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The Effect of Indicators of Systemic Inflammatory Response on Survival in Glioblastoma Multiforme

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ABSTRACT

AIM: To evaluate the prognostic value of preoperative neutrophil-to-lymphocyte ratio and platelet-lymphocyte ratio in glioblastoma multiforme patients.

MATERIAL and METHODS: A total of 75 patients retrospectively analysed. The complete blood count of the patients was analysed before surgery. In our study, cut-off values for PLR 150 (platelet-lymphocyte ratio) and NLR 4 (neutrophil-to-lymphocyte ratio) were found to be significant by creating the ROC curve. Overall survival (OS) was calculated from surgery to death or the last contact. Progression-free survival (PFS) was calculated from surgery to progression. The last follow-up was November 2018.

RESULTS: The median OS was significantly shorter in PLR>150 patients (p=0.005; 10 vs 17 months). And the median OS was significantly shorter in NLR>4 patients too (p=0.010; 11 vs 17 months). In multivariate analysis, Karnofsky performance score <70 (HR:2.96, 95% CI:1.68-5.21; p<0.001), type of surgical resection (HR:2.32, 95% CI:1.35-3.98; p=0.002) were statistically significant for PFS. In multivariate analysis, KPS<70 (HR:2.72, 95% CI:1.30-5.67; p<0.007), type of surgical resection (HR:2.09, 95% CI:1.10-3.95; p=0.023), NLR>4 (HR:2.14, 95% CI:1.11-4.14; p=0.023) were statistically significant for OS were found to be independent prognostic factor.

CONCLUSION: The presence of 70<KPS and type of surgical resection in patients with GBM had a negative effect on PFS. NLR>4, 70<KPS, type of surgical resection were independent prognostic factors that negatively affect for the OS.

KEYWORDS: Glioblastoma multiforme, Pretreatment neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, Survival

INTRODUCTION

The World Health Organization describes glioblastoma as a malignant, class IV tumour with a high degree of mitosis and necrosis (10). The most common malignant primary brain tumour in adults is glioblastoma (10). Glioblastoma multiforme (GBM), all cancer related deaths 3-4% of that causes the most malignant form (10). The median survival after diagnosis is 12 months just radiotherapy and 14,5 months with radiochemotherapy in GBM patients (15). The standard therapy for GBM is maximum total resection followed by radiation therapy concurrent with temozolomide (TMZ) and subsequent adjuvant TMZ chemotherapy (Stupp protocol) (15). Recently, evidence has shown that preoperative haematological markers related to nutrition, clotting and inflammation are predictive and prognostic factors of cancers (7,13). Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), haematological indicator of systemic inflammation. Studies in many various cancers have demonstreated the relationship between high NLR and PLR and poor prognosis. A high NLR and PLR gastrointestinal tumours, such as prostate cancer and lung cancer is closely related to a poor prognosis in solid malignancies (3-5,16-18,20,22). PLR and NLR as prognostic marker in glioblastomas in recent years has been described. NLR and PLR are the determinants of host inflammation (1,9,14).

MATERIAL and METHODS

In this study, 122 GBM patients were admitted to our institution

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between the years 2011-2018 for postoperative radiotherapy purposes. 75 of them had the conditions to be analysed. We took medical records indicating the patient's age, gender, histopathology, magnetic resonance imaging (MRI) and computed tomography (CT) scans and follow-up data in our clinical files. Patients with complete blood count results prior receiving corticosteroid therapy and surgery were incorporated in the study. The exclusion criteria were: 1)-hematological diseases, 2)-autoimmune diseases, 3)-metabolic diseases, 4)-existing infections, 5)-patients treated with glucocorticoid or anti-inflammatory drugs.

Overall survival was defined from surgery to death or the last contact, and was determined as the last follow-up of November 2018. Progression-free survival (PFS) was calculated from surgery to progression. Tumor diameter was measured based on preoperative MRI scans. Newly improving or worsening neurological symptoms, tumour growth of 25% in the MRI were assumed as progression.

Complete blood count and biochemical tests, was performed with XN-900 Haematology analyser (Symex,Japan). The normal reference range for neutrophils 1,56-6,13 × 10^9 / L, for lymphocytes to 1.18–3,57 × 10^9 / L and platelets for 142-424 × 10^9 / L. 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.

This study was approved by the local Ethics Committee (2018 /1598).

