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Neutrophil-to-Lymphocyte Ratio as a Microbiota-Dependent Indicator of Immune Dysfunction and a Long-Term Prognostic Factor in Patients with Cirrhosis

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Aim: to evaluate the neutrophil-to-lymphocyte ratio (NLR) as a microbiota-dependent indicator of immune dysfunction and a long-term prognostic factor in patients with cirrhosis.
Materials and methods. A prospective study included 47 patients with cirrhosis. Gut microbiota was analyzed using *16S* rRNA gene sequencing. Long-term survival prognosis was assessed over a 4-year follow-up period, and medium-term survival prognosis was assessed over 1 year follow-up period.
Results. During the 4-year follow-up period, 15 patients died, including 6 who died within the first year. Deceased patients had a higher neutrophil-to-lymphocyte ratio compared to survivors. This was significant for both long-term and medium-term prognoses (p = 0.021 and p = 0.048, respectively). Multivariate regression analysis identified a high NLR and low serum albumin levels as independent predictors of mortality for both long- and medium-term outcomes. The NLR was inversely correlated with the abundance of *Roseburia, Alistipes, Rikenellaceae, Parabacteroides, Robinsoniella, Paraprevotella,* and *Odoribacter* in the gut microbiota, and positively correlated with the cumulative level of ethanol-producing bacteria. NLR values did not differ significantly between patients who received glucocorticosteroids and those who did not.
Conclusions. The neutrophil-to-lymphocyte ratio correlates with the composition of pro- and anti-inflammatory taxa of the gut microbiota and serves as an independent factor for medium- and long-term prognosis in patients with cirrhosis.
Keywords: gut microbiota, gut-liver axis, infectious complications, cirrhosis, prognosis
Conflict of interest: the authors declare no conflict of interest.

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Отношение нейтрофилов к лимфоцитам как микробиота-зависимый показатель иммунной дисфункции и фактор долгосрочного прогноза у больных циррозом печени

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Цель: оценить отношение нейтрофилов к лимфоцитам как микробиота-зависимый показатель иммунной дисфункции и фактор долгосрочного прогноза у больных циррозом печени.
Материалы и методы. В проспективное исследование были включены 47 пациентов с циррозом печени. Кишечная микробиота изучена с помощью секвенирования гена *16S* рРНК. Долгосрочный прогноз для жизни был оценен в течение периода наблюдения длительностью 4 года, среднесрочный — 1 год.
Результаты. За 4-летний период наблюдения из 47 пациентов, включенных в исследование, умерли 15 пациентов, в том числе 6 в течение первого года. У умерших пациентов отношение нейтрофилов к лимфоцитам было выше, чем у выживших. Это было справедливо как в отношении долгосрочного, так и в отношении среднесрочного прогноза (p = 0,021 и p = 0,048 соответственно). При проведении многофакторного

регрессионного анализа высокие цифры отношения нейтрофилов к лимфоцитам и низкий уровень альбумина в крови были независимыми предикторами летального исхода при оценке долго- и среднесрочного прогноза. Отношение нейтрофилов к лимфоцитам обратно коррелировало с содержанием в кишечной микробиоте *Roseburia, Alistipes, Rikkenellaceae, Parabacteroides, Robinsoniella, Paraprevotella, Odoribacter* и прямо коррелировало с совокупным уровнем бактерий, которые образуют этанол. Значение отношения нейтрофилов к лимфоцитам значимо не различалось между пациентами, принимавшими и не принимавшими глюкокортикостероиды.

Выводы. Отношение нейтрофилов к лимфоцитам коррелирует с содержанием в кишечной микробиоте про- и противовоспалительных таксонов, а также является независимым фактором, определяющим средне- и долгосрочный прогноз у пациентов с циррозом печени.

Ключевые слова: кишечная микробиота, ось «кишка — печень», инфекционные осложнения, цирроз, прогноз

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Introduction

Cirrhosis affects not only the liver itself but also other systems, including the immune system. In particular, production of lymphocytes that are the key cells of the adaptive immune system decreases, leading to a compensatory increase in neutrophil production, which are part of the innate immune system [1]. Therefore, the neutrophil-to-lymphocyte ratio (NLR) serves as an indirect biomarker of immune dysfunction in cirrhosis. This dysfunction reduces the resistance to infections, worsening the prognosis for these patients. It was demonstrated in patients with cardiac, renal, and oncological diseases [2, 3], as well as in relation to short-term prognosis for cirrhosis [4].

The gut microbiota is a complex community of microorganisms residing in the human intestine [5]. In recent years, it has attracted significant research attention [6]. Studies have shown that cirrhosis is associated with an increase in harmful *Proteobacteria* and a decrease in beneficial microorganisms in the gut microbiota [7–10]. This imbalance is known as gut dysbiosis and leads to bacterial translocation, that is the migration of gut bacteria and their components from the intestinal lumen into regional lymph nodes, the portal vein system, and subsequently into the liver tissue, where they further exacerbate cirrhotic transformation [11–14]. Additionally, bacterial translocation alters the immune system function, and as mentioned above, the NLR is one of key indicators of this.

Although a high NLR has already been identified as a predictor of poor short-term survival in patients with cirrhosis [4], its correlation with medium- and long-term prognosis, as well as its relationship with gut microbiota composition, has not yet been evaluated. Investigating these associations is the aim of this study.

