

Prognostic significance of pre-treatment neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in patients with glioblastoma

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Abstract. Glioblastoma multiforme (GBM) is the most common and aggressive primary brain tumour in adults. Identification of accessible and cost-effective prognostic factors may better guide adjuvant treatment-related decisions. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are markers of host inflammatory response, and their increase has recently been shown to be a poor prognostic factor in several malignancies. The aim of the present study was to investigate the prognostic value of preoperative NLR and PLR in GBM patients. Between 2012 and 2017, 104 patients who had undergone surgery for GBM were considered for adjuvant therapy in our institution. Of those, 80 patients with evaluable pre-corticosteroid full blood count results were identified and included in the final analysis. The Eastern Cooperative Oncology Group performance status, localization, radiochemotherapy and second-line systemic therapy were found to be independent prognostic indicators for progression-free and overall survival. The median overall survival was 13.2 months. Patients with NLR <4 had a better median overall survival of 10.7 vs. 7.8 months in patients with NLR >4; however, this difference was not statistically significant (P>0.05). Overall survival also did not differ significantly between patients with low and those with high PLR values (10.2 vs. 15.2 months, respectively; P=0.105). In conclusion, the results of the present study suggest that pre-treatment NLR and PLR do not have prognostic value in GBM patients; however, large-scale trials are required to confirm these findings.

Introduction

Glioblastoma multiforme (GBM) is the most common malignant brain tumour in adults (1). The current standard of first-line therapy is maximal safe resection followed by radiation therapy concurrent with temozolomide and subsequent adjuvant temozolomide chemotherapy (2). However, almost all patients experience relapse after adjuvant therapy and overall survival (OS) is dismal, despite the best available treatment modalities (3). New adjuvant treatment strategies, better patient selection and personalized therapy are crucial for improving clinical outcomes.

Clinical factors such as age at presentation, tumour location, Karnofsky performance status, extent of surgery and isocitrate dehydrogenase (IDH) status are well-known prognostic factors for GBM (4). Identification of more accessible and cost-effective prognostic factors may better guide adjuvant treatment decisions. The neutrophil-to-lymphocyte ratio (NLR) is a marker of host inflammatory response, and its elevation has recently been shown to be a poor prognostic factor in a number of malignancies, including colon, prostate, lung and bladder cancer (5-9). The platelet-to-lymphocyte ratio (PLR) is another inflammatory marker, although it has been less extensively investigated as a prognostic factor in cancer patients compared with NLR.

A limited number of studies have evaluated the role of NLR and PLR in GBM prognosis and survival, but the results are controversial. Some studies found that higher NLR values were associated with worse OS at the time of first diagnosis or prior to second surgery, whereas one study demonstrated that lower NLR values were associated with better prognosis only in IDH wild-type patients. In addition, other studies did not observe any association between NLR values and clinical outcome.

A total of 3 studies evaluated the prognostic effect of PLR in GBM patients: One of those studies reported a negative prognostic effect of increased PLR values, whereas the remaining 2 studies did not identify any association between PLR and OS.

The aim of the present study was to evaluate the prognostic value of NLR and PLR for OS in a cohort of patients with GBM.

Patients and methods

Patient information. In this retrospective, single-centre study, a total of 80 patients who were diagnosed between

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January 2012 and June 2017 at the Departments of Radiation Oncology and Medical Oncology of Samsun Training Hospital (Samsun, Turkey) were evaluated. The Stupp protocol (primary radiotherapy with a total of 60 Gy with concomitant temozolamide and subsequent temozolamide) was used for all patients as the postoperative radiochemotherapy regimen. The protocol of the present study was approved by the local Ethics Committee.

Demographic data, clinicopathological data and treatment parameters (i.e., extent of surgical resection, radiotherapy and use of chemotherapy) were obtained from medical records. Data on patient death were obtained from the National Electronic Death Registration System, Turkey.

