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Research Article

Optimizing Patient Selection for Bevacizumab Plus Irinotecan in Recurrent High Grade Glioma: Superiority of the Neutrophil-to-Lymphocyte Ratio Over Other Systemic Inflammation Indices

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Abstract

Objectives: Recurrent high-grade gliomas (rHGG) pose a significant challenge with poor prognosis. While bevacizumab plus irinotecan (BEV+IRI) is a frequent salvage regimen, clinical outcomes exhibit substantial inter-patient heterogeneity. Therefore, accessible prognostic biomarkers are needed to identify patients most likely to benefit.

Methods: This retrospective, single-center study enrolled adults with recurrent WHO grade 3–4 gliomas treated with BEV+IRI. Pre-treatment laboratory data were used to calculate Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), Systemic Immune-Inflammation Index (SII), Pan-Immune-Inflammation Value (PIV), and hemoglobin, albumin, lymphocyte, platelet (HALP) scores. Optimal cut-offs were determined via receiver operating characteristics (ROC) analysis. Survival was analyzed using Kaplan-Meier and Cox regression models.

Results: In 43 patients, median overall survival (OS) was 9.6 months; median progression free survival (PFS) was 5.8 months. Patients with high pre-treatment NLR (≥6.74) had significantly shorter OS (4.4 vs. 11.4 months; p<0.001). Multivariate analysis confirmed high NLR as a strong independent risk factor for mortality (HR: 9.31, 95% CI: 3.18–27.28; p<0.001). Conversely, PIV, SII, PLR, and HALP scores showed no prognostic significance. While generally tolerable, the regimen caused vascular events in 14%.

Conclusion: Among various inflammation indices, pre-treatment NLR emerged as a consistent and clinically relevant prognostic biomarker in rHGG patients treated with BEV+IRI. NLR-based stratification could optimize patient selection and reduce unnecessary toxicity.

Keywords: Bevacizumab-Irinotecan, Neutrophil-to-Lymphocyte Ratio, Recurrent Gliomas

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Gliomas represent the most prevalent primary malignant brain tumors in adults, constituting a group of neoplasms characterized by marked histopathological and molecular heterogeneity. According to the current 2021 WHO classification, High Grade Gliomas (HGG) encompass isocitrate dehydrogenase (IDH) wild type glioblastoma (grade 4), IDH mutant grade 3 and 4 astrocytoma, and IDH mutant 1p/19q-codeleted grade 3 oligodendroglioma.[1] Despite distinct histological and molecular subtypes, this group of tumors shares a common clinical trajectory defined by diffuse infiltration, high recurrence rates, and a therapy-resistant, aggressive nature. Within this spectrum, oligodendrogliomas, despite an initially more indolent course driven by IDH mutation and 1p/19q codeletion, can eventually undergo malignant transformation (anaplastic conversion), evolving into an aggressive phenotype.[2] Regardless of the specific histological subtype, all such HGG at the recurrent stage exhibit shared biological features, including diffuse infiltration, intense neovascularization, and resistance to treatment. Glioblastoma multiforme (GBM), beyond being the most frequent primary brain tumor in adults, is a notoriously aggressive malignancy where recurrence is inevitable despite standard multimodal therapies comprising maximal surgical resection, radiotherapy, and temozolomide.[3] Following recurrence, therapeutic options are limited, and the prognosis is unfortunately grim. In this setting, the combination of BEV+IRI is a frequently utilized salvage regimen, largely due to the high radiological response rates observed in early-phase trials.[4,5] However, recent large-scale data have cast doubt on whether the addition of irinotecan confers a clear survival advantage, highlighting significant heterogeneity in treatment responses.[6] Consequently, predicting which patients will genuinely benefit from this potentially toxic combination remains one of the most critical unmet needs in clinical practice.

It is well established that the inflammatory response significantly shapes the tumor microenvironment and contributes to treatment resistance.[7] Based on this pathophysiological premise, readily available parameters such as the NLR have been shown to correlate with survival in this patient cohort.[8] Similarly, the HALP score, which incorporates nutritional status, has recently been reported to hold prognostic significance in GBM patients.[9]