Materials and methods

Patients

A total of 47 patients with cirrhosis undergoing treatment at the V.Kh. Vasilenko Clinic of Internal Diseases, Gastroenterology and Hepatology (Sechenovskiy University), were enrolled in this prospective study. All potential participants were informed about the study procedures and provided written informed consent. The study protocol was approved by the local ethics committee of the University.

Inclusion criteria were as follows: a diagnosis of cirrhosis confirmed by liver biopsy or based on a combination of clinical, laboratory, and instrumental data; age between 18 and 70 years.

Exclusion criteria included: the use of lactulose, lactitol, other prebiotics, probiotics, antibiotics, or metformin within the past 6 weeks; alcohol consumption within the past 6 weeks; inflammatory bowel disease, cancer, or any other serious disease.

Gut microbiota analysis

On the first day of hospitalization, stool samples were collected from each patient in sterile containers and subsequently frozen at –80 °C. DNA was extracted from the stool samples using the MagNa Pure Compact Nucleic Acid Isolation Kit, following the manufacturer's instructions. Sequencing libraries were prepared using two cycles of PCR amplification. In the first PCR step, specific primers targeting the v3–v4 region of the *16S* ribosomal RNA (rRNA) gene were used: 16S-F: TCGTCGGCA-GCGTCAGATGTGTATAAGAGACAGCCTACGGGNGGCWGCAG и 16S-R: GTCTCGTGGGCTCGGAGATGTGTATAAGAGACAGGACTACHVGGGTATCTAATCC.

After the initial PCR amplification, samples were purified using AMPure XP magnetic beads. A second PCR step was then performed to attach

Table 1. Main characteristics of the patients included in the study
Таблица 1. Основные характеристики включенных пациентов

Parameter / *Параметр*	**Value / *Значение***
Etiology of liver cirrhosis, *n* *Этиология цирроза печени, n*	Alcohol / *Алкоголь* — 15 Viral hepatitis / *Вирусный гепатит* — 15 Other / *Прочая* — 10 Mixed / *Смешанная* — 7
Age, years / *Возраст, лет*	51 (39–59)
BMI, kg/m^2 / *ИМТ, кг/м^2*	24.2 (22.7–27.7)
Child — Pugh scores / *Баллы по Чайлду — Пью*	8 (6–9)
Erythrocytes, 10^{12}/L *Эритроциты, 10^{12}/л*	3.86 (3.55–4.27)
Leukocytes, 10^9/L *Лейкоциты, 109/л*	3.7 (2.8–5.2)
Neutrophils, 10^9/L *Нейтрофилы, 10^9/л*	2.1 (1.6–2.9)
Lymphocytes, 10^9/L *Лимфоциты, 10^9/л*	1.1 (0.7–1.5)
Neutrophil/lymphocyte ratio *Отношение нейтрофилы/лимфоциты*	2.0 (1.7–2.8)
Platelets, 10^9/L *Тромбоциты, 10^9/л*	81.0 (57.8–109.0)
Erythrocyte sedimentation rate, mm/h *Скорость оседания эритроцитов, мм/ч*	12 (8–25)
Prothrombin index, % *Протромбиновый индекс, %*	63 (53–70)
Total protein, g/L *Общий белок, г/л*	71.2 (63.1–77.0)
Albumin, g/L *Альбумин, г/л*	35.9 (30.5–40.2)
Creatinine, mg/L *Креатинин, мг/л*	0.72 (0.62–0.88)
Glucose, mmol/L *Глюкоза, ммоль/л*	5.2 (4.7–5.6)
Total bilirubin, μmol/L *Общий билирубин, мкмоль/л*	35.5 (25.7–62.3)
Sodium, mmol/L *Натрий, ммоль/л*	141 (138–144)
Cholesterol, mmol/L *Холестерин, ммоль/л*	3.53 (3.12–4.09)
Cholinesterase, IU/L *Холинэстераза, МЕ/л*	3042 (2273–4183)
Alanine aminotransferase, IU/L *Аланинаминотрансфераза, МЕ/л*	35 (23–61)
Aspartate aminotransferase, IU/L *Аспартатаминотрансфераза, МЕ/л*	50 (32–71)
Alkaline phosphatase, IU/L *Щелочная фосфатаза, МЕ/л*	220 (166–310)
Gamma-glutamyl transferase, IU/L *Гамма-глутамилтрансфераза, МЕ/л*	77 (34–136)
C-reactive protein, mg/L *С-реактивный белок, мг/л*	5.2 (0.8–13.1)
Ascites, grades 0/1/2/3 *Асцит, степени 0/1/2/3*	21/11/10/5
Esophageal varices, grades 0/1/2/3 *Варикозное расширение вен пищевода, степени 0/1/2/3*	10/15/12/10
Hepatic encephalopathy, minimal/overt *Печеночная энцефалопатия, минимальная/явная*	19/16

specific adapters and enable sample multiplexing. Following the two amplification steps, samples were further purified using magnetic beads. Illumina index primers and adapter sequences were added, and library quantities were assessed using HiFi HotStart ReadyMix. The prepared sequencing libraries were quantified using the Qubit 2.0 fluorometer (Invitrogen, USA), and their quality was assessed with an Agilent Bioanalyzer (Agilent Technologies, USA). Libraries were pooled in equal proportions and diluted to the required concentration for sequencing on the MiSeq platform (Illumina, USA). Paired-end sequences of 300 + 300 nucleotides were obtained. Sequences were trimmed at the 3' end using Trimmomatic (Illumina, USA) and subsequently merged into a single amplicon [15, 16] using the MeFiT tool. Amplicon nucleotide sequences were classified using the Ribosomal Database Project (RDP) classifier and the RDP database [17].