Patients with complete blood count results before receiving corticosteroid therapy or surgery were included in the study. NLR was calculated by dividing the neutrophil count by the lymphocyte count, and the PLR was defined as the absolute platelet count divided by the absolute lymphocyte count.

Statistical analysis. Progression-free survival (PFS) was calculated as the time interval between the date of the initial surgery and the detection of tumour progression documented on magnetic resonance imaging or the date of death. The time interval between the date of diagnosis and the date of death, or of the last follow-up for surviving patients, was defined as the OS. Kaplan-Meier curves were used to calculate OS and PFS. Patients who were alive at the last visit were censored in the analysis. Univariate and multivariate analyses were performed using the Cox proportional hazards model to evaluate the effect of variables on PFS and OS. Both the NLR and PLR were evaluated as continuous or dichotomous variables. A cut-off value of 4 for NLR was selected according to previous trials, as it had been shown to correlate with clinical outcomes in GBM patients. $P < 0.05$ was considered to indicate statistically significant differences. All analyses were performed using SPSS version 23 software (IBM SPSS, Armonk, NY, USA).

Results

Study population. Between 2012 and 2017, 104 patients with GBM were assessed for consideration of adjuvant therapy at our institution, among whom 80 patients with evaluable pre-corticosteroid full blood count results were identified and included in the present study. Of the 80 patients, 39 (48.7%) were male and 41 (51.3%) were female, with a mean age of 56.8 ± 13.1 years. The median tumour diameter was 42.3 ± 14.8 mm. The majority of the patients (85%) had received concurrent chemoradiotherapy after surgery. In addition, the majority of the patients (72.5%) subsequently received adjuvant temozolamide. Gross total excision was achieved in over half of the patients (52.5%). The most common tumour localization was the temporal lobe (27.5%). The median follow-up time was 12 months (range, 3-55 months).

The mean pre-treatment neutrophil, platelet and lymphocyte counts were $7.9 \pm 3.7 \times 10^9/l$ (range, 2.4 - $21.6 \times 10^9/l$), $259.1 \pm 65.7 \times 10^9/l$ (range, 133 - $462 \times 10^9/l$), and $1.7 \pm 0.7 \times 10^9/l$ (range, 0.5 - $3.6 \times 10^9/l$), respectively.

The mean pre-treatment NLR was 6.3 ± 5.5 (median, 4.39; range, 1.03-30.29), and the mean pre-treatment PLR was 182.9 ± 95.4 (median, 163.1; range, 56.8-607.9). Baseline demographic data are presented in Table I.

Table I. Demographic and clinical characteristics.

Characteristics	n	%
Sex		
Female	41	51.3
Male	39	48.7
Age (years), mean \pm SD	80	56.8 ± 13.1
Tumour location		
Temporal	22	27.5
Parietal	13	16.3
Frontal	13	16.3
Frontoparietal	9	11.3
Parietooccipital	10	12.5
Frontotemporal	5	6.3
Occipital	3	3.8
Other	5	6.4
Primary/secondary		
Primary	77	96.3
Secondary	3	3.8
Hemisphere		
Right	32	40
Left	45	56.3
Midline	3	3.8
Type of operation		
Total	42	52.5
Subtotal	30	37.5
Biopsy	7	8.8
Unknown	1	1.3
Adjuvant treatment		
Chemoradiotherapy	68	85
Radiotherapy	5	6.3
No treatment	3	3.7
Unknown	2	2.5
Chemoradiotherapy + Cyberknife	2	2.5
Temozolamide		
Yes	58	72.5
No	11	13.8
Unknown	11	13.8
Preoperative NLR, mean \pm SD	80	6.3 ± 5.5
Preoperative PLR, mean \pm SD	80	182.9 ± 95.4

SD, standard deviation; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

PFS. The median PFS was 9.1 months. On univariate analysis, PFS did not differ significantly according to sex, laterality, or pre-treatment neutrophil, lymphocyte and platelet counts. However, age < 65 years, Eastern Cooperative Oncology Group (ECOG) performance status 1 and 2, administration of concurrent radiotherapy compared with radiotherapy alone, administration of second- and third-line systemic therapy, and frontal compared with occipital tumour localization were considered as prognostic factors. PFS did not differ significantly between patients with higher (> 4) and those with lower (< 4) NLR values.

