. They rated their pain before and after hip arthroplasty using a 10-point scale (where 0 is no pain whatsoever and 10 is the most severe pain imaginable); the results were as follows: the mean score was 5.1 before the procedure and 2.5 after the procedure. The ranges of motion in the joints increased. When asked whether hip arthroplasty had improved their quality of life, 27 study patients answered "yes". Twenty-two patients received a cementless endoprosthesis, 6 patients received a cemented one and 2 patients received a hybrid endoprosthesis.

The results obtained in study patients were statistically analysed using the PQStat statistical software, version 1.8.2.156.

The results obtained in the visual analogue scale (VAS) before and after the procedure were compared using the Wilcoxon matched-pairs test.

The results of mobility assessments performed before and after the procedure were compared using the Bowker test.

The test probability was deemed significant at $p<0.05$ and highly significant at $p<0.01$.

RESULTS

The majority (63.33%) of study patients were women in age 66 to 80 years (Table 1).

Table 1. Distribution of answers to question about sex and age

Sex	Number	Percentage
Woman	19	63.33%
Man	11	36.67%
Age	Number	Percentage
Below 50 years	2	6.67%
51-65 years	4	13.33%
66-80 years	19	63.33%
Over 80 years	5	16.67%

Table 2. Place of residence and employment status

Place of residence	Number	Percentage
City with over 100,000 residents	0	0%
Town with 50,000-100,000 residents	11	36.67%
Town with under 50,000 residents	5	16.67%
Village	14	46.67%
Please describe your employment status before surgery	Number	Percentage
Manual worker	15	50%
Intellectual worker	8	26.67%
Pensioner/on disability pension	5	16.67%
Unemployed	2	6.67%

The answers showed that 46.67% of study patients were from rural areas, 16.67% were from small towns and 36.67% were from larger towns. A half of study patients were manual workers and 26.67% were intellectual workers (Table 2).

The answers showed that 46.67% of study patients weighed between 71 and 90 kg and 26.67% of study patients weighed over 90 kg. The height of study patients was as follows: up to 150 cm in 3.33% of study patients, between 151 and 170 cm in 56.67%, and between 171 and 190 cm in 40% (Table 3).

The majority (93.33%) of patients underwent hip arthroplasty due to hip osteoarthritis (Table 4).

A highly significant ($p<0.01$) change was found in the level of hip joint pain after the procedure as compared with the score recorded before the procedure. The level of pain after the procedure was considerably lower (Table 5).

Fig. 3. Distribution of answers to question "Please rate your level of hip joint pain on a scale from 0 to 10, where : 0-no pain, 1-3 mild pain, 4-6 moderate pain, 7-10 severe pain.

The results in the "extension" scale did not change significantly ($p>0.05$) after *vs*. before the procedure. The results in the "flexion" scale changed significantly ($p<0.05$) after *vs*. before the procedure (Table 6).

The results in the "ADDUCTION" scale did not change significantly ($p>0.05$) after *vs.* before the procedure (Table 7).

The results in the "external rotation" scale did not change significantly ($p>0.05$) after *vs.* before the procedure (Table 8).

Table 3. Distribution of answers to question about weight and height

Weight	Number	Percentage
Up to 50 kg	1	3.33%
51-70 kg	7	23.33%
71-90 kg	14	46.67%
Over 90 kg	8	26.67%
Height	Number	Percentage
Up to 150 cm	1	3.33%
151-170 cm	17	56.67%
171-190 cm	12	40%
Over 190 cm	0	0%

Table 4. Distribution of answers to question: "Please tick the reason for your hip arthroplasty"

Please tick the reason for your hip arthroplasty	Number	Percentage
Hip osteoarthritis	28	93.33%
Femoral neck fracture	1	3.33%
Osteoporosis	0	0%
Other	1	3.33%

The majority (90%) of study patients confirmed that hip arthroplasty had improved their quality of life (Table 9).

Cemented endoprostheses were implanted in 20% of study patients while the majority (73.33%) received a cementless endoprosthesis; 6.67% of study patients received a hybrid endoprosthesis (Table 10).

DISCUSSION

Coxarthrosis is more common in women and its main predisposing factors are obesity and overweight. Obesity is theoretically the easiest factor to control in the context of the risk of osteoarthritis [4-8].

Patients with coxarthrosis face severe periarticular pain every day and their ability to perform everyday activities is limited.

Articular pain is the most common symptom leading to an osteoarthritis diagnosis. The pain intensifies when the patient is moving, using stairs or carrying heavy objects, and has a tendency to subside once the physical activity has stopped and during rest. During the study, the vast majority of patients reported difficulty performing certain activities, such as walking and using stairs.

The conservative treatment of this disorder involves physical therapy and rehabilitation. It is aimed at maintaining or increasing the range of mobility and the muscle strength. The physical therapy uses such methods as low-frequency currents, ultrasound therapy, laser therapy, cryotherapy, shockwave therapy and magnetic field therapy [25-29].

Table 5. Distribution of answers to question: "Please rate your level of hip joint pain on a scale from 0 to 10, where 0 means no pain whatsoever and 10 means the most severe pain imaginable"

VAS		Before procedure		After procedure
		Number	Percentage	Number
0		0	0%	0
1		1	3.33%	11
2		1	3.33%	11
3		3	10%	0
4		12	40%	4
5		3	10%	1
6		1	3.33%	1
7		3	10%	2
8		4	13.33%	0
9		1	3.33%	0
10		1	3.33%	0
Arithmetic mean		5.1		2.4667
Median		4		2
Standard deviation		2.187		1.8144
Minimum		1		1
Maximum		10		7
Lower quartile		4		1
Upper quartile		7		3.5
Wilcoxon test for dependent groups	Z	3.5045		
	p	0.0005		

However, if conservative treatment does not help the patient in any way and the osteoarthritis is advanced, patients are offered total hip arthroplasty.

The study was conducted in 30 patients, the vast majority of whom were women, which is consistent with the suggested relationship between the predisposition to coxarthrosis and sex. Overweight and obesity are also factors that strongly predispose patients to osteoarthritis. The vast majority of study patients were overweight or obese based on their BMI.

When study patients were asked about their work, the most common answer was manual labour. Overload and mechanical injury are factors that predispose patients to the development of osteoarthritis. The results of the study may thus be interpreted as a confirmation of this relationship. The majority of study patients also believed that hip osteoarthritis limited their physical activity and their ability to perform activities of daily living, which might have also resulted in a forced limitation or change to one's type of work.

The vast majority of study patients were able to walk short distances of about 80 to 100 metres without needing to rest. After arthroplasty, the distance patients were able to walk without rest increased to 1,000 metres and more. These results can be interpreted as a considerable improvement in the health and quality of life of study patients.

As shown by the study, patients were considerably happier with their quality of life after arthroplasty and rehabilitation and their overall physical fitness had improved. When comparing their physical activity to that recorded before the procedure, study patients pointed out that the quality of their gait had considerably improved. The distance they were able to walk without painful discomfort after arthroplasty was definitely longer than the distance measured before the procedure. Patients who were not able to work before the surgery managed to start working again after the surgery and rehabilitation.

An analysis of the present study showed that hip arthroplasty had a positive effect on the health and quality of life in the majority of patients. Study patients achieved an extraordinary improvement in their physical and mental state since the severe chronic pain they used to experience had been affecting their everyday life.

According to the research conducted by Kieszkowska-Grudny A., Maleszewska J., Siwy-Hudowska A., Nawrocki S., described in a paper titled "Assessment of quality of life and strategies of coping with disease in a group of patients undergoing hip arthroplasty",

Table 6. Distribution of answers to question "extension" and "flexion"

Extension (scale in degrees)			Before procedure		After procedure
			Number	Percentage	Number
30 and more			5	16.67%	14
29-20			21	70%	13
19-10			4	13.33%	3
Below 10			0	0%	0
Bowker test	χ^2	3.6667			
	df	3			
	p	0.2998			
			After procedure		
			1	2	3
Before procedure	Number	1	2	3	0
		2	11	7	3
		3	1	3	0
	% of row	1	40%	60%	0%
		2	52.38%	33.33%	14.29%
		3	25%	75%	0%
	% of column	1	14.29%	23.08%	0%
		2	78.57%	53.85%	100%
		3	7.14%	23.08%	0%
	% of sum	1	6.67%	10%	0%
		2	36.67%	23.33%	10%
		3	3.33%	10%	0%
Flexion (scale in degrees)			**Before procedure**		**After procedure**
			Number	**Percentage**	**Number**
120 and more			1	3.33%	12
119-110			27	90%	16
109-99			2	6.67%	2
Below 99			0	0%	0
Bowker test	χ^2	8.1			
	df	3			
	p	0.044			
			After procedure		
			1	2	3
Before procedure	Number	1	1	0	0
		2	10	15	2
		3	1	1	0
	% of row	1	100%	0%	0%
		2	37.04%	55.56%	7.41%
		3	50%	50%	0%
	% of column	1	8.33%	0%	0%
		2	83.33%	93.75%	100%
		3	8.33%	6.25%	0%
	% of sum	1	3.33%	0%	0%
		2	33.33%	50%	6.67%
		3	3.33%	3.33%	0%

Table 7. Distribution of answers to question "abduction" and "adduction"

Abduction (scale in degrees)			Before procedure		After procedure
			Number	Percentage	Number
40 and more			6	20%	0
39-30			21	70%	0
29-20			3	10%	0
Below 20			0	0%	30
Adduction (scale in degrees)			**Before procedure**		**After procedure**
			Number	**Percentage**	**Number**
30 and more			5	16.67%	12
29-20			23	76.67%	16
19-10			2	6.67%	2
Below 10			0	0%	0
Bowker test	χ^2		5.6429		
	df		3		
	p		0.1303		
				After procedure	
			1	2	3
	Number	1	5	0	0
		2	7	15	1
		3	0	1	1
	% of row	1	100%	0%	0%
		2	30.43%	65.22%	4.35%
		3	0%	50%	50%
	% of column	1	41.67%	0%	0%
		2	58.33%	93.75%	50%
		3	0%	6.25%	50%
	% of sum	1	16.67%	0%	0%
		2	23.33%	50%	3.33%
		3	0%	3.33%	3.33%

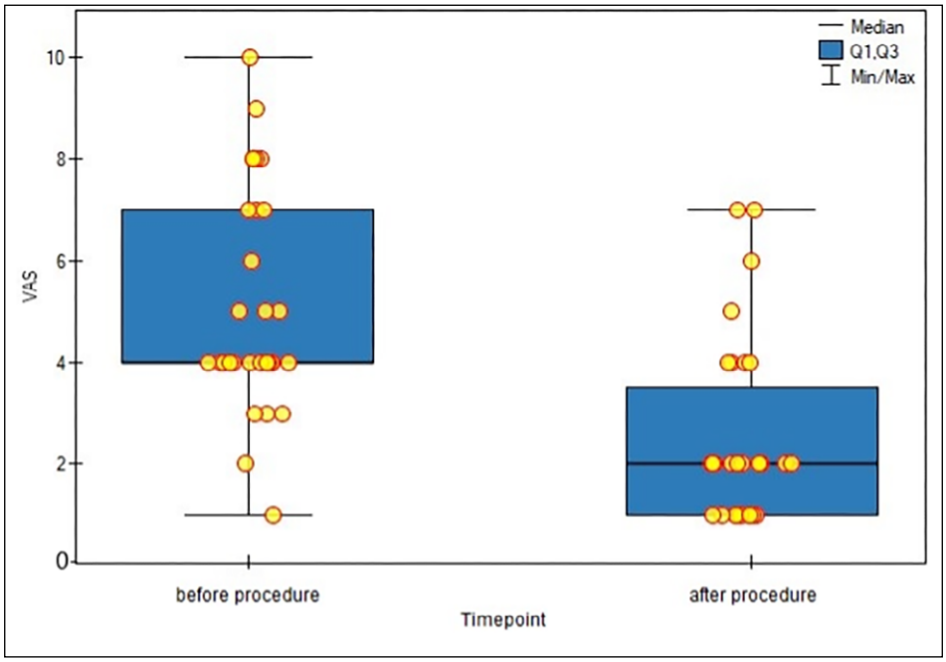

Fig. 3. Distribution of answers to question "Please rate your level of hip joint pain on a scale from 0 to 10, where : 0-no pain, 1-3 mild pain, 4-6 moderate pain, 7-10 severe pain.

Table 8. Distribution of answers to question "external rotation" and "internal rotation"

External rotation (scale in degrees)			Before procedure		After procedure
			Number	Percentage	Number
40 and more			6	20%	12
39-30			21	70%	15
29-20			3	10%	3
Below 20			0	0%	0
Bowker test	χ^2		3.2		
	df		3		
	p		0.3618		
				After procedure	
			1	2	3
Before procedure	Number	1	6	0	0
		2	5	15	1
		3	1	0	2
	% of row	1	100%	0%	0%
		2	23.81%	71.43%	4.76%
		3	33.33%	0%	66.67%
	% of column	1	50%	0%	0%
		2	41.67%	100%	33.33%
		3	8.33%	0%	66.67%
	% of sum	1	20%	0%	0%
		2	16.67%	50%	3.33%
		3	3.33%	0%	6.67%

Internal rotation (scale in degrees)	Before procedure		After procedure
	Number	Percentage	Number
30 and more	7	23.33%	0
29-20	21	70%	0
19-10	2	6.67%	0
Below 10	0	0%	30

Table 9. Distribution of answers to question: "Did hip arthroplasty improve your quality of life?"

Did hip arthroplasty improve your quality of life?	Number	Percentage
Yes	27	90%
No	3	10%

Table 10. Distribution of answers to question: "Type of endoprosthesis used"

Type of endoprosthesis used	Number	Percentage
Cemented endoprosthesis	6	20%
Cementless endoprosthesis	22	73.33%
Hybrid endoprosthesis	2	6.67%

arthroplasty has a positive influence on the quality of life, improving the range of hip joint mobility and reducing hip joint pain [20].

Based on the present study and the results reported by the authors mentioned above, one can conclude that hip arthroplasty contributes to an improvement in the quality of life. This is partly due to a reduction in pain, an increase in the range of joint mobility and an increase in overall physical fitness. The studies showed that patients were satisfied with their surgery. After the procedure, patients enjoyed more independence; the fact that they did not have to depend on other people and orthopaedic aids anymore contributed to an improvement in their satisfaction and quality of life.

CONCLUSIONS

1. Coxarthrosis is a difficult clinical problem.
2. Hip arthroplasty resulted in the elimination of pain or its radical reduction.
3. After the procedure, study patients showed a considerably better level of physical fitness as compared to baseline and were able to walk a longer distance without pain.
4. The patients are happy and satisfied with the effects of hip arthroplasty.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Gene expression profile of immune-check point in response to Trastuzumab therapy in patients with HER-2 positive breast cancer

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ABSTRACT

Aim: To clarify the association between response to Trastuzumab and molecular expression of TIM-3 and FOXP-3 immune checkpoints.

Materials and Methods: FOXP-3 and TIM-3 expression in peripheral blood was analyzed using qPCR, and the serum level of Trastuzumab was estimated using an immune sorbent enzyme assay.

Results: During treatment with Trastuzumab, the FOXP-3 gene expression showed a significant decline throughout one year of treatment, going from 0.85 at cycle 9 to 0.75 at cycle 17. While the TIM-3 gene expression showed a significant up regulation at cycle 9 to 2.8 fold, followed by a reduction in the fold change from 2.8 to 1.7 in the font of reference gene expression.

Conclusions:FOXP-3 and TIM-3 have the potential to be suggestive markers that can anticipate the response to Trastuzumab, but they are not capable of predicting the likelihood of recurrence**.**

KEY WORDS: breast cancer; immune checkpoints, HER-2, FOXP-3, TIM-3, Trastuzumab

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INTRODUCTION

Breast cancer (BC) is the most frequent female cancer [1]. It increased recently in women worldwide, and represent 25% of all malignancies in females [2]. In Basrah, 16.8% of all malignancies and 30.2% of female cancers are breast cancer [3, 4]. Recently, it considered the second common cause of death in women [5]. This tumor is highly diverse in terms of its genetic profile, cell composition, and biological function. This lead to variations in the response and clinical outcomes to conventional treatments. Human epidermal growth factor receptor-2 positive (HER-2+) are aggressive, brain metastasize, and have poor prognoses [6]. 20-30% of breast cancers express the HER-2/ERBB2 receptor [7]. Different modalities of drugs that target HER2 receptors are currently available, including monoclonal antibodies (Trastuzumab, Pertuzumab), tyrosine kinase inhibitors (Lapatinib, Neratinib), and antibody-drug conjugates (Ado-Trastuzumab, Emtansine) [8, 9]. However, after adjuvant treatment including chemotherapy and Trastuzumab about twenty percent of patients with HER-2+ BC still develop recurrence and metastasis [10]. The challenge here is the difficulty of identifying patients with a high risk of recurrence. Many clinical oncologists can only suspect the risk of recurrence based on many factors like lymph node metastasis, age of onset, clinicopathologic investigations; tumor size, and receptor expression [10, 11]. Immune checkpoint molecules like PD-1 (programmed cell death-1), TIM-3 (T cell immunoglobulin and mucin-domain-containing-3), V-domain Ig suppressor of T cell activation (VISTA), FOXP3 (Fork head box P3), and LAG-3 (lymphocyte activation gene-3) are leukocyte differentiation antigens that are trans-membrane receptors of T cells [12, 13]. These checkpoint molecules are essential regulators of T cell function in the tumor microenvironment. The new development of immune checkpoint therapy, which blocks these inhibitory molecules and can promote anti-tumor immune responses, has remarkably revolutionized cancer treatment patterns [14]. Clearly, tumor cells can evade immune surveillance and immune killing and promote self-growth by overexpressing immune checkpoint molecules and relevant ligands.

AIM

In the present study we aimed to clarify the association between response to Trastuzumab and molecular expression of TIM-3 and FOXP-3 immune checkpoints.

MATERIALS AND METHODS

Study population: fifty women with newly diagnosed HER-2-positive BC were included in the current prospective study through the period from May 2021 to August 2022. All patients aged 20 years and older were referred to Basra Cancer Center (southern Iraq). A blood specimen was collected from the patients before starting chemotherapy, radiation, or immunotherapy. Pregnant women, smokers, and patients with chronic diseases were excluded.

STUDY DESIGN AND ETHICAL CONSIDERATIONS

This study was designed as a prospective cohort study. A signed informed consent was obtained from all patients whose blood samples and clinical data were used in this study. All patients were followed up for a year (over 17 cycles) of Trastuzumab treatment.

