TSH and thyrotropic agonists: key actors in thyroid homeostasis. Journal of thyroid research. 2012. 351864. doi: 10.1155/2012/351864.

7. Dietrich J.W.C. Der hypophysen-schilddrüsen-regelkreis: Entwicklung und klinische anwendung eines nichtlinearen modells. Logos-Verlag, 2002.

8. Galloway V.A., Leonard W.R., Ivakine E. Basal metabolic adaptation of the Evenki reindeer herders of Central Siberia. American Journal of Human Biology: The Official Journal of the Human Biology Council. 2000; 1(12): 75–87. doi: 10.1002/(SICI)1520-6300(200001/02)12:1<75::AID-AJHB9>3.0.CO;2-G

9. Leslie R.D.[et al.]. Hypothalamo-pituitary-thyroid function in anorexia nervosa: influence of weight gain. Br Med J. 1978; 2(6136): 526–8. 10.1136/bmj.2.6136.526

10. International Obesity Task Force. Obesity: Managing the Global Epidemic: Report of the World Health Organization (WHO) Consultation; World Health Organization: Geneva, Switzerland, 1997.

11. Karatsoreos I.N., McEwen B.S. Psychobiological allostasis: resistance, resilience and vulnerability. Trends in cognitive sciences. 2011; 15(12): 576-584.

12. Levy S.B., Bribiescas R.G. Hierarchies in the energy budget: Thyroid hormones and the evolution of human life history patterns. Evolutionary Anthropology: Issues, News, and Reviews. 2023; 5(32): 275-292. doi: 10.1002/evan.22000

13. Mahwi, T.O., Abdulateef D.S. Relation of Different Components of Climate with Human Pituitary-Thyroid Axis and FT3/FT4 Ratio: A Study on Euthyroid and SCH Subjects in Two Different Seasons. International Journal of Endocrinology. 2019; 1–9. doi:10.1155/2019/2762978.

14. McEwen B.S., Wingfield J.C. The concept of allostasis in biology and biomedicine. Hormones and behavior. 2003; 1(43): 2-15. doi: 10.1016/s0018-506x(02)00024-7

15. Opstad K. Circadian rhythm of hormones is extinguished during prolonged physical stress, sleep and energy deficiency in young men. Eur J Endocrinol. 1994; 131(1): 56–66. 10.1530/eje.0.1310056

16. Schorr M., Miller K.K. The endocrine manifestations of anorexia nervosa: mechanisms and management. Nat Rev Endocrinol. 2016; 13(3): 174–86. 10.1038/nrendo.2016.175

17. Spencer L. [et al.]. Screening and subsequent management for thyroid dysfunction pre-pregnancy and during pregnancy for improving maternal and infant health. Cochrane Database Syst Rev. 2015; 2015: CD011263. https://doi.org/10.1002/14651858.CD011263.pub2.

18. Evseeva S.A. [et al.]. Seasonal changes in the pituitary - thyroid system in children of the Arctic region of Yakutia. Yakut medical journal 2021; 71: 89-91. doi:10.25789/YMJ.2021.74.23

19. Leonard W.R. [et al.]. Seasonal variation in basal metabolic rates among the Yakut (Sakha) of Northeastern Siberia. American Journal of Human Biology. 2014; 4(26):437-445. doi:10.1002/ajhb.22524

20. Sentis S.C., Oelkrug R., Mittag J. Thyroid Hormones in the Regulation of Brown Adipose Tissue Thermogenesis. Endocr Connect. 2021; 10: R106–R115. doi:10.1530/EC-20-0562.

21. Nikanorova A.A. [et al.]. Signs of Polar T3 Syndrome in young men in Yakutia. Yakut medical journal. 2024; 1:5-8.

22. Silva J.E. Physiological Importance and Control of Non-Shivering Facultative Thermogenesis. Front Biosci. 2011;3:352–371. doi:10.2741/s156.

23. Silva J.E. Thermogenic Mechanisms and Their Hormonal Regulation. Physiological Reviews. 2006; 86:435–464. doi:10.1152/physrev.00009.2005.

24. Sterling P. Principles of allostasis: optimal design, predictive regulation, pathophysiology and rational therapeutics. In: Schulkin J, editor. Allostasis, Homeostasis, and the Costs of Physiological Adaptation. Cambridge: Cambridge University Press. 2004; 17–64.

