DOI: 10.21294/1814-4861-2025-24-5-40-52
УДК: 616-006.484+616-002+616.155.32

Для цитирования: *Скляр С.С., Нечаева А.С., Улитин А.Ю., Мацко М.В., Олюшин В.Е., Самочерных К.А.* Клеточные маркеры воспаления в крови у пациентов с глиомами различной степени злокачественности. Сибирский онкологический журнал. 2025; 24(5): 40–52. – doi: 10.21294/1814-4861-2025-24-5-40-52
For citation: *Sklyar S.S., Nechaeva A.S., Ulitin A.Yu., Matsko M.V., Olyushin V.E., Samochernykh K.A.* Cellular immune inflammation markers in the blood of patients with gliomas of different malignancy grades. Siberian Journal of Oncology. 2025; 24(5): 40–52. – doi: 10.21294/1814-4861-2025-24-5-40-52

CELLULAR IMMUNE INFLAMMATION MARKERS IN THE BLOOD OF PATIENTS WITH GLIOMAS OF DIFFERENT MALIGNANCY GRADES

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Abstract

Inflammatory blood markers are vital for immune responses and predicting cancer outcomes. Their roles in brain gliomas remain unclear. **The aim of this study** is to evaluate the diagnostic significance of these markers in patients with gliomas, taking into account various histological subtypes and malignancy grades. **Material and Methods.** This prospective study enrolled 139 patients with newly diagnosed supratentorial adult-type diffuse gliomas. The cohort was stratified based on tumor grade and genetic mutations, comprising 25 cases of grade 2 diffuse gliomas (of them 7 with oligodendroglioma), 25 cases of gliomas grade 3 (of them 8 with oligodendroglioma) or 4 and 89 patients with glioblastoma. The pre-operative neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR) and platelet-lymphocyte ratio (PLR) were calculated. Results. The LMR in the glioma grade 2 group was higher than that in the glioma grade 3, 4 and glioblastoma groups (3.71 *vs* 3.09 *vs* 3; p<0.05) with areas under the curve (AUCs) of 0.6552 (0.4930–0.8174) and 0.6586 (0.5583–0.7590) respectively. LMR was higher in patients with IDH1/2-mutation gliomas (3.44 *vs* 3.0; p=0.039). No differences in LMR were observed between patients with oligodendroglioma and glioma without codeletion 1p/19q (3.43 *vs* 3.19; p=0.76). LMR in all cohorts was not affected by use of corticosteroids. The NLR was higher in glioblastoma patients than in patients with glioma grade 2 (2.9 *vs* 1.96, p<0.05). Increase of NLR in glioblastoma patients were correlated with the corticosteroids (3.7 *vs* 8.0, p<0.05 and 1.95 *vs* 3.79, p<0.05, respectively). **Conclusion.** Thus, LMR has the potential to serve as a promising, additional, independent of the appointment of corticosteroids, diagnostic biomarker for diffuse gliomas of the adult type. An increase in the malignancy grade is associated with a decrease in LMR. NLR is not a reliable biomarker. Corticosteroids can increase NLR during steroid treatment, potentially affecting its reliability as a biomarker.

Key words: brain tumors, glioma, inflammatory blood markers, lymphocyte-monocyte ratio.

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КЛЕТОЧНЫЕ МАРКЕРЫ ВОСПАЛЕНИЯ В КРОВИ У ПАЦИЕНТОВ С ГЛИОМАМИ РАЗЛИЧНОЙ СТЕПЕНИ ЗЛОКАЧЕСТВЕННОСТИ

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Аннотация

Клеточные маркеры воспаления, являющиеся ключевыми медиаторами иммунного ответа, уже продемонстрировали свою прогностическую значимость при различных онкологических заболеваниях. Однако их роль в патогенезе и прогрессировании глиом остается неизученной. **Цель исследования –** оценить диагностическую ценность данных биомаркеров при разных гистологических типах глиом и различных степенях их злокачественности. **Материал и методы.** В исследование включено 139 пациентов с впервые диагностированными диффузными глиальными опухолями взрослого типа супратенториальной локализации. Стратификация пациентов проводилась по степени злокачественности опухоли, наличию мутации в генах IDH1/2 и коделеции 1p19q. Согласно гистологической верификации, в когорте выявлено 25 случаев диффузной глиомы grade 2, 25 случаев диффузной глиомы grade 3 или 4, у 89 пациентов верифицирована глиобластома. Анализировались наличие сопутствующих заболеваний, текущая медикаментозная терапия, включая применение глюкокортикостероидов, молекулярно-генетические и морфологические особенности опухоли. В предоперационном периоде выполнялся развернутый клинический анализ периферической крови с определением абсолютных показателей моноцитов, нейтрофилов, лимфоцитов, а также значений клеточных маркеров воспаления (NLR (нейтрофильно-лимфоцитарное соотношение), LMR (лимфоцитарно-моноцитарное соотношение), PLR (тромбоцитарно-лимфоцитарное соотношение). **Результаты.** Значение LMR в группе с глиомой grade 2 было выше, чем у пациентов с глиомой grade 3, 4 и глиобластомой (3,71 *vs* 3,09 *vs* 3; p<0,05) с площадями под кривой (AUCs) of 0,6552 (0,4930–0,8174) и 0,6586 (0,5583–0,7590) соответственно. Выявлены значимо более высокие показатели LMR у пациентов с глиомами с наличием мутаций IDH1/2 по сравнению с IDH-wild type (3,44 *vs* 3,0; p=0,039). Примечательно, что терапия ГКС не оказала существенного влияния на уровень LMR ни в одной из исследуемых подгрупп. При глиобластомах уровень NLR был выше, чем у пациентов с глиомами grade 2 (2,9 *vs* 1,96, p<0,05). Повышение уровня NLR прямо коррелировало с назначением ГКС (3,7 *vs* 8,0, p<0,05 и 1,95 *vs* 3,79, p<0,05, respectively). При статистическом анализе определена положительная корреляция между применением ГКС и повышением NLR в группах пациентов с глиобластомой и глиомами grade 2 (3,7 *vs* 8,0, p<0,05 и 1,95 *vs* 3,79, p<0,05, соответственно). **Заключение.** Полученные данные позволяют рассматривать LMR в качестве перспективного, дополнительного, не зависящего от назначения ГКС, диагностического биомаркера при диффузных глиомах взрослого типа. С повышением степени злокачественности регистрировалось уменьшение LMR. NLR не является достоверным диагностическим показателем. Увеличение данного биомаркера сопряжено с назначением пациентам ГКС, что снижает его ценность.