All patients underwent screening to ensure they met the criteria for inclusion, and a questionnaire formula was completed. Age, parity, menstrual status, history of concurrent cancer, history of diabetes mellitus, history of hemolytic disease, drug history, and history of pregnancy with concomitant cancer were also recorded. For diagnosis and staging tests, all patients have histopathology, immunohistochemical, tumor markers, and imaging. All participants underwent a one-year period of follow-up, starting at zero time before cycle 1, then cycle 9, and cycle 17 of immunotherapy. Along with measuring the serum concentration of Trastuzumab therapy. Five mL of blood specimens were drawn from each participant and used for the investigation of:

1. Gene expression of immune checkpoints FOXP3 and TIM3 in peripheral blood.
2. Serological investigations: Trastuzumab.

A tumor marker was measured from all patients; it is routinely measured at the oncology lab as requested by the oncologist. CA15-3 is a surrogate marker for tumor load and is used to follow up on tumor recurrence and monitor metastasis.

RELATIVE GENE EXPRESSION

From each peripheral blood specimen, total RNA was extracted at three Trastuzumab therapy cycles: zero time (before treatment), after 9 cycles; and at 17 cycles. 200 µl of peripheral blood was aspirated from EDTA blood specimens and completed the procedure according to the manufacturer's kit (Genome Kite: China). The purity and concentration of RNA were determined by an Optizen Nanodrop by measuring its absorption at 260 and 280 nanometers. The cDNA was kept at -80°C (Nuair: Japan). The synthesis of the first strand of DNA (cDNA) was conducted according to manufactured instructions (Applied Biosystems, USA), with a standard volume of extracted RNA of about 5–10 µl in RT Fdmix (Hexamer) and adding 15 µl of DEPC water as a step in the synthesis of cDNA. The gene expression of FOXP3 and TIM3 was achieved using a real-time PCR instrument using a SYBR green master mix, where the Actin gene was employed as an internal control or housekeeping gene to normalise the amplified target genes. The PCR reactions were carried out in a total volume of 20 µl containing 2 µl of the cDNA added to 1 µl of forward and 1 µl of reverse primers in the presence of 10 µl SYBR-green and 6 µl of nuclease-free water.

Thermal cycling for all the genes was initiated with a denaturation step at 95°C for 10–15 min, followed by 30 cycles (denaturation at 95°C for 15 s, annealing at 60°C for 30 s, and elongation at 60°C for 60 s when fluorescence appeared).

Primer sequences were designed by Primer3 software (Source forge, USA).

Forward and reverse primers of β-Actin, FOXP3 [15] and TIM3 [16] genes for real-time PCR amplification were designed as follow:

1. B-actin: Forward GGACTTCGAGCAAGAGATGG
Reverse AGCACTGTGTTGGCGTACAG
2. FOXP3: Forward CCACTTGCAGACACCATTTG
Reverse CATGATCAGCCTCACACCAC
3. TIM3: Forward CCATGTTTTCACATCTTCCC
Reverse GAGTCCCGTAAGTCATTGG

SEROLOGICAL TESTS

Quantitative determination of Trastuzumab (Herceptin) levels in human serum for all women included in this study by sandwich enzyme immunoassay (ELISA), epitope diagnostics Inc USA ELISA/V2/US/2015-07. The process is carried up according to the manufacturer's guidelines in the kit from Epitope Diagnostics Inc.: USA.

STATISTICAL ANALYSIS

All analyses used SPSS 21.0. Shapiro-Wilk tested variables for normality. Kruskal-Wallis was used for non-parametric variables and one-way ANOVA for parametric data. P-values below 0.05 indicate statistical significance, qRT-PCR data analysis employed the Livak method (Delta-Delta CT).

Table 1. Clinical and pathological characteristics of patients

		Number	Percentage
Age (years)	Less than 50	30	60
	50 and more	20	40
Menopausal status	Premenopausal	24	48
	Menopausal	26	52
Parity	Positive	34	68
	Negative	10	20
	Unmarried	6	12
Family history of breast cancer	Positive	9	18
	Negative	41	82
Smoking history	Non-smoker	50	50
	Smoker	0	0
Stage	I	2	4
	II	27	54
	III	21	42
Grade	Grade 2	25	50
	Grade 3	25	50
Estrogen receptor	Positive	9	18
	Negative	41	82
Progesterone receptor	Positive	9	18
	Negative	41	82
Type of chemotherapy	ACT	33	66
	ACD	17	34
Develop recurrence	Yes	6	12
	No	44	88
BMI	Normal (less 25)	9	18
	Overweight (25-29.9)	17	34
	Obesity (30-39.9)	24	48

RESULTS

This follow-up longitudinal descriptive observational cohort study recruited fifty women with HER-2 positive breast cancer. Sixty percent of them were under the age of 50, 24(48%) were pre-menopausal, 34 (68%) of the women were fertile with more than one child, while 20% had no children and six were single. Nine of the patients (18%) have a positive family history of breast cancer (Table 1).

Histopathological and clinical features of the patients are summarized in table 1. Tumor node metastasis (TNM) staging of breast cancer found that 4% of patients were in stage I, 54% were in stage II, and 42% were in stage III. Half of the tumors were classified as grade II, while the other half were classified as grade III. Regarding the chemotherapy, 33 of them were given ACT (Adriamycin and Taxol), whereas 17 (34% of the total) were given ACD (Adriamycin and Docitaxol). Only 18% of patients had a body mass index (BMI) within the normal range, 34% were overweight, and 48%, were obese. Twelve percent of participants in this research developed recurrence after one year of Trastuzumab treatment. Various fold changes in gene expression of immune checkpoints FOXP-3 and TIM-3 in patients participated in this study (Table 2). During treatment with Trastuzumab, the FOXP-3 gene expression fold showed a significant decline throughout one treatment, going from 0.85 at cycle 9 to 0.75 at cycle 17 (Fig. 1.). While the TIM-3 gene expression showed a significant reduction in the fold change from 2.8 to 1.7 in the font of reference gene expression (Fig. 2). FOXP-3 and TIM-3 gene expression have no statistical significance between patients who experienced recurrence and those who do not show such recurrence.

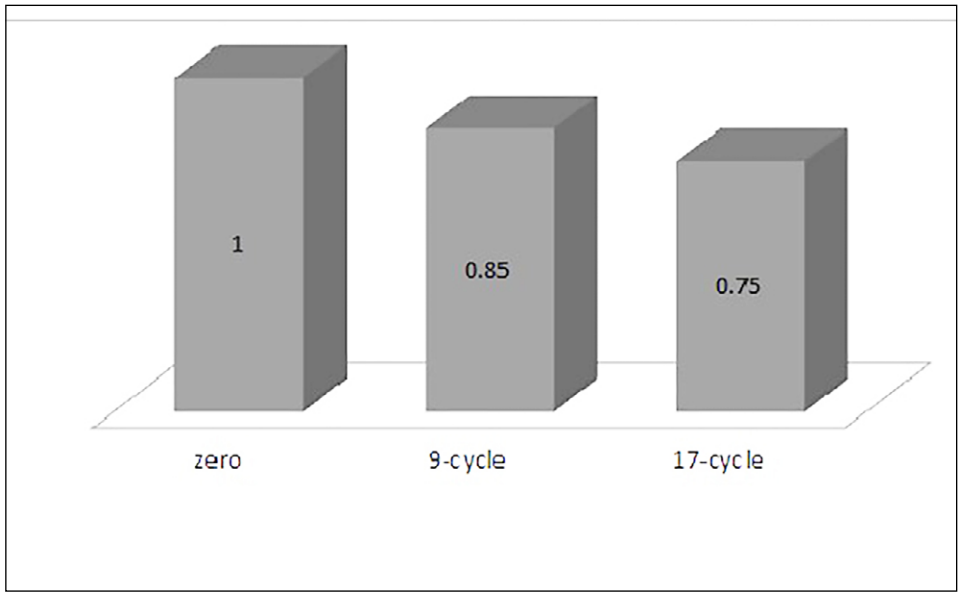

Fig. 1. FOXP-3 fold-change analysis in peripheral cells from patients with HER-2-positive breast cancer during a course of trastuzumab therapy.

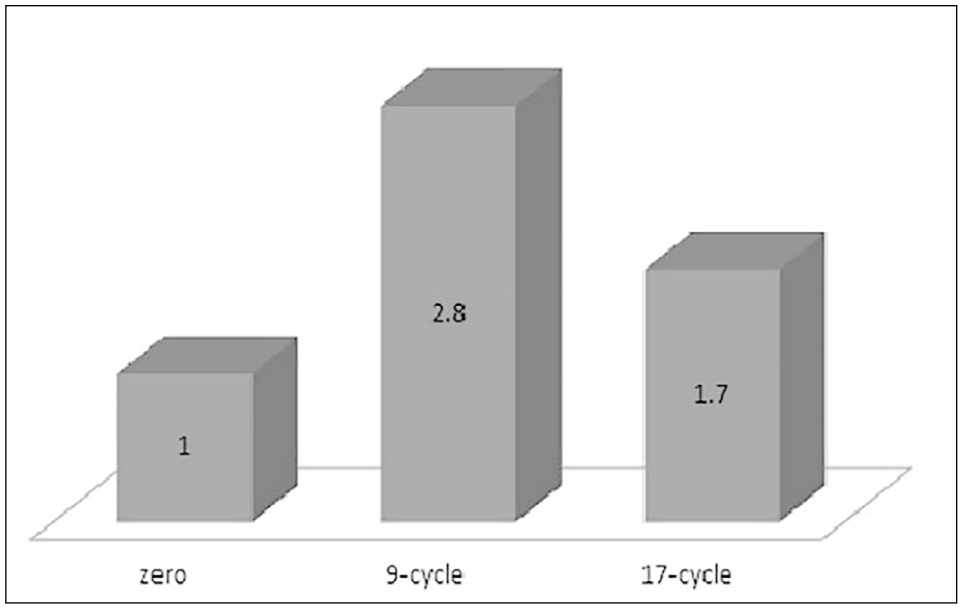

Fig. 2. TIM-3 fold-change analysis in peripheral mononuclear cells among patients with HER-2-positive breast cancer during the course of Trastuzumab therapy.

FOXP-3 mRNA levels in total RNA were estimated by RT-qPCR, normalized to beta actin, and shown here relative to the zero cycle. The treatment down-regulated the FOXP3 mRNA, when it was 0.85, and it continued to down-regulate until it reached cycle 17 to 0.

TIM-3 mRNA levels in total RNA were estimated by RT-qPCR, normalized to beta actin, and shown here relative to the zero cycle before Trastuzumab. The treatment upregulated the TIM-3 mRNA when it was 2.8 at cycle 9 of Trastuzumab therapy, and it continued to downregulated until it reached 1.7 at cycle 17 to 1.7. Trastuzumab levels were low at cycle 9 and increased significantly at cycle 17, p-value 0.002 (Table 3). However, there is no statistical difference in Trastuzumab level among patients who have recurrence and those who do not develop recurrence at cycles 9 and 17 (Table 4).

CA15-3 at cycle zero was higher than normal and showed significant reduction after complete Trastuzumab therapy. However, CA15-3 serum levels decreased dramatically in non-recurrence patients but remained high in recurrence patients (Tables 5, 6).

DISCUSSION

Trastuzumab has several mechanisms of action that depend on host competency of immune status [7]. Immune checkpoints such as FOXP-3 and TIM-3 have evolved in the immune system to tackle autoimmune response by developing tolerance to self-antigens [8-11]. However, the tumor cells escape immune recognition by several mechanisms, especially down-regulating immune response itself [18, 19]. Tumor checkpoints down-regulate the immune response to weaken antitumor responses, allowing them to avoid

Table 2. Fold change in expression of FOXP-3 and TIM-3

Fold change expression		No.	Mean	P value
FOX-3	cycle zero	50	1	0.0001*
	cycle 9	50	0.85	
	cycle 17	50	0.75	
TIM-3	cycle zero	50	1	0.0001*
	cycle 9	50	2.81	
	cycle 17	50	1.73	
* Friedman Test				

Table 3. Trastuzumab serum level at cycles 9 and 17 of treatment

	Trastuzumab cycle-9 [µg/ml]	Trastuzumab cycle 17 [µg/ml]
N	50	50
Median	51.8	126.9
Std. Deviation	91.89	112.9
P value	0.002	

Table 4. Trastuzumab level between recurrence and non-recurrence patients

Develop recurrence		Trastuzumab (9 cycle)	Trastuzumab (17 cycle)
Yes	N	6	6
	Median	17.15	30.36
No	N	44	44
	54.05		134.47
P value	Median	0.12	0.263

Table 5. Serum level of CA15-3 in beginning and end of Trastuzumab treatment

	CA15-3 zero [u/ml]	CA15-3 cycle17 [u/ml]
N	50	50
Median	33.3	25.9
S.D	10.9	42.7
P value	0.0001*	

*Mann Whitney test

identification and eradication by the immune system [20]. Furthermore, immune checkpoint inhibitors open new treatment strategies and introduce recent oncology therapeutic agents [21]. FOXP-3 is a transcription factor and a hallmark of regulatory T cells (Tregs), which mediate tumor immune escape [22]. FOXP-3 is also a tumor suppressor gene in breast cancer [23]. Treatment with Trastuzumab down-regulated FOXP-3 expression, and this may be attributed to the decrease in Treg cells. The results are consistent with Qiu et al. who report a reduction in the number of Treg cells after trastuzumab therapy [24]. FOXP-3 is able to inhibit the transcription of the HER-2/ErbB2 gene as a result of its interaction with the fork head DNA binding motifs that are located in the promoter of the ErbB2 gene [25, 26]. On the other hand, there are no significant differences between the expression of FOXP-3 among those patients who develop recurrence and those with no recurrence. Hence, FOXP-3 could be a suggestive marker to anticipate the response to Trastuzumab but not for predicting the possibility of recurrence. Regarding high TIM-3 expression, which is related to increased metastatic potential, advanced cancer grades, and shorter survival; there may be increased CD80 expression on cells [27]. The up-regulation of mRNA TIM-3 at cycle 9 and may be related to a shortage of Trastuzumab treatment for 3-5 weeks in the oncology center. This might explain upregulation in TIM-3 expression in those patients, and this agrees with the low serum level of Trastuzumab at the same cycle, followed by significant downregulation at cycle 17, where the serum level of Trastuzumab increased significantly at this cycle, and this may explain these changes in gene expression. Accordingly, TIM-3 reduction goes with the possible response of the patients to treatment. However, there is no significant change in the expression of TIM-3 among recurrence patients, so its role in prediction of the occurrence of metastasis is of no value among those patients. On the other hand, CA15-3, which was requested by the oncologist as a routine marker to follow-up the response to treatment

Table 6. Difference in CA15-3 blood levels between individuals with and without recurrence

Develop recurrence		Ca15-3 zero [u/ml]	Ca15-3 end [u/ml]
Yes	N	6	6
	Median	40	38
No	N	44	44
	Median	32.7	20.2
Sig.*		0.003	0.002

Mann Whitney test

and monitor the metastasis [28], showed a significant reduction at cycle 17 which reflects the fact that this may agree with our finding that down-regulation of FOXP-3 and TIM-3 was related to Trastuzumab therapy responsiveness.

CONCLUSIONS

In conclusion, our results indicate that FOXP-3 and TIM-3 have the potential to be suggestive markers that can anticipate the response to Trastuzumab, but they are not capable of predicting the likelihood of recurrence.

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ETHICAL APPROVAL

The present study's protocol was reviewed and approved by the University of Basrah's College of Medicine, which is affiliated with the Ministry of Higher Education and Scientific Research.

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REVIEW ARTICLE

CONTENTS

Latest research in nootropic therapy of patients with chronic cerebral circulation insufficiency

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ABSTRACT

Aim: To analyze latest research on the usage of choline alfoscerate and ethylmethylhydroxypyridine succinate (EMHPS) as nootropic therapy for patients with chronic cerebral circulation insufficiency (CCCI).

Materials and Methods: Bibliosemantic, comparative and system analysis methods were used in the study. The proposed recommendations are developed on the basis of the analysis of modern literature, the results of randomized studies and meta-analyses, authoritative studies devoted to the study of the CCCI problem.

Conclusions: The combination of EMHPS with choline alfoscerate for the complex treatment of CCCI and associated syndromes improves the functions of the endothelium, leads to asthenic syndrome, indicators of stress, depression and anxiety decreasing has a positive effect on the cognitive impairment and complications' progress reduction.

KEY WORDS: chronic cerebral circulation insufficiency, metabolic syndrome, choline alfoscerate, ethylmethylhydroxypyridine succinate

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INTRODUCTION

In an ever-increasing world where productivity and mental abilities are of great importance, many people are looking for ways to improve their cognitive functioning. Nootropics, or "smart drugs", have become the subject of interest and considerable research, particularly in the context of their use to improve memory, attention, concentration, and other cognitive functions. Also, the high prevalence of cardiovascular and cerebrovascular diseases (CVD), as well as MS, and their high comorbidity lead to an increase in the number of difficult-to-treat patients with various combined pathologies, which determines the need for a more detailed examination and a thoughtful systemic approach to the therapy of this category of patients with mandatory taking into account all comorbid pathologies [1].

AIM

The aim of the study was to analyze latest research of the usage of choline alfoscerate and EMHPS as nootropic therapy for patients with CCCI.

MATERIALS AND METHODS

Bibliosemantic, comparative and system analysis methods were used. The proposed recommendations are developed on the basis of analysis of modern literature, the results of randomized studies and meta-analyses, authoritative studies devoted to the study of the CCCI problem.

REVIEW AND DISCUSSION

Arterial hypertension (AH), DM, obesity, and dyslipidemia remain the main risk factors of the circulatory system diseases and are mortality leading causes in the world, and its combination is likely leading to more rapid progress of cardio- and cerebrovascular pathologies, such as myocardial infarction and ischemic stroke (IS) [2]. The mentioned diseases associated with MS – j-systemic damage as a result of various diseases and the presence of clinical symptoms and laboratory and instrumental data: abdominal obesity, insulin resistance (IR) – have a leading role in the pathogenesis of hyperglycemia, hyperlipidemia and AH.