Table II. Univariate and multivariate analysis for progression-free survival.

Variables	Univariate			Multivariate		
	HR	95% CI	P-value	HR	95% CI	P-value
Age	0.508	0.300-0.859	0.012 ^a	0.845	0.421-1.695	0.635
Sex	0.869	0.546-1.384	0.555			
ECOG PS						
1-2						
3-4	0.220	0.130-0.371	0.000 ^a	6.629	3.096-14.194	0.000 ^a
Localization						
Frontal						
Parietal/temporal	1.293	0.764-2.189	0.339	1.926	1.057-3.510	0.032 ^a
Occipital	5.936	1.632-21.596	0.007 ^a	3.965	0.829-18.950	0.084
Other	3.579	1.306-9.807	0.013 ^a	2.320	0.782-6.884	0.129
Laterality						
Right						
Left	0.719	0.440-1.173	0.187			
Midline	1.590	0.480-5.261	0.448			
Type of operation						
Biopsy						
Subtotal	0.803	0.307-2.106	0.656			
Gross total	0.408	0.157-1.064	0.067			
Radiotherapy						
Concurrent						
Alone	3.007	1.187-7.620	0.020 ^a	4.201	1.292-13.657	0.017 ^a
Temozolamide						
Yes						
No	1.366	0.706-2.645	0.355			
Second-/third-line systemic therapy						
Yes						
No	0.331	0.196-0.558	0.000 ^a	0.292	0.161-0.527	0.000 ^a
NLR						
>4						
<4	1.374	0.858-2.202	0.186			
PLR						
>135						
<135	0.724	0.444-1.182	0.197			
Pre-treatment neutrophils	1.000	1.000-1.000	0.07			
Pre-treatment lymphocytes	1.000	1.000-1.001	0.236			
Pre-treatment platelets	1.000	1.000-1.000	0.556			
Pre-treatment NLR	1.015	0.968-1.065	0.532			
Tumour size	0.993	0.972-1.014	0.525			

^aStatistically significant. HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

On multivariate analysis, ECOG performance status, localization, radiochemotherapy and second-line systemic therapy remained as independent prognostic indicators (Table II).

OS. A total of 53 patients had succumbed to the disease by the time of the analysis. The OS was 13.2 months in

the entire study population. Univariate and multivariate analyses demonstrated that patients with ECOG 1-2, and those receiving concurrent chemoradiotherapy or additional systemic therapy, had longer OS. On multivariate analysis, frontal localization was also a significant predictor of survival (Table III).

Table III. Univariate and multivariate analysis for overall survival.

Variables	Univariate			Multivariate		
	HR	95% CI	P-value	HR	95% CI	P-value
Age	1.416	0.807-2.485	0.225			
Sex	0.847	0.486-1.478	0.559			
ECOG PS						
1-2						
3-4	2.647	1.505-4.658	0.001 ^a	2.526	1.256-5.080	0.009 ^a
Localization						
Frontal						
Parietal/temporal	1.197	0.652-2.197	0.562	2.006	0.963-4.179	0.063 ^a
Occipital	4.042	0.872-18.733	0.074	5.432	1.034-28.533	0.046 ^a
Other	8.331	2.078-33.403	0.003 ^a	2.394	0.513-11.178	0.267
Laterality						
Right						
Left	0.747	0.416-1.338	0.326			
Midline	6.154	0.742-51.067	0.092			
Operation type						
Biopsy						
Subtotal	0.672	0.198-2.278	0.524			
Gross total	0.395	0.116-1.345	0.137			
Radiotherapy						
Concurrent						
Alone	6.752	2.164-21.072	0.001 ^a	7.127	1.768-28.740	0.06 ^a
Temozolamide						
Yes						
No	1.864	0.901-3.855	0.093			
Second-/third-line systemic therapy						
Yes						
No	0.176	0.091-0.341	0.000 ^a	0.085	0.036-0.205	0.000 ^a
NLR						
>4						
<4	1.258	0.727-2.179	0.412			
PLR						
>135						
<135	0.649	0.365-1.125	0.121			
Pre-treatment neutrophils		1.000	1.000-1.000	0.074		
Pre-treatment lymphocytes		1.000	1.000-1.001	0.236		
Pre-treatment platelets		1.000	1.000-1.000	0.556		
Pre-treatment NLR		1.015	0.968-1.065	0.532		
Tumour size		0.993	0.972-1.014	0.525		