Ключевые слова: церебральные опухоли, глиомы, маркеры воспаления, LMR.

Introduction

According to global epidemiological data, approximately 320,000 new cases of primary central nervous system (CNS) tumors are diagnosed every year, with an estimated mortality of about 250,000 patients affected by these neoplasms [1]. Among primary intracerebral tumors, diffuse gliomas are the most common subtype [2]. The 5th edition of the WHO classification of CNS tumors categorizes astrocytomas as grades 2, 3, and 4, oligodendrogliomas as grades 2 and 3, and gliob-

lastomas as grade 4 [3]. Notably, all grade 2gliomas are classified as low-grade tumors; conversely, grade 3 and 4 diffuse gliomas as well as glioblastomas, are associated with a significantly poor prognosis and are classified as malignant neoplasms.

Treatment of diffuse glioma patients includes neurosurgical procedures, adjuvant radiation therapy and systemic anti-tumor therapies, including chemotherapy and targeted therapy [4, 5]. It is important to note that the specific anti-tumor regimen is not only adapted to the histological subtype of diffuse glioma but is also strongly influenced by the extent of resection [4]. The extent of tumor resection can substantially impact the necessity for subsequent anti-tumor therapy, particularly in cases of low-grade diffuse glioma. For histological classifications such as grade 3 and 4 astrocytomas, grade 3 oligodendrogliomas and glioblastomas, radiation and chemotherapy are required regardless of surgical outcome. Although glioblastoma has distinctive radiographic characteristics, it is often difficult to differentiate diffuse gliomas of varying grades of malignancy using MRI data. Therefore, there is an urgent need for pre-operative confirmation of histological diagnosis to facilitate optimal neurosurgical planning and comprehensive treatment of the patient.

Advanced imaging techniques such as magnetic resonance imaging (MRI) and positron emission tomography (PET) have been developed in recent years and have made it easier to improve the accuracy of pre-operative diagnostics [6, 7]. Liquid biopsy has proven to be a very promising diagnostic approach in general oncology and neuro-oncology [8]. Circulating nucleic acids have been identified as having significant diagnostic potential in gliomas of different malignancies [9]. However, the high costs associated with these techniques limit their availability in many health care settings. Therefore, there is still a critical need for a cost-effective, rapid and unambiguous method of differential diagnosis of brain gliomas.

Research suggests that systemic immune inflammation plays a key role in the oncogenic process [10–12]. The primary focus of the study was to assess the local immune response within tumors. Reprogrammed immune cells have been shown to contribute approximately 30 percent of the cellular composition of malignant gliomas, facilitating tumorogenesis [13]. In addition, intracellular inflammatory signaling pathways were clarified and key cytokines were characterized. However, research on systemic immune inflammation in gliomas is still in its early stages and should be further explored.

Numerous studies have been carried out to evaluate the diagnostic and prognostic relevance of cellular inflammatory markers in patients with glioma [14–18]. It should be stressed that most of these studies did not stratify tumors according to histological classification and grade of malignancy. Moreover, the existing literature largely ignored the effect of glucocorticosteroid (GCS) therapy on patients, despite its significant impact on the dynamics of the immune system. The prognostic effects of inflammatory biomarkers in patients with glioblastoma have been previously assessed, including the effects of GCS [19].

This study aimed to assess the diagnostic utility of systemic inflammatory markers – including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) – across histological subtypes and malignancy grades of glioma, with particular consideration of GCS.

Material and Methods

The research involved 139 patients, all newly diagnosed with supratentorial adult-type gliomas. Patients underwent surgery in the Department of Brain and Spinal Cord Tumor Surgery at the National Research Medical Centre of Almazov in the period from 2021 to 2024. Before being included in the study, informed consent was obtained from each of the participants. The exclusion criteria included diagnosis of immunodeficiency, autoimmune disease or neoplasms outside the central nervous system.

The study also excluded individuals who had previously undergone radiation therapy, chemotherapy, or immunotherapy. Each patient included in the research was assessed by a team of specialists: a general practitioner, otolaryngologist, dentist and neurologist. The presence of acute or chronic inflammatory conditions during the period of exacerbation, use of antibacterial agents and antibiotics at the time of enrolment and continued treatment with anticonvulsants were also considered disqualifying factors.

Venous blood samples were collected from patients three days prior to surgical intervention in the morning, followed by a comprehensive clinical haematological examination and the quantification of C-reactive protein (CRP). Patients with CRP levels above 5 ng/ml were excluded from the study cohort. Clinical haematological analysis, including extended leukocyte differentiation, was performed with the use of the Sysmex XN-550 haematological analyser, using Sysmex reagents and control materials sourced from Japan. Inflammatory markers, including the NLR, LMR and PLR, were calculated from absolute counts of lymphocytes, neutrophils, monocytes, and platelets to evaluate the systemic inflammation in neuro-oncologic diseases.

The study included only patients who underwent scheduled neurosurgical interventions. Histopathological diagnosis was made by analyzing surgical tumor samples according to standardized criteria described in the Fifth Edition of the World Health Organisation Central Nervous System Tumor Classification [3]. Histological sections were stained with haematoxylin and eosin, in addition to immunohistochemistry (IHC) panels including anti-GFAP (poly, DakoCytomation), anti-ATRX (Abcam), anti-EGFR (Abcam), anti-MGMT (NovusBiologics), anti-Ki-67 (Dako), anti-

IDH1R132H (Dianova), and for differential diagnosis Syn (DakoCytomation) and NB (Leica), CD99 (12E7, DakoCytomation). Fluorescence in situ hybridization (FISH) was used to assess for the presence of a 1p/19q codeletion. FISH was performed using two-color DNA probe test systems to detect deletions of the SRD (1p36) (Cytocell) and GLTSCR1 (19q13) (Fast Probe, Wuhan Healthcare) genes. Mutational analysis of the IDH1 (exon 4) and IDH2 (exon 4) genes was performed via high-resolution melting analysis (HRMA) of PCR products, followed by subsequent DNA sequencing to elucidate genetic alterations. The prepared specimens were viewed and evaluated by two independent pathologists. The final diagnosis was made by a multidisciplinary team including a pathologist, an oncologist, a neurosurgeon and a radiologist, based on the results of a molecular-histological conclusion of the biopsy material, taking into account the clinical course of the disease, the radiological appearance and the macroscopic intraoperative features of the tumor.