Follow-Up

Patients included in this study were contacted by phone every three months to verify their survival status. If the patient could not be reached, their relatives were contacted to obtain this information. In cases where neither the patient nor their relatives could be reached, electronic medical records were reviewed in the Unified Medical Information and Analytical System of Moscow, which contains death registration data. The follow-up period lasted 4 years.

Statistical analysis methods

Statistical analysis was conducted using Statistica 10 (StatSoft Inc., USA) and SPSS Statistics (SPSS: An IBM Company, USA) software. Data are presented as medians with interquartile ranges. Differences between continuous variables were assessed using the Mann — Whitney *U* test, while differences between categorical variables were evaluated using Fisher's exact test. Patient survival was analyzed using the Kaplan — Meier method. To assess the impact of various factors on patient survival, a Cox regression model was constructed. A *p*-value of ≤ 0.05 was considered statistically significant.

Results

The study included 47 patients. During the 4-year follow-up period, 15 of them died (long-term prognosis), including 6 during the first year of follow-up (medium-term prognosis). The main characteristics of the included patients are presented in Table 1.

NLR was higher in the deceased patients than in the survivors. This was true for both the long-term and medium-term prognosis ($p = 0.021$ and $p = 0.048$, respectively; Fig. 1).

ROC analysis showed that, using a cut-off point of 1.98, NLR determines the unfavorable long-term prognosis of patients with cirrhosis with a sensitivity of 86.7 % and a specificity of 62.5 % (AUC = 0.712 [0.559–0.866]; Fig. 2).

Another ROC analysis revealed that using a cutoff point of 2.12, NLR predicts poor medium-term survival (death within the first year of follow-up) in patients with cirrhosis with a sensitivity of 100.0 % and a specificity of 63.4 % (AUC = 0.752 [0.604–0.900]; Fig. 3).

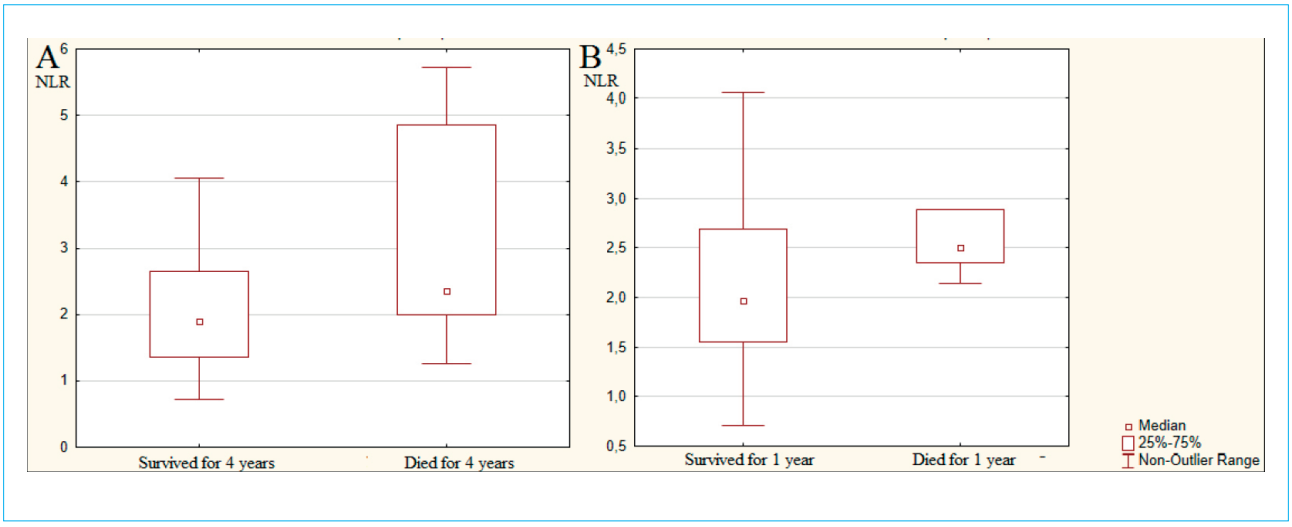

Figure 1. Neutrophil to lymphocyte ratio in patients with liver cirrhosis who died during the follow-up period (A — 4 years, B — 1 year) and who survived

Рисунок 1. Отношение нейтрофилов к лимфоцитам у пациентов с циррозом печени, которые умерли в течение периода наблюдения (А — 4 года, В — 1 год) и которые его пережили