^aStatistically significant. HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

NLR and PLR. Patients with an NLR value of <4 had a longer PFS when compared with patients with higher NLR values (10.7 vs. 7.8 months, respectively), but the difference was not statistically significant (Fig. 1). The PFS for patients with low PLR values was 7.4 months as compared with 10.02 months for those with

high PLR values, but the difference was not statistically significant (P=0.166).

Patients with NLR <4 had a better OS of 14.5 vs. 11.6 months in patients with NLR >4. The difference was not statistically significant (P>0.05; Fig. 2). OS did not differ significantly between patients with low and those

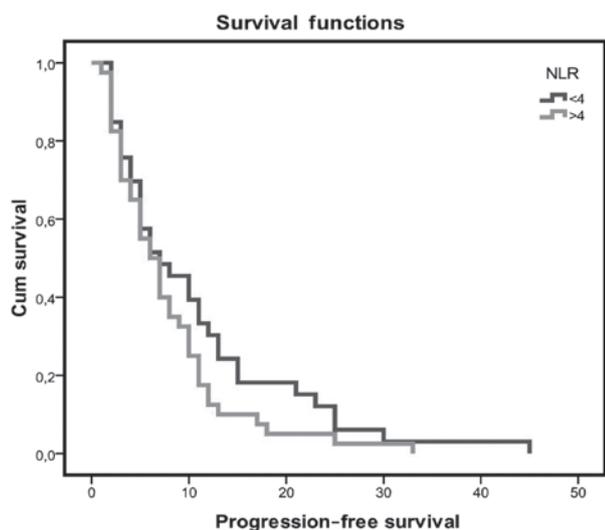


Figure 1. Kaplan-Meier curves for progression-free survival. NLR, neutrophil-to-lymphocyte ratio.

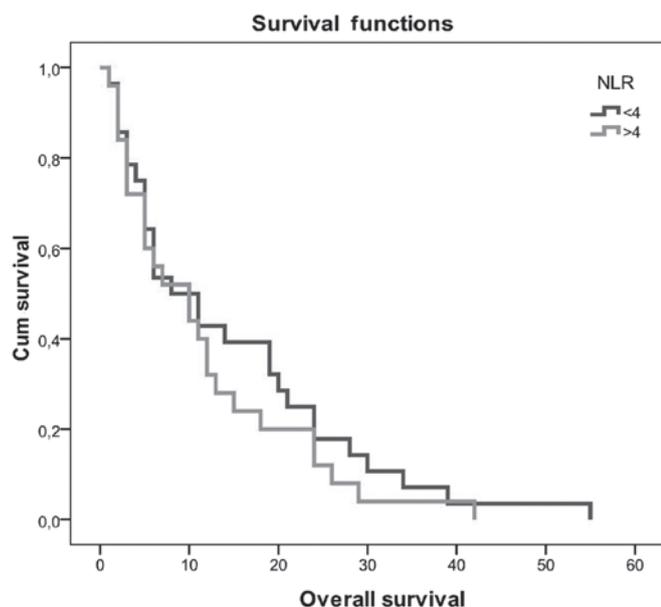


Figure 2. Kaplan-Meier curves for overall survival. NLR, neutrophil-to-lymphocyte ratio.

with high PLR values (10.2 vs. 15.2 months, respectively; $P=0.105$).