25. Sterling P., Eyer J. Allostasis: a new paradigm to explain arousal pathology. In: Fisher S., Reason J.T., editors. Handbook of Life Stress, Cognition, and Health. Chichester, NY: Wiley; 1988; 629–49.

26. Dietrich J.W. [et al.]. The AQUA-FONTIS study: protocol of a multidisciplinary, cross-sectional and prospective longitudinal study for developing standardized diagnostics and classification of non-thyroidal illness syndrome. BMC Endocrine Disorders. 2008; 8:1-9. doi: 10.1186/1472-6823-8-13.

27. Snodgrass J.J. [et al.]. The influence of basal metabolic rate on blood pressure among indigenous Siberians. American journal of physical anthropology. 2008; 2(137):145-155. doi: 10.1002/ajpa.20851

28. Rothenbuchner G. [et al.]. The influence of total starvation on the pituitary-thyroid-axis in obese individuals. Acta Endocrinol Suppl (Copenh). 1973; 173:144.

29. Opstad P.K. [et al.]. The thyroid function in young men during prolonged exercise and the effect of energy and sleep deprivation. Clin Endocrinol (Oxf). 1984; 20(6): 657–69. 10.1111/j.1365-2265.1984.tb00116.x

30. Chatzitomaris A. [et al.]. Thyroid Allostasis-Adaptive Responses of Thyrotropic Feedback Control to Conditions of Strain, Stress, and Developmental Programming. Front. Endocrinol. 2017;163(8): 273787. doi: 10.3389/fendo.2017.00163.

31. Dietrich J.W. [et al.]. Thyrotropic feedback control: evidence for an additional ultrashort feedback loop from fractal analysis. Cybernetics and Systems: An International Journal. 2004. №4(35). 315-331. https://doi.org/10.1080/01969720490443354

32. Snodgrass J.J. [et al.]. Total energy expenditure in the Yakut (Sakha) of Siberia as measured by the doubly labeled water method. The American Journal of Clinical Nutrition. 2005. №4(84). 798–806. doi: 10.1093/ajcn/84.4.798

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RATIO OF NEUTROPHILS TO LYMPHOCYTES AND APOPTOSIS OF LYMPHOCYTES IN PATIENTS WITH HBV AND HCV DEPENDING ON THE STAGE OF LIVER FIBROSIS

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A common complication of HBV and HCV is liver cirrhosis, which is based on chronic systemic inflammation associated with immune dysfunction that affects the progression of the disease. **The purpose of the study.** Determination of NLR and lymphocyte apoptosis index as a marker of the degree of inflammation and systemic immuno-inflammatory response in various degrees of liver fibrosis in patients with viral hepatitis.

Materials and methods. 107 patients underwent the study, of which 53 patients were diagnosed with HBV and 54 with HCV. The blood levels of leukocytes, neutrophils, and lymphocytes were studied in the studied patients and the neutrophil/lymphocyte ratio (NEU/LYM) was determined. In order to verify structural changes in the liver, ultrasound elastometric examination was performed on a 2D – Supersonic Aixplorer SWE device (France) for all persons with es-Tableished viral hepatitis. The examination of patients was carried out according to the Cut–off scale, and liver fibrosis was determined by the METAVIR scale. A group of 10 practically healthy individuals was selected as a comparison group. The values of the indicators were expressed in kPa, the value of the indicator 7.1 kPa corresponded to F2, 9.2 kPa – F3, F4≥13.5 kPa. Verification of HBV and HCV was carried out by PCR on the device “Rotor Qene Q” (Germany).

The results obtained showed an increase in the absolute number of lymphocytes with a decrease in the NLR indicator against the background of a decrease in the apoptosis marker of CB95+ lymphocytes with varying degrees of liver fibrosis. A decrease in this marker reflects the damaging effect of hepatotropic viruses, which is indirectly confirmed by the detected leukocytosis.

Keywords: viral hepatitis, liver cirrhosis, systemic inflammation, neutrophil to lymphocyte ratio, prognostic marker.

Introduction. Hepatitis B and C virus (HBV and HCV) infection remains a global problem that seriously threatens human health and is the main cause of terminal liver diseases, including cirrhosis of the liver (CL) and hepatocellular carcinoma [11]. According to WHO estimates, in 2019, there were 290 million people infected with HBV and HCV worldwide, and about 1.5 million people were newly infected every year [17].