A primary limitation of the current literature, however, is that standard indices often reflect only a subset of the inflammatory cell population. For instance, the NLR fails to account for platelets and, more critically, monocytes, both of which play pivotal roles in tumor progression and immunosuppression. In GBM pathophysiology, circulating monocytes are recruited to the tumor site where they differentiate into Tumor-Associated Macrophages (TAMs); constituting 30-50% of the total tumor mass, these cells orchestrate an immunosuppressive microenvironment and drive angiogenesis.[10] Similarly, neutrophils are not merely passive indicators of inflammation; they actively facilitate tumor cell migration and blood-brain barrier disruption through the release of Neutrophil Extracellular Traps (NETs).[11] Furthermore, platelets support tumor growth by secreting vascular endothelial growth factor (VEGF) and platelet drived growth factor, while simultaneously shielding circulating tumor cells from immune destruction.[12] Accordingly, in the context of recurrent GBM, a malignancy characterized by heterogeneity, intense vascularization, and an immunologically 'cold' phenotype, a more comprehensive evaluation incorporating all these hematological lineages is warranted.

In this context, the PIV offers a more holistic overview by integrating neutrophil, platelet, monocyte, and lymphocyte counts into a single comprehensive metric.[13] In recent years, easily calculable peripheral blood indices such as the NLR, PLR, and PIV have demonstrated prognostic utility across a variety of solid tumors.[14] Therefore, the primary objective of this study was to compare the prognostic power of these distinct inflammatory indices in patients with rHGG receiving BEV+IRI, while simultaneously delineating the real-world toxicity profile of this regimen.

Methods

This retrospective study enrolled adult patients diagnosed with rHGG who were followed at our clinic and treated with a salvage regimen of BEV+IRI between January 2017 and February 2022. The study cohort comprised patients with histopathologically confirmed WHO grade 3 or 4 gliomas who experienced radiological or histopathological recurrence or progression following adjuvant therapies (radiotherapy, chemotherapy, or chemoradiotherapy) or follow-ups. Inclusion criteria were defined as follows: an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2 at the initiation of treatment, age ≥18 years, and the availability of complete baseline complete blood count (CBC) and serum albumin data in medical records. Conversely, patients with a history of a second primary malignancy, those with active infections or autoimmune diseases capable of confounding inflammatory indices, and patients with inaccessible follow-up data were excluded from the study.

Patients were administered intravenous bevacizumab (10 mg/kg) and irinotecan (125 mg/m^2) on days 1 and 15 of a 28-day cycle. The irinotecan dosage was adjusted based on the patients' concomitant use of enzyme-inducing versus non-enzyme-inducing antiepileptic drugs. Treatment response was assessed via cranial magnetic resonance imag-

ing (MRI) performed every 2 to 3 cycles, while toxicity was graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 5.0.[15]

Demographic characteristics, ECOG performance scores, molecular markers (specifically IDH mutation status), comorbidities, history of prior treatments (including radiotherapy and adjuvant therapies), and pre-treatment hemogram parameters were extracted from the hospital's electronic medical records. Inflammatory and nutritional indices were calculated using baseline neutrophil, lymphocyte, monocyte, and platelet counts (x 10^9/L), as well as hemoglobin (g/dL) and albumin (g/dL) levels obtained within the two weeks prior to BEV+IRI administration, according to the following formulas:

- **NLR (Neutrophil-to-lymphocyte ratio):** Absolute Neutrophil Count / Absolute Lymphocyte Count
- **PLR (Platelet-to-lymphocyte ratio):** Platelet Count / Absolute Lymphocyte Count
- **SII (Systemic immune-inflammation index):** (Absolute Neutrophil Count x Platelet Count) / Absolute Lymphocyte Count
- **PIV (Pan-immune-inflammation value):** (Absolute Neutrophil Count x Platelet Count x Absolute Monocyte Count) / Absolute Lymphocyte Count
- **HALP score:** (Hemoglobin x Albumin x Absolute Lymphocyte Count) / Platelet Count

Crucially, these samples were drawn at the time of recurrence documentation, prior to the initiation of corticosteroids for symptomatic brain edema, ensuring that the indices reflect a pre-steroid baseline.

Statistical Analysis

Statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) version 26.0 (IBM Corp., Armonk, NY, USA) and Python (SciPy library). The normality of continuous variables was assessed using the Shapiro-Wilk test; normally distributed data were expressed as mean ± standard deviation, while non-normally distributed data were presented as median (minimum-maximum). Categorical variables were summarized as frequencies (n) and percentages (%). For survival analyses, the primary endpoint was defined as OS, calculated from the initiation of BEV+IRI therapy to the date of death or last follow-up. The secondary endpoint was PFS, defined as the time from treatment initiation to disease progression or, in the absence of progression, the last follow-up. The optimal cut-off values for inflammatory indices (NLR, PLR, PIV, HALP, SII) in predicting survival were determined via ROC curve analysis and the Youden Index (Sensitivity + Specificity - 1). Survival curves were estimated using the Kaplan-Meier method, and differences between groups were compared using the Log-rank test. Univariate and multivariate Cox proportional hazards regression models were employed to identify independent prognostic factors. A p value of <0.05 was considered statistically significant.