Statistical analysis was performed using thePrism GraphPad 10 program (GraphPad Software, USA). The normality test was performed using Kolmogorov–Smirnov, Shapiro–Wilk tests. We used the mean ± standard deviations for normally distributed data, and median (rank) for non-normally distributed data. Nonparametric group comparisons were conducted using the Mann–Whitney U test. The diagnostic accuracy of preoperative inflammatory markers was evaluated using ROC curve analysis, with AUC quantification. Statistical significance was set at $p<0.05$. The resulting graphs were performed using the Prism GraphPad 10 program (GraphPad Software, USA).

Results

Patients were stratified into three cohorts based on histopathological classification: grade 2 glioma (n=25, of them 7 with oligodendroglioma), IDH1 mutated grade 3 and 4 gliomas (n=25, of them 8 with oligodendroglioma), and glioblastoma (n=89) (Table 1).

The grade 2 glioma and grade 3 and 4 glioma (IDH1-mt) cohorts also included patients diagnosed with oligodendroglioma (7 and 8 patients, respectively). Notably, patients exhibiting IDH1-positive tumor status in grades 2, 3, and 4 glioma were significantly younger than those diagnosed with glioblastoma (Table 1). The mean age of patients with grade 2 glioma was 42.5 ± 12.5 years, comprising 14 (56 %) males and 11 (44 %) females. Conversely, the mean age of patients with 3 and 4 glioma (IDH1-mt) was 46 ± 11 years, with 7 males (28 %) and 18 females (72 %). In the glioblastoma cohort, the mean age was 60 ± 12.5 years, with 51 (57.31 %) males and 38 (42.69 %) females.

A significant proportion of patients diagnosed with grade 2 and grade 3 gliomas did not receive glucocorticoid therapy (dexamethasone) prior to surgery, with rates of 76 % and 56 %, respectively. In contrast, in the glioblastoma cohort, only 25.85 % of cases were not administered glucocorticoids, as shown in Table 1.

Comparison of preoperative inflammatory blood markers for glioma of different subtypes

There were no statistically significant differences observed in lymphocyte, platelet, or platelet-lymphocyte ratio (PLR) levels across the three studied cohorts (Fig. 1b, 1d, and 1g). Notably, the counts of neutrophils and monocytes in grade 2 glioma cohort

Table 1/Таблица 1

Preoperative characteristics of 139 patients with cerebral gliomas

Характеристики 139 пациентов с церебральными глиомами на дооперационном этапе лечения

Parameters/Параметры	Grade 2 glioma/ Глиома grade 2 (n=25)	Glioma grade 3, 4 IDH-mutant/ Глиома grade 3, 4 с мутацией IDH (n=25)	Glioblastoma/ Глиобластома (n=89)
Age, years/Возраст, лет	**42.5 ± 12.5[b]**	**46 ± 11[b]**	60 ± 12,5
Male/Муж	14 (56 %)	7 (28 %)	51 (57.31 %)
Female/Жен	11 (44 %)	18 (72 %)	38 (42.69 %)
Taking dexamethasone/Принимают дексаметазон			
Yes/Да	6 (24 %)	11 (44 %)	66 (74.15 %)
No/Нет	19 (76 %)	14 (56 %)	23 (25.85 %)
Laboratory dates/Лабораторные показатели			
Neutrophils/Нейтрофилы (×10⁹/L)	**4.01 (1.54–15.0)[b]**	5.30 (1.53–16.80)	7.42 (1.85–24)
Lymphocytes/Лимфоциты (×10⁹/L)	2.11 (1.20–4.0)	2.0 (1.01–2.7)	2.07 (0.66–4.82)
Monocytes/Моноциты (×10⁹/L)	**0.52 (0.2–1.50)[b]**	0.60 (0.01–2.1)	0.81 (0.2–2.0)
Platelets/Тромбоциты (×10⁹/L)	226 (158–401)	268 (108–408)	245 (117–487)
NLR	**1.96 (0.64–8.30)[b]**	2.0 (0.76–16.63)	2.9 (0.62–34.25)
LMR	**3.71 (2.4–9.230)[a–b]**	3.09 (0.99–8.33)	3.0 (0.53–8.48)
PLR	104 (49.58–199.2)	114 (70.13–348.5)	117 (32.05–358.9)

Notes: mt – mutant; [a] – *vs* grade 3,4 (IDH1-mt) ($p<0.05$); [b] – $p<0.05$ *vs* glioblastoma ($p<0.05$); created by the authors.

Примечания: mt – мутация; [a] – по сравнению с глиомами grade 3, 4 (IDH1-mt) ($p<0,05$); [b] – по сравнению с глиобластомами ($p<0,05$); таблица составлена авторами.

Table 2/Таблица 2

Preoperative inflammatory markers and dexamethasone intake in glioma patients

Предоперационные маркеры воспаления и прием дексаметазона у пациентов с глиомой

Parameters/ Параметры	Grade 2		Grade 3,4 (IDH-mt)		Glioblastoma/Глиобластома	
	Without dexamethasone/ Без дексаметазона (n=19)	With dexamethasone/ С дексаметазоном (n=6)	Without dexamethasone/ Без дексаметазона (n=14)	With dexamethasone/ С дексаметазоном (n=11)	Without dexamethasone/ Без дексаметазона (n=23)	With dexamethasone/ С дексаметазоном (n=66)
Neutrophils/ Нейтрофилы ($\times 10^9$/L)	3.43 (1.54–11.69)	5.20 (4.40–9.6)	**4.0 (1.53–5.52)**	**10.0 (3.05–16.80)[a]**	**3.70 (1.85–7.55)**	**8.0 (2.14–24)[b]**
Lymphocytes/ Лимфоциты ($\times 10^9$/L)	2.0 (1.20–3.25)	3.48 (2.06–4.0)	2.0 (1.20–2.5)	2.20 (1.01–2.7)	1.76 (1.10–4.70)	2.18 (0.66–4.82)
Monocytes/ Моноциты ($\times 10^9$/L)	0.50 (0.20–1.0)	0.57 (0.39–1.50)	0.52 (0.30–2.10)	0.72 (0.01–1.21)	**0.59 (0.20–1.0)**	**0.82 (0.23–2.0)[b]**
NLR	1.86 (0.64–3.56)	2.1 (1.37–2.59)	**1.86 (0.76–4)**	**5 (1.15–16.63)[a]**	**1.95 (0.62–5.0)**	**3.79 (0.80–34.35)[b]**
LMR	3.75 (2.4–9.23)	3.74 (2.47–8.33)	3.1 (0.99–6.67)	2.5 (1.0–4.58)	3.6 (1.3–8.2)	2.88 (0.53–8.48)

Notes: mt – mutant, [a] – *vs* glioma grade 3,4 (IDH1-mt) without dexamethasone ($p<0.05$); [b] – *vs* glioblastoma without dexamethasone ($p<0.05$); created by the authors.