Statistical Method

The descriptive statistics were performed using of the data mean, standard deviation, median-minimum-high frequency and ratio values. The distribution of the variables was measured using Kolmogorov Smirnov test. Independent quantitative data analysis Mann-Whitney U test was used. Independent qualitative data analysis chi-square test, chi-square test conditions are not provided, were compared using Fischer's test. The domain level and the cut off value by ROC curve were investigated. Kaplan Meier survival analysis (log-rank) was used. Univariate and multivariate Cox proportional hazards models were made. Statistical analysis were performed using SPSS software version 22.0 (IBM SPSS, Armonk, NY, USA) and the level of significance was taken as a p value less than 0.05.

RESULTS

Among the 75 patients analysed, 28 (%37) were female and 47 (%63) were male. Median age of the patients was 58.0 ± 13.02 years (range:19-78). The median follow-up was 12.0 ± 12.95 (6-84) months. The median tumour diameter was 4.0 ± 1.49 cm (2.5-9 cm). The most common symptom was headache in 25 (33%) patients. Lesion lateralisation was the left hemisphere in 35 (47%) patients and the right hemisphere in 40 (53%). The most common tumour localisation was temporal lobes in 25 (33%) patients. The parietal lobe 17 (23%), frontal lobe 14 (19%) and others 19 (25%), respectively. The most common symptom was headache 25 (33%), then power loss 12 (16%), speech disorder 10 (13%), balance problems 9 (12%), vision problems 8 (11%), nausea and vomiting 6 (8%), amnesia 3 (4%), seizure 2 (3%) respectively. Comorbid diseases were observed in 17 (23%) patients. Essential hypertension (n=9) were the most common comorbid disease. 3 patients had chronic obstructive lung disease, 2 patients cardiac diseases and 3 patients mixed diseases.

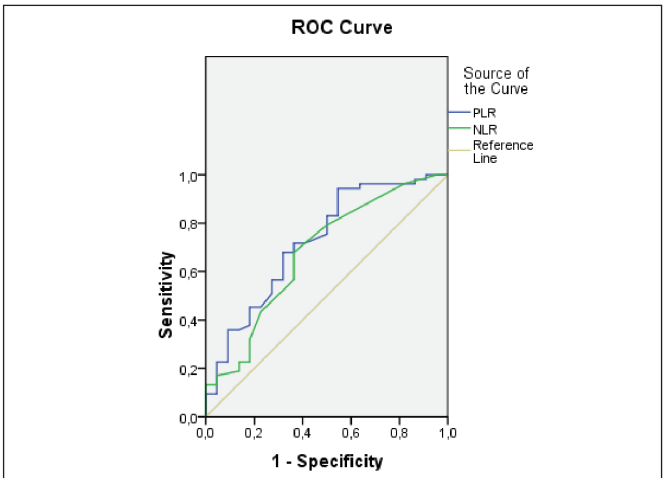
Gross total resection was performed in 31 (41%) patients, subtotal resection was performed 44 (59%) patients. Postoperatively, all patients received chemoradiotherapy and 69 (92%) patients received adjuvant chemotherapy. Adjuvant temozolomide was given to 69 (92%) patients and median adjuvant treatment cycle was 6 (range: 3-9).

The salvage treatment methods applied to patients after progression were not the same. Chemotherapy, radiotherapy, surgical options one of them applied together or alone. 25 (33%) patients underwent chemotherapy, 4 (5%) patients underwent radiosurgery, 8 (11%) underwent surgery, and 7 (10%) patients underwent no treatment because of their general condition. No recurrence was observed in 36 (48%) patients.

In our study, cut-off values for PLR 150 and NLR 4 were found to be significant by creating the ROC curve (Figure 1).

NLR>4 values were present in 53 (71%) patients and NLR<4 values in 22 (29%) patients. The demographic comparisons of the patients according to NLR ratios are shown in Table I.

Based on PLR>150 values were present in 46 (61%) patients and PLR<150 in 29 (39%) patients. The demographic comparisons of the patients according to PLR ratios are shown in Table II.



Test variable	AUC	p	95 % CI
NLR	0.724	0.002	0.593-0.855
PLR	0.677	0.017	0.538-0.816

Figure 1: ROC curves for neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR).