Ethical Statement

Our study was conducted under the institutional research committee's ethical standards and with the 1964 Helsinki Declaration. This study was approved by the clinical research ethics committee of the Bursa Uludag University, Faculty of Medicine (Decision No: 2022-5/25, dated March 2, 2022).

Results

The study cohort comprised 43 patients diagnosed with rHGG who received combination therapy with BEV+IRI. Analysis of histopathological subtypes at initial diagnosis revealed that 24 (55.8%) of the patients had GBM, 13 (30.3%) had oligodendroglioma, 5 (11.6%) had anaplastic astrocytoma, and 1 (2.3%) had gliosarcoma. The median age of the cohort was 54 years (range: 21–82), and 28 (65.1%) were male. Regarding performance status at the time of recurrence, the majority of patients (n=30, 69.8%) had an ECOG score of 1, and 28 (65.1%) received this regimen as their first-line treatment for recurrence (first recurrence). In terms of tumor localization, the frontal and temporal lobes were the most frequently involved sites, affecting 12 patients (27.9%) each, followed by the parietal lobe in 10 patients (23.2%) and the occipital lobe in 3 patients (7.0%). Multifocal or other localizations were detected in 6 cases (14.0%). Regarding molecular characteristics, IDH mutation was positive in 14 patients (32.6%) and wild type in 11 patients (25.5%), while the mutation status was unknown for 18 patients (41.9%). The median Ki-67 proliferation index was determined to be 30% (range: 5–80%). A total of 34 patients (79%) had previously received adjuvant temozolomide therapy, with a median duration of 6 cycles (range: 1–8). Following disease progression under BEV+IRI therapy, 37 of the 43 patients (86%) received no further treatment, while 3 patients (7%) received carmustine chemotherapy, and 3 patients (7%) underwent palliative stereotactic body radiation therapy (SBRT). Although 74.4% (n=32) of patients received concomitant corticosteroids (dexamethasone) at treatment initiation, baseline blood samples used for inflammatory index calculations were obtained prior to the initiation of steroid therapy, as specified in the methods section. Regarding baseline inflammatory indices, the median NLR was calculated as 3.15, and the median PIV was 279 (Table 1).

Table 1. Demographic and clinical characteristics of patients

Characteristic	Number of patients (n)	Percentage (%)
Age (median, min-max)	54.0 (21.0 - 82.0)	
Sex		
Male	28	65.1
Female	15	34.9
ECOG performance score (At relaps)		
0	10	23.2
1	30	69.8
2	3	7.0
Ki-67, % (median, min-max)	30 (5.0 – 80.0)	
Pathological subtype (at diagnosis)		
Anaplastic astrocytoma	5	11.6
Oligodendroglioma	13	30.3
GBM	24	55.8
Gliosarcoma	1	2.3
Tumor localization		
Frontal lobe	12	27.9
Temporal lobe	12	27.9
Parietal lobe	10	23.2
Occipital lobe	3	7.0
Other/Multifocal	6	14
IDH mutation status		
Wild-type	11	25.5
Mutant	14	32.6
Unknown	18	41.9
Adjuvant treatment		
Std. stupp protocol	31	72.1
RT only	2	4.6
RT + TMZ	3	7
Follow-up	7	16.3
Line of bevacizumab plus irinotecan treatment		
First recurrence (1st Salvage)	28	65.1
Second recurrence (2nd Salvage)	15	34.9
Concomitant corticosteroid use		
Yes (Dexamethasone)	32	74.4
No	11	25.6

n: Number of patients; min-max: Minimum-maximum; ECOG: Eastern Cooperative Oncology Group; IDH: Isocitrate dehydrogenase; RT: Radiotherapy; TMZ: Temozolomide; GBM: Glioblastoma Multiforme.