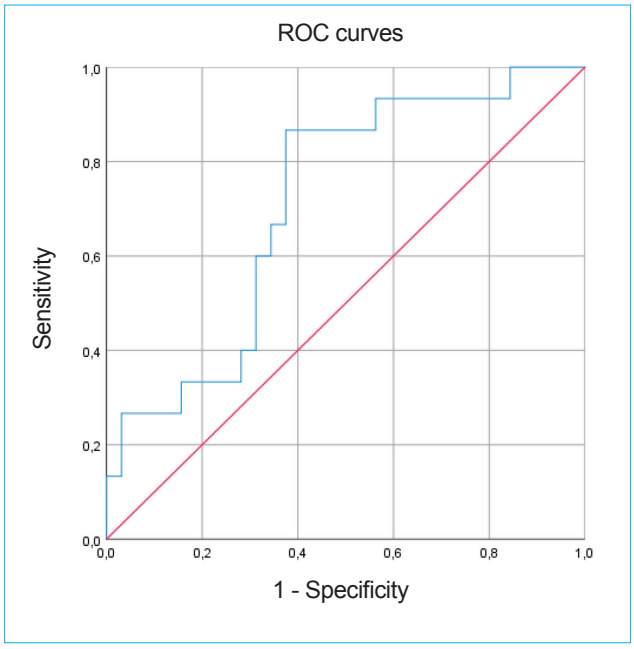

Figure 2. ROC analysis of the use of neutrophil-to-lymphocyte ratio as a predictor of poor long-term survival in patients with liver cirrhosis

Рисунок 2. ROC-анализ использования отношения нейтрофилов к лимфоцитам как предиктора неблагоприятного долгосрочного прогноза для жизни у пациентов с циррозом печени

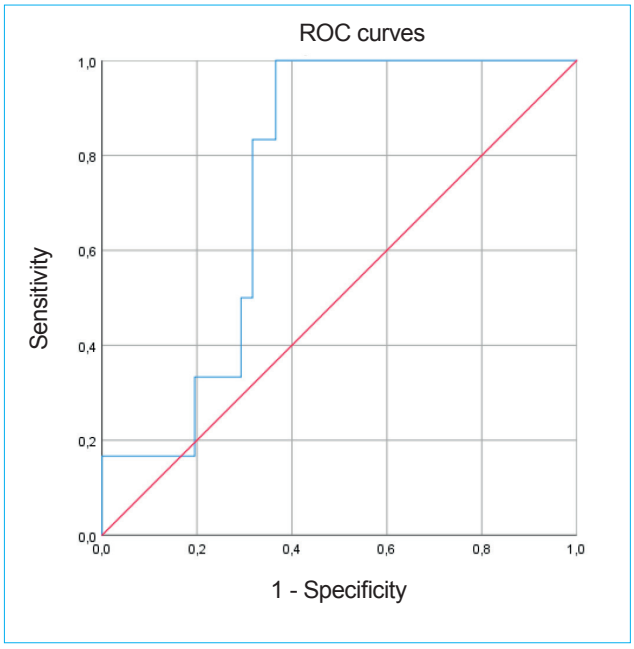

Figure 3. ROC analysis of the use of neutrophil-to-lymphocyte ratio as a predictor of poor mid-term survival in patients with liver cirrhosis

Рисунок 3. ROC-анализ использования отношения нейтрофилов к лимфоцитам как предиктора неблагоприятного среднесрочного прогноза для жизни у пациентов с циррозом печени

In patients with NLR above 1.98, mortality within 4 years was 52 %, while in those with a lower ratio it was 9.1 % (p = 0.002; Fig. 4).

In patients with NLR above 2.12, mortality during the first year of follow-up was 28.6 %, while in those with a lower ratio it was 0 (p = 0.004; Fig. 5).

Multivariate regression analysis revealed that high NLR and low serum albumin levels were independent predictors fatal outcome in the assessment of long- and medium-term prognosis (Table 2).

NLR inversely correlated with the abundance of *Roseburia* (r = –0.299; p = 0.041), *Alistipes* (r = –0.343; p = 0.018), *Rikkenellaceae* (r = –0.310; p = 0.035), *Parabacteroides* (r = –0.328; p = 0.025), *Robinsoniella* (r = –0.290; p = 0.049), *Paraprevotella* (r = –0.388; p = 0.007), *Odoribacter* (r = –0.324; p = 0.026) and directly correlated with the total abundance of bacteria that form ethanol (r = 0.340; p = 0.020).

In patients with NLR above 1.98, the gut microbiota had lower abundance of *Roseburia* (p = 0.044), *Alistipes* (p = 0.021), *Rikkenellaceae* (p = 0.038), *Parabacteroides* (p = 0.027), *Bilophyla* (p = 0.007), *Paraprevotella* (p = 0.005) and *Odoribacter* (p = 0.030) than that in patients with values below this threshold. The opposite changes were observed with regard to ethanol-producing bacteria (Fig. 6).

Since taking glucocorticosteroids changes NLR, namely it increases the neutrophils level and reduces the lymphocytes count, we divided our patients into subgroups who took and did not take these drugs. There were 5 patients with autoimmune hepatitis in the first group, and all other patients in the second group. NLR did not significantly differ between these groups of patients (Fig. 7). None of the patients taking glucocorticosteroids died during the follow-up period (Fig. 8), but the difference between the groups in life expectancy was still insignificant (p = 0.138), possibly due to the small number of participants.

