

## RESEARCH ARTICLE

# Prognostic Significance of Indicators of Systemic Inflammatory Responses in Glioblastoma Patients

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### Abstract

**Background:** High-grade gliomas, with glioblastomas as the most frequently observed histologic subtype, are the most common primary brain tumours in adults. It is considered that inflammatory responses play a major role in malignancies, including tumour progression. This study aimed to determine the prognostic significance of the neutrophil to lymphocyte ratio (NLR) and the thrombocyte to lymphocyte ratio (PLR) as indicators of systemic inflammatory response (SIR) in glioblastoma patients. **Methods:** A total of 90 patients treated for glioblastoma were retrospectively evaluated. Absolute counts were used to generate NLR and PLR. A SIR was considered to be present with an NLR  $\geq 5$  and/or PLR  $\geq 150$ . **Results:** Median follow-up time was 11.3 months (range: 1-70 months). The 1-year and 2-year overall survival rates were 55.2% and 19.5%, respectively. Univariate analysis showed that there was no correlation between overall survival and gender ( $p=0.184$ ), comorbid disease ( $p=0.30$ ), clinical presentation ( $p=0.884$ ), or tumour lateralization ( $p=0.159$ ). Multivariate analysis showed that overall survival was significantly correlated with SIR based on NLR (HR: 2.41), and ECOG performance status (HR: 1.53). The prognostic factors that affected survival, other than SIR, were Eastern Cooperative Oncology Group (ECOG) performance status ( $p=0.003$ ), and tumour localization ( $p=0.006$ ). **Conclusion:** The present findings confirm that NLR based on peripheral blood counts prior to treatment can be used as a prognostic factor in patients with glioblastoma. Since tumour aggression increases and survival decreases as the NLR value rises, choice of treatment modality is facilitated for glioblastoma patients.

**Keywords:** Glioblastoma- prognosis- neutrophil to lymphocyte ratio- thrombocyte to lymphocyte ratio

*Asian Pac J Cancer Prev*, 18 (12), 3287-3291

### Introduction

High-grade gliomas, among which glioblastomas are the most frequently observed histologic subtype, are the most common primary brain tumours in adults. The incidence of glioblastoma in adults is 3-4/100,000 patients, versus 1/1,000,000 in children (Van Gool, 2015). The standard treatment for glioblastoma consists of maximal safe resection, followed by concomitant chemoradiotherapy using temozolomide and adjuvant temozolomide therapy, which is known as the Stupp protocol (Stupp et al., 2005). Despite advances in treatment, median survival in patients with glioblastoma is 12-15 months. Due to the high rate of mortality in patients with glioblastoma, researchers have been searching for prognostic factors other than age, Karnofsky Performance Status (KPS), etc.

In addition to such benign disorders as infectious and autoimmune diseases, malignancies can also cause chronic inflammation (Turkdogan et al., 2016; Hussein

and Ahmed, 2005). It was reported that the inflammatory response plays a major role in malignancy, including tumour progression (Grivennikov, 2010). Neutrophils and lymphocytes are immune cells, and are a part of the tumour microenvironment that plays a regulatory role in carcinogenesis. Even though the precise mechanism of systemic inflammatory response (SIR) in cancer patients is not known, hypoxia due to tumour necrosis, changes in neuroendocrine metabolism, synthesis of interleukin, and acute phase proteins are considered possible causes of SIR. SIR is reported to be associated with poor prognosis in patients with a variety of solid tumours (Forrest et al., 2003).

Recently, numerous studies reported that the neutrophil to lymphocyte ratio (NLR), based on the neutrophil and lymphocyte counts in peripheral blood, is a good indicator of SIR (Gunaldi et al., 2015; Atzpodien et al., 2003; Fogar et al., 2006). The neutrophil and lymphocyte counts in peripheral blood are also correlated with immune cell counts in tumour stroma (Pollard, 2004). As such, it was

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concluded that NLR is a simple and inexpensive method for detecting SIR. In addition to NLR, the thrombocyte to lymphocyte ratio (PLR) has also been investigated as an indicator of SIR (McMillan, 2009). The present study aimed to determine the prognostic role of the SIR indicators, NLR and PLR, in patients with glioblastoma.