Примечание: mt – мутация; [a] – по сравнению с глиомами grade 3,4 (IDH1-mt) без дексаметазона ($p<0,05$); [b] – по сравнению с глиобластомами ($p<0,05$); таблица составлена авторами.

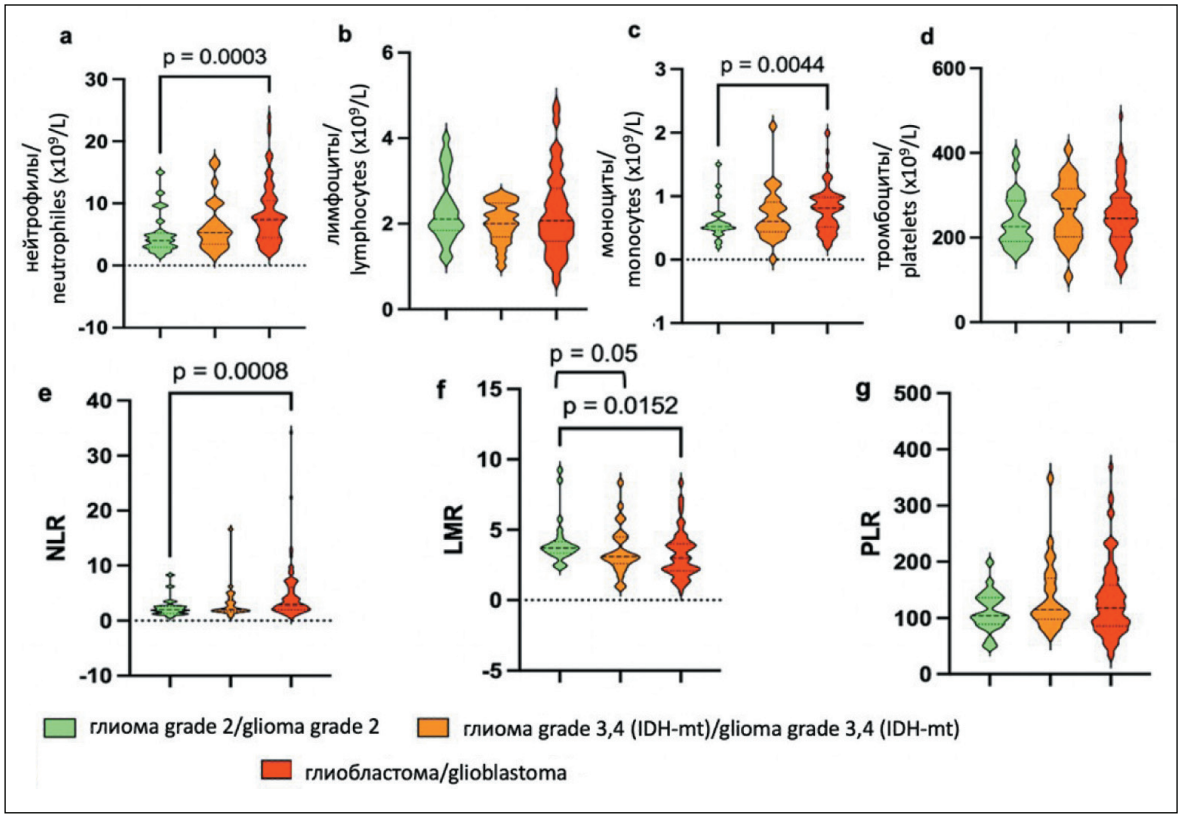

Fig. 1. Violin diagram illustrating the distribution of preoperative inflammatory marker levels in different grades of glioma groups. Notes: the central dashed line indicates the median value, while the flanking dashed lines demarcate the first and third quartiles; a – neutrophils, b – lymphocytes, c – monocytes, d – platelets, e – NLR, f – LMR; g – PLR; created by the authors

Рис. 1. Диаграмма, иллюстрирующая распределение предоперационных уровней маркеров воспаления в различных группах глиом grade 2, 3 и 4 (IDH1-mt) и глиобластом. Примечания: центральная пунктирная линия указывает на среднее значение, в то время как боковые пунктирные линии разграничивают первый и третий квартили; a – нейтрофилы, в – лимфоциты, c – моноциты, d – тромбоциты, e – NLR, f – LMR, g – PLR; рисунок выполнен авторами

[4.01 (1.54–15.0) and 0.52 (0.2–1.50), respectively] were significantly lower compared to those in the glioblastoma cohort [37.42 (1.85–24) and 0.81 (0.2–2.0), respectively] (Fig. 1a, 1c).

The analysis revealed that the NLR and LMR exhibited no significant differences between grade 3 and 4 glioma (IDH-mutant) and glioblastoma groups. Notably, the LMR was found to be significantly higher in the grade 2 glioma group with a mean value of 3.71 (range: 2.4–9.230) than in the grade 3 and 4 glioma (IDH-mutant) and glioblastoma groups (3.09, range: 0.99–8.33 and 3.0 (range: 0.53–8.48), respectively (Fig. 1f). Conversely, the highest NLR values were recorded in glioblastoma patients, with a mean of 2.9 (range: 0.62–34.25), demonstrated a statistically significant difference compared to the NLR in low-grade glioma patients, which was 1.96 (range: 0.64–8.30) (Fig. 1e).

The analysis of hematological parameters, specifically neutrophils, lymphocytes, monocytes, NLR and LMR, was conducted in relation to the administration of GCS prior to surgical intervention (Table 2). In patients receiving GCS, a statistically significant elevation in neutrophil counts was observed in the grade 3 and 4 glioma and glioblastoma cohorts (Fig. 2a). Furthermore, NLR values were markedly increased in patients with gliomas undergoing treatment with dexamethasone (Fig. 2d). The administration of dexamethasone was found to influence monocyte levels exclusively in the glioblastoma patient group (Fig. 2c). Notably, the LMR index exhibited no significant variation between patients receiving dexamethasone and those who were not across all three patient categories (Fig. 2e).