Table I: The Demographic Comparisons of the Patients According to NLR Ratios

	NLR≤4		NLR>4		p
	n	%	n	%	
Age					
≤50	9	41	12	23	0.109
>50	13	59	41	77	
Gender					
Female	6	27	22	41	0.246
Male	16	73	31	59	
KPS					
<70	18	82	28	53	**0.019**
≥70	4	18	25	47	
Operation type					
Total resection	9	41	22	41	0.962
Subtotal resection	13	59	31	59	
Postoperative treatment					
Chemoradiotherapy	21	96	51	96	0.877
Only chemotherapy	1	4	2	4	
Adjuvan chemotherapy					
Present	21	96	48	91	0.477
Absent	1	4	5	9	
Ki-67 ratio					
≤10	6	27	11	21	0.539
>10	16	73	42	79	
IDH					
Positive	11	50	27	51	
Negative	10	46	25	47	0.809
Unknown	1	4	1	2	
ATRX					
Positive	11	50	20	38	
Negative	1	4	4	7	0.597
Unknown	10	46	29	55	
EGFR					
Positive	10	46	19	36	
Negative	6	27	8	15	0.189
Unknown	6	27	26	49	

NLR: *Neutrophyl to lymphocyte ratio,* ***KPS:*** *Karnofsky performance score,* ***IDH:*** *Isocitrate dehydrogenase,* ***ATRX:*** *α thalassemial mental retardation syndrome X-linked,* ***EGFR:*** *Epidermal growth factor.*

Table II: The Demographic Comparisons of the Patients According to PLR Ratios

	PLR≤150		PLR>150		p
	n	%	n	%	
Age					
≤50	14	48	7	15	**0.002**
>50	15	52	39	85	
Gender					
Female	10	35	18	39	0.685
Male	19	65	28	61	
KPS					
<70	26	90	20	44	**<0.000**
≥70	3	10	26	56	
Operation type					
Total resection	12	41	19	41	0.995
Subtotal resection	17	59	27	59	
Postoperative treatment					
Chemoradiotherapy	28	97	44	96	0.846
Only chemotherapy	1	3	2	4	
Adjuvan chemotherapy					
Present	28	97	41	89	0.249
Absent	1	3	5	11	
Ki-67 ratio					
≤10	8	28	9	20	0.419
>10	21	72	37	80	
IDH					
Positive	15	52	23	50	
Negative	13	45	22	48	0.926
Unknown	1	3	1	2	
ATRX					
Positive	14	48	17	37	0.494
Negative	1	3	4	9	
Unknown	14	48	25	54	
EGFR					
Positive	10	35	19	41	
Negative	7	24	7	15	0.609
Unknown	12	41	20	44	

PLR: *Platelet to lymphocyte ratio,* ***KPS:*** *Karnofsky performance score,* ***IDH:*** *Isocitrate dehydrogenase,* ***ATRX:*** *α thalassemial mental retardation syndrome X-linked,* ***EGFR:*** *Epidermal growth factor.*

The median PFS for PLR<150 was 9 months, NLR<4 was 9 months too. These were not statiscically significant. Median PFS was 11 months in patients undergoing total resection and 10 months for Karnofsky performance scare (KPS)≥70 patients. In univariate analysis KPS≥70 (p=0.002), total surgical resection (p=0.040) were statistically significant for PFS (Table III).

In multivariate analysis, KPS≥70 (HR:2.96, 95% CI:1.68-5.21; p<0.001), type of surgical resection (HR:2.32, 95% CI:1.35-3.98; p=0.002) were statistically significant for PFS (Table IV).

The median OS for PLR<150 was 17 months (p=0.005), NLR<4 was 17 months (p=0.001) too. These were statiscically significant. Age, gender, Ki-67 ratio, adjuvant chemotherapy apply, IDH-ATRX-EGFR molecular analysis were not statistically significant. Median OS was 17 months in patients undergoing total resection (p=0,032) and KPS≥70 patients (p<0.001).

In univariate analysis PLR<150 (p=0.005), NLR<4 (p=0.010), KPS≥70 (p<0.001), total surgical resection (p=0.032) were statistically significant for OS (Table V).

In multivariate analysis, KPS≥70 (HR:2.72, 95% CI:1.30-5.67; p<0.007), type of surgical resection (HR:2.09, 95% CI:1.10-3.95; p=0.023), NLR>4 (HR:2.14, 95% CI:1.11-4.14; p=0.023) were statistically significant for OS were found to be independent prognostic factor (Table VI).

The median OS was significantly shorter in PLR>150 patients (10 vs 17 months; p=0.005) (Figure 2).

The median OS was significantly shorter in NLR>4 patients (11 vs 17 months) (p=0.010) (Figure 3).