## Materials and Methods

### Patients and Methods

Patients diagnosed as glioblastoma that were treated between 2011 and 2015 at Süleyman Demirel University, Department of Radiation Oncology, Isparta, Turkey, and Medicalpark Gaziantep Hospital, Gaziantep, Turkey, were retrospectively evaluated. Patients with a high-grade glioma other than glioblastoma, patients that had undergone blood transfusion  $\leq 3$  months prior to diagnosis, and those with active bleeding, bleeding diathesis, hyper or hypothyroidism, infection, disseminated intravascular coagulation, heparin treatment, or connective tissue diseases were excluded from the study. Patients that underwent a complete blood count and biochemical analysis, including liver and renal function tests, prior to receiving any treatment including steroids was analysed. NLR was calculated as the ratio of the absolute neutrophil count to the absolute lymphocyte count, and PLR was calculated as the ratio of the absolute thrombocyte count to the absolute lymphocyte count. SIR was considered to be present in patients with an  $NLR \geq 5$  and/or  $PLR \geq 150$ . Statistical analysis was performed using SPSS for Windows v.15.0 (SPSS, Inc., Chicago, IL). The logrank test was used for univariate analysis of survival. Prognostic factors for survival were analysed via Cox regression analysis (multivariate analysis). Survival rates were calculated using KaplanMeier survival analysis. Results were considered statistically significant when the type 1 error was  $< 0.05$ .

## Results

**Patient and tumour characteristics** Among the 90 patients analysed, 39 (43%) were female and 51 (57%) were male. Median age of the patients was 58.5 years (range: 16-93 years) (Table 1). Eastern Cooperative Oncology Group (ECOG) performance status was as follows: 0 (n = 34 (37.8%)); 1 (n = 16 (17.8%)); 2 (n = 25 (27.8%)); 3 (n = 15 (16.7%)). Comorbid disease was noted in 25 patients, and type II diabetes mellitus (n = 6) and essential hypertension (n = 6) were the most common. In total, 6 patients had both type II diabetes mellitus and essential hypertension.

Headache was the most common symptom at presentation (n = 35 (38.9%)). Neurological deficit, epileptic seizures, and syncope were observed in 30 (38.9%), 17 (18.9%), and 5 (8.9%) patients, respectively. In total, 87 (96.7%) patients were diagnosed as primary glioblastoma and 3 (3.3%) as secondary glioblastoma. Lesion lateralisation was the left hemisphere in 44 (48.9%) patients and the right hemisphere in 40 (44.4%). Tumour localisation was the frontal, temporal, and occipital lobes in 30%, 30%, and 6.7% of the patients, respectively.

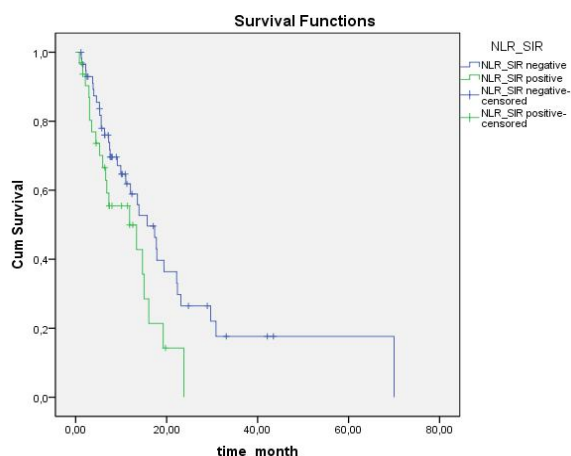


Figure 1. All Patients Survival

Tumour localisation could not be determined in 7 patients. Gross total excision was performed in 38 (53.3%) patients, whereas 34 (37.8%) patients underwent subtotal excision. In 6 patients biopsy only was performed. In 18 patients diagnostic procedures information was failed to obtain. Postoperatively, 11 patients received radiotherapy only, and 75 (83.3%) received chemoradiotherapy. Adjuvant temozolomide was given to 65% (n = 59) of the patients, and the median number of adjuvant treatment cycles was 6 (range: 1-12). Adjuvant treatment data were missing for 3 of the patients.

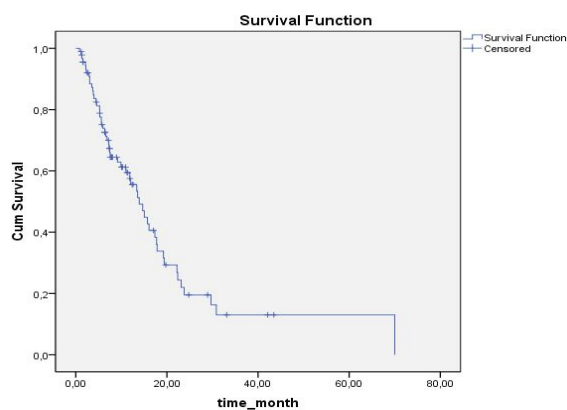


Figure 2. Survival According to SIR Based on NLR

Table 1. Laboratory Values of Patients

	Mean. Standard Deviation	Median
Age	55.7±16.3	58.5
AST (U/L)	22.2±10.8	20
ALT (U/L)	34.8±24.4	30
BUN (mg/dl)	17.3±8.3	15
Cre (mg/dl)	0.89±0.07	0.78
WBC (10 <sup>3</sup> /mm <sup>3</sup> )	8.34±3.31	7.6
HGB (g/dl)	12.9±1.6	13
PLT (10 <sup>3</sup> /mm <sup>3</sup> )	249.8±74.9	245
Neutrophils	7.89±5.0	6.1
Lymphocytes	1.84±1.06	1.7

