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Can Platelet-to-Lymphocyte Ratio (PLR) and Neutrophil-to-Lymphocyte Ratio (NLR) Help Predict Outcomes of Patients With Recurrent Glioblastoma?

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Abstract. *Background/Aim: In patients with recurrent glioblastoma, very little data are available regarding the prognostic value of platelet-to-lymphocyte (PLR) and neutrophil-to-lymphocyte (NLR) ratios. This study investigated potential associations between PLR or NLR and treatment outcomes. Patients and Methods: PLR and NLR at diagnosis of recurrence plus 10 additional characteristics were retrospectively analyzed for associations with progression-free survival (PFS) and overall survival (OS) in 75 patients with recurrent glioblastoma. Results: On multivariate analyses, maximal cumulative diameter of recurrent lesion(s) <40 mm (p=0.015) and systemic therapy (p<0.001) were associated with improved PFS. On multivariate analysis of OS, improved outcomes were significantly associated with PLR ≤150 (p=0.029), maximal cumulative diameter <40 mm (p=0.030), and systemic therapy (p=0.010). Conclusion: In addition to other characteristics, PLR at the time of recurrence was identified as an independent predictor of OS in patients with recurrent glioblastoma. PLR may be useful when designing personalized treatment approaches or clinical trials.*

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The majority of patients with newly diagnosed glioblastoma receives multimodal therapy including maximal safely achievable resection followed by chemoradiation and maintenance chemotherapy (1). Selected patients may benefit from additional therapy with tumor treating fields (2). Despite improvements in the primary treatment of glioblastoma, a considerable number of these patients develop a recurrence after a comparably short time, namely within the first year following primary treatment (3, 4). Patients with recurrent glioblastoma often have limited prognoses and may benefit from personalized treatment concepts. A personalized approach ideally considers different individual factors including the patient's remaining lifespan. The knowledge of prognostic factors of overall survival (OS) can facilitate the process of selecting the most appropriate individual treatment regimen. Several clinical and treatment-related predictors of improved survival have already been identified for patients experiencing a recurrence of glioblastoma (5-21). In addition, pre-clinical factors such as inflammatory markers may be helpful. The prognostic role of platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) have already been investigated in patients with newly diagnosed glioblastomas (22-37).

However, only three studies have investigated the prognostic value of NLR, and none have investigated the role of PLR in patients with recurrent glioblastomas (38-40). Thus, additional studies are required to better define the prognostic role of PLR and NLR in these patients. Therefore, the present study was conducted to investigate potential associations between these two inflammatory markers and treatment outcomes in terms of progression-free survival (PFS) and OS.

Patients and Methods

This retrospective study included the data of 75 patients who experienced a recurrent glioblastoma between 2014 and 2024 and

Table I. *Characteristics analyzed for associations with progression-free survival and overall survival following the diagnosis of recurrent glioblastoma.*

Characteristic	Subgroup	Number of patients (%)
Platelet-to-lymphocyte ratio	≤150	25 (33)
	>150	50 (67)
Neutrophil-to-lymphocyte ratio	≤4	28 (37)
	>4	47 (63)
Age at diagnosis of recurrence	≤60 Years	36 (48)
	≥61 Years	39 (52)
Sex	Female	35 (47)
	Male	40 (53)
Karnofsky performance score at diagnosis of recurrence	≤80	47 (63)
	90-100	28 (37)
Interval between end of primary radiotherapy and diagnosis of recurrent glioblastoma	≤4 Months	38 (51)
	≥5 Months	37 (49)
Number of recurrent lesions	1	44 (59)
	≥2	28 (37)
	Unknown	3 (4)
Maximal cumulative diameter of recurrent lesion(s)	<40 mm	34 (45)
	≥40 mm	38 (51)
	Unknown	3 (4)
Site(s) of recurrent lesion(s)	Old site(s)	49 (65)
	New site(s)	9 (12)
	Both	14 (19)
	Unknown	3 (4)
Resection of recurrent lesion(s)	No	54 (72)
	Yes	21 (28)
Re-irradiation of recurrent lesion(s)	No	58 (77)
	Yes	17 (23)
Systemic therapy for recurrent lesion(s)	No	20 (27)
	Yes	53 (71)
	Unknown	2 (3)

for whom PLR and NLR were available at the time of recurrence. The study was originally approved by the Ethics Committee at the University of Lübeck, Germany, in 2022 (file 2022-509), and the last amendment was approved in March 2024 (same file number).