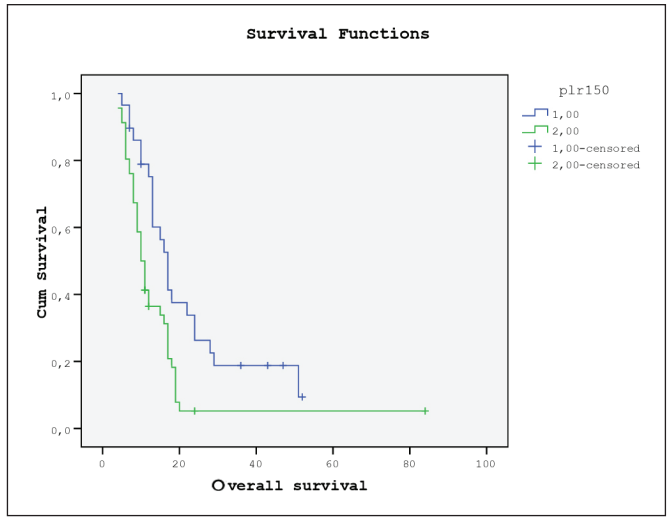


Figure 2: OS for PLR>150 and PLR≤150 patients.

Table III: Univariate Cox Regression Analyses for Progression Free Survival

Univariate analyses	1 year PFS (%)	2 year PFS (%)	Median PFS (month)	p
PLR				
≤150	41	11	9	0.060
>150	24	5	8	
NLR				
≤4	32	16	9	0.068
>4	27	4	8	
Surgery				
Total resection	47	7	11	**0.040**
Subtotal resection	16	6	7	
KPS				
≥70	41	11	10	**0.002**
<70	9	-	7	

PLR: *Platelet to lymphocyte ratio,* ***NLR:*** *Neutrophyl to lymphocyte ratio,* ***KPS:*** *Karnoffsky performance score.*

Table IV: Multivariate Cox Regression Analyses for Progression Free Survival

Multivariate analyses (PFS)	HR	95% CI	p
Surgery			
Total resection	1		
Subtotal resection	2.32	1.35-3.98	**0.002**
KPS			
≥70	1		
<70	2.96	1.68-5.21	**<0.001**

KPS: *Karnofsky performance score.*

Table V: Univariate Cox Regression Analyses for Overall Survival

Univariate analyses	1 year OS (%)	2 year OS (%)	Median OS (month)	p
PLR				
≤150	75	34	17	**0.005**
>150	41	5	10	
NLR				
≤4	76	41	17	**0.010**
>4	45	7	11	
Age				
≤50	82	19	17	0.070
>50	47	16	11	
Gender				
Female	46	12	11	0.327
Male	59	20	17	
Ki-67 ratio				
≤10	45	10	11	0.225
>10	57	18	15	
KPS				
≥70	67	27	17	**<0.001**
<70	35	-	9	
Surgery				
Total resection	80	14	17	**0.032**
Subtotal resection	35	14	10	
Adjuvant chemotherapy				
Absent	17	-	10	0.343
Present	57	18	13	
IDH				
Negative	47	11	11	0.066
Positive	61	22	17	
ATRX				
Negative	60	20	17	0.901
Positive	58	14	16	
EGFR				
Negative	43	9	10	0.286
Positive	62	21	17	

PLR: *Platelet to lymphocyte ratio,* ***NLR:*** *Neutrophyl to lymphocyte ratio,* ***KPS:*** *Karnofsky performance score,* ***IDH:*** *Isocitrate dehydrogenase,* ***ATRX:*** *α thalassemial mental retardation syndrome X-linked,* ***EGFR:*** *Epidermal growth factor.*

Table VI: Multivariate Cox Regression Analyses for Overall Survival

Multivariate analyses (OS)	HR	95% CI	p
Surgery			
Gross total resection	1		
Subtotal resection	2.09	1.10-3.95	**0.023**
NLR			
≤4	1		
>4	2.14	1.11-4.14	**0.023**
KPS			
≥70	1		
<70	2.72	1.30-5.67	**0.007**

NLR: *Neutrophyl to lymphocyte ratio,* ***KPS:*** *Karnofsky performance score.*

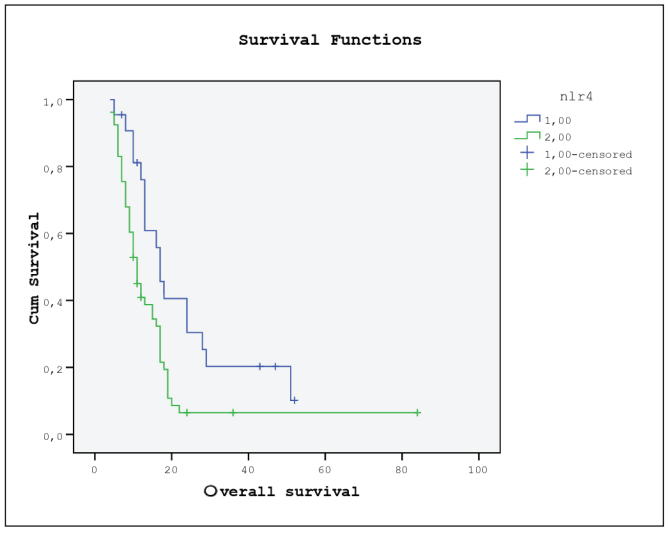


Figure 3: OS for NLR>4 and NLR≤4 patients.