Diagnostic value of inflammatory blood markers in glioma diagnosis and glioma grading

According to the ROC analysis, two biomarkers showed significant diagnostic value: NLR and LMR (Fig. 3). The optimal ratio of sensitivity and specificity for the diagnosis of grade 2glioma compared to glioblastoma was observed for NLR value <2.5 (72.0 % and 61.3 %, respectively) and for LMR >3.57 (64 %

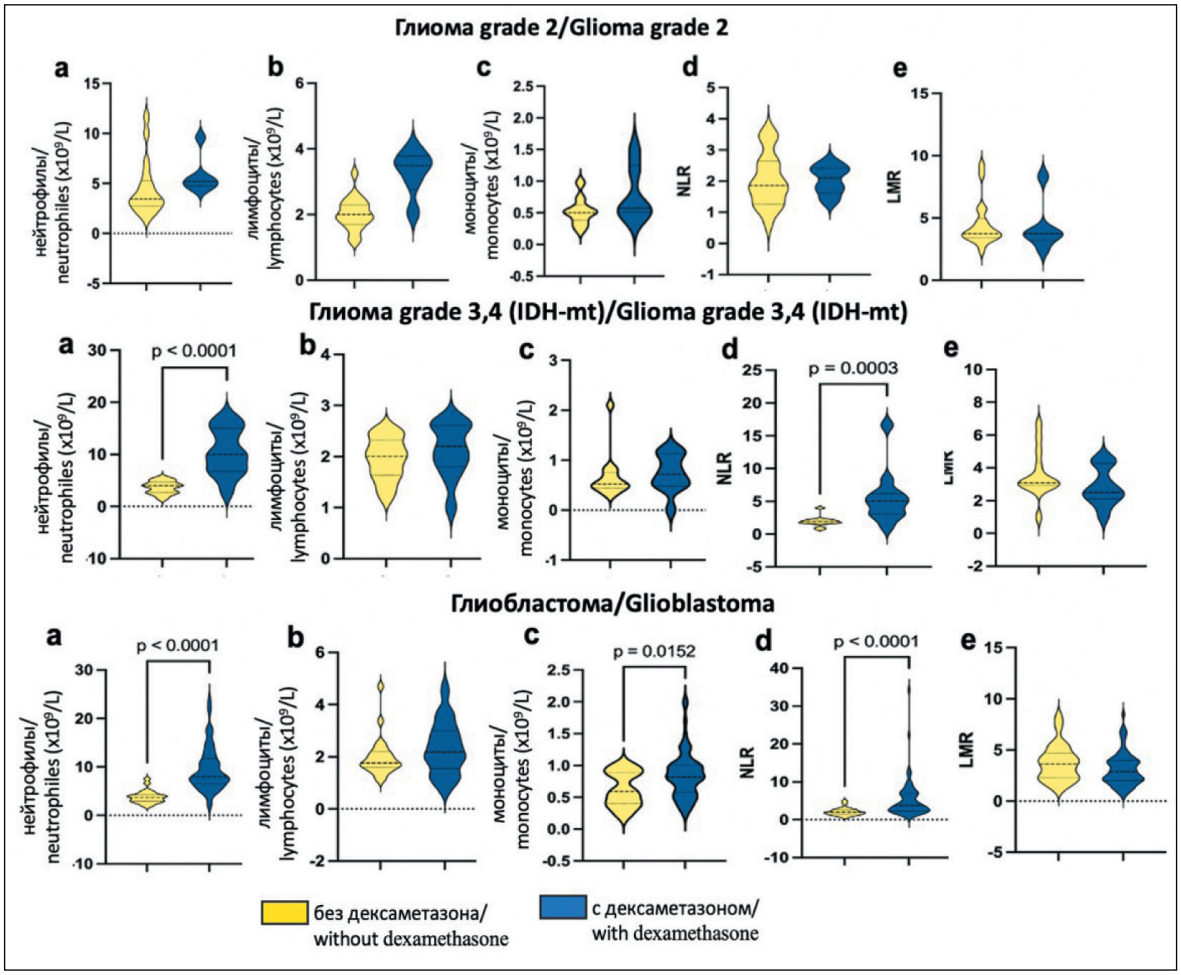

Fig. 2. Violin diagram comparing preoperative inflammatory marker levels across glioma grades, stratified by dexamethasone administration status. Notes: central lines represent medians, with outer boundaries indicating interquartile ranges; a – neutrophils, b – lymphocytes, c – monocytes, d – NLR, e – LMR; created by the authors

Рис. 2. Диаграмма, на которой сравниваются уровни дооперационных маркеров воспаления в зависимости от гистологического подтипа глиомы и приема дексаметазона. Примечания: центральные линии представляют медианы, внешние границы указывают на межквартильные интервалы; a – нейтрофилы, в – лимфоциты, c – моноциты, d – NLR, e – LMR; рисунок выполнен авторами

and 59 %, respectively). The area under the ROC curve (AUC) was 0.7157 (95 % CI: 0.6087–0.8227) for NLR and 0.6586 (95 % CI: 0.5583–0.7590) for LMR, which characterized the quality of the model as satisfactory (Table 3, Fig. 3). However, NLR values were influenced by the administration of GCS (Table 2), whereas LMR was unaffected by this therapeutic intervention, establishing LMR as a more robust independent marker. When differentiating the diagnosis of grade 2 glioma from more aggressive glial tumors (grade 3 and 4 with IDH1 mutation and glioblastoma), the optimal ratio of sensitivity and specificity (72 % and 58 %, respectively) was observed at LMR levels >3.4 (AUC 0.6579, 95 % CI: 0.5635–0.7522). In the differential diagnosis of grade 2 glioma from grade 3 and 4 glioma with IDH1 mutation, satisfactory sensitivity and specificity (72 % and 68 %, respectively) were also maintained at LMR > 3.4 (AUC 0.6552, 95 % CI: 0.4930–0.8174). The study showed that LMR, compared with other cellular biomarkers, has significant diagnostic value for patients diagnosed with low-grade glioma.