Discussion

The syndrome of immune dysfunction associated with cirrhosis manifests as an alteration in the composition and function of various immune cells. Among other things, neutrophil chemotaxis, phagocytosis, and bactericidal activity are reduced [18–23], and lymphocyte function is altered. Many of these changes have been associated with

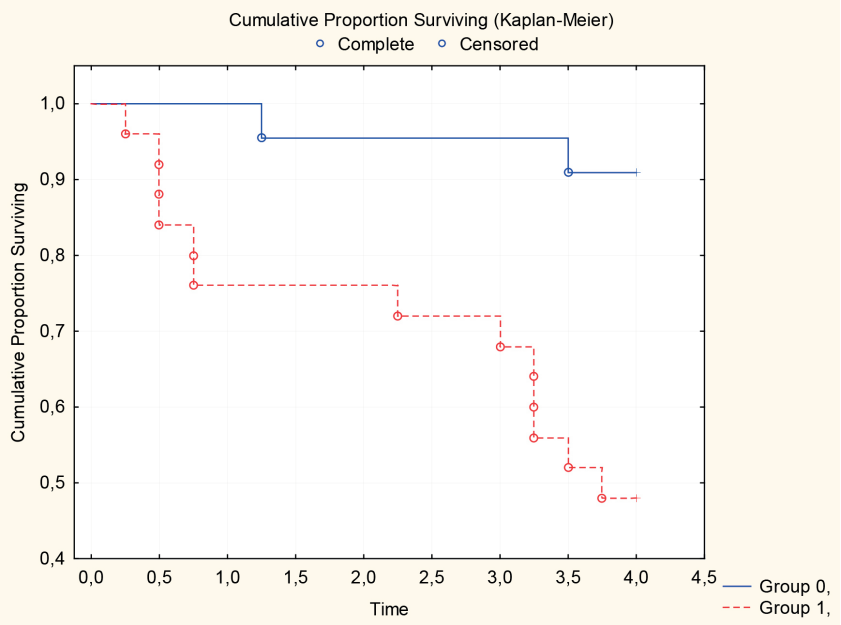

Figure 4. Survival curves (in years) of patients with liver cirrhosis (long-term prognosis) whose neutrophil to lymphocyte ratio was above and below the threshold (Group 1 and Group 0, respectively)
Рисунок 4. Кривые выживаемости (в годах) пациентов с циррозом печени (долгосрочный прогноз), у которых отношение нейтрофилов к лимфоцитам было выше и ниже порогового (Group 1 и Group 0 соответственно)

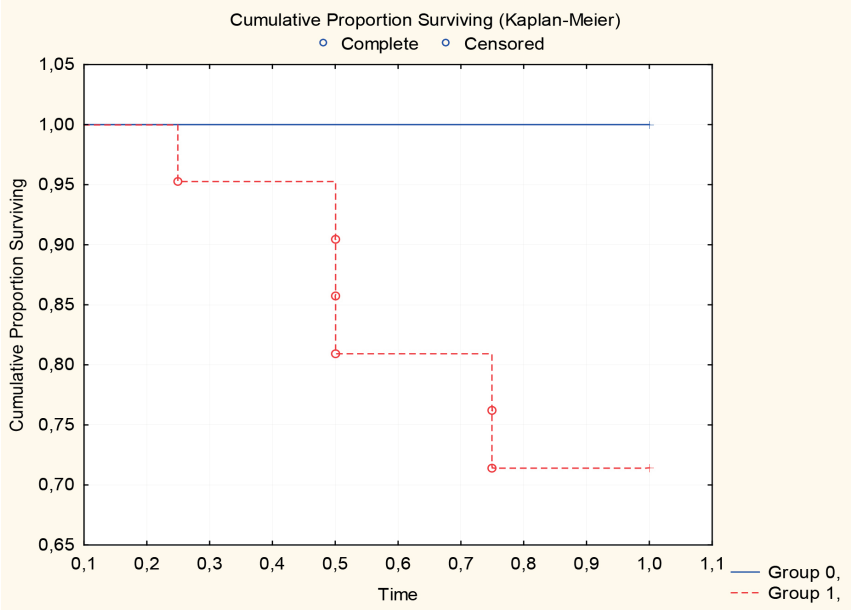

Figure 5. Survival curves (proportions of the first year of observation) of patients with liver cirrhosis (medium-term prognosis), in whom the neutrophil-to-lymphocyte ratio was above and below the threshold (Group 1 and Group 0, respectively)
Рисунок 5. Кривые выживаемости (доли первого года наблюдения) пациентов с циррозом печени (среднесрочный прогноз), у которых отношение нейтрофилов к лимфоцитам было выше и ниже порогового (Group 1 и Group 0 соответственно)