Treatment of recurrent glioblastoma included a resection in 21 patients (28%), with 11 undergoing gross tumor resection and 10 undergoing subtotal resection. A second course of radiotherapy was performed in 17 patients (23%). Depending on the radiation dose of the primary radiotherapy administered to the organs at risk, the dose-fractionation regimens of re-irradiation varied and included radiotherapy with one fraction of 1.6-2.5 Gy per day with or without a simultaneous integrated boost (SIB) in six patients and hyper-fractionated or accelerated hyper-fractionated radiotherapy using two fractions of 1.1-1.5 Gy per day with or without a SIB in 11 patients, respectively. In 16 patients, total doses ranged between 21 Gy and 55.8 Gy (median dose=34.8 Gy); in one patient, radiation therapy was terminated early after 4.8 Gy. Fifty-three patients (71%) received systemic therapy for the recurrence. Regimens used for systemic therapy included temozolomide (TMZ) alone in 28 patients, TMZ plus lomustine in one patient, TMZ plus procarbazine/lomustine (PC) in two patients, TMZ plus PC and bevacizumab in one patient, lomustine alone in one patient, PC alone in 16 patients, PC plus vincristine (PCV) in one patient, PC plus bevacizumab in one patient, and bevacizumab alone in two patients. In another two patients (3%), it remained unclear whether the recommended systemic therapy was administered.

PLR (≤150 *vs.* >150) and NLR (≤4 *vs.* >4) at the time of recurrence plus 10 additional characteristics were analyzed with respect to associations with PFS and OS (Table I). The additional characteristics included age at diagnosis of recurrence (≤60 *vs.* ≥61 years, median=61 years), sex (female *vs.* male), Karnofsky performance score (KPS) at diagnosis of recurrence (≤80 *vs.* 90-100), interval between primary radiotherapy and diagnosis of recurrent glioblastoma (≤4 *vs.* ≥5 months, median=4 months), number of recurrent lesions (single *vs.* two or more), maximal cumulative diameter of recurrent lesion(s) (<40 *vs.* ≥40 mm), site(s) of recurrent lesion(s) (old *vs.* new *vs.* both), resection of recurrent lesions(s) (no *vs.* yes), re-irradiation of recurrent lesions(s) (no *vs.* yes), and systemic therapy for recurrent lesions(s) (no *vs.* yes).

PFS and OS were calculated from the day of diagnosis of recurrent glioblastoma. For univariate analyses, the Kaplan–Meier method and the log-rank test were used. After Bonferroni adjustment for 12 tests, *p*-values <0.0042 were significant and represented an alpha level of <5%. In addition, a *p*-value of <0.05 was considered indicating a strong trend for an association with PFS or OS. Factors indicating significance or a strong trend on univariate analyses were included in multivariate analysis, namely a Cox proportional hazards model. In the multivariate analysis, a *p*-value

Table II. *Progression-free survival rates at 6 and 12 months following the diagnosis of recurrent glioblastoma (univariate analyses).*

Characteristic	Subgroup	At 6 months (%)	At 12 months (%)	*p*-Value
Platelet-to-lymphocyte ratio	≤150	42	28	0.15
	>150	25	15	
Neutrophil-to-lymphocyte ratio	≤4	35	27	0.28
	>4	29	16	
Age at diagnosis of recurrence	≤60 Years	30	15	0.93
	≥61 Years	32	26	
Sex	Female	27	21	0.23
	Male	35	18	
Karnofsky performance score at diagnosis of recurrence	≤80	20	13	**0.002**
	90-100	48	31	
Interval between primary radiotherapy and diagnosis of recurrent glioblastoma	≤4 Months	31	22	0.75
	≥5 Months	31	18	
Number of recurrent lesions	1	34	21	0.50
	≥2	30	21	
Maximal cumulative diameter of recurrent lesion(s)	<40 mm	53	36	**0.004**
	≥40 mm	15	9	
Site(s) of recurrent lesion(s)	Old site(s)	35	25	0.29
	New site(s)	14	0	
	Both	37	18	
Resection of recurrent lesion(s)	No	21	14	0.024
	Yes	55	34	
Re-irradiation of recurrent lesion(s)	No	30	22	0.56
	Yes	34	10	
Systemic therapy for recurrent lesion(s)	No	11	5	**<0.001**
	Yes	37	24	