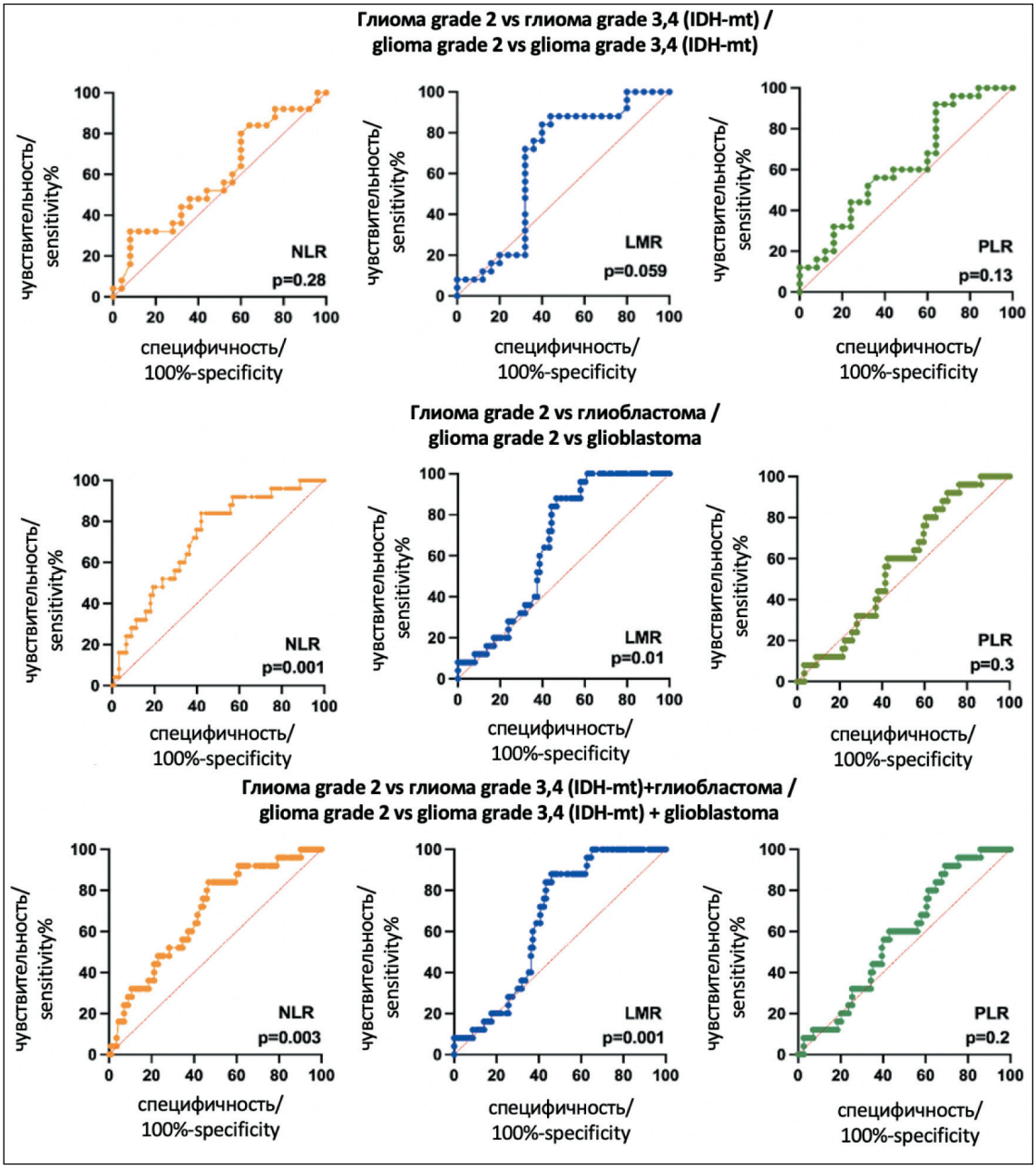

Fig. 3. The diagnostic value of preoperative inflammatory markers in glioma diagnosis. Grade 2 glioma *vs* grade 3 and 4 glioma (IDH-mt), grade 2 glioma *vs* glioblastoma, grade 2 glioma *vs* grade 3 and 4 glioma (IDH-mt) + glioblastoma.
Notes: created by the authors

Рис. 3. Диагностическая ценность предоперационных маркеров воспаления в диагностике глиомы. Глиомы grade 2 *vs* глиомы grade 3, 4 (IDH-mt); глиома grade 2 *vs* глиобластомы; глиома grade 2 *vs* глиомы grade 3, 4 (IDH-mt) + глиобластома.
Примечание: рисунок выполнен авторами

Table 3/Таблица 3

Diagnostic value of various inflammatory markers in glioma diagnosis

Диагностическая ценность различных маркеров воспаления в диагностике глиомы

Markers/ Маркеры	Grade 2 *vs* grade 3,4 (IDH-mt)		Grade 2 *vs* glioblastoma/ Grade 2 *vs* глиобластома		Grade 2 *vs* grade 3, 4 (IDH-mt) + glioblastoma/ Grade 2 *vs* grade 3, 4 (IDH-mt) + глиобластома	
	AUC (95 % CI)	p-value	AUC (95 % CI)	p-value	AUC (95 % CI)	p-value
NLR	0.5888 (0.4292–0.7484)	0.28	0.7157 (0.6087–0.8227)	0.001	0.6876 (0.5798–0.7954)	0.003
LMR	0.6552 (0.4930–0.8174)	0.059	0.6586 (0.5583–0.7590)	0.01	0.6579 (0.5635–0.7522)	0.001
PLR	0.6232 (0.4670–0.7794)	0.13	0.5676 (0.4546–0.6807)	0.30	0.5798 (0.4708–0.6888)	0.20

Notes: AUC – Area Under the ROC Curve; created by the authors.

Примечания: AUC – площадь под кривой ROC; таблица составлена авторами.

Table 4/Таблица 4

Preoperative LMR in glioma patients

Предоперационная LMR у пациентов с глиомой

Patients/Пациенты (n=139)	LMR	p-value
1p/19q-codeletion status/с коделецией 1p/19q		
Oligodendroglioma/Олигодендроглиома (n=15)	3.43 (0.99–6.67)	0.7690
Glioma without 1p/19q-codeletion / Глиома без коделеции 1p/19q (n=124)	3.19 (0.53–9.23)	
IDH1/2-mutation status/с мутацией IDH1/2		
Glioma grade 2, 3, 4 IDH-mt/ Глиома grade 2, 3, 4 IDH-mt (n=50)	3.44 (0.99–9.23)	0.0392
Glioblastoma IDH-wt/Глиобастома IDH-wt (n=89)	3.0 (0.53–8.48)	

Notes: wt – wild type, mt – mutant; created by the authors.

Примечания: wt – дикий тип, mt – мутация; таблица составлена авторами.