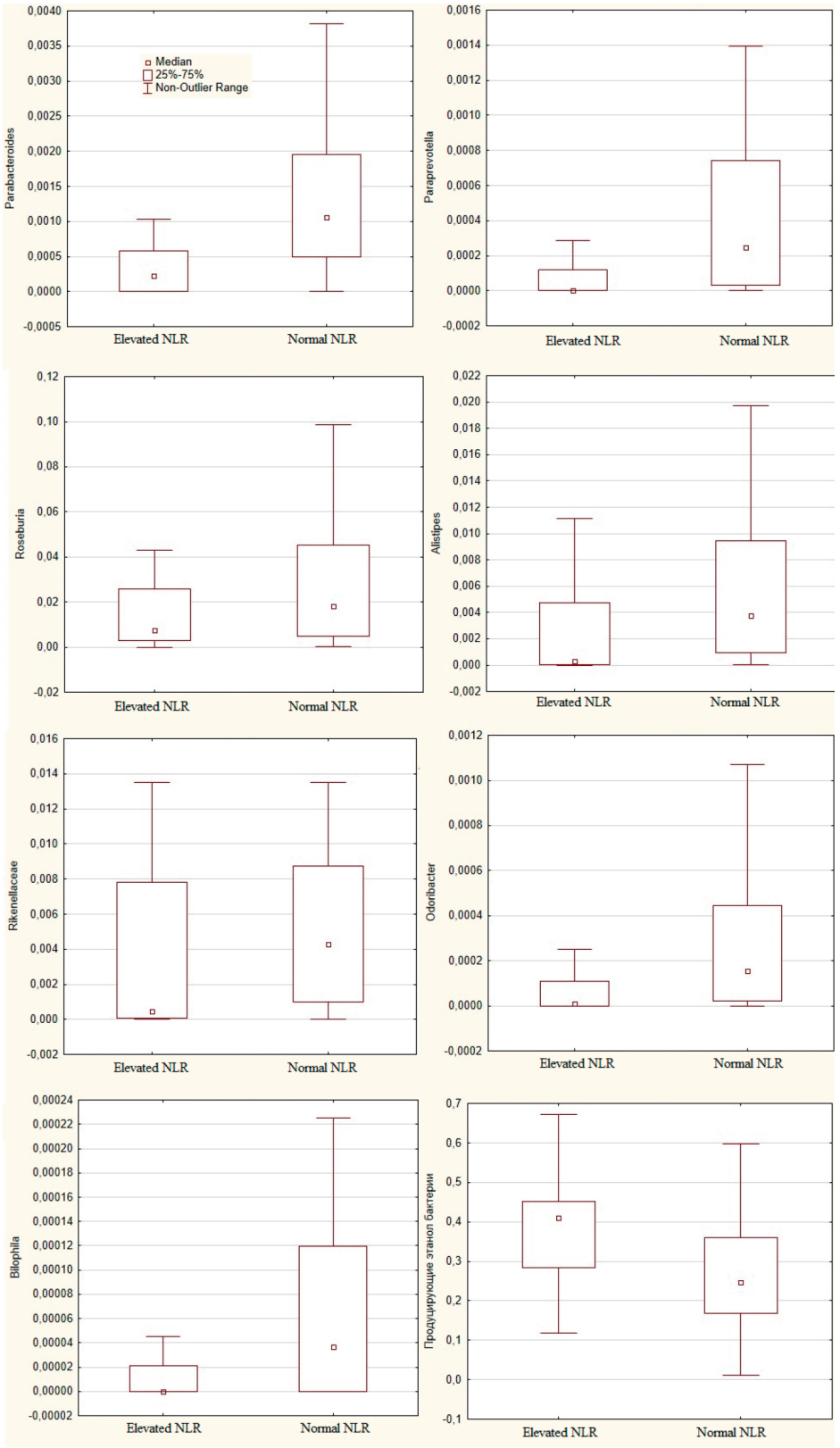

Figure 6. Gut microbiota taxa significantly different between patients with neutrophil to lymphocyte ratio values above and below the threshold (1.98)

Рисунок 6. Таксоны кишечной микробиоты, значимо различающиеся между пациентами со значениями отношения нейтрофилов к лимфоцитам выше и ниже порогового (1,98)

Table 2. Results of multivariate regression analysis of factors determining unfavorable long- and medium-term prognosis in patients with liver cirrhosis

Таблица 2. Результаты многомерного регрессивного анализа факторов, определяющих неблагоприятный долго- и среднесрочный прогноз больных с циррозом печени

Parameter / *Параметр*	Long-term forecast *Долгосрочный прогноз*		Short term forecast *Краткосрочный прогноз*	
	p	HR	*p*	HR
Neutrophil to lymphocyte ratio *Отношение нейтрофилов к лимфоцитам*	0.024	1.27 (1.03–1.57)	0.021	1.38 (1.05–1.83)
Blood albumin level, g/L *Уровень альбумина в крови, г/л*	0.039	0.88 (0.78–0.99)	0.061	0.77 (0.58–1.01)
Ascites of the 2nd–3rd grade *Асцит 2–3 ст.*	0.264		0.561	
Esophageal varices > 1st degree *Варикозное расширение вен пищевода > 1 ст.*	0.786		0.381	
Hepatic encephalopathy *Печеночная энцефалопатия*	0.751		0.767	

endotoxemia and partially regressed after the use of probiotics [24–26].

In patients with cirrhosis, memory B-cells were found in the blood much less frequently than in healthy individuals. Their level correlates with laboratory markers of liver disease progression. Dysfunction of these cells correlates with levels of lipopolysaccharide and bacterial DNA in the environment [27–30].