A difficult clinical task consists not only of detection time of the disease and correct diagnosis, but also of choosing the safest and the most effective drug, which is associated with a possible risk of side effects or aggravation of existing comorbid conditions, especially when the patient has CVD. For patients with MS and CVD we need to use drugs with systemic pleiotropic and

multimodal effects on metabolism, especially, lipid metabolism, and on a wide range of pathological processes of the circulatory system, in particular on tissue hypoxia, oxidant stress, endothelial dysfunction, microangiopathy, etc. In this sense, it is justified to use as part of complex therapy drugs that have antioxidant and antihypoxic activity and contain mitochondrial substrates – succinic acid (succinate), a prominent representative of which is EMHPS [1]. EMHPS is a derivative of pyridoxine, which is used as an antioxidant and membranotropic agent. The presence of two separate chemical groups – 3-hydroxypyridine and succinate – in the composition of EMHPS makes this substance a promising therapeutic agent for the treatment of metabolic pathological conditions caused by endothelial dysfunction. It is known for its ability to improve cognitive function and protect the brain from oxidative stress and toxins, which can be achieved through several mechanisms, in particular by the production increasing of neurotransmitters such as norepinephrine and dopamine, which are responsible for the transmission of signals between neurons. Studies have shown that EMHPS have a positive effect on brain function – attention and concentration increasing, learning and memory improving and age-related changes of cognitive function reducing. EMHPS has a wide range of potential therapeutic properties: from vasotropic (anti-ischemic, cardioprotective and antiatherogenic) to neurotropic (neuroprotective, nootropic and anticonvulsant) [3].

The study of M.M. Tanashyan et al. [4] shows the effectiveness of EMHPS in 39 patients with CCCI and MS associated with DM (80%), AH (97%) and cerebral non-stenotic atherosclerosis (72%). All patients received therapy taking into account chronic diseases (antihypertensive, hypoglycemic, cardiac and antithrombotic drugs) along with EMHPS. A clear positive effect of administrating EMHPS as a part of basic therapy was convincingly demonstrated regarding the main biochemical indicators of MS: IR and carbohydrate and lipid metabolism disorders. In particular, there was an improvement in glycemic indicators (in 50% of patients), a significant reduction of hyperinsulinism, and a significant decrease of IR index and C-peptide level.

The complex effect of the EMHPS (antithrombotic, antiplatelet, hypoglycemic, hypolipidemic, and possibly antiatherogenic) on the main pathogenetic links of cerebrovascular pathology occurring on the background of MS demonstrated in this study shows the feasibility of more active use of the drug, including in the form of disorders of carbohydrate metabolism and vascular pathology.

In a number of studies with DM, MS and CVD, the positive effect of the EMHPS as part of basic therapy on indicators of carbohydrate and lipid metabolism, in particular on the reduction of indicators of glycated hemoglobin, IR and gamma-glutamyltrans, was confirmed. This drug is an effective hepatoprotector. The use of the EMHPS in the complex treatment prescribed for type 2 diabetes and diabetic angiopathy led to a statistically significant decrease in glycaemia (another 5.8-10% in the morning) and lipid spectrum and was considered by the authors of the study as a means of preventive therapy for the further development of diabetic foot. It should be noted that the presence of lactose monohydrate in the dosage form of the drug the EMHPS does not significantly affect the biochemical indicators of blood, but is the most optimal auxiliary substance, taking into account its much smaller (compared to glucose) negative effect on glycaemia [1].

Clinical studies show that the use of EMHPS contributes to a reliable improvement of cognitive and motor functions of patients with CCCI, as well as an improvement in the assessment scales for patients' condition after IS, such as the Rankin scale and the Barthel index [5]. Through elimination of oxidative stress, inclusion of EMHPS in the complex treatment of CCCI, IS, craniocerebral injuries and their consequences, mild cognitive impairment due to atherosclerosis, anxiety disorders, acute myocardial infarction improves the treatment results and helps to reduce the complications number [4].

EMHPS' addition to AH therapy contributed to significant increasing of endothelium-dependent vasodilatation index with the most vivid effect for patients with a resistant course of AH and was accompanied by a tendency to restore the function of the endothelium and the bone marrow ability to produce endothelial cells' progenitors following ischemia [5].

The *in vitro* experiments by Trofimova S.A. et al. [6] demonstrated the highest total antioxidant and antiradical activity of cytoflavin, similar, but somewhat less pronounced activity of vinpocetine, while EMHPS and actovegin – only the nonspecific superoxide dismutase activity which was times lower than that of cytoflavin and vinpocetine.

Choline is an essential nutrient for proper functioning of human organism. It is a main unit of cell and organelle membranes and takes part in numerous physiological processes including signal transduction, DNA and histone methylation, and nerve myelination. Choline is a different metabolites precursor – such as acetylcholine (ACh), phosphatidylcholine (PC), sphingomyelin and betaine [7].

In 1998 the Food and Drug Administration US (FDA) identified choline as an essential nutrient.

Choline alfoscerate (C8H20NO6P) or alpha-glycerophosphocholine (α-GPC, or GPC) is a ACh precursor

commonly used as a food supplement. GPC is considered one of the most common choline sources due to its high choline content and its ability to cross the blood-brain barrier [8]. The organism's choline level decreasing can lead to impaired memory, learning and other cognitive functions.

Through oral administration GPC is readily metabolized to PC – an active form of choline that is able to increase the neurotransmitter ACh release and brain-derived neurotrophic factor (BDNF) [9]. GPC enhances the brain cognitive function and is well-known for its effectiveness in the several neurodegenerative and vascular diseases treatment – such as Alzheimer's disease and dementia. GPC is known to be more effective in combination with cholinesterase inhibitors (ChEI) [10]. GPC administration as treatment of aged rats resulted in restoration of muscarinic M1 receptors number to levels found in the striatum and hippocampus from young animals. In the acute cerebral ischemia model in rats, GPC increased the neurons' tolerance to circulation insufficiency and slowed the execution of the apoptosis. Also, there were findings that have shown that GPC increases proliferation [11].

Also, cholinergic precursors are one of the first drugs used in attempting to relief cognitive impairment in dementia-related disorders [12].

The effects of GPC related to cerebrovascular events remain controversial. A multicenter clinical trial revealed the excellent therapeutic role of GPC on cognitive recovery of patients with acute IS or transient ischemic attack (TIA) [13]. At the same time, a recent research has shown that GPC's consumption is associated with a higher 10-year incident IS risk after adjusting for traditional cerebrovascular risk factors [14]. A potential explanation for these different findings is different GPC supplementation effects on the microbial community structure of the guts: in that case, a recent preclinical research demonstrated that GPC can cause the murine microbiota shift, characterized by Ruminococcus, Bacteroides and Parabacteroides increased abundance and Roseburia, Lactobacillus and Akkermansia decreased abundance [15].

In summary, GPC and other forms of choline supplementation have beneficial effects in terms of improved endothelial function and cognitive functions. However, further dedicated studies are warranted to throughly investigate different effects of the currently available forms of choline supplementation [16].

The numerous clinical studies have demonstrated the effectiveness of GPC for dementia [17]. The patients suffered from degenerative, vascular or combined dementia (Alzheimer's type dementia, vascular dementia and acute cerebrovascular diseases – transient ischemic attack or IS). The treatment duration was 3 or 6 months for oral administration and 3 months for parenteral administration. The obtained results confirmed that GPC improved the clinical condition of patients, in particular, memory and attention [18].

In the study of S.I. Gavrilova et al. [19] psychometric measures showed a significant improvement after treatment with GPC. ApoE4 allele noncarriers performed in immediate and delayed reproduction tests of 10 words. Although, most achieved indicators were decreased in the end of therapy course – 7-9 months after treatment, the level of cognitive functioning remained at a higher level than before GPC treatment. A repeated GPC treatment course prevents the further increasing of cognitive impairment during the follow-up period (10-12 months).

In conclusion, GPC is well-tolerated, safe and is recommended for dementia preventive treatment in patients with high Alzheimer's disease risk, in particular in elderly patients with mild cognitive impairment [19].

The study of I.V. Kolykhalov [20] showed a good therapeutic effect over the GPC treatment course, both in cognitive functioning and a number of immunological parameters in 30 patients with mild cognitive impairment, aged 56 to 82 years (mean age 68.8±9.4 years), received GPC therapy course in 400 mg capsules 3 times a day (1200 mg per day) for 3 months. Evaluation of therapeutic efficacy through psychometric tests and scales was carried out 3 times (the 0th, 45th and 90th day) immunological parameters of leukocyte elastase (LE) and α1-protease inhibitor (α1-PI) were evaluated twice on therapy days 0th and 90th. Significant clinical and immunological correlations included both cognitive functions improvement (according to MMSE and the Boston Naming Test) and LE activity level increasing after a GPC therapy course completion, which suggests that LE functional activity increasing can be shown as a marker of a positive therapeutic response to GPC treatment for patients with mild cognitive impairment [20].

The EMHPS and GPC combination in which these substances complement each other, creating a synergy that improves cognitive function. EMHPS provides neurotransmitter production increasing, while GPC provides precursors for the ACh synthesis. In the result, we have the improvement of signal transmission between neurons and strengthening of memory, learning and other cognitive functions. Modern studies also prove the effectiveness of combined neuroprotection to increase the survival of neurons after IS, on the model 440 non-linear male rats with acute IS. It has been experimentally proven that intensive therapy of acute IS with neuroprotective complexes (NPC): cerebrolysin + EMHPS; cerebrolysin + citicoline; cerebrolysin + edaravone; cerebrolysin + choline alfoscerate initiated within the "therapeutic window" helps to reduce processes of neurodestruction and neuroglioproliferation, which subsequently reduces mortality and neurological deficits [21].

In the State Institution of Science «Research and Practical Center of Preventive and Clinical Medicine» State Administrative Department (Kyiv, Ukraine) we carried out neurological and neuropsychological examination according to the data of scientific research fragment: "Peculiarities of the clinical symptoms and neuropsychological impairment of patients with discirculatory encephalopathy during the war". We used drug combination, targeted effect of which is aimed at overcoming cholinergic insufficiency: EMHPS with choline alfoscerate. In the result of 38 patients with a diagnosis of CCCI and comorbidity examination using such scales as MANND [22], MMSE, DASS-21, FAS and providing treatment combination of ChEI and choline precursors decreasing severity of neurological symptoms, regression of anxiety and depression indicators, and the most significant regression of stress and fatigue indicators were observed.

Complex therapy of CCCI includes a strategy for the prevention of CCCI and its complications, an important place is reduction of regulated risk factors for its development, which primarily include AH and atherogenic dyslipidaemia. Correction of AH was carried out according to general rules, taking into account age and concomitant diseases. The goal of hypotensive therapy is to reduce blood pressure in all patients under the age of 65 to normal, i.e. below 140/90 mm Hg. or to as close as possible to this indicator, a well-tolerated level [23]. The principle of treatment of atherogenic dyslipidaemia is a differentiated therapy based on the results of a comprehensive study aimed at clarifying the causes of its development – hereditary or secondary (caused by diabetes, hypothyroidism, dysproteinaemia, nephrotic syndrome, etc.). The possibilities of non-drug therapy, including diet therapy, physical activity, and weight control, must be used. If these measures are ineffective, medical correction with statins is added within three months.

Supplementing the treatment protocol for patients with CCCI with a drug complex aimed at eliminating cholinergic insufficiency, the appointment of ChEI (neurocytin) in combination with choline precursors (choline alfoscerate) leads to the correction of disorders in the emotional and volitional sphere due to CCCI. To mitigate cognitive impairment, it is necessary to develop a longer, personalized and complex approach, taking into account comorbidity and degree of neurological and neuropsychological deficit. The authors point out positive effects of choline precursors in CCCI – acetylcholine increased production, release of acetylcholine from terminals in response to drug administration [24].

CONCLUSIONS

1. The problem of determining the most effective methods of treatment for patients with CCCI aimed at preserving neurons by improving and developing effective methods of nootropic therapy remains relevant.
2. The complex effect of EMHPS (antithrombotic, antiaggregant, hypoglycemic, hypolipidemic and possibly antiatherogenic) indicates the expediency of more active use of the drug, especially for patients with carbohydrate metabolism disorders and cardiovascular pathology.
3. The inclusion of EMHPS in the combined therapy of CCCI and associated syndromes improves the results of treatment for patients and helps to reduce the number of complications.
4. GPC and other forms of choline supplementation have beneficial effects in terms of improved endothelial function and cognitive functions.
5. Nootropic therapy using EMHPS and GPC is a promising approach for improving cognitive functions and the brain tissue protection.
6. The appointment of combination of ChEI with choline precursors as targeted cholinergic insufficiency therapy leads to reduction of asthenic syndrome, indicators of stress, depression and anxiety, and, as a result to reduction of cognitive impairment.

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The authors adhere to the standards of the Helsinki Declaration of the World Health Organization association, as well as Interdisciplinary norms and regulations on the use of animals in research, testing and educational programs, which are published by the appropriate committee dealing with animal research at the Academy of Sciences in the city of New York. The submitted manuscripts relate to the work patients and prepared in accordance with ethical standards. The study was performed as a fragment of the complex scientific project of the Scientific Department of Internal Medicine (State Institution of Science «Research and Practical Center of Preventive and Clinical Medicine» State Administrative Department) «Improvement of patient-oriented approaches to the management of patients with cardiovascular and cerebrovascular diseases with comorbid conditions, in particular in those suffered from COVID-19» (state registration number 0122U000234; term: 2022-2024).

CONFLICT OF INTEREST

The Authors declare no conflict of interest

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REVIEW ARTICLE

CONTENTS

The influence of parenteral nutrition on the condition of the oral cavity: literature review

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ABSTRACT

Oral health plays a pivotal role in the overall well-being of patients. This article delves into the intricate interplay between oral health and systemic health outcomes in various patient populations, including those undergoing parenteral nutrition in childhood, individuals with impaired swallowing function, and those reliant on long-term enteral or parenteral nutrition. Through a comprehensive review of existing literature, the multifaceted role of oral health maintenance in optimizing nutritional therapy outcomes and enhancing overall quality of life is explored. Alternative forms of nutrition have a profound impact on Oral microbiota, which in turn is reflected in general health and wellbeing. Despite its significance, the importance of systematic oral health assessments and nurse involvement in providing holistic care to patients with complex medical needs has been underestimated. By elucidating critical connections between oral health and systemic health outcomes, this article aims to underscore the significance of oral health in comprehensive patient care and stimulate further research to advance our understanding of this crucial aspect of healthcare management.

KEY WORDS: parenteral nutrition, enteral nutrition, microbiota

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INTRODUCTION

The evaluation and maintenance of oral health are crucial aspects of caring for patients in intensive care units, as evidenced by numerous clinical studies confirming its effectiveness in preventing ventilation-associated pneumonia, aspiration pneumonia, or hospital-acquired pneumonia [1]. The oral cavity, serving as a dynamic ecosystem, undergoes continual changes in its microflora composition, influenced by various factors including maternal microorganisms, living conditions, dietary habits, and health status. Emerging evidence highlights the profound impact of oral health on overall well-being, with implications extending beyond traditional considerations of digestion and swallowing [2].

This article explores the intricate interplay between oral health and systemic health outcomes in various patient populations, including those undergoing parenteral nutrition (PE) in childhood, individuals experiencing impaired swallowing function, and those reliant on long-term enteral or parenteral nutrition. Through a comprehensive review of existing literature, this article delves into the multifaceted role of oral health maintenance in mitigating risks associated with systemic diseases, optimizing nutritional therapy outcomes, and enhancing overall quality of life [3].

The importance of systematic oral health assessments and nurse involvement in providing holistic care to patients with complex medical needs has been underestimated in recent decades [4-5]. By clarifying these critical connections, this article aims to underscore the significance of oral health in comprehensive patient care and stimulate further research to advance our understanding of this crucial aspect of healthcare management.

WHAT IS PARENTERAL NUTRITION?

Parenteral nutrition (PN) serves as a vital intervention in patients where enteral or oral nutrition is either unfeasi-

ble or inadequate. European and American Guidelines prioritize enteral nutrition (EN) over PN whenever the gastrointestinal tract remains functional and accessible, except in cases of intestinal failure due to various conditions such as short bowel syndrome, inflammatory bowel diseases, high-output fistulas, severe intestinal obstruction, or when the gastrointestinal tract is inaccessible [6-7].

Intestinal failure, characterized by reduced gut function hindering nutrient absorption, necessitates parenteral supplementation, with its severity classified into acute (type I), prolonged acute (type II), and chronic (type III) forms. Type I patients typically receive short-term PN in hospitals, whereas type II and III patients require PN over weeks to months or months to years, often administered at home [8].

Malnutrition, common in hospitalized patients, especially the critically ill, surgical, and cancer patients, necessitates nutritional support, with PN indicated for those with non-functional or inaccessible gastrointestinal tracts. While PN provides crucial nutrition for patients unable to be fed orally or enterally, it comes with complexities and potential complications such as hepatobiliary, infectious, and mechanical issues, alongside metabolic disturbances [9-10]

A study by Salama et al. examined the impact of total parenteral nutrition (TPN) on teething in premature infants, finding that TPN, particularly the intralipid component, is associated with earlier tooth eruption. Conducted on 85 preterm infants, the study underscores the need for further investigation into TPN's effects on dental development, with gender also influencing the timing of tooth eruption. This novel research sheds light on a poorly studied aspect of premature infant care, emphasizing the importance of nutritional considerations in neonatal care protocols [11].

AIM

This article aims to underscore the significance of oral health in comprehensive patient care and stimulate further research to advance our understanding of this crucial aspect of healthcare management.

REVIEW AND DISCUSSION

IMPAIRED SWALLOWING

The relationship between oral health and swallowing function is closely intertwined, with prolonged use of EN or PN increasing the risk of declining oral health and subsequent impairment of swallowing. A systematic review by Drancourt et al. explored this association in individuals over 65, highlighting factors such as dental status, saliva secretion, and oral motility. Their findings revealed that weakened tongue strength and restricted tongue mobility were significantly linked to diminished swallowing ability. Maintaining optimal oral health, particularly dental health, is crucial for lifelong well-being. Many patients receiving EN are unable to orally consume food, necessitating additional supportive measures, yet the oral hygiene of these individuals is often subpar [12].

GENERAL ORAL HEALTH STATUS

A study investigating oral health status in home parenteral nutrition (HPN) outpatients revealed poorer oral health compared to the UK norm, with higher rates of decay, fewer teeth, and increased risk factors for caries and oral infection, despite similar dental attendance. The findings suggest a need for increased awareness and management of oral health risk factors among HPN patients, including consideration of complications related to bisphosphonates, anticoagulant therapy, and parenteral antibiotic prophylaxis [13].