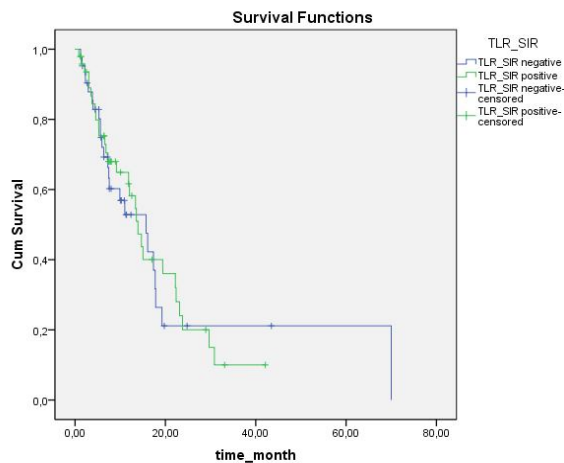


Figure 3. Survival According to SIR Based on PLR

### NLR, PLR, and SIR

Based on NLR values, SIR was present in 32 (35.6%) patients and absent in 58 (64.4%). Based on PLR values, SIR was present in 48 (53 %) patients and absent in 42 (46.7%). Median duration of follow up was 11.3 months (range: 1-70 months). The 1-year overall survival (OS) rate was 55.2%, versus 2-year OS of 19.5% (Figure 1). OS was significantly correlated with SIR based on NLR ( $P=0.048$ ) (Figure 2). In SIR-negative patients (according to NLR) median survival was  $15.7 \pm 2.5$  months (95% CI: 10.6-20.7), versus  $11.8 \pm 4.7$  months (95% CI: 10.4-18.9) in SIR positive patients (according to NLR). SIR based on PLR was not significantly correlated with OS ( $P = 0.854$ , Figure 3): however, OS in patients with SIR based on PLR tended to be shorter than in patients without SIR ( $13.9 \pm 1.5$  months (95%CI: 10.4-17.3) and  $15.7 \pm 3.8$  months (95% CI: 8.1-23.3), respectively). When the presence of SIR was based on NLR and PLR values above the limits mentioned above SIR was a prognostic factor for poor survival ( $P = 0.026$ ) (Figure 4). Median survival was  $16 \pm 2.2$  months (95% CI: 11.7-20.4) in patients without SIR, versus  $11.8 \pm 4.7$  months (95% CI: 2.6-21) in those with SIR. Univariate analysis showed that there wasn't a correlation between OS and gender ( $p = 0.184$ ), comorbid disease ( $p = 0.30$ ), clinical presentation ( $p = 0.884$ ), or tumour lateralisation ( $p = 0.159$ ). The only prognostic factors other than SIR that affected survival were ECOG performance status ( $p = 0.003$ ) and tumour localisation ( $p = 0.006$ ). Multivariate analysis showed that OS was significantly correlated with the presence of SIR (based on NLR) (HR: 2.41; 95% CI: 1.26-4.58) and ECOG performance status (HR: 1.53; 95% CI: 1.15-2.05).

### Discussion

The present retrospective study analysed the correlation between SIR and survival in patients with glioblastoma. The presence of SIR was a poor prognostic factor and OS was significantly shorter in patients with SIR. This correlation was stronger when SIR was based on the NLR value. PLR- another marker of SIR- was not significantly correlated with survival, but there was

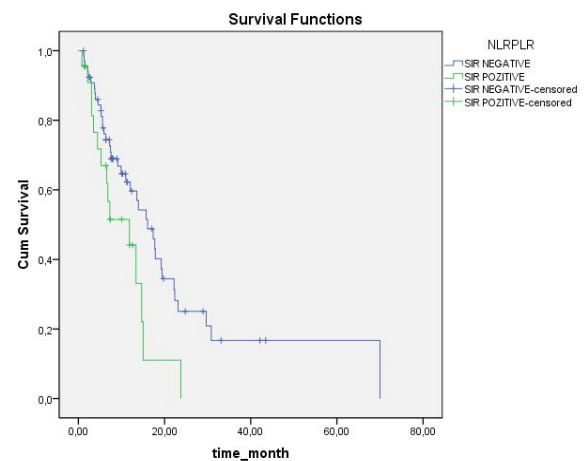


Figure 4. Survival According to SIR was Based on NLR and PLR Values Above the Limits Mentioned Above SIR

a trend toward shorter survival in the patients with SIR based on PLR. Recent studies reported the prognostic role of NLR in patients with a variety of solid tumours, including lung, gastric, extrahepatic cholangiocarcinoma, ovarian, and colorectal cancer, and in patients with liver metastasis of colorectal cancer (Halazun, et al., 2008; Sharma et al., 2008, Kitano et al., 2017). Inflammatory cells play a major role in tumour progression and an elevated neutrophil count in tumour stroma is a poor prognostic factor (Turkdogan et al., 2016). Cytokines and chemokine secreted by neutrophils increase tumour angiogenesis, which induces tumour progression and metastasis. NLR obtained via the peripheral blood count is a good indicator of inflammation in tumour stroma, and as an elevated neutrophil count in tumour biopsy specimens is prognostically important, inflammation based on NLR in peripheral blood is also of prognostic importance (Balkwill and Mantovani, 2001).