After Bonferroni adjustment, *p*-values <0.0042 were considered significant and given in bold; *p*-values <0.05 indicated a trend.

Table III. *Multivariate analysis of progression-free survival following the diagnosis of recurrent glioblastoma (Cox proportional hazards model).*

Characteristic	Hazard ratio	95% Confidence interval	*p*-Value
Karnofsky performance score (≤80 *vs*. 90-100)	0.60	0.34-1.06	0.078
Maximal cumulative diameter (<40 *vs*. ≥40 mm)	2.10	1.16-3.82	**0.015**
Resection of recurrent lesion(s) (no *vs*. yes)	0.53	0.27-1.04	0.067
Systemic therapy for recurrent lesion(s) (no *vs*. yes)	0.23	0.12-0.46	**<0.001**

Significant *p*-values are given in bold.

of <0.05 was regarded significant, and a *p*-value of <0.10 was considered indicating a trend for an association with PFS or OS.

Results

On univariate analyses of PFS (Table II), significant associations were found between improved outcomes and the characteristics KPS 90-100 (p=0.002), maximal cumulative diameter of recurrent lesion(s) <40 mm (p=0.004), and systemic therapy for the recurrence of glioblastoma (p<0.001). Moreover, a strong trend was observed for resection of recurrent lesions(s) (p=0.024). In the subsequent Cox proportional hazards model (Table III), improved PFS was significantly associated with maximal cumulative diameter <40 mm (p=0.015) and systemic therapy (p<0.001). Trends for associations with better PFS were found for KPS 90-100 (p=0.078) and resection (p=0.067).

On univariate analyses of OS (Table IV), a better outcome was significantly associated with systemic therapy for recurrent glioblastoma (p=0.002). Trends for such an association were found for PLR ≤150 (p=0.017, Figure 1), KPS 90-100 (p=0.008), and maximal cumulative diameter of recurrent lesion(s) <40 mm (p=0.016). In the Cox proportional hazards model (Table V), improved OS was significantly associated with PLR ≤150 (p=0.029), maximal cumulative diameter <40 mm (p=0.030), and systemic therapy (p=0.010). In addition, KPS 90-100 showed a trend (p=0.061) towards improved OS.

Table IV. *Overall survival rates at 6 and 12 months following the diagnosis of recurrent glioblastoma (univariate analyses).*

Characteristic	Subgroup	At 6 months (%)	At 12 months (%)	*p*-Value
Platelet-to-lymphocyte ratio	≤150	71	55	0.017
	>150	60	33	
Neutrophil-to-lymphocyte ratio	≤4	71	53	0.15
	>4	59	32	
Age at diagnosis of recurrence	≤60 Years	64	40	0.47
	≥61 Years	63	40	
Sex	Female	49	34	0.33
	Male	76	46	
Karnofsky performance score at diagnosis of recurrence	≤80	51	26	0.008
	90-100	82	61	
Interval between primary radiotherapy and diagnosis of recurrent glioblastoma	≤4 Months	58	36	0.15
	≥5 Months	70	45	
Number of recurrent lesions	1	69	45	0.13
	≥2	62	37	
Maximal cumulative diameter of recurrent lesion(s)	<40 mm	82	53	0.016
	≥40 mm	51	31	
Site(s) of recurrent lesion(s)	Old site(s)	70	48	0.11
	New site(s)	61	0	
	Both	56	37	
Resection of recurrent lesion(s)	No	58	34	0.17
	Yes	76	55	
Re-irradiation of recurrent lesion(s)	No	60	38	0.20
	Yes	74	46	
Systemic therapy for recurrent lesion(s)	No	37	19	**0.002**
	Yes	72	47	

After Bonferroni adjustment, *p*-values <0.0042 were considered significant and given in bold; *p*-values <0.05 indicated a trend.