By the end of the mean follow-up period, death had occurred in 76.7% (n=33) of the patients. Kaplan-Meier analysis for the entire cohort revealed a median OS of 9.6 months and a median PFS of 5.8 months (Fig. 1a, 1b). In the survival analysis stratified by the determined cut-off value, patients with a high pre-treatment NLR (≥6.74) had a median OS of 4.4 months, whereas those with a low NLR (<6.74) achieved a median OS of 11.4 months. This difference between the groups was statistically highly significant (Log-rank p<0.001, Fig. 1c). Conversely, stratification based on the PIV score yielded no significant difference in survival between the groups (p=0.356, Fig. 1d).

Receiver operating characteristic curve analysis, conducted to evaluate the success of inflammatory indices in predicting survival, demonstrated that only NLR exhibited statistically significant performance (Fig. 2). The optimal cut-off value for NLR in predicting OS was determined to be 6.74 (AUC: 0.576); the "High NLR" group above this threshold showed a specificity of 100% for predicting mortality. In contrast, no significant prognostic threshold values could be established for the PIV, HALP, SII, and PLR indices (Table 2).

In the univariate Cox regression analysis evaluating factors affecting OS, high NLR (≥6.74) was found to significantly increase the risk of death by 5.04-fold (95% CI 2.11–12.05, p<0.001). A total of 33 death events occurred during the follow-up period. In the multivariate analysis, which was parsimoniously constructed using only three variables

Table 2. Hematological parameters and systemic inflammatory indices at diagnosis

Parameter / index	Median (min-max)
Hematological parameters	
Neutrophils (10^3/μL)	4.86 (1.50-12.85)
Lymphocytes (10^3/μL)	1.46 (0.33-10.00)
Monocytes (10^3/μL)	0.52 (0.16-1.25)
Thrombocytes (10^3/μL)	187 (52-379)
Hemoglobin (g/dL)	13.3 (10.2-16.2)
Albumin (g/dL)	4.1 (3.0-5.1)
Inflammatory indices	
NLR	3.15 (0.30-20.45)
PLR	147 (23-489)
SII	598 (70-5331)
PIV	279 (38-3710)
HALP	0.39 (0.09-4.57)

NLR: Neutrophil-to-Lymphocyte Ratio; PLR: Platelet-to-Lymphocyte Ratio; SII: Systemic Immune-Inflammation Index; PIV: Pan-Immune-Inflammation Value; HALP: Hemoglobin, Albumin, Lymphocyte, and Platelet score; μL: microliter; g/dL: Gram per desiliter.