Limitations

Some prejudices may be in this study. This was a retrospective research, first of all. And we were not analyze different prognostic factors and connections between in this study,like IDH-1 mutations, EGFR, ATRX etc. These crucial parameters are not known for all patients. MGMT status was not known too. Yet, this study concentreated on the connection between preoperatively hematological markers and clinical outcomes in GBM. When we look at these, they illustrate our limitations.

DISCUSSION

The relationship between hematological parameters for the prognoses of patients with GBMs are little known. NLR and PLR of GBM patients for PFS and OS were assessed limited number of studies, but the results are not clear. Some studies have demonstrate that high preoperative NLR is connected with bad prognosis and lower survival in GBM patients.PLR, another inflammatory marker, has been less researched as a prognostic factor in cancer patients compared to NLR.

As we know, 70< KPS value is worse survival indicator than the 70≥KPS value. In Simpson et al.'s study, in patients with gross total resection, in the frontal region of the tumor and high KPS ratio and < 40 years in GBM patients were observed the best OS (14). In our study, we observed better OS in patients with gross total resection and KPS ≥70 in accordance with the literature.

The outcomes of present study assess the relationship among with preoperative neutrophil-to-lymphocyte ratio and platelet-lymphocyte ratio, progression free survival and overall survival in patients with GBM. In our study, we observed that patients with high NLR values were associated with a poor OS and this was statistically significant. NLR elevation is associated with poor survival. The other marker, PLR was not significantly correlated with progression free survival or overall survival.

According to Lopes et al. in the subgroup analysis of patients who completed the stupp protocol, a higher NLR>7 was an independent prognostic factor in GBM patients for a poor overall survival (9). Mason et al. analyzed NLR values in postoperative GBM patients who generally taken corticosteroids, which effect the NLR values, and referred a cut-off value of 7.5. (11) That NLR values is very high compared ours. In our study, we found cut off value 4 for NLR.

Han et al. during a study conducted by 154 patients with glioblastoma, NLR was reported to be associate independent prognostic factor for survival (6). But, PLR was not significant prognostic factor for survival in multivariate analysis. We found that high NLR are related to poor prognosis and PLR is'nt significant prognostic factor as in Han et al.'s results.

Kaya et al. have confirmed that NLR may be used as a prognostic factor in glioblastomas patients based on peripheral blood counts prior to treatment, like us (8).

Neutrophil and lymphocyte counts are non-specific parameters which will be littered with coincident conditions like infection, inflammation, and medications (22). The blood-brain barrier is usually impaired in glioblastomas, which permit circulating lymphocytes to pass through (12). In cancer patients the quantitiy of neutrophils increases. This brings a relative decrease in the lymphocyte diversity. Thus, the tumour cells are suppress the immune cells. The mechanism of the increase in neutrophils and the decrease in lymphocytes has not been obviously detected (21,23). In present study, we found that the median lymphocyte level was lower with 1.6 (range:0.5-3.0) and also the neutrophil level was higher with 7.0 (range:2.4-22.0).

Zadora et al. retrospectively examined 424 patients with brain tumors and determinant a major relationship between tumour grade and NLR. The cut-off value of NLR was upper in glioblastoma patients and was 2,5 (21). This was lower than our study.

Bambury et al. examined the effect of SIR on prognosis in glioblastoma patients based on a retrospective evaluation of the patients. They considered SIR to be present in patients with NLR> 4. They also reported that the based on multivariate analysis the presence of SIR was an independent poor prognostic factor (2). In this study, we found that the prognosis was badly in patients with NLR> 4 patients.

Wang et al. taking into account the incidence of IDH mutation, assessed the prognostic value of NLR, PLR and LMR in glioblastoma patients, In patients with GBM, PLR and NLR have independent prognostic values (19). Hematological markers NLR, PLR were not related with IDH mutations in our study.

CONCLUSION

In present study, we found that prognostic factors that could be effective in GBM and our results in terms of progression free survival and overall survival were consistent with literature. In the future, we think that the findings of our retrospective

study will be confirmed by prospective studies. Preoperative higher NLR value is meaningful prognostic indicator for GBM patients.

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