Discussion

The results of the present study demonstrated that patients with lower NLR values exhibited a longer OS compared with patients with higher NLR values, but the difference was not statistically significant. PLR was not prognostic for clinical outcome. Although NLR is an easily available and cost-effective test, its clinical use in patients with GBM is associated with some challenges. NLR should be calculated prior to steroid therapy and surgery, as both these interventions may increase the neutrophil count and lead to misinterpretation of the value (10). NLR may also be affected by various factors,

such as hypertension, autoimmune diseases, cardiovascular diseases and insulin resistance. In addition, the optimal cut-off value has not been established.

The identification of prognostic factors is crucial for GBM patients and may guide clinical treatment. Several studies have demonstrated an association between inflammatory status and cancer development. Pre-treatment neutrophil, lymphocyte and platelet counts are indicators of cancer-associated inflammation. High neutrophil count has been demonstrated to be an independent negative prognostic marker for recurrence and survival in gastric cancer, metastatic renal cell carcinoma, metastatic melanoma and advanced non-small-cell lung cancer (11). NLR is considered to reflect the balance between activation of the inflammatory pathway and the anti-tumour immune function (12).

As a marker of systemic inflammation, the prognostic significance of pre-treatment NLR in GBM patients remains unclear. NLR values <4 were shown to be significantly correlated with a better OS for GBM patients in 3 retrospective studies (10,13,14). By contrast, 2 retrospective studies did not identify any association between NLR values and OS, in accordance with our results. Mason *et al* evaluated NLR values in postoperative GBM patients who mostly received corticosteroids, which affect the NLR values, and used a cut-off value of 7.5 (15). Lopes *et al* also did not observe any correlation of NLR with OS, but they reported a shorter OS in patients with an NLR value >7 who completed the Stupp protocol (16).

McNamara *et al* assessed the prognostic value of NLR prior to second surgery in GBM patients and demonstrated that low NLR values were associated with longer OS after the second surgery compared with high NLR values (17).

PLR is also described as a prognostic factor in different cancer types; however, it is less extensively investigated compared with NLR in GBM patients. A total of 3 retrospective studies evaluated the prognostic value of PLR in GBM patients: Wang *et al* reported that PLR had independent prognostic value in GBM patients (10). Conversely, the other 2 trials could not find any association between PLR and clinical outcome in GBM patients (14,16).

Of the known prognostic factors in our study population, ECOG performance status, localization, combined therapy and second-line systemic treatment were identified as prognostic factors for clinical outcome.

There were certain limitations to the present study. First, this was a retrospective study and the sample size was not sufficient to reach statistical significance for survival due to worse disease outcomes; the results should be confirmed in a prospective study. Second, the O^6 -methylguanine-DNA methyltransferase methylation status of the patients was not known. Moreover, the post-progression salvage treatments were heterogeneous. Finally, cardiovascular diseases, infection, or drug treatments may also have affected the neutrophil and lymphocyte counts; however, we could not detect all confounders for patients with such medical history.

In conclusion, pre-treatment NLR and PLR values were not associated with prognosis in GBM patients and do not appear to be useful markers for predicting prognosis in GBM patients. There remains an unmet need to identify better prognostic factors for GBM patients.

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Availability of data and materials

The datasets used and analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

OY made substantial contributions to conception and design, and acquisition of data, and interpretation of data; EO made substantial contributions to conception and acquisition of data; OO made substantial contributions to acquisition of data; YK involved in drafting the manuscript and revising it critically for important intellectual content.

Ethics approval and consent to participate

Samsun Research and Training Hospital approval no. 2017/14.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no potential competing interests to disclose.

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