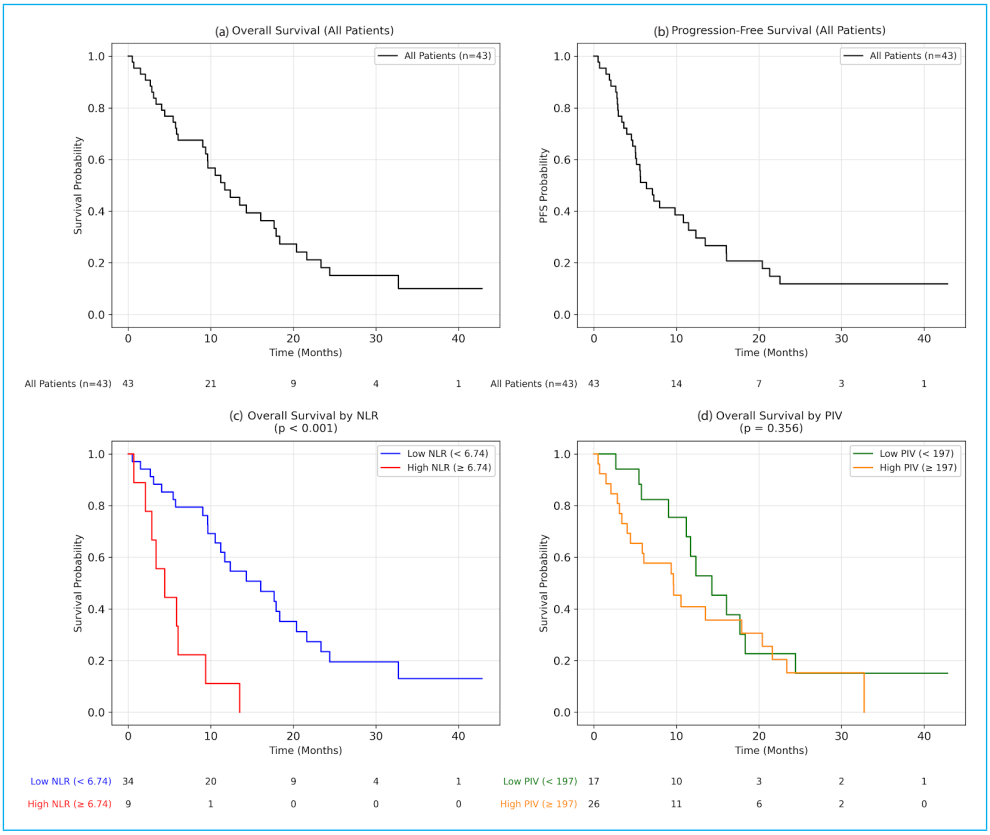

Figure 1. Kaplan-Meier estimates of overall survival (OS) and progression-free survival (PFS) in patients with recurrent high grade gliomas treated with bevacizumab plus irinotecan. **(a)** Overall survival curve for the entire study cohort (n=43), showing a median OS of 9.6 months. **(b)** Progression-free survival curve for the entire cohort, with a median PFS of 5.8 months. **(c)** Overall survival stratified by the pretreatment Neutrophil-to-Lymphocyte Ratio (NLR). Patients with a high NLR ≥6.74) had significantly shorter survival compared to those with a low NLR (<6.74) (Median OS: 4.4 vs. 11.4 months, Log-rank p<0.001). **(d)** Overall survival stratified by the Pan-Immune-Inflammation Value (PIV). No statistically significant difference was observed between high and low PIV groups (Log-rank p=0.356). The number of patients at risk for each 10-month interval is provided in the tables below the X-axes for all panels.

(Age, ECOG performance score, and NLR) to ensure model stability, the prognostic power of NLR remained highly significant (HR: 9.31, 95% CI: 3.18–27.28, p<0.001). Furthermore, the multivariate model indicated that advanced age also independently increased the mortality risk (HR: 1.04, 95% CI 1.01- 1.07, p=0.011) (Table 3).

The BEV+IRI regimen demonstrated a generally tolerable safety profile, with no treatment-related toxic deaths (grade 5) recorded. Among hematological toxicities, neutropenia was the most common (34.9%), yet the rate of grade 3-4 neutropenia remained limited to 4.7%. Regarding non-hematological adverse events, nausea (72.1%) and vomiting (55.8%) were most frequently observed, and there were no unmanageable side effects (Table 4).

A notable finding during the treatment course was the occurrence of vascular/thromboembolic events in 14.0% (n=6) of the patients. Detailed analysis of these cases revealed that 5 patients developed ischemic cerebrovascular accidents (CVA) and 1 patient developed pulmonary embolism (PE). Regarding bevacizumab-related bleeding complications, intracranial or systemic hemorrhage was observed in 4.7% (n=2) of patients, but these events were not life-threatening. The incidence of hypertension was recorded as 14.0%, and no patient exhibited severe hypertension (grade 3-4) requiring treatment discontinuation (Table 5). An exploratory comparison between patients who developed vascular events (n=6) and those who did not (n=37) showed no significant difference in median age (49.5 vs. 56.0 years; p=0.410) or bevacizumab exposure (median cycles: 6 vs. 5; p=0.711). Baseline cardiovascular comorbidity was not more frequent among event cases (16.7% vs. 29.7%; p=0.659). Given the limited number of events, these analyses were descriptive and multivariable modeling was not feasible.

Table 3. Prognostic performance of inflammatory and nutritional indices

Index	Median (min - maks)	Optimal Cut-off	AUC (%95 CI)	Sensitivity	Spesifity	p (Log-Rank)
NLR	3.15 (0.30 - 20.45)	≥ 6.74	0.576	%27.3	%100	<0.001*
PIV	279 (38 - 3710)	≥ 197.28	0.536	%81.8	%30.0	0.356
HALP	0.39 (0.09 - 4.57)	0.4	0.603	%51.5	%70.0	0.125
PLR	147 (23 - 489)	150	0.615	%48.5	%80.0	0.341
SII	598 (70 - 5331)	312.54	0.527	%24.2	%90.0	0.806

AUC: Area Under the Curve; HR: Hazard Ratio; CI: Confidence Interval; OS: Overall Survival; NLR: Neutrophil-to-Lymphocyte Ratio; PLR: Platelet-to-Lymphocyte Ratio; SII: Systemic Immune-Inflammation Index; PIV: Pan-Immune-Inflammation Value; HALP: Hemoglobin, Albumin, Lymphocyte, and Platelet score.