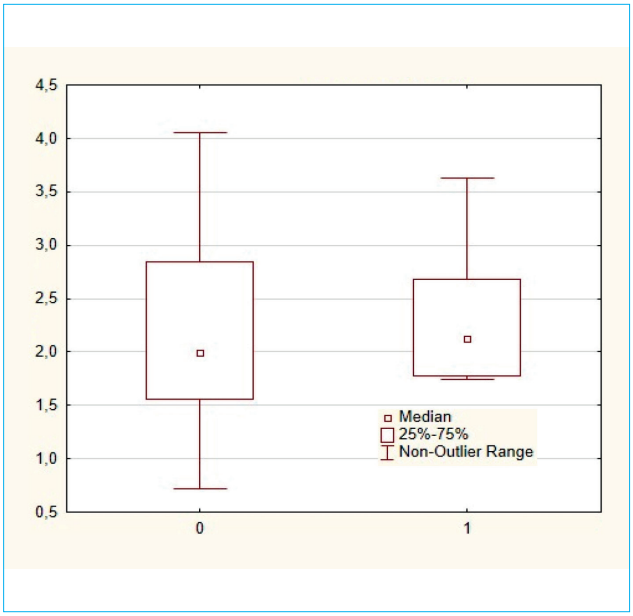

Figure 7. Neutrophil to lymphocyte ratio in patients who took glucocorticosteroids and those who did not take these drugs (Groups 1 and 0, respectively)

Рисунок 7. Отношение нейтрофилов к лимфоцитам у пациентов, которые принимали глюкокортикостероиды, и тех, кто не принимал данные препараты (группы 1 и 0 соответственно)

A high antigen load resulting from bacterial translocation may contribute to prolonged activation and subsequent exhaustion of T lymphocytes. Significant reduction in the overall number of T cells in peripheral blood is observed in patients with cirrhosis and ascites. The proportion of activated $CD4^+$ T cells and aging $CD8^+$ T cells significantly increases. Additionally, the proportion of $CD4^+$ and $CD8^+$ populations expressing apoptosis markers ($CD95^+$) is higher in patients with cirrhosis compared to healthy individuals from the control group. A reduction in the level of co-stimulatory molecules of lymphocytes, such as CD28, has also been found. Thus, it can be assumed that these changes in adaptive immunity may play a role in the immunosuppression observed in cirrhosis, leading to increased susceptibility to bacterial infections [31, 32]. A low level of T cells is not associated with the etiological factor of cirrhosis and a negative correlation it with the presence of splenomegaly has been noted [32]. A previous study showed that T cell immunodeficiency in cirrhosis is associated with a defect in lymphopoiesis in the thymus, which is exacerbated by cell deposition in the spleen and activation of cell death caused by bacterial translocation [34].

Lipopolysaccharide enhances the systemic inflammatory response by activating Toll-like receptors 2 and 4 and stimulates the mass production of cytokines, which in turn leads to increased secretion of reactive oxygen species that further increase the permeability of the intestinal barrier, enhancing bacterial translocation [35].

The significant enhancement of production of cytokine and reactive oxygen species, leading to increased intestinal permeability and bacterial translocation, highlights the importance of developing therapeutic strategies to overcome

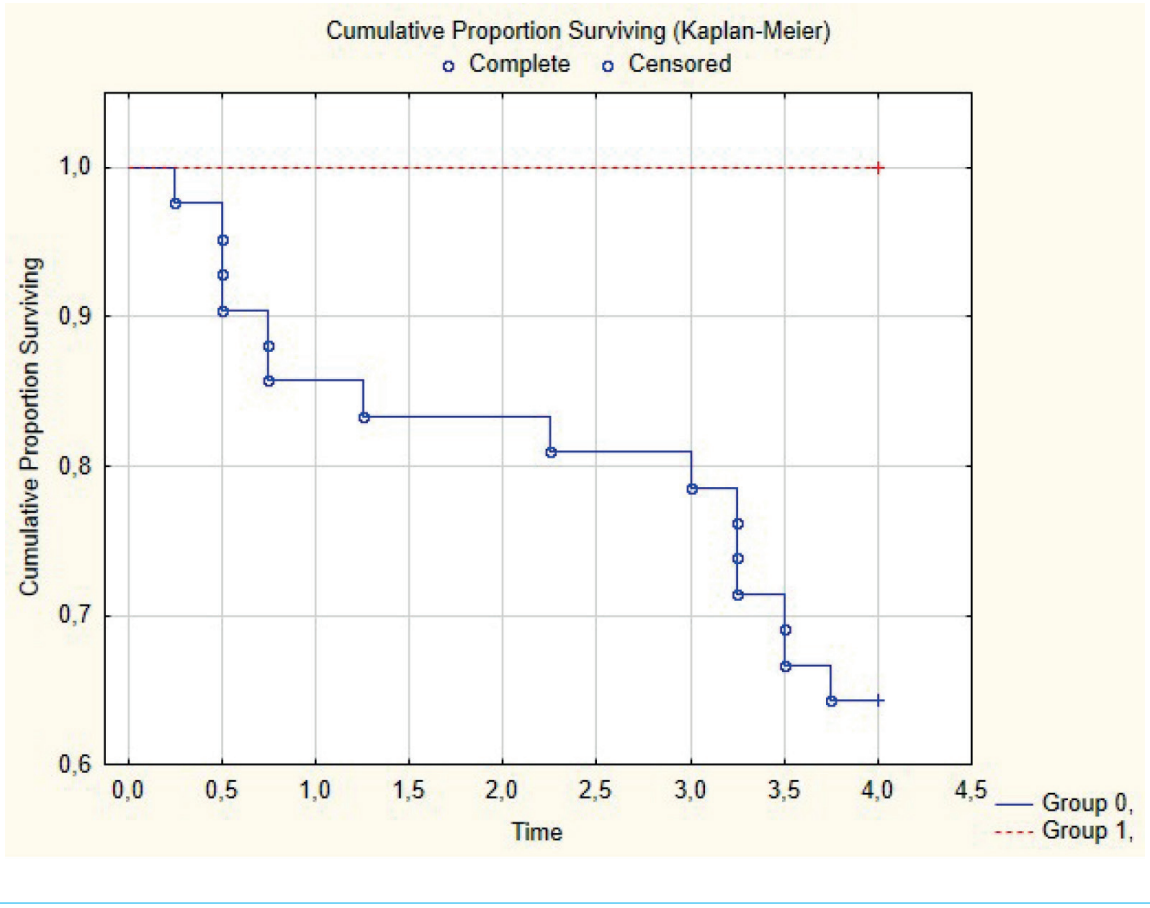

Figure 8. Survival of patients who took glucocorticosteroids and those who did not take these drugs (Group 1 and Group 0, respectively)