Comparison of LMR for glioma of different IDH1-mutation and 1p/19q-codeleted status

The LMR index was evaluated when all patients (n=139) were divided into groups depending on the presence of the IDH1 gene mutation and the presence of 1p/19q-codeletion (table 4). No significant differences in the value of LMR were found in the group of patients with oligodendroglioma and glioma without 1p/19q codeletion (Fig. 4a). However, in patients with glioma with a mutation in the IDH1 gene, the LMR value was significantly higher than in patients in the glioblastoma IDH-wt group (Fig. 4b).

The LMR was assessed in a cohort of 139 patients stratified based on the presence of the IDH1/2 mutation and the occurrence of 1p/19q codeletion (Table 4). No statistically significant differences in LMR values were observed between the oligodendroglioma and other glioma (without 1p/19q codeletion) patient groups (Fig. 4a). Conversely, patients harboring the IDH1/2 mutation exhibited a markedly elevated LMR compared to those with glioblastoma IDH-wildtype (Fig. 4b).

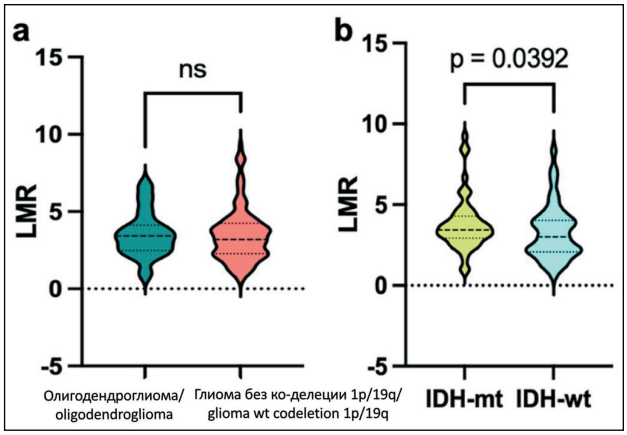

Fig. 4 Preoperative LMR in glioma patients. Violin diagram showing comparative results of LMR in oligodendroglioma vs glioma without codeletion 1p/19q (a); glioma IDH1/2-mt vs glioma IDH-wt (b). The dashed line in the middle represents the median and the dashed lines on both sides represent the interquartile range. Notes: wt – wild type, mt – mutant, ns – nonspecific; created by the authors

Рис. 4. Предоперационная LMR у пациентов с глиомой. Диаграмма, показывающая сравнительные результаты LMR при олигодендроглиоме и глиоме без кодирования 1p/19q (a); глиоме IDH1/2-mt и глиобластоме (b). Пунктирная линия посередине представляет собой медиану, а пунктирные линии с обеих сторон представляют межквартильный диапазон. Примечания: wt – дикий тип, mt – мутант, ns – неспецифический; рисунок выполнен авторами

Discussion

The hypothesis that there is a relationship between inflammatory responses and tumorigenesis was first proposed by Rudolf Virchow in the 19th century, who

elucidated the infiltration of leukocytes into neoplastic tissue [10, 11]. Recent decades have produced considerable evidence that inflammation is a key factor in the development and etiology of neoplastic diseases. Inflammatory processes are mediated by active involvement and regulation of immune cells, including neutrophils, lymphocytes and monocytes, in addition to platelets. Numerous studies have highlighted the important diagnostic and prognostic implications of these blood markers in different malignancies, in isolation or in combination [20–24].

The re-evaluation of immunological deficits associated with the central nervous system, together with the role of the immune system in tumorigenesis, has stimulated research into the inflammatory mechanisms underlying intracerebral neoplasms, in particular diffuse gliomas [13, 25–27]. At the same time, there has been a worldwide interest in the local immune microenvironment to understand its complexity and its implications for tumor behavior [13, 28, 29]. Recent research has shown that the tumor microenvironment in gliomas has features similar to chronic inflammation, suggesting that there is a significant interaction between tumor biology and the immune response [29–31].

Gliomas are known to express chemokines that facilitate the recruitment of immune cells that differentiate into tumor-associated macrophages, neutrophils, and myeloid suppressor cells, which are also affected by cytokines. These immune components contribute to tumorigenesis while simultaneously impairing the effector lymphocytes' ability to function. In view of these findings, it is reasonable to assume that systemic inflammatory markers such as NLR, LMR and PLR can serve as reliable and sensitive biomarkers for the diagnosis and prognostic evaluation of glioma.

Numerous clinical studies have been conducted to elucidate the diagnostic and prognostic relevance of NLR and LMR in glioma [14–18, 32–34]. In addition, consensus research has identified NLR as the most relevant and reliable biomarker in this context [14, 15, 17, 18, 34]. NLR serves as an indicator of both a non-specific neutrophil-mediated immune response and a specific adaptive immune response against cancer, mediated by lymphocytes. NLR has already been shown to be of diagnostic value in glioma patients compared to neoplasms such as meningioma, schwannoma and adenoma [17, 18, 35].

In preoperative diagnosis of gliomas of different grades of malignancy, a positive correlation has been established between NLR and tumor grade [14, 18, 34, 35]. However, these studies did not account for the administration of GCS by patients, despite evidence indicating that dexamethasone, commonly prescribed to reduce peritumoral edema, affects immune system functioning [36]. In our study, statistically significant differences in median NLR values were observed when comparing patient groups with grade 2 glioma and glioblastoma (1.96 *vs* 2.9; $p<0.05$) (Table 1, Fig. 1). However, it should be noted that in patients with glioblastoma, as well as in the group with grade 3 and 4 gliomas receiving GCS, there was an observed increase in neutrophils and NLR compared to patients who were not administered this therapy (8.0 *vs* 3.7, $p<0.05$; 3.79 *vs* 1.95, $p<0.05$; 10.0 *vs* 4.0, $p<0.05$; 5.0 *vs* 1.86, $p<0.05$, respectively) (Table 2, Fig. 2). The NLR median was almost identical for patients not receiving dexamethasone in the groups with grade 2, 3 and 4 glioma and glioblastoma (1.86 *vs* 1.86 *vs* 1.95; $p>0.05$). Therefore, our data show that NLR is a biomarker that is dependent on GCS, which significantly reduces its diagnostic value (Tables 1 and 3).