The other studies underscore the compromised oral health status of Percutaneous endoscopic gastrostomy (PEG) patients, revealing poorer oral health indices compared to the general population even before gastrostomy, with further deterioration observed over three months of exclusive enteral feeding, suggesting the importance of heightened focus on oral hygiene [14].

XEROSTOMIA

The prolonged use of EN and PN can indirectly affect the oral cavity's environment and health. Malnutrition and dehydration, prevalent in patients with conditions like inflammatory bowel disease or extensive small intestine resection, contribute to reduced salivation. Lee et al. reported that 81% of respondents experienced oral discomfort during PN therapy, leading to a persistent change in food choices for 27% ($p<0.05$) of these patients [15]. Additionally, another study echoed these findings by indicating a higher prevalence of xerostomia among patients with restricted oral intake, weight loss, and reduced independence [16].

IMPORTANCE OF CHEWING

Mastication, the initial and pivotal stage of digestion, necessitates coordination among the tongue, facial muscles, jaw, and teeth, playing a vital role beyond food intake as the masticatory system is closely linked to speech production and overall health, with chewing

also promoting saliva production, thereby indirectly affecting digestive processes [17].

Chronic stress exposure can lead to physical and mental health issues globally, but mastication serves as an effective coping mechanism, potentially modulating stress response pathways, including the hypothalamic-pituitary-adrenal axis and autonomic nervous system, thereby attenuating stress-induced physiological and neurological changes in both animal models and humans [18].

Chewing not only aids in swallowing and digestion but also contributes to stress relief and cognitive regulation, particularly in sustaining attention, as evidenced by the majority of studies reviewed, suggesting its potential utility in enhancing cognitive function, though further research is warranted to elucidate its mechanisms and applications [19].

Temporal changes in cerebral blood flow during jaw movement were investigated through bilateral transcranial Doppler ultrasound examination during clenching, gum chewing, and tooth tapping in healthy volunteers, revealing significant increases in middle cerebral artery blood flow velocity during clenching and gum chewing, indicating the influence of muscle contraction intensity on task-induced cerebral blood flow changes [20].

Onozuka et al. proved chewing leads to a bilateral increase in blood oxygenation levels in areas including the sensorimotor cortex, cerebellum, thalamus, supplementary motor area, and insula [21]. Chuhuaicura et al. proved chewing ability might serve as a protective element in individuals affected by cognitive decline and neurodegenerative disorders, potentially through mechanisms such as enhancing cerebral blood flow [22].

ROLE OF SALIVARY DEFENCES IN MAINTAINING A HEALTHY ORAL MICROBIOTA

The findings of Pedersen et al. emphasise the critical role of saliva in maintaining the delicate equilibrium of the oral microbiota, emphasizing its multifaceted contributions to oral health and symbiosis. Dysfunctions in salivary gland activity and composition can disrupt this balance, increasing the risk of oral diseases such as gingivitis, caries, and fungal infections [23].

Chewing serves as a fundamental mechanism to stimulate salivary flow, thereby contributing significantly to oral health. Salivary glands are activated during mastication, releasing saliva into the mouth. This increased salivary flow serves several important functions that help prevent the development of dental caries [24].

Saliva helps to neutralize acids in the mouth. When we consume acidic foods or beverages, such as citrus fruits or soda, the pH level in our mouth drops, creating an environment conducive to the erosion of tooth enamel and the proliferation of acid-loving bacteria. Saliva contains bicarbonate ions, which act as a buffer to neutralize these acids, helping to restore the mouth's pH balance and mitigate the harmful effects of acidity on the teeth [25].

Saliva contains antimicrobial components, such as enzymes and antibodies, which help to inhibit the growth of bacteria and fungi in the oral cavity. By promoting saliva production through chewing, these antimicrobial properties are enhanced, further reducing the risk of oral infections and dental diseases [26].

In a study by Pedroso et al., 17 patients, aged 64 ± 10 years, who underwent percutaneous endoscopic gastrostomy due to head or neck cancer (76%) or neurological disorders (24%) were examined. Following a month of exclusive EN, colonization rates of yeast or lactose fermenting gram-negative organisms remained similar. However, there was an increase in patients colonized with candida species (from 76% to 88%) and lactose fermenting gram-negative bacteria (from 24% to 29%). Conversely, lactose non-fermenting gram-negative bacteria or *Staphylococcus* species showed decreased occurrences. Fewer than 30% of subjects exhibited increased colony-forming units, with only two patients showing increased microbiological load across all tested media. Notably, there was a higher rate of isolation of beta-haemolytic bacteria (from 53% to 94%). Overall, the study suggests a reduction in isolation rates and microbial load in the oral cavity after one month of EN, with further follow-up needed to explore these findings in depth [27-29].

PARENTERAL NUTRITION IN CHILDHOOD

The oral cavity in humans constitutes a dynamic ecosystem, where the oral microflora develops during early childhood and undergoes continual changes over time. Initially, maternal microorganisms such as *Lactobacillus* spp., *Staphylococcus* spp., *Streptococcus* spp., Bifidobacterium spp., and Gram-negative rod-shaped bacteria of the *Enterobacterales* contribute significantly to its formation. As time progresses, the composition and stability of the oral bacterial flora are influenced by various factors including external elements like living conditions and dietary patterns, as well as internal factors such as health status and genetic predispositions [30].

A study by Olczak-Kowalczyk et al. concludes that PN in childhood increases the likelihood of dental developmental abnormalities, which are influenced by factors such as malnutrition and antibiotic therapy during infancy while limiting the frequency of meals

and cariogenic snacks, and likely reducing antibiotic use, decreases the risk of caries [31].

A study by Kumaraguru et al. found that compared to the general UK paediatric population, oral issues were less frequent among children in our study who received home parenteral nutrition (HPN), unlike adult patients on intravenous nutrition who exhibited greater oral health concerns than the general public. Nonetheless, the overall prevalence of these issues was similar among both adult and paediatric populations receiving long-term HPN, underscoring the necessity for targeted health guidance in this patient cohort [32].

CONCLUSIONS

The intricate relationship between oral health and systemic well-being is increasingly recognized as a crucial aspect of comprehensive patient care, particularly in populations with complex medical needs such as those undergoing PN, experiencing impaired swallowing, or reliant on long-term EN. The available literature highlights the multifaceted impact of oral health maintenance on optimizing nutritional therapy outcomes and enhancing overall quality of life.

From the influence of early childhood nutrition on dental development to the implications of xerostomia and compromised oral health in patients receiving EN or PN, this article emphasises the profound significance of oral health in holistic healthcare management. Moreover, it underscores the importance of systematic oral health assessments and the involvement of nurses in providing comprehensive care to patients with diverse medical conditions.

Despite recent strides in understanding the connections between oral health and systemic health outcomes, there remains a need for further research to deepen our understanding and refine clinical practices. By continuing to explore these critical connections and implementing evidence-based interventions, healthcare professionals can better address the oral health needs of patients, ultimately improving overall health outcomes and enhancing the quality of care

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REVIEW ARTICLE

CONTENTS

Seasonal influenza in children: complications, treatment, prevention (subject publication review)

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ABSTRACT

Aim: To study the specificity of seasonal flu in children, in particular, in young children, as well as treatment, prevention and complications of seasonal flu.
Materials and Methods: For the methodological justification of the article, we used the pool of research technologies. Methods of theoretical analysis, system-analytical, comparative methods provided us with the opportunity to characterize the features of influenza incidence in children.
Conclusions: A distinctive feature of influenza is the high lability of the genes of the infectious agent. In this regard, it is extremely important to timely update information about new strains of the pathogen, creation of new types of vaccines and antiviral drugs, as well as changes in the course of the disease. Our literature review is intended to improve the medical community.

KEY WORDS: influenza virus, acute respiratory viral infections, pneumonia, sinusitis, vaccine

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INTRODUCTION

Seasonal influenza, an acute respiratory viral infection, creates health problems for both individuals and the population as a whole, provoking the development of epidemics and pandemics. This places a significant burden on the healthcare system [1, 2].

The human influenza virus (type A and type B) is most active during the autumn-winter period [3-5]. The most dangerous virus for humans is the influenza virus type A. This virus has a more intense ability than others to mutate, change the genotype and, accordingly, has a greater ability to infect large masses of people and animals, provoking the development of not only epidemics, but also pandemics (the so-called bird flu, swine flu). Viruses are classified and recognized based on two surface proteins, hemagglutinin and neuraminidase [4, 5]. We know of two lineages of influenza type B: Victoria and Yamagata. These strains mutate more slowly, affect only humans, and provoke the development of seasonal epidemics [4, 5]. Influenza virus type C affects only humans; the symptoms of this disease are more mild and create seasonal epidemics [4, 5]. Influenza virus type D affects cattle; there are no known cases of human infection [4, 5].

When analyzing the epidemic situation for the autumn-winter 2019-2020, the following facts were established: the majority of patients admitted to the intensive care unit (94%) were infected with influenza virus type A, of which A(H3N2) accounted for 58% of cases. For somatic departments, the percentage remained similar and was, respectively, 94% of cases of influenza virus type A, strain A (H3N2) 65% of cases [6]. The development of severe acute respiratory infections was more often provoked by influenza virus type B (57%) [6].

AIM

To study the specificity of seasonal flu in children, in particular, in young children, as well as treatment, prevention and complications of seasonal flu.

MATERIALS AND METHODS

For the methodological justification of the article, we used the pool of research technologies. Methods of theoretical analysis, system-analytical, comparative methods provided us with the opportunity to characterize the features of influenza incidence in children. The author group adheres to the principles of the 1964 Declaration of Helsinki as amended. Patients whose data were used in the preparation of this literature review provided voluntary written and oral informed consent

for the processing of personal data, treatment, and examination. While working with patients, all principles of bioethics were observed and all permits were obtained from the relevant regulatory authorities. The team of authors used methods of comparative and theoretical analysis, as well as system analytical algorithms.

REVIEW AND DISCUSSION

Seasonal influenza incidence peaks in the northern hemisphere in February, with epidemic rates remaining elevated from October to April [7]. This phenomenon is due to the increased survivability of the influenza virus in cool climates. We should not forget about the accumulation of people in insufficiently ventilated areas during the autumn-winter period. All this determines the pronounced seasonality of outbreaks of infection [8]. For example, the increase in influenza incidence in the 2019- 2020 season began much earlier than usual in some regions due to an early decrease in ambient temperatures [6].

The mechanism of transmission of the influenza virus is airborne. This means that a person who sneezes infects not only those around him at that moment within a meter radius, but also those who subsequently come into contact with surfaces on which mucus particles have settled. For example, with a door handle or handrails in public transport. The outbreak of infection spreads especially quickly between family members and in closed groups, such as a kindergarten group, a school class, or a hospital department [8].

Symptoms of influenza infection are intoxication, fever, headache, cough, muscle pain. The severity of the disease varies from mild to severe [9]. Most patients overcome the infection within 5 days [9], some may develop severe complications, some of which can be life-threatening and result in death [10]. The most serious – and deadly – influenza complication is pneumonia [8], which is either primary influenza virus pneumonia or secondary bacterial pneumonia [9]. Extrapulmonary complications of influenza infection include damage to the cardiovascular system, in particular viral myocarditis, and damage to the nervous system, in particular the development of sensorineural hearing loss [11]. The development of complications from ENT organs, such as otitis media, sinusitis, laryngitis, is also typical [10].

Young children, elderly people, people suffering from various chronic diseases, and pregnant women are at risk for developing complications of influenza infection [12, 13]. An additional risk group consists of persons with a complicated medical history. These are children with various congenital pathologies and infections. Patients with chronic diseases of the blood system (sickle cell anemia), endocrine system (diabetes mellitus), urinary system (glomerulonephritis). Children and adults with various metabolic disorders and people with HIV positive status or AIDS [14, 15]. Naturally, patients from a high-risk group require preventive vaccination [8].

In Ukraine, half of children hospitalized for influenza infection are not at risk [15]. Among somatically healthy children, influenza infection is considered a disease requiring symptomatic treatment and not requiring hospitalization [16].

Influenza virus is the main pathogen leading to the development of acute respiratory infection in young children [9, 17]. It is also the main cause of the development of viral pneumonia under the age of two years [18]. In children under seven years of age, influenza infection accounts for a significant percentage of diagnoses during hospitalization [19].

The most dangerous complication of influenza infection is viral pneumonia. This is an inflammatory disease of the bronchopulmonary tract, characterized by the accumulation of exudate in the alveoli and making the gas exchange mechanism in the damaged area of the lung impossible. This leads to the development of hypoxia of varying severity [21]. Pneumonia is extremely dangerous for children with congenital defects of the bronchopulmonary and cardiovascular systems [22]. HIV positive status increases the risk of developing pneumonia.

All cases of viral pneumonia in childhood require hospitalization [20]. If we talk about the risks of developing complications from viral pneumonia, then the first place should be the addition of a bacterial infection and the development of lobar pneumonia. In second place are heart and liver failure [20]. The symptoms of viral and bacterial pneumonia are similar. In both cases, a wet cough, coarse and fine bubbling wheezing, and tachypnea will be noted. An X-ray image reveals a shadow with an enhanced pulmonary pattern. A general blood test is characterized by leukocytosis and increased ESR. Differential diagnosis relies on history and a specific test for influenza virus. One should be wary of febrile hyperthermia in young children it can provoke convulsions [21]. Basically, viral pneumonia resolves on its own, without medical intervention [23].

In approximately 25% of patients, especially young children, the course of acute respiratory viral infections can be complicated by the development of acute otitis media [24]. Otitis media is the second most common diagnosis in pediatric emergency departments, behind upper respiratory tract infections. Most often, children aged 6-24 months suffer from otitis media [25, 26], which is explained by age-related features of the structure and functioning of the Eustachian tube [27].

Otitis media includes some variants. First of all, we would like to note two diseases that are closely related to each other, but completely different in the nature of development – acute otitis media (OMA) and otitis media with effusion (OME). OMA is basically inflammatory in nature of bacterial etiology, while OME is characterized by the presence of fluid in the middle ear without obvious signs of inflammation. As a rule, patients with OME do not present any complaints, but it should be remembered that symptoms such as ear congestion or hearing impairment are possible. It is important to understand that OMA and OME are two different diseases and their treatment is radically different [28]. OMA requires timely antibacterial therapy, otherwise it can lead to the generalization of a bacterial infection to neighboring organs with the development of such complications as tympanic membrane (TM) perforation, mastoiditis, meningitis, brain abscess, hearing loss, and others [25, 26]. Chronic otitis media may occasionally be accompanied by damage to the inner ear with persistent hearing loss and dizziness [24].

The second most common ear, nose and throat complication of flu is sinus infection. Sinusitis is known as a widespread disease with typical clinical symptoms [29] including fever, headache, discomfort or pressing pain in the projection area of the sinuses, purulent discharge from the sinuses and nose, congestion and blockage of nasal breathing [30]. There may be a disturbance in the sense of smell [31]. The proximity of the nasal sinuses to such vital organs as the eyes and brain determines the severity of development and the severity of potential complications [32], such as meningitis, periorbital cellulitis, cavernous sinus thrombosis, epidural abscess or brain abscess [30, 31]. The appearance of severe headache, confusion, pain in the eyeballs, periorbital edema due to sinusitis should alert the leading doctor to possible complications [30].

The best way to prevent pneumonia, ear and sinus infections and other complications is to prevent flu [24]. Prevention of influenza includes specific and nonspecific prevention measures. Nonspecific prevention is aimed at isolating a person sick with influenza, introducing a mask regime to protect others, frequent ventilation of rooms, measures to strengthen the immune system (healthy meal, adequate sleep, physical activity, reducing stress factors, etc.).

However, all these measures taken together are significantly inferior in effectiveness to vaccination as a measure of specific prevention of influenza. Today, the use of the influenza vaccine is the single most significant way to prevent the incidence of influenza [15, 16]. There are national programs for immunization against influenza, in which the need to vaccinate people at risk for developing post-influenza complications is a common thread [9]. Both types of vaccines are widely used to prevent influenza: inactivated influenza vaccine (IIV) and live attenuated influenza vaccine (LAIV) [33, 34]. In IIV a non-live influenza virus is used, such vaccines are administered by injection. In LAIV a live weakened influenza virus is used, the vaccine is administered intranasally as a spray. Nasal vaccines are indicated exclusively for children over 2 years of age. Children under 2 years of age or children under 5 years of age with a history of bronchial asthma or stenos of larynges are prohibited from administering the vaccine in the form of an intranasal spray [24].

The continuous mutation of the influenza virus causes a decrease in the effectiveness of previously produced vaccines and every season requires updated influenza vaccines [15, 35] with predominant protection against the main strains of influenza A and influenza B, which are expected to dominate the current season [36].

Food and Drug Administration's (FDA's) Vaccines and Related Biological Products Advisory Committee in 2019-2020 recommended that trivalent influenza vaccines include the following: (1) an A/Brisbane/02/2018 (H1N1) pdm09-like virus; (2) an A/Kansas/14/2017 (H3N2)-like virus; (3) a B/Colorado/06/2017-like virus (B/Victoria lineage) [36].

It is advisable to vaccinate against influenza in advance – 2 weeks before the expected onset of illness, since this time is necessary for the production of anti-influenza antibodies, which will protect the child [24]. The most optimal time for anti-influenza vaccination is considered to be October and November [37], however, receiving the vaccine is also possible in the winter months [8].

The Public Health Organization (WHO) and the Centers for Disease Control (CDC) recommend annual influenza vaccination for anyone over 6 months of age [3, 5, 35, 37]. The exceptions are children in the first six months of life and people with a history of allergies. If you have Guillain-Barré syndrome, you should consult a doctor before vaccination [3, 38].

WHO especially recommends vaccination for people who are at risk of developing complications from influenza [3, 37, 38]. Children aged 6-59 months and pregnant women are included in the priority groups for influenza immunization [37]. The body of a pregnant woman who has received a dose of the vaccine produces antibodies, which the mother passes on to the fetus in the last trimester of pregnancy and during breastfeeding. These antibodies will protect the baby from the flu for some time after birth [35, 39]. For children under 8 years of age, the first vaccination is accompanied by the administration of 2 doses of vaccines at once. After

reaching 8 years of age and older, 1 dose of the vaccine is administered annually [15, 34, 39].

Parents concerns about vaccinating their children against influenza are usually associated with possible adverse reactions after vaccination [15, 40]. When an inactivated vaccine is administered by injection, most often no side effects occur; sometimes there may be mild pain at the injection site and low-grade fever, which go away on their own after a short time. After administration of the nasal vaccine, the temperature may rise to low-grade levels, there may be nausea, runny nose, and wheezing [24].