Cirrhosis of the liver is a complex chronic disease that causes hepatocyte fibrosis and the development of portal hypertension and synthetic liver dysfunction [7.10].

One of the consequences of cirrhosis of the liver (CL) is a dysfunction of the immune system, which affects both innate and adaptive responses and is associated with systemic inflammation and immunodeficiency. In patients with advanced CL, chronic inflammation occurs as a result of activation of immune system cells by bacterial infection, followed by endotoxemia and increased production of inflammatory cytokines [14].

The persistence of systemic inflammation is associated with the progression of the disease, the appearance of complications and an unfavorable prognosis [6].

Despite the fact that inflammation plays an important prognostic role in patients with structural changes in the liver, clinical verification of the inflammatory status is somewhat difficult, mainly due to the lack of routine cytokine assessment outside research institutions [9].

Simple and accessible markers for assessing the severity and stage of inflammatory status would be of great value to practitioners. Recently, there has been increased interest in affordable and reliable biomarkers that not only contribute to the early diagnosis of the disease, but also determine its severity, reflect the dynamics of the pathological process and facilitate differential diagnosis. In addition to the traditional pro–inflammatory markers - erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), procalcitonin and fecal calprotectin also belong to them [16]. In their study, Moreau and co-authors [13] showed that the number of leukocytes and CRP levels progressively varied depending on the degree of CL, with the highest values observed in patients with grade III CL who had an unfavorable prognosis. Thus, the authors suggested that CRP levels and the number of leukocytes can be used as markers of inflammation and an unfavorable prognosis in patients with liver damage [9]. The ratio of lymphocytes to monocytes has been proposed as another surrogate marker of inflammation, which is a promising predictor of decompensation and mortality in patients with CL of viral HBV etiology [8,19].

Currently, a number of indicators have been proposed that allow us to judge the severity of inflammatory changes in the body. One of these methods can be the ratio of neutrophils to lymphocytes (NLR), a convenient and easy-to-use parameter that reflects the imbalance between various components of the immune system and can be easily implemented in everyday clinical practice. This indicator is a marker of systemic inflammation and emphasizes the connection between two immune pathways: the number of neutrophils indicates ongoing (or progressive) inflammation, whereas the number of lymphocytes reflects the activity of immunoregulatory pathways [12, 18].

To calculate NLR, the absolute number of neutrophils must be divided by the absolute number of peripheral blood lymphocytes [3]. An analysis of the literature in recent years has shown that NLR is used as an indicator of inflammation and is an accurate prognostic indicator of decompensated CL: with an increase in NLR, the prognosis and survival of patients deteriorates [5,15,20].

The purpose of the study. Determination of NLR and lymphocyte apoptosis index as a marker of the degree of inflammation and systemic immuno-inflammatory response in various degrees of liver fibrosis in patients with viral hepatitis.

Materials and methods. From 2020 to 2023, 107 patients were examined on an outpatient basis at the Central Research Laboratory(CRL) of the A. Aliyev Institute of Advanced Medical Education and the Medikus Clinic Medical Center in Baku, of which 53 patients were diagnosed with HBV and 54 with HCV. Clinical diagnosis of patients: Chronic viral hepatitis B/C. Cirrhosis of the liver, compensated/subcompensated stage (class A/B). The decompensated stage of cirrhosis (class C) was not included in this study, due to the very low immune status of patients at this stage and the difficulty of verifying the data obtained. The surveyed, aged 18 years and older, were from both Baku and the regions of the Republic The average age of hepatitis B patients: men - 37.7 ± 0.6 years, women - 38.7 ± 0.8 years; hepatitis C patients: men - 44.7 ± 0.6 years, women - 42.7 ± 0.6 years. As a control group, 10 practically healthy individuals of both sexes were examined, with an average age of 34.6 ±0.9 years. The inclusion criteria were patients with confirmed viral hepatitis – HBV and HCV.

At the same time, F0 corresponded to the absence of fibrosis, F1 – underdeveloped fibrosis, F2 – moderate fibrosis, F3 – severe fibrosis, F4 – cirrhosis.