Table V. *Multivariate analysis of overall survival following the diagnosis of recurrent glioblastoma (Cox proportional hazards model).*

Characteristic	Hazard ratio	95% Confidence interval	*p*-Value
Platelet-to-lymphocyte ratio (≤150 *vs.* >150)	2.10	1.08-4.07	**0.029**
Karnofsky performance score (≤80 *vs.* 90-100)	0.55	0.29-1.03	0.061
Maximal cumulative diameter (<40 *vs.* ≥40 mm)	1.96	1.07-3.61	**0.030**
Systemic therapy for recurrent lesion(s) (no *vs.* yes)	0.43	0.22-0.82	**0.010**

Significant *p*-values are given in bold.

Discussion

Many patients with recurrent glioblastoma have poor prognoses and would likely benefit from treatment regimens considering an individual patient's specific situation and remaining lifetime. Patients with poor expected survival should preferably be treated with short and little burdensome regimens. In case of very poor prognoses, patients may even be considered for best supportive care (BSC) alone. For optimal relief of symptoms caused by edema, BSC should be supplemented with the administration of corticosteroids. Patients with more favorable survival prognoses should be considered for a more intensive, if possible multimodal, treatment of their recurrence. Multimodal treatment would ideally include maximal safely possible re-resection followed by re-irradiation plus concurrent systemic therapy and sequential systemic therapy. If a patient is selected for re-irradiation, the previous course of radiotherapy and the cumulative equivalent dose in 2 Gy fractions (EQD2) administered to the organs at risk need to be considered (41, 42). In the retrospective study of Stiefel *et al.* who investigated re-irradiation in patients with recurrent brain tumors or recurrent brain metastases, a second course of radiotherapy appeared safe if the cumulative EQD2 was <100 Gy_2 to the brainstem and <75 Gy_2 to chiasm and optic nerves (43, 44). In addition to the cumulative EQD2, the patient's

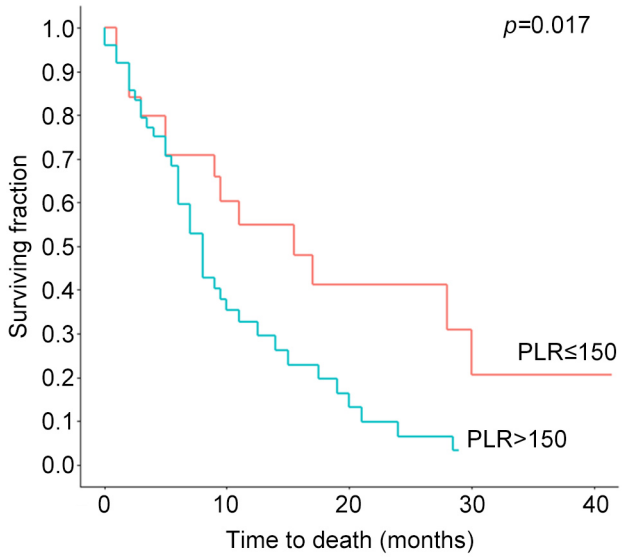

Figure 1. *Comparison of platelet-lymphocyte ratio (PLR) ≤150 vs. >150 regarding overall survival following the diagnosis of recurrent glioblastoma (univariate analysis).*

remaining survival time should be considered when selecting the dose-fractionation regimen of re-irradiation. Patients with less favorable prognoses should receive hypo-fractionated (doses per fraction >2 Gy) or even ultra-hypo-fractionated (doses per fraction ≥5 Gy) regimens, if reasonably possible, to allow them to spend as many days as possible of their remaining lifespan without treatment (45, 46). In contrast, patients with longer estimated survival can benefit from re-irradiation with lower doses per fraction that are known to be associated with less radiation-related late toxicity (41). In this context, one should bear in mind that the risk of experiencing late toxicity increases with the patient's lifetime.