Currently, LMR is recognized as a biomarker for anti-cancer immunological activation in general oncology. The increase in its value is related either to the high number of effector lymphocytes, which leads to an adequate immune response, or to the reduction in monocytes. Monocytes play a dual role in the pathology of cancer. After differentiation, these cells can either play a protective function by helping to destroy the neoplasm or reprogramme themselves to support the growth of the tumor. Our data reveal no correlation between blood lymphocyte levels in patients and glioma grade (Table 1, Fig. 1, Table 3, Fig. 3). As expected, glucocorticoids were not found to affect lymphocyte levels ($p>0.05$) (Table 2, Fig. 2). However, absolute monocyte counts increased with tumor malignancy (0.52 *vs* 0.60 *vs* 0.81) (Table 1, Fig. 1, Table 3, Fig. 3). Statistical significance was reached only when comparing values for low-grade diffuse glioma (grade 2) and glioblastoma (0.52 *vs* 0.81; $p=0.0044$) (Table 1, Fig. 1). Notably, dexamethasone increased monocytes, but only in the glioblastoma patient's group (0.59 *vs* 0.82; $p=0.0152$) (Table 3, Fig. 3).

The relevance of LMR in glioma patients remains controversial in the neurooncology community. Although some studies have questioned its predictive effects, others have demonstrated its relevance [15, 17, 18, 33, 35]. A key observation is that many studies evaluating LMR did not stratify patients with glioma by histological subtype or grade of malignancy or considered the effect of dexamethasone. Our previous cohort study in glioblastoma patients identified LMR as a key biomarker predictive of the risk of early relapse, independent of dexamethasone therapy [19]. This analysis revealed a correlation between increasing grade and decreasing LMR. In particular, the median LMR for grade 2 glioma was 3.71, while for grade 3 and 4 gliomas, the median LMR was 3.09, and for glioblastoma patients, it was 3.05 ($p<0.05$). It should be noted that LMR levels remained unchanged with corticosteroid treatment in all patient groups.

The findings suggest that there is no correlation between the number of lymphocytes and tumor malignancy; however, there is a correlation with increased monocytes. This suggests that the LMR is primarily driven by absolute monocyte counts. Notably, in the glioblastoma cohort, monocytes were significantly increased in patients receiving corticosteroids, although

the LMR was not affected. These results highlight the complex mechanisms and interactions between the immune cell populations and support the use of composite biomarkers for diagnostic evaluation rather than relying on absolute monocytes and lymphocytes alone.

In addition, the LMR was assessed in cohorts of patients stratified by presence or absence of IDH/2 gene mutations and 1p/19q codeletion (Table 4, Fig. 4). According to the fifth edition of the WHO classification system, these genetic alterations are critical to the definitive histological diagnosis. No statistically significant differences in LMR values were observed between patients with and without oligodendroglioma (3.43 *vs* 3.19; p=0.76). Conversely, in a cohort of patients without IDH1 and IDH2 mutations, LMR was found to be significantly lower (3.44 *vs* 3.0; p=0.039). These findings highlight the differential immune responses associated with low-grade and high-grade gliomas. In neurooncology, it has been well documented that platelets activate neoplastic cells through cytokine signaling, which is important for thrombosis, angiogenesis, cell migration and dissemination of cancer.

In addition, platelets contribute to evasion of immunological surveillance and are involved in inflammatory responses [37]. Consequently, the presence of thrombosis and increased platelet counts in patients with oncological diseases correlate with poor prognosis. However, the specific role of platelets in glioma progression and clinical course remains unclear. Our findings suggest that there is no significant correlation between the number of platelets and the histological grade of gliomas (226 *vs* 268 *vs* 245; p>0.05) (Table 1, Fig. 1).

The PLR Inflammatory Index is recognized as a reliable independent biomarker indicating the progression of cancer. Its diagnostic and prognostic usefulness has been demonstrated in various malignancies, including esophageal and gastric cancer, lung cancer and colorectal cancer [20, 23, 24, 37]. In a previous study involving a cohort of patients with glioblastoma, PLR was shown to be of significant prognostic importance [19]. However, its diagnostic effectiveness in distinguishing gliomas of different malignancies is still limited. Although an increasing trend in PLR values was observed with increasing grade of glioma, statistical significance was not reached (104 *vs* 114 *vs* 117; p>0.05) (Table 1, Fig. 1).

Conclusion

The immune system plays a dual role in tumorigenesis: it can prevent cancer through antitumor functions, and it can also promote tumor growth. Inflammatory cell markers are key agents in these mechanisms and their prognostic and diagnostic relevance warrants investigation. Our results suggest that LMR is an additional potential diagnostic marker in glioma patients regardless of corticosteroid therapy. Of course, it seems incorrect to make a preliminary diagnosis based on LMR alone, but this biomarker may be an additional tool in the pre-operative differential diagnosis. NLR is correlated to corticosteroid use, thereby reducing its diagnostic utility. In addition, the PLR showed no significant correlation with the grade of malignancy. Thus, the increased LMR levels observed in low-grade gliomas, as opposed to malignant gliomas, indicate increased activation of the immune response. This may explain the favorable and prolonged clinical course often observed with low-grade diffuse glioma, which may reflect underlying immunological mechanisms, and require further investigation.

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Поступила/Received 23.06.2025
Одобрена после рецензирования/Revised 03.10.2025
Принята к публикации/Accepted 16.10.2025

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Konstantin. A. Samochernykh: making critical comments, final approval of the manuscript version.
All authors approved the final version of the manuscript prior to publication and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

Funding
This study required no funding.
Conflict of interests
The authors declare that they have no conflict of interest.
Compliance with Ethical Standards
The study was conducted in accordance with ethical principles outlined in the Declaration of Helsinki approved by Ethics Committee of Almazov National Medical Research (2, Akkuratova St., Saint Petersburg, 197341, Russia), protocol No. 3-21 dated March 10, 2021.
Voluntary informed consent
Written informed voluntaries consents were obtained from the patients for the publication of data in medical journal.

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ВКЛАД АВТОРОВ

Скляр Софья Сергеевна: разработка концепции и планирование научной работы, сбор данных, интерпретация полученных результатов, написание черновика статьи.
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Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью и добросовестностью любой части работы.

Финансирование
Это исследование не потребовало дополнительного финансирования.

Конфликт интересов
Авторы заявляют об отсутствии конфликта интересов.

Соответствие принципам этики
Проведенное исследование соответствует стандартам Хельсинкской декларации, одобрено независимым этическим комитетом Национального медицинского исследовательского центра им. В.А. Алмазова (Россия, 197341, г. Санкт-Петербург, ул. Аккуратова, 2), протокол № 3-21 от 10.03.21.

Информированное согласие
Все пациенты подписали письменное информированное согласие на публикацию данных в медицинском журнале, включая его электронную версию.