107 patients underwent the study, of which 53 patients were diagnosed with HBV and 54 with HCV. The blood levels of leukocytes, neutrophils, and lymphocytes were studied in the studied patients and the neutrophil/lymphocyte ratio (NEU/LYM) was determined. In order to verify structural changes in the liver, ultrasound elastometric examination was performed on a 2D – Supersonic Aixplorer SWE device (France) for all persons with esTableished viral hepatitis. The examination of patients was carried out according to the Cut–off scale, and liver fibrosis was determined by the METAVIR scale. The stages of fibrosis were estimated from F0 to F4. At the same time, F0 corresponded to the absence of fibrosis, F1 – underdeveloped fibrosis, F2 – moderate fibrosis, F3 – severe fibrosis, F4 – cirrhosis. The values of the indicators were expressed in kPa, the value of the indicator 7.1 kPa corresponded to F2, 9.2 kPa – F3, F4≥13.5 kPa. Verification of HBV and HCV was carried out by PCR on the device "Rotor Qene Q" (Germany).

According to the results of a comprehensive examination, all patients were divided into comparison groups according to the stage of liver fibrosis: HBV -fibrosis stage – F0-1-14 patients, F- 2-14, F-3-14 and F-4-11 patients; HCV-fibrosis stage – F0-1 -10, F-2-15, F-3-15 and F-4-14 patients. A group of 10 practically healthy individuals was selected as a comparison group.

The syndrome of systemic inflammatory response was not esTableished in the study groups. During the examination, the following criteria were taken into account: body temperature >38 ° C or <36 ° C, respiratory rate >20 per minute, heart rate >90 beats. in min. and the

leukocyte level is >12 thousand/μl or < 4 thousand/μl.

The number of lymphocytes with the marker of their apoptosis CD95⁺ was determined in peripheral blood. The procedure for phenotyping lymphocytes with the CD95⁺ marker was carried out according to the attached instructions. Smear microscopy was performed on a Lumam luminescent microscope at a magnification of 5x100. A panel of monoclonal antibodies from Sorbent LLC (Moscow) was used for CD95⁺ immunophenotyping. In practical healthy individuals, the expression of the CD95⁺ marker on blood lymphocytes averaged 51.7±2.0%.

Statistical processing of the obtained data was carried out using the analytical program Microsoft Excel–2010. The Student's t–criterion and the Mann–Whitney criterion (U) were calculated. The correlation analysis was carried out according to Pearson's double criterion.

The results of the study and their discussion. The analysis of laboratory data depending on the stage of liver fibrosis in patients with HBV and HCV revealed some significant differences in the indicators of clinical blood analysis (Fig).

In the groups of patients with HBV and HCV, the number of circulating leukocytes was mainly lower compared to the group of healthy individuals (6.9±03x10⁹/l) (Fig), except for patients with HBV at stage F0-1, however, these differences were statistically unreliable. There was no fundamental difference in the studied indicator between the different stages of fibrosis, except for a statistically significant increase in leukocytes in patients with HCV (5.6±0.2) compared with HBV (5.0±0.1) at stage F4. In patients with HBV and HCV with progressive fibrosis, a decrease in the number of leukocytes was revealed.