These considerations show that it is important to be able to estimate a patient's remaining lifetime as precisely as possible. To achieve this goal, prognostic factors can be very helpful. In previous studies, a variety of clinical and treatment-related factors significantly associated with improved survival have already been identified for patients with recurrent glioblastoma. These factors included better performance status, younger age, smaller size or volume of recurrent lesions, single recurrence, frontal location, re-resection, particularly gross tumor resection of recurrent lesions, adjuvant treatment for recurrent glioblastoma, and longer interval between resection of primary glioblastoma and re-resection (5-21).

In addition to these predictive factors, the inflammatory markers PLR and NLR may play a prognostic role in patients with recurrent glioblastoma. Several studies and meta-analyses suggested associations between PLR and/or NLR and outcomes in patients treated for newly diagnosed glioblastoma (22-37). However, no study was identified during our literature research that investigated the prognostic role of PLR for patients with recurrent glioblastoma. In addition, only three studies have evaluated the prognostic value of NLR for these patients (38-40). In 2014, McNamara *et al*. presented a retrospective study of 107 patients who received re-resection of glioblastoma for tumor progression (38). Median OS times were 9.7 months in patients with NLR ≤4 (prior to re-resection) compared to 5.9 months in patients with NLR >4 (p=0.02). On multivariate analysis, NLR prior to re-resection proved to be an independent predictor of OS following the second surgery (time ratio 1.65, 95% confidence interval=1.15-2.35, p<0.01). In 2021, Haksoyler *et al*. retrospectively evaluated the role of NLR in 103 patients receiving bevacizumab plus irinotecan for recurrent glioblastoma (39). In this study, the optimal cut-off value for NLR considering the area under the curve, sensitivity, and specificity was 3.04. Patients of the lower-NLR group had a significantly longer median OS (15.8 *vs*. 9.3 months, p=0.015) and better 1-year OS (61% *vs*. 30%). In addition, lower NLR was an independent predictor of better OS in the corresponding multivariate analysis (hazard ratio 1.63, p=0.023). In 2023, Deng *et al*. presented the retrospective data of 764 patients with newly diagnosed glioblastoma (40). In those 609 patients who developed a recurrence during the period of follow-up, high NLR at the time of first recurrence was negatively associated with OS (adjusted hazard ratio 1.69, 95% confidence interval 1.25–2.27, p<0.001). In the present study, we did not find a significant association between NLR and treatment outcomes in terms of OS and PFS. However, patients with NLR ≤4 had a non-significantly better 1-year OS than patients with NLR >4 (53% *vs*. 32%, p=0.15). These OS rates were similar to those found in the study of Haksoyler *et al*. (39). Possibly, the lower sample size in our study hampered the achievement of significant results. When compared to the previous studies, our study was the first to investigate the prognostic role of PLR at the time of recurrence for patients with recurrent glioblastoma. According to its results, PLR ≤150 at the time of recurrence was significantly associated with improved OS on multivariate analysis. Thus, PLR may be considered a potential predictor of OS for patients with recurrent glioblastoma that may support physicians when designing individualized treatment programs for these patients. However, the retrospective nature of our study associated with a risk of hidden selection biases needs to be considered when incorporating our results into the decision process. This limitation applies also to the previous studies that investigated the prognostic role of NLR (38-40). Thus, prospective studies are urgently needed to properly define the prognostic value of PLR and NLR for patients with recurrent glioblastoma.

In summary, PLR at the time of recurrence was found to be an independent predictor of OS in patients with recurrent glioblastoma. PLR may be useful for physicians who aim to create individualized treatment programs for these patients. Moreover, PLR may contribute to the proper design of future clinical trials. In contrast to other studies, a significant association between NLR and treatment outcomes was not found. Considering the retrospective design of this study and previous studies, it becomes obvious that prospective trails are required to properly define the role of PLR and NLR in patients with recurrent glioblastoma.

Conflicts of Interest

The Authors report no conflicts of interest related to this study.

Authors' Contributions

The study was designed by all Authors. Data were collected by O.Z. and D.R., and analyzed by D.R. and N.Y.Y. The manuscript was drafted by D.R., and reviewed and finally approved by all Authors.

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