Inflammatory cells direct the interaction between tumour cells and the tumour microenvironment (Grivennikov et al., 2010; Del Prete et al., 2011). Hanahan and Weinberg (2011) showed that uncontrolled inflammation is a critical factor for tumour proliferation. Even though the underlying mechanisms are not fully known, the neutrophil count does increase in patients with cancer. Some hypothesised that inflammatory cytokines or reactive oxygen species secreted by tumour cells cause the neutrophil count to increase, both in tumour stroma and in peripheral blood. This increase in the neutrophil count causes a decrease in lymphocytes and lymphocyte apoptosis. In patients with locally advanced lung cancer a decreased lymphocyte count has been shown to be a poor prognostic factor and it was postulated that an elevated NLR could be a sensitive marker of tumour recurrence (Gregory and Houghton, 2011; McMillan, 2008).

The role of host immunity in glioblastoma biology was first suggested in an epidemiological study in which it was observed that the incidence of glioblastoma was lower in patients with a history of allergy (Schlehofer et al., 1999). Another study that evaluated pathological specimens of patients with glioblastoma reported that effector T-cell infiltration in tumour stroma was a good prognostic factor (Lohr et al., 2011). The underlying mechanisms of

the role of an elevated NLR in cancer prognosis are not fully understood. One possible mechanism is the driving force of systemic inflammation on secretion of angiogenic factors, growth factors, and other proneoplastic signals, as proposed by Hanahan and Weinberg (2011). An increase in the neutrophil count causes a decrease in the lymphocyte count, and as a result cellular immunity in other words, immunity against tumour cells is depressed (Zadora et al., 2015). Bambury et al., (2013) studied the effect of SIR on prognosis in patients with glioblastoma, based on retrospective evaluation of 84 patients. They considered SIR to be present in patients with an NLR >4. They also reported that based on multivariate analysis the presence of SIR was an independent poor prognostic factor. Furthermore, they showed that when NLR was added to nomograms that included age, ECOG performance status, and extension of surgical resection the index's concordance increased. Another retrospective study by Han et al., (2015) that included 154 patients with glioblastoma reported that NLR was an independent prognostic factor for survival. They reported that there was a significant correlation between NLR and PLR values, but that based on multivariate analysis PLR was not a significant prognostic factor for survival. They also studied the concordance between NLR, and the neutrophil count and CD3+ T-lymphocyte infiltration in tumour tissue, reporting that patients with an NLR >4 had an elevated neutrophil count and decreased CD3+ T-lymphocyte infiltration in tumour tissue. McNamara et al., (2014) reported the importance of NLR prior to reoperation for glioblastoma. They reported that patients with an NLR ≤4 had significantly longer survival (9.7 months) than those with an NLR >4 (5.9 months) (P = 0.02). Zadora et al., (2015) retrospectively studied 424 patients with brain tumours, and observed a significant correlation between tumour grade and NLR. The NLR cut-off value was highest in patients with glioblastoma and was 2.579 in patients with high-grade lesions.

The prognostic importance of NLR and PLR varies according to tumour type. Whereas PLR is a better prognostic factor for oesophageal cancer, NLR is a significantly better prognostic factor for endometrial cancer (Feng et al., 2014; Haruma et al., 2015). It has been shown that NLR is an important prognostic factor for glioblastoma (Han et al., 2015). In accordance with the literature, the present findings show that NLR is a better prognostic factor than PLR in patients with glioblastoma. The difference between the cut-off value noted in the present study and that in earlier studies might be due to differences in the populations studied.

The NLR cut-off value also varies according to tumour type; 5 for lung cancer, versus 2.56 for gastric cancer (Gunaldi et al., 2015; Kaya et al., 2013). Our study was done with patients from two separate centers. Blood count devices were different but, we think that our study does not affect the results of using different blood count devices because it contains the ratio for neutrophil lymphocytes and platelets. Furthermore, the present findings confirm that NLR based on the peripheral blood count prior to treatment can be used as a prognostic factor in patients with glioblastoma. As tumour aggression increases and

survival decreases as the NLR value increases, aggressive treatment modalities (such as new targeted therapies or immunotherapy) can be used in this selected patient population.

#### Conflict of interest

No conflict of interest.

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