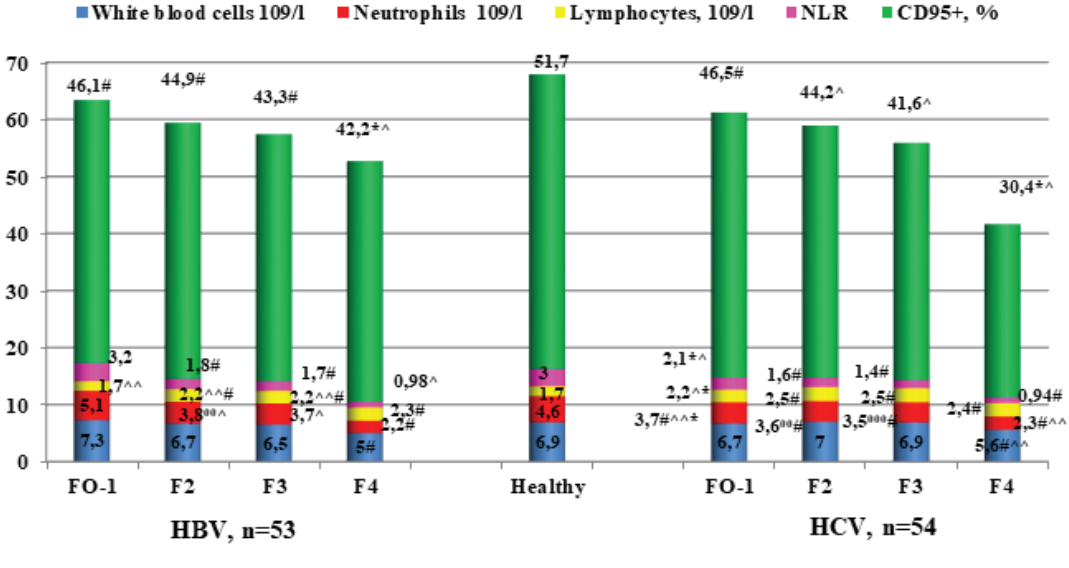
The absolute number of neutrophils in peripheral blood in patients with viral hepatitis was lower than in healthy individuals (with the exception of HBV patients at the stage of fibrosis F0-1–5.1±03x10⁹/l versus 4.6±03x10⁹/l). There were no statistically significant differences between the groups of patients with HBV and HCV in terms of neutrophil levels. At the same time, a decrease in neutrophils was determined depending on the severity of fibrosis. A statistically sTable relationship was determined in HBV patients between the stages of fibrosis F2 - F4 (p<0.001), F3 - F4 (p<0.001).

The study revealed an increase in the absolute number of peripheral blood lymphocytes in comparison with the group of healthy individuals (1.7±01x10⁹/l), as well as their high level in HCV patients in relation to patients with HBV. Comparison of these lymphocyte levels between groups using the Mann-Whitney criterion revealed a statistically significant increase in the absolute number of lymphocytes in HCV patients at stages F0-1, F2 and F3 relative to patients with HBV. The detected lymphocytosis in both etiological variants of chronic hepatitis is quite expected, because many viral infections are accompanied by an increase in the number of lymphocytes [4]. In our study, an increase in the number of lymphocytes with the progression of fibrosis was determined. Lymphocyte levels were inversely correlated with neutrophil levels in HBV patients (F0-1, r=-0.37; F2- r= -0.72; F3- r= -0.74; F4-r= -0.3) and in HCV patients (F0-1r= -0.4; F2- r=-0.72; F3- r= -0.74; F4- r=-0.25).

As the results of our studies show, in patients with HBV and HCV, there is a decrease in the absolute number of neutrophils and an increase in the absolute number of lymphocytes, and, accordingly, a decrease in NLR. The results obtained are consistent with the data of I.V. Mannova, who esTableished inverse correlations between these hematological parameters [4].

According to Table 1, the NLR index in the groups of patients with HBV and HCV was statistically significantly reduced relative to healthy individuals, and its decrease was determined depending on the stage of fibrosis. In the two studied groups of patients, a statistically significant decrease was determined at the stage of fibrosis F2, F3 and F4 (p<0.001). In patients with HBV with CL, there was a decrease in the NLR index by 3.1 times (p<0.001), and in patients with HCV - by 3.2 times (p<0.001).

It is known from the literature that the persistence of HBV and HCV increases the proliferative potential of lymphocytes and reduces the level of apoptosis of these cells [2]. Among the numerous protective antiviral mechanisms, one of the key places belongs to apoptosis, which helps to prevent viral replication and persistence [1]. Apoptosis is a universal biological mechanism. In viral hepatitis, apoptosis can lead to excessive death of not only hepatocytes, but also other cell populations. This mechanism reflects either a systemic immuno-inflammatory response to infection or extrahepatic persistence of the virus [1].



The indicators of the general blood test and the marker of CD95+ lymphocyte apoptosis in patients with HBV and HCV, depending on the stage of fibrosis (M±m)

In this regard, in our study, the study of the marker of apoptosis ($CD95^+$) of peripheral blood lymphocytes in patients with HBV and HCV at various stages of fibrosis was of particular interest. In patients with HBV and HCV and in healthy individuals, the number of peripheral blood lymphocytes in a state of apoptosis with the $CD95^+$ marker was determined immediately after isolation. It was found that $CD95^+$ levels were elevated in patients with HBV and HCV compared to controls. There was no statistically significant difference between the groups of patients with HBV and HCV. A decrease in the $CD95^+$ marker was determined in two groups of patients, depending on the severity of fibrosis. At stage F4, the $CD95^+$ level in HBV patients was 42.2±0.9%, and in HCV - 30.4±2.6%, which was 1.4 times higher ($p<0.05$).