People who did not take care of influenza prevention and managed to get sick can use the following drugs aimed at suppressing virus replication to treat influenza [6, 13, 41]. There are 4 medicines that can help treat flu and are recommended by CDC for use in children during the 2019-2020 flu season. They are neuraminidase inhibitors. Oseltamivir (trade name Tamiflu) can be used to treat influenza in children 2 weeks of age and older. Available in tablet form and liquid form. The use of oral oseltamivir in children during the first 14 days of life is not indicated. Zanamivir (trade name Relenza) is a powder for inhalation. Can be used in children over 7 years of age, however, the drug is contraindicated in patients with chronic diseases of the respiratory tract (bronchial asthma, etc.). Inhaled zanamivir is administered through a special inhaler (Diskhaler). Peramivir (trade name Rapivab) is used as an intravenous injection and is indicated for the treatment of influenza in children aged 2 years and older. Baloxavir (trade name Xofluza) is available in tablet form and is used once for patients 12 years of age and older [15, 42]. All currently circulating influenza viruses are resistant to adamantane antiviral drugs (such as amantadine and rimantadine), and these are therefore not recommended for monotherapy [13].

The effectiveness of the following antiviral drugs depends on the timeliness of their administration – they must be taken in the first 2 days from the moment of illness! The question of prescribing the drug to a patient admitted later than the first 48 hours from the onset of the disease is decided individually with the doctor [13]. The duration of treatment with antiviral drugs is usually 5 days, but if necessary, it can be extended until clinical improvement [13]. In some cases, these drugs are prescribed to high-risk patients who have been in contact with someone who has the flu to prevent the development of the disease. However, it should be remembered that these drugs are used for prophylactic purposes in exceptional cases and are not a replacement for the influenza vaccine [15, 42].

The issue of using corticosteroids is decided individually; they cannot be used continuously (unless there is an indication for it, for example, bronchial asthma), since this leads to immunosuppression, prolonged viral clearence and the addition of a secondary bacterial or fungal infection [13].

CONCLUSIONS

A distinctive feature of influenza is the high lability of the genes of the infectious agent. In this regard, it is extremely important to timely update information about new strains of the pathogen, creation of new types of vaccines and antiviral drugs, as well as changes in the course of the disease. Thus, our literature review is intended to improve the awareness of the medical community on the issues of the specificity of seasonal flu in children, its complications, treatment and prevention.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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REVIEW ARTICLE

CONTENTS

Etiology of gingival recession – a literature review

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ABSTRACT

Gum recession is a common problem that in most cases does not cause any bothersome symptoms to the patient. They can affect people of any age and are most often diagnosed on the vestibular surfaces of the teeth. They are manifested by the exposure of part of the root through the apical migration of the gingival margin. Its etiology is not fully understood, but it is known that it consists of many factors. The authors discussed such factors as inflammation, gum biotype, patient's age, mechanical and chemical damage, smoking, presence of tartar, cervical defects and their reconstruction, orthodontic treatment, occlusal overload and iatrogenic factors. Additionally, important risk factors also include genetic predispositions and abnormalities in the immune system. In addition, certain hygiene habits, such as improper brushing techniques or lack of regular check-ups at the dentist, may also contribute to the development of gum recession. Understanding the comprehensive nature of these factors is crucial to the effective treatment and prevention of this common condition. It is also worth taking into account the importance of educating patients on proper oral hygiene and regular dental check-ups to prevent gum recession.

KEY WORDS: gingival recession, stomatology, medical prevention

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INTRODUCTION

Gum disease is one of the most common conditions that dentists encounter in their offices. It is rare for a patient to come to the doctor citing the occurrence of gum recession as the main problem. In most cases, it proceeds without bothersome symptoms for the patient, or at least they are not associated with the problem [1]. Gingival recession is defined as apical migration of the gingival margin toward the cemento-enamel junction (CEJ) [2]. This condition, although not associated with increased tooth loss, is considered an aesthetic problem and is often associated with dentin hypersensitivity and carious/non-carious cervical lesions on the exposed root surface. It can also lead to excessive abrasion of the root surface and even, in extreme cases, tooth loss [3,4].

According to Rodier [5], 17% of recessions have no obvious clinical etiology. However, two groups of etiological factors can be distinguished:

- predisposing factors, which are necessary for the occurrence of recession and which are essentially anatomical;
- initiating factors, which in the risk area will promote the occurrence of recession. These are mainly related to the behavior of the patient or practitioner [6].

Gingival recessions are most often observed in mandibular incisors (43.0%), followed by maxillary molars (13.2%), mandibular premolars (12.2%), maxillary incisors and premolars (8.9%), mandibular molars (4.9%), maxillary canines (4.6%) and mandibular canines (4.3%). Recession was more frequently observed in the mandibular arch (66%) than in the maxillary arch (34%) [7].

The current classification of gingival recessions was proposed in 2011 by Cairo et al. It was based on the loss of connective tissue attachment (CAL - Clinical Attachment Loss) in the interdental spaces [8]. This classification was incorporated into the new WWC2017 classification as follows (Table 1) [4].

AIM

The aim of this study is to develop an understanding of the multi-faceted factors influencing gum recession

Table 1. WWC2017 standings

Recession type 1 (RT1)	- Gingival recession without loss of interdental attachment. - The interdental CEJ is clinically undetectable in both the mesial and distal parts of the tooth.
Recession type 2 (RT2)	- Gingival recession associated with loss of attachment in the interdental spaces. - The amount of interdental CAL (measured from the interdental enamel-cementum junction to the depth of the interdental sulcus/pocket) is less than or equal to the loss of buccal attachment (measured from the buccal CEJ to the apical end of the buccal sulcus/pocket).
Recession type 3 (RT3)	- Gingival recession associated with loss of interdental attachment. - The magnitude of the interdental CAL (measured from the interdental CEJ to the apical end of the fissure/cheekbone) is greater than the loss of buccal attachment (measured from the buccal CEJ to the apical end of the fissure/cheekbone).

and to examine their role in the development of this common condition.

REVIEW AND DISCUSSION

CAUSES OF GINGIVAL RECESSIONS

INFLAMMATION OF THE GINGIVAL TISSUES

The main etiological factors associated with the occurrence of gingival recession are periodontal inflammation associated with bacterial plaque accumulation due to poor oral hygiene [7].

GINGIVAL BIOTYPE

The term gingival biotype refers to the width of the gingiva in the vestibulopontine segment, which is genetically determined [9]. In the 20-35 age group, 43.25% of individuals were found to have a thin gingival biotype. Such a condition requires special care during aesthetic, restorative and periodontal therapy. Patients are more prone to connective tissue loss and epithelial damage. Treatment for them should be atraumatic, while they should use appropriate oral hygiene techniques adapted to their mucosal condition on a daily basis [10]. Thin gingival biotypes are less stable, and the occurrence of papillary and marginal recession is more common in them [3,10]. Das and Shenoy determined that there is a relationship between gingival thickness and cigarette smoking. Smokers were observed to have significantly less gingival thickness [9]. However, biotype alone does not affect the effectiveness of surgical coverage of recessions [11]. Yared et al (2006) found that 93% of teeth in which recession developed had a gingival thickness of less than 0.5 mm [12].

MECHANICAL INJURIES

Tooth brushing

An incorrect brushing technique, or too much pressure of the toothbrush against the tooth surface, are among the most common etiological factors associated with the development of gingival recessions. It has been observed that when the method was corrected, there was a halt in the progression of recession development [13]. In addition to technique and pressure, the timing of brushing, the hardness of the bristles in the toothbrush and the frequency of toothbrush replacement are also important [14].

Prosthetic restorations

Incorrectly designed or cemented fixed dental restorations result in areas that promote plaque accumulation, making it difficult to maintain proper hygiene. This leads to local inflammation, as well as tartar deposition. The same is true for poorly made or fitted partial dentures or their retaining components. Inadequate oral hygiene and the denture itself leads to inflammation of the gums and plaque accumulation. In addition, gingival recession occurs at the junction of the denture plate and/or its retention elements with the tooth as a result of their pressure on the surrounding tissues. This sets the stage for developing periodontal disease. In addition, if the restoration does not meet the patient's expectations in terms of aesthetics then the patient may experience discomfort and avoid proper oral hygiene, which increases the risk of inflammation and the development of recession. This is why it is so important not only to make but also to fit the prosthetic restoration accurately, but also to have regular dental check-ups and proper oral hygiene [15].

Oral self-inflicted injuries

Oral self-injuries can be intentional, accidental or the result of an unusual habit. These injuries are usually the result of the presence of parafunctions or the presence of a foreign body in the mouth , which cause erosion of the gingival tissue in a specific area [16]. Dilsiz and Aydin described a case of gingival recession of the lower incisors after habitual scratching of this area with a nail [17].

Gingival retraction

Phatale et al. stressed the need for special care when performing the gingival retraction procedure with mechanical methods, as recessions of the exposed gingiva can occur if care is not taken and the surrounding tissues are traumatized [18]. When using conventional retraction sutures, healthy epithelium can be damaged not only by using too much force, but also by too long a retraction time. The recommended time for placing the floss in the gingival crevice is between 5 and 15 minutes [19]. Both rotary curettage and electrosurgical methods of gingival retraction are also associated with the postoperative occurrence of gingival recession [20]. A meta-analysis by Yijing et al. showed that retraction pastes such as Expasyl or FoamCord are a much safer alternative to popular retraction threads [21]. In contrast, Kazakova et al. identified erbium yag and diode lasers as safe tools for performing gingival retraction [22].

IMPACT OF TOBACCO PRODUCTS

Cigarettes

A study from the Baltimore Longitudinal Study of Aging found that cigar and/or pipe users had more missing teeth and more sites with severe loss of connective tissue attachment and advanced recession compared to non-smokers [23]. The nicotine in cigarettes causes blood vessels to shrink, so less blood reaches the tissues causing gingival recession. It can also cause the formation of gingival pockets , the presence of which leads to inflammation of the area, decreased epithelial attachment, infection and other health complications [24].

Tobacco chewing

Gingival recessions and loss of connective tissue attachment can also be caused by the local effects of tobacco during snuff chewing. In such situations, recessions are most often located unilaterally within the lower dental arch [23]. It has been shown that patients who chew tobacco were twice as likely to have gingival recessions compared to the rest of the patients. This is related to the fact that chewing tobacco also contains large amounts of fermentable sugars, which stimulate the development of plaque, a direct factor responsible for the formation of gingival recessions [25].

AGE

Based on the studies conducted by Woofter, it can be assumed that the formation of gingival recessions may also be a result of the physiological aging process of the soft and bony tissues of the alveolar process. Studies conducted by other authors also show that the incidence and frequency of gingival recessions increase with age [26].

A long period of exposure to risk factors leading to gingival recessions may explain the association between the occurrence of gingival recessions and age. In younger patients, there is a predominantly local occurrence of gingival recessions at single teeth, which is associated with various etiological factors, paraphunctures characteristic of this age group (e.g., nail biting, holding a pencil in the mouth). In adults, on the other hand, the presence of common gingival recessions may be the result of a multifactorial effect of certain etiological factors, such as previous periodontal therapies combined with traumatic brushing [27].

TOOTH OCCLUSAL OVERLOAD

The relationship between gingival recession and occlusion, although often discussed in dentistry, is a contentious issue. Solnit and Stambaugh [28]. reported spontaneous partial or complete root coverage after occlusal alignment of 25 teeth with gingival recession. However, Harrel and Nunn showed no statistically significant difference between occlusal overload and gingival height, or between correction of occlusal height and change in gingival height. They conclude that there is no relationship between occlusal overload and gingival recession [29]. Similar results were obtained by Dodwad, who indicated that occlusal overload only in interaction with other factors can cause the occurrence of gingival recession [30]. Tayman and Sarıçam, however, showed that chronic stress on the lower incisors has the effect of increasing the incidence of gingival recessions [31].

ORTHODONTIC TREATMENT

Orthodontic braces can damage periodontal tissues by creating retention areas for plaque. Even with excellent oral hygiene, braces cause a change in the oral microflora, leading to the growth of bacteria similar to those present in areas affected by periodontal disease. Orthodontic treatment affects some of the periodontal problems, such as deepening the depth of probing pockets, loss of connective tissue attachment and gingival recessions [32]. Amid et al. in their meta-analysis showed that the incidence of recession with orthodontic treatment is inversely proportional to the width of the keratinized gingiva and the thickness of the gingiva [32]. These findings were confirmed in the 2023 study by Koppolu et al [33].

IATROGENIC CHEMICAL DAMAGE

Gingival recessions can also occur through iatrogenic chemical damage to the soft tissues around the treated tooth. The substance causing such damage can be an etchant or a self-etching bonding system [34]. Such effects

can also occur with chemomechanical gingival retraction [18]. Ozcelik et al. also described the occurrence of gingival recession after inadvertent soft tissue contact with formocresol and ferrous sulfate [35].

NON-CARIOUS CERVICAL LESIONS OF CARIOUS ORIGIN

Non-carious cervical lesions (NCCLs) involve destruction of the hard tissue in the cervical area of the tooth crown and underlying root surface by pathologies other than caries (without microbial involvement) [36].

On clinical examination, NCCLs manifest as deep, round or wedge-shaped craters close to the CEJ [37]. Such lesions affect the structural integrity of the tooth, facilitate the persistence of bacterial plaque and contribute to tooth sensitivity. This is often associated with gingival recession, which causes architectural fragility associated with a low crown-to-root ratio [36]. The cervical part of the tooth differs morphologically and histologically from the crown and root. The enamel gradually becomes thinner approaching the CEJ, and because of this, the cervical area becomes the most sensitive area where dentin can be exposed to irritants. If the NCCL involves only the crown of the tooth then only conservative treatment is possible, while if it also involves the root or only the root itself, surgical treatment is necessary [38].

FILLINGS OF CERVICAL DEFECTS

In the case of improperly performed restorations in the cervical region, the edges of the fillings may be located subgingivally. They can then directly cause mechanical trauma to the soft tissues. When improperly shaped cervical restorations are present, plaque retention and accumulation causing inflammation can be facilitated. Teeth with minimal or no keratinized gingival tissues and restored with abnormal subgingival cervical margins have been shown to be more predisposed to gingivitis, leading to the development of gingival recession [39]

DENTAL CALCULUS

Tartar has been shown to be an important factor in the etiology of gingival recessions, and especially in young patients [40]. Dodwad has shown that subgingival tartar is a much stronger determinant of recession than supragingival tartar. Regular tartar removal may therefore be an effective prophylaxis in the formation of gingival recessions [30].

CONCLUSIONS

Analysis of gingival recession reveals its complex nature, resulting from many potential causes and risk factors. It is influenced both by patient behavioral factors, such as toothbrushing technique, the type of toothbrush used or smoking, as well as by genetic determinants of the gingival biotype. Age, bite overload, orthodontic treatment and chemical and mechanical damage can also contribute to the problem. Understanding these correlations is key to effective management and prevention of gingival recession to ensure patients' long-term oral health.

The quest to avoid gingival recession requires a holistic approach that combines educational, preventive and therapeutic aspects. Preventing gum recession plays a key role in maintaining oral health and preventing many dental problems.

The primary step in recession prevention is patient education. Patients should be informed about proper tooth brushing technique, flossing and rinsing, as well as the impact of parafunctions, (such as smoking) on gum health. Regular check-ups with the dentist allow earlier detection of problems and implementation of appropriate preventive and therapeutic measures.

When gingival recession occurs , appropriate therapies are essential. This may include surgical techniques such as gingival grafts to restore tissue integrity and reduce hypersensitivity. However, proper planning and execution of cervical restoration also plays a key role, minimizing the risk of recession recurrence and further damage.

It is worth noting that prevention of gingival recession is important for both the aesthetics of the smile and oral health. Prevention of gingival recession has a positive impact on the overall health of patients, reducing the risk of periodontal and systemic diseases. Therefore, regular dental care, proper education and attention to oral hygiene are key to maintaining healthy gums and an aesthetically pleasing smile.

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CONFLICT OF INTEREST

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REVIEW ARTICLE

CONTENTS

The influence of vitamin and mineral consumption on the course of coronavirus disease (COVID-19)

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ABSTRACT

Aim: The study of the role of micronutrients in the prevention of the severe course of the coronavirus disease.

Materials and Methods: In order to fulfill the task, there was conducted an analytical review of medical and biological publications in English in the electronic databases PubMed Medline of the US National Library of Medicine (NLM), Embase, Cochrane Database of Systematic Reviews for the period from 2015 to November 2023, where included 50 published articles, 28 preprints and 109 trials. In the course of the study, the bibliographic-semantic research method was used according to the "Preferred Reporting Elements for Systematic Reviews and Meta-Analyses" (PRISMA) protocol. According to this protocol, identified literary sources were sequentially analyzed by title, keywords, abstract and full text of articles. Based on the results of 16 searches, 2650 articles from PubMed, Cochrane Database of Systematic Reviews and Embase, 3162 articles from preprint servers and 237 trials were rejected. In the final article synthesis, we included 50 published articles, 28 preprints, and 109 trials.

Conclusions: The most effective in preventing complications of the coronavirus disease are vitamins A, D, E, K, C, B_3, B_6, B_9, B_{12} and such mineral substances as Mg, Se and Zn. The consumption of appropriate bioactive complexes and source products can be considered a clinically and economically effective strategy for the prevention of a severe course of the coronavirus disease.

KEY WORDS: micronutrients, vitamins, minerals, prevention, severity of the course of coronavirus infection

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INTRODUCTION

The rapid spread of the incidence of COVID-19 in the world presented health care specialists with new tasks related to the effective prevention of this infection. One of the key questions is to find out the reasons for the greater susceptibility of the patient's body to the coronavirus disease COVID-19, the degree of impaired immune response of patients, the role of rational nutrition and specific micronutrients in supporting the immune functions of the patient's body [1, 2]. A significant risk factor for a severe course development of progressive disease of COVID-19 is the presence of low-grade systemic inflammation, which is observed in diabetes, metabolic syndrome, and cardiovascular diseases and can be triggered by nutrient deficiencies [3]. Despite the large number of clinical studies on the patients' use of the supplements of vitamins and minerals with COVID-19, the aspect of nutritional prevention of the severe course of the coronavirus disease remains insufficiently studied in the world.

AIM

The aim of the research, in connection with the above, was to study the role of micronutrients in the prevention of the severe course of the coronavirus disease.