Рисунок 8. Выживаемость пациентов, которые принимали глюкокортикостероиды, и тех, кто не принимал данные препараты (Group 1 и Group 0 соответственно)

these issues. Therefore, it is reasonable to assume that some of the positive effects of albumin administration in patients with cirrhosis-related spontaneous bacterial peritonitis or acute kidney injury may be largely due to its anti-inflammatory and antioxidant properties [36, 37]. Multivariate regression analysis in our study showed that NLR and albumin levels in the blood were independent predictors of long- and middle-term mortality, that supporting this hypothesis.

Earlier studies have examined the use of NLR as a predictor of unfavorable short-term prognosis in patients with decompensated cirrhosis. Exceeding a threshold value of 4 was found to be an independent risk factor for fatal outcomes [4]. The current study showed similar patterns for middle- and long-term prognosis.

The link between gut dysbiosis and long-term prognosis in cirrhosis patients has been studied before. Mortality in patients with severe dysbiosis was significantly higher than in those with moderate dysbiosis. Severe dysbiosis was an independent risk factor for death in cirrhosis patients [10]. In deceased patients, compared to survivors, there was an increased abundance of *Enterobacteriaceae, Proteobacteria,* and *Lactobacillaceae*, and a reduced content of *Firmicutes* and *Clostridia*. The number of *Bacilli, Enterococcaceae*, and *Lactobacillaceae* was higher, and the number of *Clostridia* was lower in those who died within the first year of follow-up compared to those who survived this year. The number of *Enterobacteriaceae* and *Proteobacteria* was higher in those who died in the 2nd–4th year of follow-up compared to survivors.

In this study, we evaluated the correlations between NLR and the level of various bacterial taxa in the gut microbiota. The phylum *Bacteroidetes* (*Bacteroidota* in the modern classification) includes non-spore-forming, gram-negative strict anaerobes, including the families *Rikenellaceae* and *Odoribacteraceae*, and the

genera *Parabacteroides*, *Paraprevotell*a, and *Alistipes*, some of which play a significant role in colonization resistance, have anti-inflammatory effects, and normalize metabolism. In our study, NLR was inversely correlated with the level of *Alistipes*, *Rikenellaceae*, *Odoribacter*, *Parabacteroides*, and *Paraprevotella* in the gut microbiota, indicating their association with the development of the systemic inflammatory response.

A reverse correlation with NLR was also found with *Roseburia* and *Robinsoniella*, which belong to the family *Lachnospiraceae*. Previous studies have shown that the level of these bacteria in the gut microbiota was reduced in senile sarcopenia, chronic kidney disease, asthma, multiple sclerosis, arterial hypertension, hyperlipidemia, ischemic heart disease, type 2 diabetes, obesity, and other diseases [38–46].

The content of ethanol-producing bacteria in the intestines was directly correlated with NLR. This can be explained by the fact that ethanol damages enterocytes, promoting bacterial translocation and the neutrophilic inflammatory response to it.

In our study, we did not find a significant difference in NLR between patients who took glucocorticoids and those who did not. Since all the patients who took these drugs had autoimmune hepatitis, it can be assumed that their immune systems were initially hyperreactive, and thus, glucocorticoids did not lead to immunodeficiency but restored their immune system to a normoreactive state. Further studies with a larger sample size are required to confirm this hypothesis.

The correlations found between immune dysfunction and gut microbiota in cirrhosis suggest that interventions aimed at correcting gut dysbiosis in this disease may be a promising approach for treating this complication.

Studying the gut microbiome in various diseases has become a priority in modern science but has yet to find application in everyday clinical practice. The high cost of gut microbiome sequencing and the lack of bioinformatics specialists hinder its implementation. A priority step toward incorporating gut dysbiosis studies into clinical practice is replacing this expensive method with something simpler and more accessible. PCR is an ideal option for determining the content of specific taxa in feces, followed by a comprehensive assessment of the gut microbiome.

A strong point of our study is that it is the first to describe the relationship between NLR and gut dysbiosis, confirming the hypothesis about the significant role of bacterial translocation in the development of the systemic inflammatory response. Our study is also the first to evaluate the impact of NLR on middle- and long-term survival in cirrhosis patients.

The limitation of this study was the small number of participants, which did not prevent us from obtaining significant results. Larger-scale studies are needed to verify our findings.

Conclusion

In our study, we showed that the NLR correlates with the abundance of pro-inflammatory and anti-inflammatory taxa in the gut microbiota and is an independent factor determining the middle- and long-term prognosis in patients with cirrhosis. Given the significant role of bacterial infections in the pathogenesis of this disease, correcting immune dysfunction using agents targeting the gut microbiota appears to be a promising direction for therapy.

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