At the same time, the lowest levels of the $CD95^+$ marker were observed at the F4 fibrosis stage, that is, with the progression of the fibrosis stage, a decrease in the $CD95^+$ marker was recorded. Correlations were found in HBV patients between the level of lymphocytes and $CD95^+$ markers (F0-1r=0.6; F2-r=0.71; F3-r=0.51; F4-r=0.2) and in HCV patients (F0-1r=-0.6; F2-r=-0.2; F3-r=-0.41; F4-r=-0.35). A correlation was also determined between elastometry indices and $CD95^+$ apoptosis markers in HBV patients (F0-1r=-0.2; at F4- r= -0.23) and in HCV patients (at stage F0-1r= -0.34; at F4-r= -0.21).

Thus, our study revealed some laboratory patterns, the nature and degree of previously described hematological and immunological changes in patients with $CD95^+$ with varying degrees of liver fibrosis were clarified.

Conclusions:

1. In patients with HBV and HCV with varying degrees of liver fibrosis and without systemic inflammatory response syndrome, a decrease in the absolute number of neutrophils, an increase in the absolute number of lymphocytes, a decrease in the NLR index against the background of a decrease in the level of the $CD95^+$ lymphocyte marker was revealed.

2. In patients with HBV and HCV, there is a decrease in the programmed death of peripheral blood lymphocytes, which may reflect the damaging effect of hepatotropic viruses, indirectly confirmed by lymphocytosis in patients with HBV and HCV.

3. Given the simplicity and accessibility of the NLR determination method, it can be recommended for use in everyday clinical practice as one of the diagnostic markers for assessing the course and predicting complications of liver cirrhosis in patients with HBV and HCV.

References

1. Bueverov A.O., Mayevskaya M.V. Klinicheskoe znachenie apoptoza pri hronicheskih virusnyh gepatitah [Clinical significance of apoptosis in chronic viral hepatitis]. Medicinskij vestnik Severnogo Kavkaza [Medical Bulletin of the North Caucasus. 2009; 2: 4-9 (In Russ.).]

2. Kalyuzhin O.V., Ponezheva J.B., Semenova I.V., [et al.]. Subpopuljacii limfocitov, uroven' interferonov i jekspressija ih receptorov u bol'nyh hronicheskimi gepatitami V i S: zavisimost' ot vida virusov m stepeni fibroza pecheni [Lymphocyte subpopulations, interferon levels and expression of their receptors in patients with chronic hepatitis B and C: dependence on the type of viruses and degree of liver fibrosis]. Terapevticheskij arhiv [Therapeutic Archive. 2017;11:14-20 (In Russ.).] doi.org/10.17116 / terarkh2017891114-20

3. Lunkov V.D., Mayevskaya M.V., Tsvetaeva E.K., [et al.]. Otnoshenie nejtrofilov k limfocitam kak prediktor neblagoprijatnogo ishoda u pacientov s dekompensirovannym cirrozom pecheni [The ratio of neutrophils to lymphocytes as a predictor of an unfavorable outcome in patients with decompensated cirrhosis of the liver]. Ross. zhurnal gastrojentrologii, gepatologii [Ross. journal of Gastroenterology, Hepatology. 2019; 29(1); 47-61 (In Russ.).] doi.org/10.22416/1382-4376-2019-29-1

4. Mannova I.V. Kliniko-patogeneticheskoe znachenie immunnogo statusa v formirovanii fibroza pecheni u bol'nyh hronicheskim gepatitom S [Clinical and pathogenetic significance of the immune status in the formation of liver fibrosis in patients with chronic hepatitis C]. Avtoreferat dis., k.m.n. [Abstract of the dissertation PhD. 2019; 24 (In Russ.).]