MATERIALS AND METHODS

In order to fulfill the task, there was conducted an analytical review of medical and biological publications in scientific journals, collections of scientific works, and materials of scientific and practical conferences on the research problem in the electronic databases PubMed Medline of the US National Library of Medicine (NLM), Embase and Cochrane Database of Systematic Reviews.

For each section of the article, the following is presented: 1) an overview of the relevant material; 2) systematic literature search in PubMed, Cochrane Database of Systematic Reviews and Embase databases, including a range of preprint servers on the relevant subject; 3) a screen of 5 clinical trial registries. The original studies were considered without restriction

on study design and included the following: 1) severe acute respiratory syndrome, SARS-CoV-2 coronavirus, Middle East respiratory syndrome CoV (MERS-CoV) and 2) disease susceptibility or 3) progression and/or complications of the disease, 4) micronutrients in the scheme of prevention and/or treatment of coronavirus disease. Literature searches were carried out in the period from 2020 to November 2023. We synthesized information about 12 components (nutrients) and their potential interaction with COVID-19: micronutrient deficiency in patients with coronavirus disease of such vitamins as retinol, niacin, pyridoxine, folic acid, cobalamin, ascorbic acid, calciferol, tocopherol, vitamin K, selenium, magnesium, zinc.

In the course of the study, the bibliosemantic research method was used according to the PRISMA "Preferred elements of reporting for systematic reviews and meta-analyses" protocol [4]. According to this protocol, the specified literary sources were consistently analyzed by title, keywords, abstract and full articles' text.

Considering the results of 16 searches 2650 articles from PubMed, Cochrane Database of Systematic Reviews and Embase, 3162 articles from preprint servers and 237 trials were rejected. In the final article synthesis, we included 37 published articles, 28 preprints, and 109 trials.

The most popular journals by research topic: Nutrients, Journal of Nutrition, Biological Trace Element Research, Expert Review of Anti-infective Therapy, Nutrition, Protein Journal, Practical Laboratory Medicine, International Journal for Vitamin and Nutrition Research, European Journal of Pharmacology, Biomedicine & Pharmacotherapy. The vast majority of studies were conducted by authors from the following countries: USA, United Kingdom, China, The Netherlands, Italy, Japan, Germany, Australia, France, Turkey, Mexico, India, New Zealand, etc.

REVIEW AND DISCUSSION

The coronavirus infection (COVID-19) poses a serious threat to the health and economy of humanity around the world. In connection with the rapid rate of mutation of the causative agent of COVID-19 – the SaRS-CoV-2 virus, the increase in the level of morbidity, the insufficiency of effective specific methods of treatment, it is becoming more and more relevant to study the factors of external and internal genesis which affect the antiviral immunity level of a person and the severity of COVID-19 course. Special attention, despite the existence of various markers associated with resistance to coronavirus infection, is paid to nutritional status study, namely, the effect of the use of vitamins and minerals with food products or with dietary supplements on the body's protective properties. Deficiency of micronutrients is considered one of the main causes of the progression of severe statuses, as it can significantly stimulate the development of inflammatory processes [3, 5], and the prognostic nutritional index (PNI) may be useful for risk stratification of patients of different gender, age and body mass index in relation to the severity of the course of COVID-19 [6, 7].

THE ROLE OF VITAMINS IN THE FORMATION OF THE BODY'S RESISTANCE TO VIRAL INFECTIONS

The most important for supporting adaptive and humoral immunity are such vitamins as retinol, niacin, pyridoxine, folic acid, cobalamin, ascorbic acid, calciferol, tocopherol, vitamin K [5, 6, 7]. The use of vitamin supplements alleviates the severe course of the coronavirus disease, which is accompanied by acute respiratory distress syndrome, septic shock, disseminated intravascular coagulation, anosmia, dysgeusia [8, 9].

Vitamin A modulates a wide range of immune processes, taking part in the development of T- and B-lymphocytes, therefore it is important for adaptive immunity. Its contribution to the regeneration of mucosal epithelium and the functioning of neutrophils, macrophages and natural killers makes it important for innate immunity. Vitamin A deficiency and acute infectious diseases, which temporarily suppress the concentration of retinol in the blood serum, impair the adequate immune response of the body [10]. The studies of vitamin A megadoses use as a therapy of an affordable adjunctive for COVID-19 treatment of with minimal side effects demonstrated increased angiotensin-converting enzyme (ACE-2) expression in the respiratory tract and a positive impact on patient prognosis [10, 11].

The results of bioinformatics studies of the target cells of the therapeutic action of vitamin A indicate that the main fight mechanisms against the virus of SARS-CoV-2 are the stimulation of the immune response, the suppression of inflammatory reactions and biological processes associated with the production of reactive oxygen species [10-12].

Increasing evidence points to the key immunomodulatory effect of vitamin D, stimulation of B-lymphocytes', macrophages', monocytes', T-cells', dendritic cells' adaptive immune response and inhibition of pro-inflammatory Th1 and Th17 cells, as well as enhancement of regulatory T-cells, autocrine/paracrine effect on Th1 lymphocytes [13]. The important role of cholecalciferol in gene transcription by binding to nuclear vitamin D receptors (VDR) has been proven [14, 15].

It should be mentioned that vitamin's D amount correlates with lower levels of pro-inflammatory interleukin-6 (IL-6) [14, 16], which can be a triggering factor of the cytokine storm – one of the main factors of acute respiratory distress syndrome in COVID-19. Also, the scientists discovered the autocrine/paracrine effect of vitamin D on Th1-lymphocytes, which, in turn, suppresses the secretion of pro-inflammatory IFN-γ and enhances the production of anti-inflammatory IL-10 [13, 17]. These molecular pathways could potentially be used therapeutically to inhibit hyperinflammatory cells in patients with severe form of COVID-19.

According to literature data, 77.8% of the research results showed that the occurrence of COVID-19 infection, prognosis and mortality were correlated with the level of vitamin D in the body of patients [8]. The prognostic value of significant 25(OH)D deficiency and the effectiveness of its correction on the outcome of the course of COVID-19 require further research.

Vitamin C (ascorbic acid) is an electron donor, acting as a cofactor for fifteen enzymes in mammals [18], which has drawn the attention of scientists to the antioxidant and antiviral properties of vitamin C. Researches of vitamin's C role in pneumonia and sepsis prevention and treatment are underway for tens of years. An assumption that this nutrient may be useful in the prevention and treatment of viral infections is based on two concepts, namely: 1) patients with acute infectious diseases have low levels of circulating vitamin C (probably due to a metabolic process); 2) vitamin C has favorable immunomodulatory properties in patients with viral infections, mainly due to an increase in the production of endogenous α- and β-interferons and a decrease in the level of pro-inflammatory cytokines [19, 20]. Clinical observations of the use of ascorbic acid for therapeutic purposes against coronavirus infection showed that the in-hospital mortality rate among patients who received intravenous vitamin C was 12%, compared to 17.6% in patients with respiratory failure who received invasive or noninvasive artificial ventilation of lungs. In addition, within the framework of this study, a significant decrease in inflammatory markers was noted, in particular, C-reactive protein ferritin and D-dimer [21], which accelerates the recovery time of patients. A previous meta-analysis by the World Health Organization (WHO) also found that introduction of vitamin C to patients who are critically ill can significantly reduce the duration of artificial lungs ventilation and the length of patient`s intensive care unit stay in [22].

Vitamins of group B. A review of scientific sources shows the broad therapeutic possibilities of using vitamins of group B for the purpose of prevention and alleviation of the condition of patients with COVID-19. In critically status patients, a clinical picture of septic shock with the development of multiple organ failure is often observed [23]. Early use of thiamine or vitamin B_1 (precursor of coenzymes in the catabolism of sugar and amino acids) along with corticosteroids and vitamin C has been shown to be effective in preventing progressive organ dysfunction, acute liver and kidney damage. The data from the riboflavin effect on Middle East Respiratory Syndrome Coronavirus (MERS-CoV) research demonstrate the effective reduction of the titer of MERS-CoV in human blood plasma products below the detection limit. If MERS-CoV is detected in the blood of asymptomatic donors, riboflavin and ultraviolet light can reduce the likelihood of transfusion of both platelets and plasma products [24].

In the process of a virtual screening of medical drugs which are approved by Food and Drug Administration of the US (FDA), special attention was paid to drugs whose main target is the protease of the virus of SARS-CoV-2. Vitamin $B_{12,}$ ribavirin, nicotinamide and telbivudine were found to be combined and used for successful treatment of coronavirus disease [25]. A molecular study of the interaction of vitamin B_9 with the main pathogenicity factor of the virus demonstrated that folate has the potential opportunity of forming strong hydrogen bonds with the SARS-CoV-2 protease [26].

Vitamin E. It is noted in literature sources that vitamin E strengthens the body immune response by means of mechanisms of reducing the production of nitric oxide, which leads to cyclooxygenase's-2 inhibition and a decrease in the prostaglandin E2 level, T-lymphocyte signals' initiation and modulation of the balance of Th1/Th2 immunoregulatory lymphocytes, inhibition of protein kinase C, which affects the monocytes', neutrophils', macrophages' and smooth muscle cells' proliferation and also reduces the production of superoxide free radicals. It is known that vitamin E taking reduces the production of superoxides, which can be quite relevant for the treatment of the oxidative effects of the SARS-CoV-2 virus [27].

Recent research shows that protein S, a vitamin K-dependent protein, normally prevents the cytokine storm seen in severe cases of COVID-19. Reduced activation of protein S because of the vitamin K depletion, which may be caused by pneumonia in coronavirus disease, has been correlated with higher thrombogenicity and possibly mortality in patients with COVID-19 [28, 29]. However, the role of vitamin K extends beyond the blood coagulation system. Matrix Gla protein (MGP) is considered to be a soft tissue calcification's and elastic fiber degradation's vitamin K-dependent inhibitor. Severe extrahepatic vitamin K deficiency has recently been demonstrated in patients with COVID-19, with

high levels of inactive MGP protein correlating with the rate of elastic fiber degradation, which may indicate that insufficient vitamin K-dependent activation of MGP leaves elastic fibers unprotected from proteolysis caused by the SARS-CoV-2 virus [28]. In 2021, a study was conducted on the relationship of low vitamin K levels to mortality in a group of 138 patients with COVID-19 among hospitalized ones. In the course of the analysis, dephosphorylated-uncarboxylated protein Matrix Gla (dp-ucMGP) was measured, which reflects the functional status of vitamin K in peripheral tissue. In patients, dp-uc MGP levels were significantly different from non-survivors and significantly higher compared to control group. It was showed by Cox regression survival analysis that dp-uc MGP increased levels (reflecting low vitamin K levels) were associated with an increased risk of mortality [29]. Therefore, vitamin K deficiency, which leads to a decrease in activated MGP and protein S, increases the likelihood of the development of complications such as lung damage and coagulopathies, respectively. Additional randomized clinical trials are needed to elucidate the potential vitamin's K role in the course of the disease of COVID-19.

THE ROLE OF MINERALS IN PREVENTION AND TREATMENT OF CORONAVIRUS INFECTION

Studies have shown that zinc has a significant effect on the course of viral infections, even on those involved in the pathology of the respiratory tract, affecting the penetration of viral particles, replication, translation of viral proteins and subsequent exit from cells. Insufficient income of zinc can lead to an increase in the risk of upper and lower respiratory tract infectious diseases. Although the therapeutic effect of zinc is considered as controversial, available evidence indicates the effectiveness of zinc supplements for use in the prevention of pneumonia and its complications, through inhibition of the inflammatory response, improvement of mucociliary clearance, prevention of lung damage caused by mechanical ventilation, modulation of antibacterial action [30].

In the course of molecular studies of the immunomodulatory properties of selenium (Se), the following main protective mechanisms were established: prevention of mutations in the viral genome, increased activation, proliferation and differentiation of CD4+ T-helper cells; increase in cytotoxicity of CD8+ T-suppressor cells and lytic activity of natural cells- killers NK [31]. In addition, selenium plays an important role in antibody production, its deficiency induced impaired maturation, T-cell functions, and T-cell antibody response in mice [32]. Based on the wide range of possibilities of this trace element in supporting the resistance of the immune system, scientists have assumed that the risk of mortality from COVID-19 may be associated with selenium deficiency [33]. Research results confirm the notion of an important role of Se in the recovery of COVID-19 and support the idea of prophylactic use of this trace element. It should be mentioned that the cause-and-effect relationship between the selenium level and the course of the coronavirus disease has not yet been sufficiently confirmed, which requires additional research.

Some studies have established a link between magnesium deficiency, reduced immune cell activity, and increased inflammation, which may be significant in the development of a life-threatening complication associated with COVID-19, such as cytokine storm [34, 35]. The therapeutic use of this macronutrient is determined by its structural function as a coenzyme of cytochrome P450, which is involved in the metabolism of vitamin D, therefore, thanks to the intake of the macronutrient, the severity of the disease of COVID-19 can be controlled, although this requires additional clinical and experimental studies [34, 36].

The special interest for clinical and preventive medicine is the correction of a person's immune status caused by a deficiency of the appropriate micronutrients by using the optimal amount of vitamins and minerals.

The pandemic of COVID-19, which was caused by the virus of SARS-CoV-2 forces scientists around the world to search for new effective preventive strategies. Of particular interest for clinical and preventive medicine is the correction of a person's immune status caused by a deficiency of the appropriate micronutrients by using the optimal amount of vitamins and minerals.

The addition of active derivatives of vitamin A can make a contribution to the creation of more effective protective immune response to vaccination against COVID-19, which allows it to be recommended as an effective drug for the prevention of coronavirus disease and its complications [10-12].

Given the antiviral, anti-inflammatory and protective role of vitamin D in the treatment of many viral diseases, carefully designed and controlled scientific studies are gaining popularity, which are conducted to provide the most effective new approach of implementation both to prevention and to chemotherapeutic treatment of the infection of COVID-19 with the help of micronutrients [13, 17].

Such micronutrients as calciferol, retinol, vitamins of B group (folate, pyridoxine, cobalamin), vitamin C and minerals Mg, Se and Zn make their contribution to the immune system normal functioning and prevention of a severe course of the disease of COVID-19 [5, 37].

Thus, the latest scientific researches identify the following main hypothetical mechanisms of combating the development of pathology and infection with COVID-19: creation of antimicrobial peptides in the respiratory epithelium, suppression of inflammatory reactions, antioxidant action and immunomodulatory effect; modulation of the renin-angiotensin-aldosterone system, which contributes to the protection of the tissue of the respiratory tract (lungs) [38, 39]. Such an economically rational and accessible approach requires further consideration and clinical research in the future. However, despite the evidence-based information on the effectiveness of preventive nutrition as a prevention of infectious respiratory diseases, the relationship between micronutrients level and the course of COVID-19 infection in human body is still being investigated and is more focused on elderly patient groups. Accordingly, the preventive aspect of nutrition support of young and middle-aged population groups is insufficiently covered and requires further in-depth study.

The prospects for further research lie in the study of the role of vitamins, minerals and biologically active complexes as effective and necessary means of preventing coronavirus infection. In continuation of the above, the further implementation of the principles of a balanced diet with the addition of trace elements and vitamins as a clinically and economically effective strategy for the prevention of respiratory viral diseases, including coronavirus infection, in different age groups of the population is promising.

CONCLUSIONS

The introduction of micronutrients into the body of a patient with COVID-19 in clinical studies has demonstrated their high effectiveness in the disease preventing and complications risk reduction. In this context, the most effective are such fat-soluble vitamins as retinol, calciferol, tocopherol, vitamin K and water-soluble vitamins ascorbic acid, niacin, pyridoxine, folic acid, cobalamin, as well as Mg, Se and Zn.

Eliminating the micronutrient deficiency by introducing a balanced diet with the consumption of appropriate groups of products that are sources of vitamins and minerals or additional introduction of appropriate pharmaceuticals (bioactive complexes) can be considered a clinically and economically effective strategy for the prevention of a severe course of the coronavirus disease.

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When publishing the data obtained during the research, the principles of ethics and legislative norms and requirements for legal research were fully taken into account and fulfilled, namely: the Universal Declaration of Human Rights (1948), the Declaration of Geneva (1948), the Declaration of Helsinki (2000), the Constitution of Ukraine (1996), Fundamentals of the legislation of Ukraine on health care (1992) and the International Physician's Oath.

CONFLICT OF INTEREST

The Authors declare no conflict of interest

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CASE STUDY

CONTENTS

A clinical case of Takayasu disease: emphasis on cardiac manifestations

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ABSTRACT
Takayasu arteriitis (TA) is a rare systemic vasculitis, affecting large vessels, cardiac valves and myocardium. Cardiac involvement is a major cause of morbidity and mortality in such patients. This publication presents a clinical case of a patient with severe aortic regurgitation combined with restrictive cardiomyopathy. It is emphasized that surgical treatment is associated with potential difficulties in patients with TA due to its inflammatory nature, disease activity and multiorgan involvement.

KEY WORDS: Takayasu arteriitis, aortic regurgitation, restrictive cardiomyopathy

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INTRODUCTION
Takayasu disease (non-specific aorto-arteritis – NAA) belongs to the orphan (rare) diseases. It is a chronic vasculitis of unknown etiology mainly affecting large vessels. The incidence is 1-3 cases per 1 million population per year depending on the country. NAA is more prevalent in Asian countries – Japan, Korea, China, India, Thailand and Singapore, as well as in Turkey, Israel, Central and South America. For example, about 100-200 new cases of NAA are registered in Japan every year [1]. Incidence estimates in Europe range from 0.4 to 1.5 per million, while prevalence ranges from 4.7 to 33 per million. The incidence among women is 8-9 times higher than among men. NAA is a disease of young people, mainly occurring in subjects younger than 40 years old. However, cases of NAA in children and the elderly were also described [2].

The main clinical cardiac manifestations of this disease are damage to the valves, myocardium and the coronary arteries. Any cardiac surgical intervention in such patients is always a rather difficult task, given the systemic and autoimmune component of the above-mentioned disease, as well as the need for immunosuppressive therapy [3]. Such patients have a high risk of complications during interventions, such as restenosis and graft occlusion during coronary artery bypass, detachment of the prosthetic valve, paraprosthetic leak and the occurrence of pseudoaneurysm at the anastomosis site, etc. [4]. Therefore, considering this category of patients as candidates for cardiac surgery, we must carefully weigh the risks and make decisions based on a multidisciplinary approach.