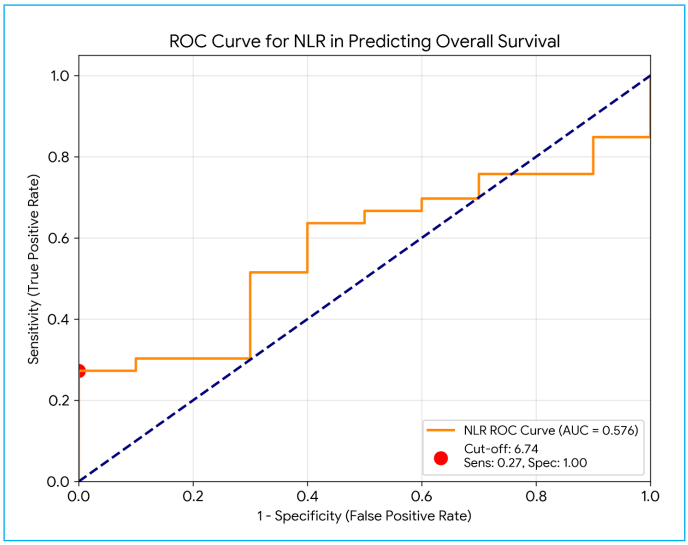

Figure 2. Receiver Operating Characteristic (ROC) curve analysis for the Neutrophil-to-Lymphocyte Ratio (NLR) in predicting overall survival. The analysis identified an optimal NLR cut-off value of 6.74 with an Area Under the Curve (AUC) of 0.576. While the sensitivity was 27.3%, this cut-off point demonstrated a 100% specificity for predicting mortality, indicating that NLR levels above this threshold are strongly associated with poor prognosis in the study population.

Table 4. Univariate and multivariate cox proportional hazards regression analysis for overall survival

Variables	Univariate analysis		Multivariate analysis	
	HR (%95 CI)	p	HR (%95 CI)	p
Age	1.02 (0.99-1.05)	0.156	1.04 (1.01-1.07)	0.011
Sex (Male vs. Female)	1.10 (0.52-2.32)	0.8	-	-
ECOG Performance Score (>0 vs 0)	1.49 (0.61-3.62)	0.38	0.74 (0.28-1.98)	0.548
Treatment Line (≥2. relapse vs. 1. relapse)	0.67 (0.32-1.39)	0.284	-	-
NLR (high ≥ 6.74 vs. low)	5.04 (2.11-12.05)	<0.001*	9.31 (3.18-27.28)	<0.001

HR: Hazard Ratio; CI: Confidence Interval; p: p-value; ECOG: Eastern Cooperative Oncology Group; NLR: Neutrophil-to-Lymphocyte Ratio. Total number of patients: 43, Total number of events (deaths): 33. To avoid overfitting, only variables with clinical significance (Age and ECOG) were included alongside NLR in the multivariate model, maintaining a ratio of 11 events per variable.

Discussion

In this study, we evaluated the prognostic value of pre-treatment systemic inflammatory indices and the safety profile of the regimen in patients with rHGG receiving BEV+IRI combination therapy. The most striking finding of our study is that the NLR, a simple and readily available marker, showed a more prominent association with OS compared to other systemic inflammation indices (PIV, SII, HALP) in our cohort. In our multivariate analysis, an NLR ≥6.74 emerged as the most potent prognostic factor, increasing the risk of death by 9.31-fold (p<0.001), independent of age and performance status.

In terms of clinical efficacy, the median OS and median PFS in our study were found to be 9.6 months and 5.8 months, respectively. These results are largely consistent with the landmark studies establishing the efficacy of bevacizumab in the treatment of rHGG. In the BRAIN study conducted by Friedman et al.[5], which formed the basis for FDA approval and included only recurrent GBM patients, the median OS and PFS for the BEV+IRI arm were reported as 9.2 months and 5.6 months, respectively. Similarly, Vredenburgh et al.[4], in a study involving patients with malignant glioma, reported a median OS of approximately 10 months. The heterogeneous nature of our cohort (inclusion of both grade 3 and 4 tumors) allows our study to better reflect real-world data. Although similar survival times were observed in the recently published study by Akbas et al. [16], which compared agents combined with bevacizumab (Temozolomide vs. Irinotecan), the prognostic power of inflammatory markers was not evaluated in that study. Our data reveal that the efficacy of the BEV+IRI regimen