5. Sarkarova M.R., Mayevskaya M.V. Prognosticheskoe i diagnosticheskoe znachenie pokazatelja otnoshenija nejtrofilov k limfocitam u pacientov s zabolevanijami zheludochno-kishechnogo trakta i pecheni [Prognostic and diagnostic significance of the ratio of neutrophils to lymphocytes in patients with diseases of the gastrointestinal tract and liver]. Medicinskij sovet [Medical advice. 2022;16(7):60-68 (In Russ.).]. doi.org/10.21518/2079-701X-2022-16-7-60-68

6. Albillos A, Lario M, Alvarez-Mon M. Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance. J Hepatol., 2014;61:1385-1396. doi:10. 1016/j. jhep.2014.08.010.

7. Asrani S.K, Devarbhavi H., Eaton J., Kamath P.S. Burden of liver diseases in the world. J Hepatol. 2019;70(1):151-71. https://doi.org/10.1016/j.jhep.2018.09.014.

8. Cai J, Wang K, Han T, Jiang H. Evaluation of prognostic values of inflammation-based makers in patients with HBV-related acute-on-chronic liver failure. Medicine (Baltimore) 2018; 97 :e13324. doi: 10.1097/MD. 0000000000013324.

9. Chiriac S., Stanciu C., Singeap AM, Sfarti C.V. et al. Prognostic value of neutrophil-to-lymphocyte ratio in cirrhotic patients with acute-on-chronic liver failure. Turk J Gastroenterol., 2020; 31(12): 868–876. doi: 10.5152/tjg.2020. 19838.

10. Hashemi S.J., Tosi M.S., Hajiani E. et. al., The Association Between Peripheral Blood Neutrophil-to-Lymphocyte Ratio and Cirrhosis Complications in Adults with Compensated Liver Cirrhosis in Ahvaz, Iran. Shiraz E-Med J.,2023;24(8):e138859. doi.org/10.5812/semj-138859.

11. Jia-Rui Zheng, Zi-Long Wang, Bo Feng. Hepatitis B functional cure and immune response. Front Immunol. 2022; Nov 17:13:1075916. doi:10.3389/fimmu. 2022.1075916.

12. Kwon JH, Jang JW, Kim YW, Lee SW, Nam SW, Jaegal D, et al. The usefulness of C-reactive protein and neutrophil-to-lymphocyte ratio for predicting the outcome in hospitalized patients with liver cirrhosis. BMC Gastroenterol. 2015;15:146.

13. Moreau R., Jalan R., Gines P. et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology, 2013;144:1426–37. doi:10.1053/j.gastro.2013.02.042.

14. Noor MT, Manoria P. Immune Dysfunction in Cirrhosis. J Clin Transl Hepatol., 2017;5:50-58. doi: 10.14218/JCTH.2016.00056.

15. Peng Y., Li Y., He Y. et. al. The role of neutrophil to lymphocyte ratio for the assessment of liver fibrosis and cirrhosis: a systematic review. Expert Rev Gastroenterol Hepatol., 2018;12 (5):503–513. https: //doi.org/10.1080/17474124. 2018. 1463158

16. Štimac D., Nardone G., Mazzari A., et al. What's New in Diagnosing Diverticular Disease. Journal of Gastrointestinal and Liver Diseases. - 2019, Dec19; 28 (4): r. 17-22. doi: 10.15403/jgld-553.

17. World Health Organization. Hepatitis V. Available at: https://www.who. int/news-room/fact-sheets/detail/hepatitis-b (Accessed October 21, 2022).

18. Xue TC, Zhang L, Xie XY, Ge NL, Li LX, Zhang BH, et al. Prognostic significance of the neutrophil-to-lymphocyte ratio in primary liver cancer: A meta-analysis. PLoS One. 2014;9(5). e96072. https://doi.org/10.1371/ journal.pone. 0096072.

19. Zhang J, Feng G, Zhao Y, Zhang J, Feng L, Yang J. Association between lymphocyte-to-monocyte ratio (LMR) and the mortality of HBV-related liver cirrhosis: a retrospective cohort study. BMJ Open, 2015; 5: e008033. doi: 10.1136/ bmjopen-2015-008033.

20. Zhang W., Aryan M., Chen Z. et. al. Prognostic value of neutrophil-to-lymphocyte ratio in cirrhosis patients undergoing transjugular intrahepatic portosystemic shunt. Eur J Gastroenterol Hepatol. 2022 Apr 1;34(4):435-442. doi: 10.1097/MEG.0000000 000002295.