CASE REPORT
Patient S., 44 years old, complained at pronounced shortness of breath during minimal exertion, swelling of the lower extremities, periodic increase in body temperature up to 37.5-38°C, general weakness and dizziness, fatigue, attacks of severe headaches with loss of visual fields and slowing of speech, pain and swelling in the neck, periodic increase of blood pressure up to 180/100 mm Hg.

She has been ill for 15 years when highly active subacute Takayasu disease was diagnosed. She took prednisone, methotrexate, acetylsalicylic acid, folic acid on a regular basis. She had a history of a subcapital fracture of the right femur due to secondary osteoporosis, which resulted in total cementless arthroplasty of the right hip joint with a Link ceramic head.

Recently she has noticed a worsening of her well-being such as increased shortness of breath, a significant decrease in exercise tolerance, emergence of pronounced swelling of the lower limbs, and an increase in abdominal size.

The condition at the examination was moderately severe. A body mass index was 19.05 kg/m^2. The skin was pale and

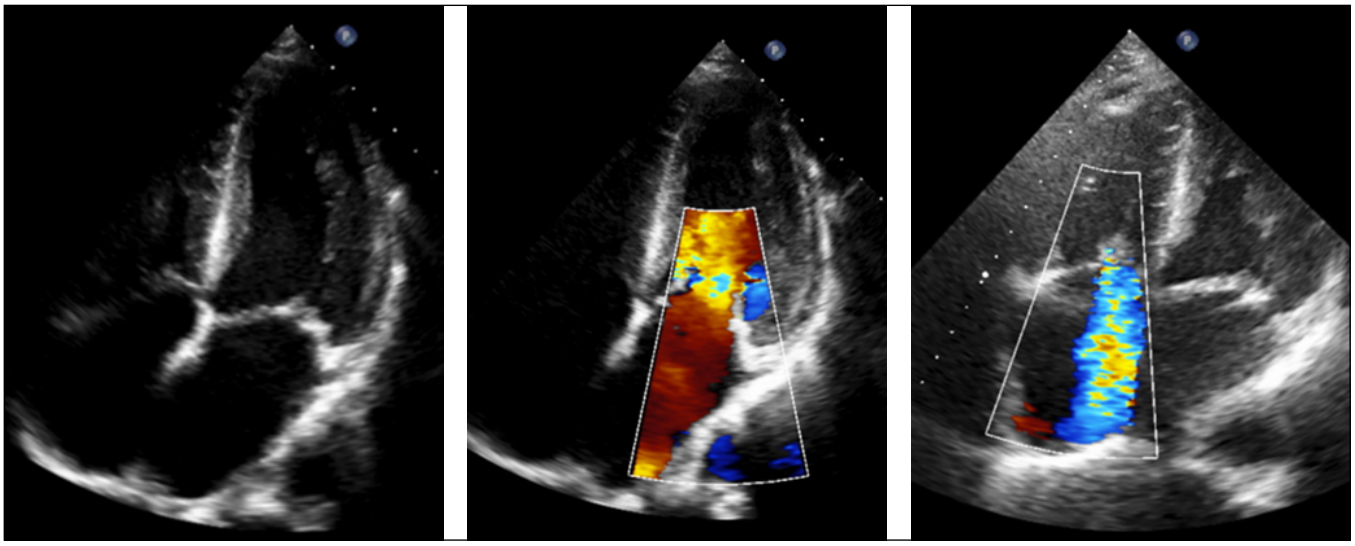

Fig. 1. Transthoracic echocardiography, apical four-chamber view. Concentric LV hypertrophy. Right atrial enlargement. Pronounced dilation of the LA with normal LV dimensions. Pronounced aortic valve regurgitation (incomplete leaflet coaptation). Relative mitral valve insufficiency, grade I-II. Pronounced tricuspid regurgitation against the background of dilation of the fibrous ring. Signs of pronounced left ventricular hypertrophy. Dilation of the ascending aorta. Thickening of the aortic walls, likely of specific etiology.

clean. Moderately pronounced lower limbs swelling was noted. At auscultation, heart tones were muffled, rhythmic, with a pronounced systolic murmur heard at all cardiac auscultation points. Blood pressure was 160/90 mmHg. In the lungs: breathing was harsh, weakened in the lower sections on both sides, more on the left, with occasional bilateral subcrepitant rales in the lower sections.

On the ECG, the rhythm was sinus, regular. Sinus tachycardia with a heart rate of 94 bpm, signs of hypertrophy of both atrial and marked left ventricular hypertrophy with systolic overload were observed.

During 24-hour Holter ECG monitoring, sinus rhythm was registered with an average HR of 84 bpm, maximum HR of 111 bpm, and a minimum HR of 58 bpm. Occasional (4) polymorphic ventricular ectopic beats, including paired, as well as occasional (22) supraventricular ectopic beats and 2 runs of supraventricular tachycardia were recorded.

Echocardiography (Fig. 1) revealed symmetric concentric hypertrophy of the left ventricular walls (up to 1.4 cm). Pronounced dilation of the left atrium (volume 99 ml, volume index 55 ml/m^2) with normal dimensions of the left ventricle (EDV 90 ml, EDV index 50 ml/m^2) and preserved left ventricular ejection fraction (LVEF) – 57 % were also found. Significant dilation of the right atrium (volume 283 ml, volume index 157 ml/m^2) was also noted in the presence of right ventricular wall thickening (up to 0.8 cm) and enlargement of its cavity (basal transverse size 4.9 cm). Pronounced insufficiency of the aortic valve in the presence of degenerative changes in the leaflets and dilation of the ascending aorta (up to 4.2 cm) and thickening of the aortic walls were also found. Pronounced relative insufficiency of the tricuspid valve and moderate relative insufficiency of the mitral valve and signs of pronounced pulmonary artery hypertension were also observed. A small amount of fluid in the pericardial cavity (leaflet separation up to 5 mm) and a moderate amount of fluid in the pleural cavities, more on the left, were detected. During the echocardiography, infiltrative cardiomyopathy was suspected, which required further examination of the patient.

There were no significant deviations in the complete blood count. Traces of protein were detected in the urinalysis. Blood chemistry showed elevated levels of C-reactive protein at 21 mg/L (normal < 5 mg/L), and NT-proBNP at 1855 pg/mL (normal < 125 pg/mL). Creatinine level was 78 µmol/L, corresponding to an estimated glomerular filtration rate (eGFR) of 83 mL/min/1.73 m^2. Total cholesterol level was 4.66 mmol/L, low-density lipoprotein (LDL) cholesterol 2.48 mmol/L, triglycerides 0.89 mmol/L, and glucose 4.4 mmol/L. Thyroid-stimulating hormone (TSH) was 2.04 µIU/mL (normal 0.27-4.2 µIU/mL), and ferritin was 24.1 µg/L (normal 11-306 µg/L).

Duplex scanning of the brachiocephalic arteries revealed the following results. On the right: the intima-media complex (IMC) of the common carotid artery (CCA) exhibited concentric, uneven thickening up to 1.6-1.7 mm. In the proximal section of the CCA, the IMC thickened concentrically up to 2.3-2.9 mm with a stenosis of the lumen in the aforementioned segment up to 95-98 % (subocclusion – lumen diameter 1.0-1.3 mm). The IMC thickness in the internal carotid artery (ICA)

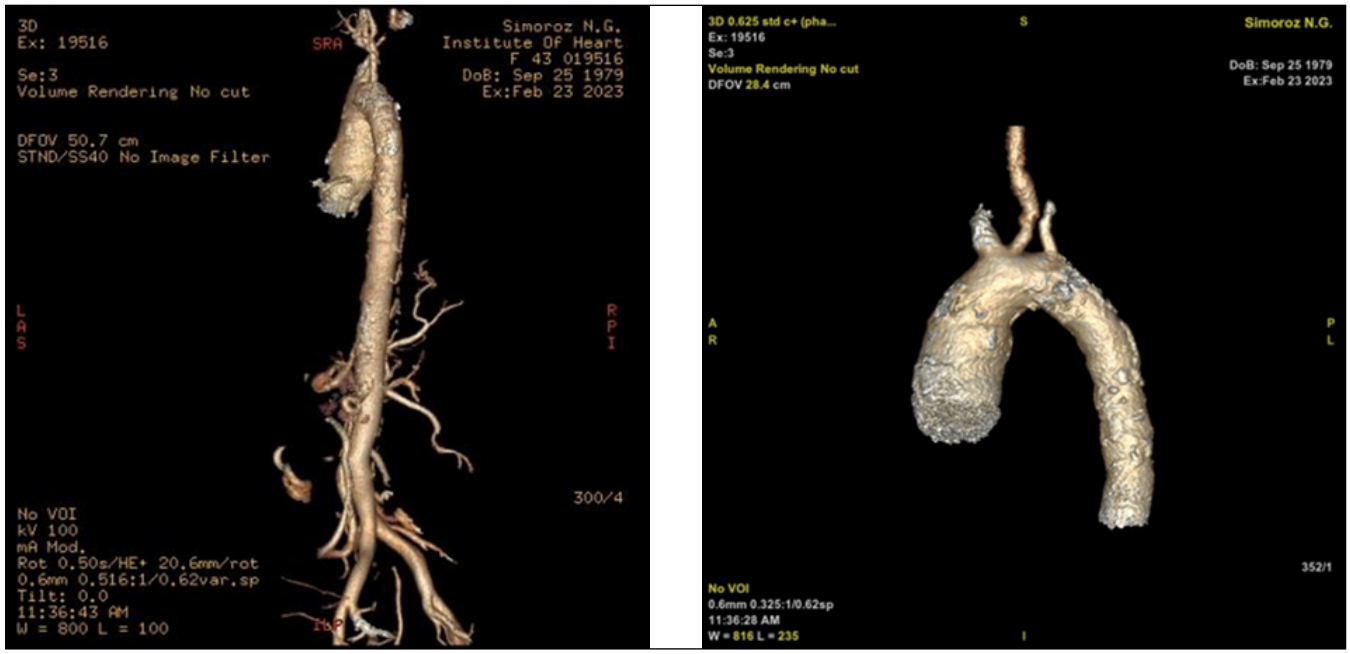

Fig. 2. MSCT – aortography. CT features of non-specific aortoarteritis (Takayasu) with signs of occlusion of the right CCA and both subclavian arteries, dilation of the ascending aorta, the superior mesenteric artery not visualized, occlusion cannot be ruled out.

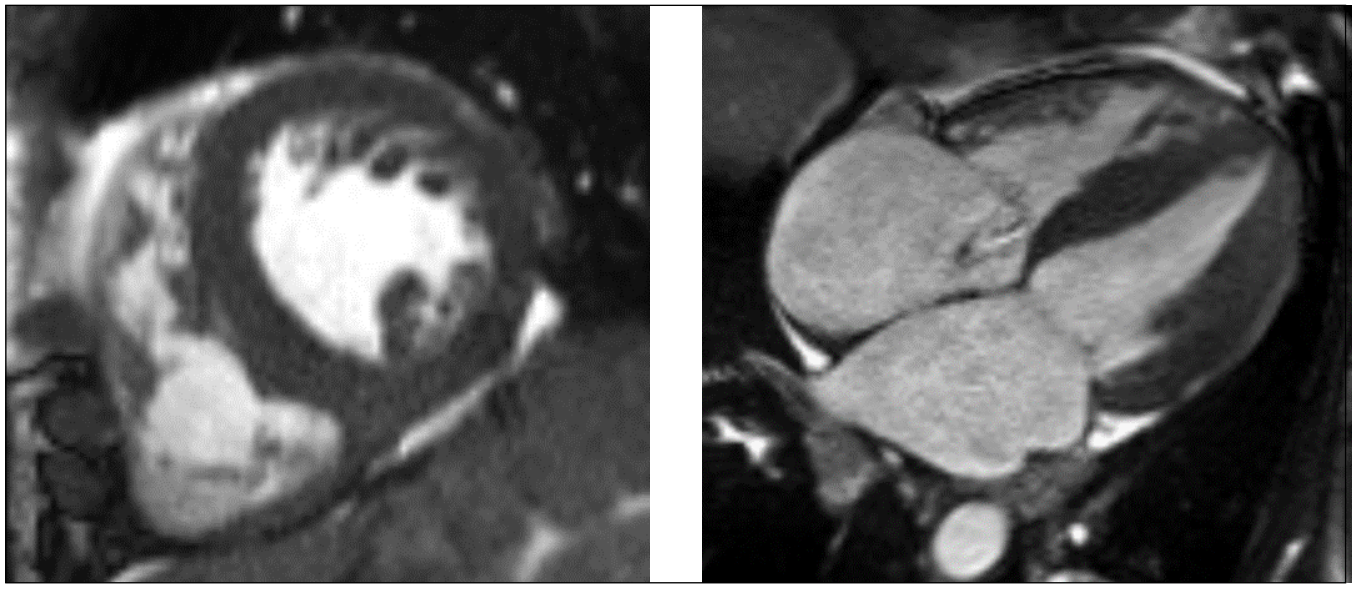

Fig. 3. Cardiac MRI with intravenous contrast. MRI signs of restrictive cardiomyopathy, high likelihood of infiltrative myocardial damage (amyloidosis). There were no findings consistent with myocardial fibroelastosis or constrictive pericarditis. MRI did not reveal signs of edema, inflammatory infiltration, or post-inflammatory/post-ischemic fibrosis.

was 0.9-1.0 mm and in the external carotid artery (ECA) it was 1.1 mm. Retrograde filling of the CCA could not be ruled out and the velocity parameters of blood flow in the CCA, ICA, and ECA were significantly reduced.

On the left there was also concentric, uneven thickening of the CCA IMC throughout up to 1.3-1.7 mm; the IMC thickness in the ICA was 1.0-1.1 mm and in the ECA it was 1.1 mm. The velocity parameters of blood flow in the CCA, ICA, and ECA on the left were increased significantly, as a mechanism of compensation. Of note, bilateral occlusions of the subclavian arteries (SCA) were revealed, as well as their secondary hypoplasias: diameter on the right was 2.9 mm and on the left it was 3.4 mm. Signs of steal syndrome were identified. The diameter of the vertebral artery (VA) on the right was 3.4 mm with retrograde blood flow; on the left, it was 3.2 mm with antegrade blood flow, and the velocity parameters of the blood flow were reduced. The diameters of the internal jugular veins on the right were 12.3 mm; on the left – 16.8 mm.

Transcranial duplex scanning revealed decreased blood flow in the right middle cerebral artery (Vps 50

cm/sec) and a compensatory increase of flow velocity parameters in the left middle cerebral artery (Vps 180 cm/sec). Blood flow in the vertebral artery at the intracranial level was retrograde on the right and antegrade on the left; the basilar artery exhibited retrograde diastolic flow.

Multislice computed tomography (MSCT) of the aorta (Fig. 2.) detected dilation of its ascending part to 41.5 mm. The aortic arch showed partial calcification. An occlusion up to 15.0 mm long was visualized above the right CCA ostium. Circular wall thickening up to 1.8 mm was noted in the proximal part of the left CCA. Both subclavian arteries were clearly visualized in the proximal sections, with contrast medium not distinctly defined distally. The diameter of the descending aorta was up to 21.6 mm. The celiac trunk in the proximal sections had a diameter up to 4.4 mm with the presence of atherosclerotic plaques at the ostium causing up to 80 % luminal stenosis. The superior mesenteric artery was not visualized. The diameter of the infrarenal part of the aorta was up to 17.5 mm with the presence of combined atherosclerotic plaques up to 2.5 mm thick.

Given the suspected infiltrative cardiomyopathy, cardiac magnetic resonance imaging (MRI) with intravenous contrast (Fig. 3) was performed for a more detailed assessment of cardiac anatomy and function. The MRI showed a left ventricular ejection fraction (LVEF) of 50 % and right ventricular ejection fraction of 50 %. Dilation of both atria and thickening of the walls of the root and ascending aorta due to inflammatory changes were also identified. Impaired kinetics of contrast material was revealed by TI-scout imaging. Both early gadolinium enhancement (EGE) and late gadolinium enhancement (LGE) showed weak diffuse enhancement of the myocardium of both ventricles, pericardial leaflets and atrial myocardium ("granular" myocardial structure). "Traces" of pathological effusion in the pericardium (< 30 ml) and fragmentary pericardial contrast were visualized.

Since the MRI also confirmed a high likelihood of infiltrative myocardial damage, the patient was referred to the cancer clinics to rule out amyloidosis. The patient underwent biopsies of subcutaneous adipose tissue, bukal mucosa and bone marrow. No amyloid deposits were found in the examined specimens. Free light chains test (kappa and lambda) also turned out negative.

In the context of ruling out storage disease, the patient underwent a blood test for the activity of alpha-galactosidase and Lyso-GL3 (Fabry disease), which showed no pathological deviations in the indicators (Fig. 4). Therefore, we classified myocardial changes detected during echocardiography and MRI of the heart as a restrictive cardiomyopathy.

Considering the pronounced aortic valve insufficiency, the issue of surgical treatment arose. However, given the severity of the patient's condition, the activity level and duration of the underlying disease, the extent of brachiocephalic artery involvement, and the pathological changes in the myocardium identified during the MRI, cardiothoracic surgery was associated with a high risk of developing complications. Therefore, a decision was taken to manage this patient conservatively.

In addition to the basic treatment for Takayasu disease (methylprednisolone, methotrexate, folic acid) standard treatment for chronic heart failure was prescribed (loop diuretic, mineralocorticoid receptor antagonist, SGLT2 inhibitor, beta-blocker), as well as antiplatelet therapy.

Cardiovascular system involvement is one of the main causes of disability and mortality in non-specific aorto-arteritis (NAA), including young patients. The pathological process primarily involves large vessels: the aorta and its branches, the pulmonary artery, and coronary arteries [5]. At present, the etiology of NAA is not established, but there is evidence of an association of the disease with genetic predisposition, infection and environmental factors. The occurrence of the disease is probably associated with a human leukocyte antigen (HLA) system of Class I and II. There is also a registered correlation with TNF-α 308/G polymorphism [6-7].

The role of autoimmune mechanisms in the development and progression of non-specific aorto-arteritis (NAA) is well recognized, with immune-mediated inflammation playing a key role. Pathogenically activated T-lymphocytes and macrophages accumulate in the arterial wall, leading to the development of granulomatous inflammation and vascular wall damage. Patients with NAA exhibit elevated levels of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which directly correlate with the severity of the disease [8].