Table 5. Toxicity profile of bevacizumab plus irinotecan regimen

Adverse event	All grades (n, %)	Grade 3-4 (n, %)
Hematological toxicity		
Neutropenia	15 (34.9)	2 (4.7)
Trombocytopenia	11 (25.6)	1 (2.3)
Anemia	11 (25.6)	1 (2.3)
Febrile neutropenia*	9 (20.9)	0 (0.0)
Non-hematological toxicity		
Nausea	31 (72.1)	1 (2.3)
Vomiting	24 (55.8)	1 (2.3)
Diarrhea	13 (30.2)	3 (7.0)
Hypertension	6 (14.0)	0 (0.0)
Intracranial/ Systemic bleeding	2 (4.7)	-
TE events (CVA and PE)	6 (14.0)	-

n: Number of patients; %: Percentage; TE: Thromboembolism; PE: Pulmonary Embolism; CVA: Cerebrovascular Accident (Ischemic Stroke).

exhibits dramatic inter-patient variations (low NLR: 11.4 months vs. high NLR: 4.4 months), thereby demonstrating that inflammation-based patient selection is essential rather than a 'one-size-fits-all' approach. Various studies exist in the literature regarding the prognostic role of NLR in gliomas. Haksoyler et al.[8] reported that an NLR value > 4.0 was associated with poor prognosis in recurrent GBM patients. While corroborating this finding, our study demonstrated that the prognostic power of NLR is even more pronounced specifically in patients receiving BEV+IRI, with a higher cut-off value (6.74) and a significantly higher hazard ratio (HR: 9.31). A comprehensive analysis by Cavdar et al.[17] in advanced NSCLC patients evaluated multiple inflammatory and laboratory-based indices simultaneously, including NLR, SII, HALP, advanced lung cancer index (ALI), and sodium–globulin ratio (SGR), and demonstrated that NLR retained independent prognostic significance in multivariate models. Similar to their findings, we observed that among several evaluated inflammatory markers, NLR showed the most consistent prognostic association with overall survival. However, unlike NSCLC cohorts where larger patient numbers allow for more complex multivariate modeling and subgroup analyses, our study population was smaller and disease-specific (recurrent high-grade gliomas), which may explain differences in the independent prognostic performance of composite indices. Although GBM and anaplastic oligodendrogliomas have distinct molecular drivers, they converge on a common phenotype of intense angiogenesis at recurrence. Our findings suggest that NLR may serve as a global indicator of this aggressive transformation, regardless of the initial molecular subtype, though this warrants validation in molecularly stratified cohorts.

However, the principal contribution of our study to the existing literature lies in its demonstration that while confirming the prognostic superiority of NLR in patients with rHGG, newer and theoretically more comprehensive indices such as PIV, SII, and HALP failed to offer significant prognostic value in this specific cohort. This finding underscores that the prognostic utility of inflammatory indices is highly contingent upon tumor type and biological context, suggesting that they cannot be applied indiscriminately in high grade gliomas. Although the formulas for PIV and SII incorporate platelet counts alongside neutrophils and lymphocytes, this inclusion may not confer the anticipated prognostic advantage given the unique immunobiology of high grade gliomas. Unlike systemic malignancies such as colorectal or lung cancer, where systemic inflammatory responses, particularly paraneoplastic thrombocytosis, are prominent, HGGs are primarily localized, intracranial diseases. In the pathogenesis of GBM, the primary driving force appears to be neutrophils rather than platelets. The hypoxic and necrotic regions characteristic of the tumor secrete high levels of CXCL8 (IL-8), actively recruiting neutrophils into the tumor microenvironment. These infiltrating neutrophils directly trigger angiogenesis and invasion by releasing proteases (e.g., matrix metalloproteinase-9) and VEGF. Consequently, the elevation of peripheral neutrophils (high NLR) acts as a 'mirror,' directly reflecting the tumor's necrosis burden and biological aggressiveness.[18] In our cohort, baseline blood samples were intentionally collected prior to steroid administration to avoid this confounder, ensuring that the high NLR observed in the poor-prognosis group is a true biological marker of tumor-induced inflammation. In another mechanism, since neutrophils directly promote angiogenesis via NETosis (Neutrophil Extracellular Traps) and VEGF secretion within the tumor microenvironment, NLR remains a potentially consistent biological marker for predicting the efficacy of bevacizumab, an anti-angiogenic agent. Although bevacizumab targets VEGF-A, in patients with a high neutrophil burden, the cytokine release derived from neutrophils may be so intense that the resultant excessive VEGF load might challenge the neutralization capacity of the drug, theoretically rendering standard-dose bevacizumab insufficient to suppress this increased pro-angiogenic activity. The dramatic survival loss observed in the high-NLR group (>6.74) in our study (4.4 months) supports the hypothesis that in these patients, the tumor develops resistance not only through angiogenesis but also via neutrophil-mediated immunosuppression and invasion mechanisms.[11, 19]