CARDIAC MANIFESTATIONS OF NAA

Clinical signs include constitutional symptoms (characteristic of the early acute inflammatory phase – fever, general malaise, muscle pain, weight loss, anorexia), vascular involvement (e.g., weak or absent pulse, tenderness along vessels, etc.) and specific symptoms related to the affected vascular regions [9]. The rate of cardiovascular manifestations in NAA is shown in Table 1 [3].

AORTIC INSUFFICIENCY (AI) AND AORTIC ANEURYSM

A study by Ying Zhang et al. involving 1069 NAA patients indicated that more than one-third had heart

[redacted]

MEDICAL REPORT

Patient Name:	[redacted]	Date of report:	29.03.2023
DBS ID:	11175523	Sample received:	22.03.2023
Date of Birth:	**25.09.1979**	Date of sampling:	10.03.2023
Gender:	F	LAB-ID:	232008945-EFL3

Indication: a-Galactosidase (M. Fabry) and lyso-GL-3

Methods: Tandem mass spectrometry from Dried Blood Spot.

Result:

	Result	Unit	Cut-off value
alpha-Galactosidase	5.1	µmol/L/h	> 2.8
lyso-GL-3	1.2	ng/mL	0.0 - 3.5

Interpretation:

alpha-Galactosidase enzyme activity and lyso-GL-3 are negative. Therefore, Fabry disease is unlikely.

Please note: Mutations such as D313Y, A143T may not result in increased lyso-GL-3 levels (see Smid et al., Journal of Medical Genetics 2015). Lyso-GL-3 is a supplementary marker to discern classical Fabry disease from patients with mild or asymptomatic course of disease, or from patients without Fabry disease. **Only in patients still presenting with specific clinical symptoms a genetic confirmatory testing for Fabry disease is highly recommended.**

Genetic testing of females with normal a-Galactosidase enzyme activity is recommended when clinical suspicion of Fabry disease persists (Wang et al., Genetics in Medicine 2011).

Authorized by: Univ. Prof. Dr. Berthold Streubel
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Report was electronically signed and approved.

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Fig. 4. The findings of the blood test for the activity of alpha-galactosidase and Lyso-GL3 by the dry drop method.

Table 1. The rate of cardiovascular manifestations in Takayasu disease [3].

Cardiovascular manifestations	Rate
Arterial hypertension	34 %-79,2 %
Aortic insufficiency	33,20 %-38,80 %
Aortic aneurysm	15,00 %-23,30 %
Chronic ischemic heart disease	5,20 %-20,1 %
Angina	3,7-16 %
Pulmonary arteritis	7,10-18,9 %
Heart failure	6,60 %
Myocardial infarction	1,5-22,2 %

valve damage, with valve insufficiency being more common than stenosis [10]. Aortic valve insufficiency was found in 20-55 % of cases, being considered a most common heart defect in patients with NAA [11]. Dilation of the fibrous ring and ascending aorta are probably the main causes of AI. Aortitis might result in fibrous thickening of the valve leaflets, leading to their subsequent deformation. The aortic regurgitation flow can also cause morphological changes to the valve leaflets [12] .

Aortic aneurysm (AA), in turn, leads to the development of chronic heart failure (CHF), while an increase of the end-diastolic diameter of the left ventricle is a predictor of unfavorable clinical prognosis [13]. Therefore, it is logical to assume that AA requires early surgical intervention to prevent the development of CHF. However, there are certain difficulties in the surgical treatment of AA associated with NAA, because of the "fragile" inflamed tissue. While replacing the root and ascending aorta is obviously a more complex procedure, valve replacement alone may have adverse long-term postoperative consequences such as prosthesis detachment, paravalvular insufficiency, or pseudoaneurysm at the anastomosis site [14]. In different studies, the percentage of postoperative anastomotic aneurysms was 8.5 %-13.8 %, while the percentage of prosthesis detachment was 4 %-25 % [15].

The preservation or incomplete resection of inflamed tissues is considered to be the mechanism underlying late events in isolated aortic valve replacement [16]. At the same time, during valve replacement with the ascending aorta, the stress of the prosthetic valve is applied to the graft rather than directly to the aortic annulus, thereby reducing the likelihood of future complications [17].

CORONARY ARTERY IMPAIRMENT IN NAA

Frovig and Loken described impairment of the coronary arteries (CA) in NAA in 1951; Young and colleagues performed aortocoronary bypass surgery in these patients in 1971. The coronary artery impairment is classified into three types [18]:

Type I – stenotic lesions at the ostium and proximal segments of the CA, this type is most common in clinical practice;

Type II – diffuse involvement of the coronary arteries or any focal segment of the artery – skip lesions;

Type III – coronary artery aneurysm, the rarest type of involvement.

As of today, the optimal method of revascularization for NAA is unclear. The most common methods include aortocoronary bypass grafting (ACBG), angioplasty of the left coronary artery, and transaortic coronary endarterectomy [19]. Surgical angioplasty is performed using a piece of autologous pericardium treated with glutaraldehyde, a graft from the subcutaneous vein, or a patch from the internal mammary artery [20]. Transaortic coronary ostial endarterectomy can be an option in patients with localized lesions at the coronary artery ostium [21].

According to a meta-analysis, aortocoronary bypass grafting (ACBG) is associated with a lower occurrence of restenosis compared to percutaneous coronary intervention. However, the risk of stroke is higher with ACBG [22].

In the presence of macroscopic calcification of the ascending aorta, aortocoronary bypass grafting (ACBG) is not a revascularization method of choice. In this case, an alternative technique is hybrid ACBG, i.e. preoperative stent placement followed by off-pump ACBG [23].

Percutaneous transluminal coronary angioplasty (PTCA) is also possible in NAA. This procedure is recommended in high-risk patients refusing surgery or having severe pulmonary hypertension [24]. Due to inflammatory changes in the vessel wall and a higher rate of stent restenosis, interventional therapy is associated with a higher frequency of repeat interventions than surgical treatment [25].

MYOCARDIAL INVOLVEMENT AND HEART FAILURE

The main factors contributing to myocardial involvement and the development of heart failure (HF) in NAA include coronary and pulmonary artery disease, arterial hypertension, AI, and myocarditis. However, given the rarity of the disease, studies evaluating the nature of myocardial involvement in NAA are scarce.

Myocarditis is rather common in NAA, with approximately 30 % of patients having signs of subclinical myocardial inflammation in some studies [26]. Clinically significant myocarditis is a rare, but life-threatening condition. In two studies with endomyocardial biopsies, myocarditis was detected in 8 out of 18 and 24 out of 54 patients with NAA, respectively [27-28]. The mechanism of myocarditis development in NAA is unclear. Direct immune cytotoxic damage to the myocardium might be one of the factors contributing to its occurrence. Typical findings on immunohistochemical examination of cardiomyocytes include HLA class I and II, as well as ICAM-1, indicating the presence of active inflammatory processes [29].

Immunosuppressive therapy may be beneficial in treating myocardial involvement in NAA. Study by Talwar et al. demonstrated that combined therapy with prednisone (1 mg/kg) and cyclophosphamide (2 mg/kg) for 12 weeks not only improved clinical and hemodynamic parameters but also affected the myocardial morphology in patients with NAA and associated myocardial involvement [28].

CONCLUSIONS

Takayasu disease is a complex condition with a severe course and multiorgan involvement. Due to its rarity, there are no large randomized trials regarding the effectiveness and safety of various approaches in managing such patients , therefore the treatment strategy should be individualized and case specific. A particular feature of this clinical case is that changes characteristic of a storage disease were detected during echocardiography and cardiac MRI in a patient with NAA, necessitating further investigation. In Takayasu arteritis immunologic cytotoxic processes may play an important role in the genesis of myocardial dysfunction in some patients similar to those occurring with vascular cell damage. Understanding the pathophysiology of Takayasu arteritis is crucial for developing effective diagnostic and treatment strategies.

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CASE STUDY

CONTENTS

Clinical and morphological features of eccrine acrospiroma: analysis of literature data and case from practice

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ABSTRACT

Eccrine acrospiroma is a rare benign tumor of the skin arising from the epithelial cells of eccrine sweat ducts. The clinical picture is characterized by its variability, so a detailed morphological study of the operative material is necessary to establish a diagnosis. Differential diagnosis must be carried out with hemangioma, melanoma, infected sebaceous cyst, metastatic skin lesion, and other tumors from elements of the sweat gland. In the article the authors presented the clinical and morphological analysis of own case from practice of large eccrine acrospiroma on the back surface of the left thigh which was diagnosed in a 56-year-old man.

KEY WORDS: eccrine acrospiroma, clinical and morphological features, case from practice

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INTRODUCTION

Eccrine glands are the smaller, numerous glands that are diffusely distributed all over the body and derived from embryonic ectoderm [1]. They play an important role in cooling down body temperature by secreting primarily water that contains electrolytes [2, 3].

Benign and malignant tumors deriving from eccrine glands are highly heterogeneous and represent various histological entities [4]. Eccrine acrospiroma is a rare benign tumor of the skin arising from the epithelial cells of eccrine sweat ducts [5]. The term «acrospiroma» was first defined by Johnson BL Jr and Helwig EB in 1969 where «spiroma» means adenoma of sweat glands and «acro» indicates the top most or end [6]. Eccrine acrospiroma are also termed as clear cell epithelioma, clear cell myoepithelioma, nodular hidradenoma, solid-cystic hidradenoma etc. [5, 7].

Eccrine acrospiroma is twice as common in women as in men. It can develop in people of any age, but most often during the fourth and fifth decades of life [8]. This tumor can occur in any part of body, but most often it is located in face (30%), scalp (10%), trunk (14%), foot (15%), and hand (5%) [6].

The diagnosis of eccrine acrospiroma is carried out only by conducting a thorough morphological examination of the excised tumor with surrounding tissues [9]. The prognosis is favorable in the vast majority of cases. Removing the tumor provides recovery. This tumor is not associated with recurrence when adequately excised [10]. Malignant transformation of eccrine acrospiroma is rare but can arise de novo or in long standing cases [6].

There is limited information in literatures about eccrine acrospiroma considering the rarity of this tumor. In the present article, we carry out a clinical and morphological analysis of own case from practice of eccrine acrospiroma which was diagnosed in a 56-year-old man.

CASE REPORT

A 56-year-old man came to the hospital with complaints of a painless tumor on the back surface of the left thigh, which appeared two years ago and increased in size over time. The skin of the thigh above the tumor was unchanged. On palpation, the tumor was characterized by the presence of a cavity and had a soft consistency. After an objective examination, a clinical diagnosis of dermoid cyst was established. The patient underwent removal of the tumor. The surgical material was sent to the pathology department for morphological examination.

During the macroscopic examination of the surgical material, a fragment of the skin with underlying soft tissues was determined. A tumor fragment was visu-

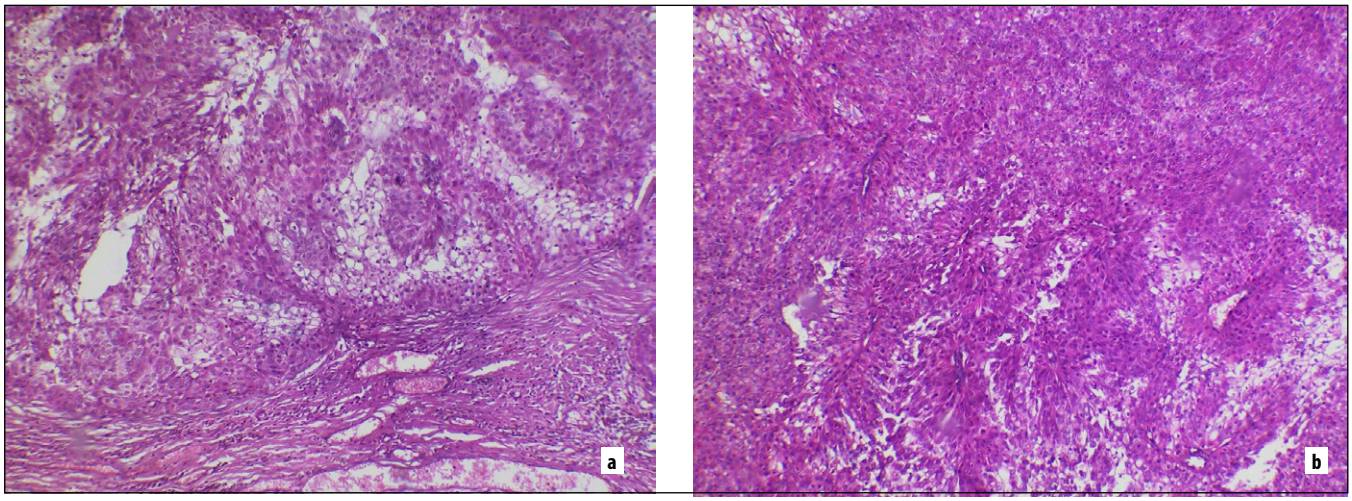

Fig. 1. The tumor is separated from the surrounding tissues by a connective tissue capsule (a). Tumor tissue is represented by spindle-shaped cells with elongated nuclei and basophilic cytoplasm; polygonal cells with rounded nuclei and light, non-staining cytoplasm; round-oval cells with clear contours, distinct light pink cytoplasm, pale colored and monomorphic nuclei (a, b). Polysade-like arrangement of cells around the vessels (b). Hematoxylin and eosin staining, a)×200, b)×200.

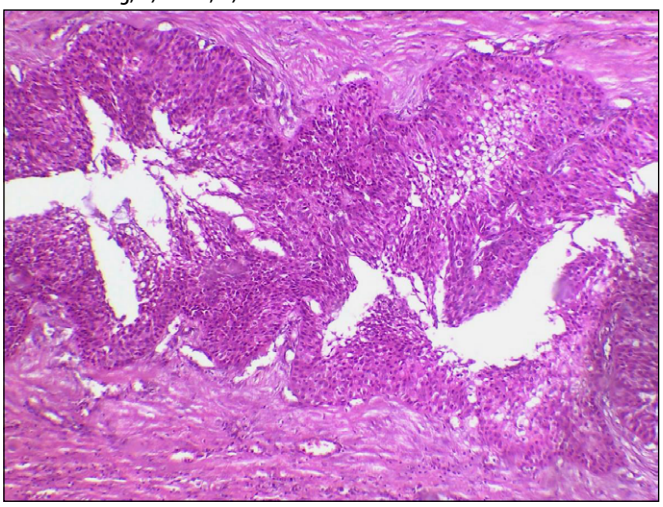

Fig. 2. The wall of the cyst with a multi-row lining of cells without a specific orientation with focal alterative changes. Hematoxylin and eosin staining, ×200.

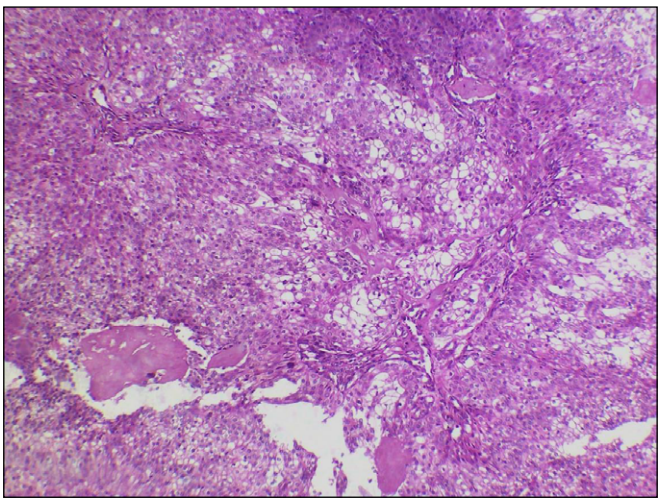

Fig. 3. Foci of hyalinosis in the tumor. Hematoxylin and eosin staining, ×200.

alized above the surface of the skin. On section, the tumor was localized above the surface of the skin and in its thickness. It was 4.5×4.0×2.5 cm in size. The tumor had a rounded shape, was encapsulated, gray-white in color with small cysts in separate areas.

A survey microscopy revealed a tumor with a well-defined connective tissue capsule with focal lymphoid-macrophage infiltration and plethoric vessels. The tumor was characterized by the presence of spindle-shaped cells with elongated nuclei and basophilic cytoplasm; polygonal cells with rounded nuclei and light, non-staining cytoplasm; round-oval cells with clear contours, distinct light pink cytoplasm, pale colored and monomorphic nuclei. In some places the cells formed trabecular structures (Fig. 1). In some of the visual fields, a polysade-like arrangement of cells was noted, which were grouped around the vessels like rosettes (Fig. 1). In some fields of view, tubular-like structures were identified, indicating ductal differentiation and represented by glandular inclusions formed by large cells with light cytoplasm. In some places, cysts were identified, which on the inner surface had a multi-row lining of cells without a specific orientation with focal alterative changes (Fig. 2). In the lumen of some cysts, homogeneous, slightly colored masses were found. Foci of hyalinosis were often visualized in the tumor (Fig. 3). The histological picture of the tumor described above corresponded to eccrine acrospiroma.

In the analyzed case from practice, eccrine acrospiroma was characterized by large size. According to literature data, this tumor presents as a small, solitary, solid, or cystic lesion measuring about 1-2 cm in size [7].

The etiopathogenesis of eccrine acrospiroma is currently an incompletely studied issue. Some scientists

emphasize the relationship between the development of this tumor and a previous skin injury [8]. Ultraviolet exposure, radiation, immunosuppression also play role in the genesis of these tumors development [4]. Other skin tumors increase the risk of developing eccrine acrospiroma [4].

Clinical symptoms of eccrine acrospiroma can be quite diverse – from the absence of pain and signs of the inflammatory process to bright manifestations of inflammation in the tumor area. The latter are manifested by hyperemia of the skin and necrotic changes development, the presence of pain, an increase in local temperature and deterioration of well-being [11]. The diagnosis of eccrine acrospiroma occurs only by morphological examination of the operative material. Sometimes the morphological diagnosis of these tumors causes difficulties and confusion even among experienced pathologists [12]. Differential diagnosis must be carried out with hemangioma, melanoma, infected sebaceous cyst, metastatic skin lesion, and other tumors from elements of the sweat gland [5, 6].

CONCLUSIONS

Eccrine acrospiroma is a fairly rare benign tumor of the skin arising from the epithelial cells of eccrine sweat ducts, which does not have characteristic clinical symptoms and is diagnosed by morphological examination of the surgical material. The correct method of treatment is surgical removal of the tumor with surrounding soft tissues. In the article the authors presented the clinical and morphological analysis of own case from practice of large eccrine acrospiroma which was diagnosed in a 56-year-old man.

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