Receiver operating characteristic analysis demonstrated a modest discriminatory performance of pretreatment NLR for overall survival in our cohort (AUC≈0.58), indicating limited global predictive accuracy. However, the cut-off value determined using the Youden index yielded high specificity, albeit at the expense of sensitivity. This pattern suggests that NLR may be more suitable for identifying a clearly high-risk subset of patients rather than serving as a high-sensitivity predictive tool for individual outcome estimation. Therefore, while NLR may not function as a standalone prognostic classifier, it may still offer practical utility in clinical risk stratification frameworks.

Regarding the safety profile, our study revealed a higher incidence of vascular events compared to similar series in the literature. Thromboembolic events occurred in 14.0% (n=6) of our patients (5 CVA, 1 PE). In the systematic review conducted by Simonetti et al.[20], the risk of bevacizumab-related arterial thromboembolism has been reported in the range of 2–5%, and venous thromboembolism in the range of 3–12%. In our exploratory analysis, vascular events (11.6% rate of ischemic stroke) were not associated with older age, longer bevacizumab exposure, or a higher prevalence of baseline cardiovascular risk factors. These findings suggest that the observed event rate may reflect the intrinsic thrombotic tendency of recurrent high-grade gliomas and the known vascular risk profile of anti-VEGF therapy rather than a clear dose-dependent toxicity pattern. However, given the small number of events, these observations should be interpreted cautiously. Furthermore, the 4.7% risk of intracranial hemorrhage is consistent with the literature and remains within acceptable limits. These findings suggest that in patients with high vascular risk who also exhibit high NLR values (expected survival <5 months), clinicians should exercise increased caution. In such cases, NLR may serve as a supplementary tool for more personalized clinical counseling, helping to weigh the potential risks of this regimen against the limited expected survival benefits.

Nevertheless, these findings should be interpreted cautiously given the retrospective design and limited sample size. Prospective validation in larger, molecularly well-annotated cohorts is required to confirm the prognostic value of NLR in this setting. Furthermore, external validation across independent institutions would be essential before integrating NLR-based stratification into clinical decision algorithms. At present, our results should be considered hypothesis-generating and exploratory rather than practice-changing.

Conclusion

In this single-center retrospective cohort of patients with recurrent high-grade gliomas treated with BEV+IRI, pretreatment NLR was associated with overall survival, whereas other composite inflammatory indices did not retain independent prognostic significance. Although the ROC discrimination was modest, the clear survival separation observed in Kaplan–Meier analyses suggests that NLR may serve as a simple and pragmatic risk-stratification marker in this setting. These findings should be considered exploratory and hypothesis-generating, and require external validation and prospective confirmation before integration into clinical decision-making algorithms.

Limitations

The primary limitation of this study is its retrospective design and relatively small sample size (n=43). While this cohort encompasses all eligible patients treated with the BEV+IRI regimen at our center over a five-year period, the limited number of events resulted in relatively wide confidence intervals in the multivariate Cox regression model, potentially affecting the precision of our effect size estimates. Consequently, our findings regarding the prognostic power of NLR should be interpreted as hypothesis-generating rather than definitive. Furthermore, the lack of an independent validation cohort and the absence of a control arm (e.g., bevacizumab monotherapy) limit the generalizability of our results. Future large-scale, prospective, multicenter studies are warranted to validate these findings and to establish standardized NLR cut-off values for patient selection in recurrent high-grade gliomas. Furthermore, the unavailability of comprehensive molecular genetic analysis results restricted the scope of molecular subgroup analyses.

Disclosures

Ethics Committee Approval: This study was approved by the clinical research ethics committee of the Bursa Uludag University, Faculty of Medicine (Decision No: 2022-5/25, dated March 2, 2022).

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Author Contributions: Concept – SOO, BO, BiO, SS; Design – SOO, EÇ, TE, ABŞ; Supervision – AD, ABŞ, BC, TE, EÇ; Findings – UH, BO, BO, SOO; Materials – UH, BO, BiO, BC; Data Collection and/or Processing – UH, SS, BO; Analysis and/or Interpretation – SS, BO, SOO; Literature Review – SOO, BO, BC, AD; Writing – SOO, BO, BiO, ABŞ; Critical Review – AD, EÇ,TE.

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