Prognostic significance of neutrophil-to-lymphocyte ratio in glioblastoma

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ABSTRACT

Aim: The neutrophil-to-lymphocyte ratio (NLR) has prognostic value in patients with a variety of cancers. The purpose of this study was to investigate the prognostic value of NLR in patients with glioblastoma. **Methods:** A prospective study was conducted on patients receiving surgery for glioblastoma. Preoperative NLR was recorded and correlated with other prognostic factors and survival. **Results:** Fifty-one patients were included in the study. The mean NLR ratio was 6.7 ± 4.6. Using receiver operating characteristic curve analysis, an NLR cut-off value of 4.7 was determined to best predict survival. Patients with NLR ratios exceeding 4.7 differed significantly from those with NLR ratios ≤ 4.7 and were associated with reduced survival. Patients with gross total tumor excision had a median survival of 18 months, whereas the median survival time was 11 months in patients with subtotal tumor excision. No significant difference in survival was observed with respect to patient age, gender, Karnofsky performance status, or tumor location. Using multivariate analysis, NLR and extent of tumor resection were identified as factors with independent prognostic power. **Conclusion:** Neutrophil-to-lymphocyte ratio is an inexpensive, widely available biomarker of glioblastoma aggressiveness and should be used alongside current glioblastoma prognostic factors.

Key words: Glioblastoma, neutrophil-lymphocyte ratio, prognosis

INTRODUCTION

Glioblastoma is by far the most common type of primary brain tumor that occurs in adults. This devastating disease is usually incurable and, despite aggressive treatment, the median survival time remains in the range of 15 months.[1] Cancer-associated inflammation has been correlated with outcome in patients with cancer.[2-4] Among the various inflammation markers, the neutrophil-to-lymphocyte ratio (NLR) has been examined in a variety of cancers and has been found to be elevated in patients with more advanced or aggressive disease.[5-8] The exact mechanisms by which neutrophilia is induced by tumors is unclear.[9,10] The secretion of angiogenesis factors and cytokines has been implicated to play a role in neutrophilia induction.[11,12] In gliomas, lymphocyte infltration around the tumor has been associated with a better prognosis.[13] To the

best of our knowledge, only one study has assessed the role of NLR in glioblastoma patients.[14] In this study, we aimed to assess the prognostic value of NLR and correlate it with other prognostic factors of glioblastoma.

METHODS

Study population

We prospectively studied patients who received surgery for glioblastoma in our institute between March 2007 and September 2013. Patients were included if they had full blood count results at first presentation, before any treatment. The extent of resection was determined by comparing magnetic resonance imaging (MRI) scans obtained before surgery with those obtained within the 1st month after surgery. Clinical variables that were analyzed included age, sex, and preoperative Karnofsky performance status score (KPS). Radiological variables included tumor lateralization, location and volume. Tumor volumes were approximated from preoperative, postgadolinium T1-weighted MRI using a modified ellipsoid volume equation $(radius_x \times radius_y \times radius_z)/2$.[15] All patients received postoperative radiotherapy with temozolomide, followed by temozolomide chemotherapy

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for up to 1-year or until recurrence. Radiotherapy was administered as fractionated focal irradiation at a dose of 2 Gy/fraction given once a day for 5 days/week over a period of 6 weeks up to a total dose of 60 Gy. Follow-up MRIs were performed every 2 months. Recurrence was defined based on MRI and/or single photon emission tomography findings.[16] The study was approved by the Institutional Review Board.

Statistical analysis

Pearson's correlation coefficient was used to assess continuous variables. Progression-free survival (PFS) was defined as the time from the initial surgery to demonstration of tumor progression on follow-up MRI or to death. Survival time was defined as the time between the date of diagnosis and the date of death for deceased patients, or to the last follow-up for surviving patients. The overall survival time was estimated using Kaplan-Meier methods, and log-rank analysis was performed to compare survival curves between groups. Patients who were still alive at last contact were treated as censored events in the analysis. Multivariate Cox regression analysis of the data was used to analyze possible prognostic factors. The forward step-wise model selection procedure was used (P value of likelihood-ratio test < 0.05 as inclusion criteria; likelihood-ratio test > 0.10 as exclusion criteria) to define the final model. The following variables were entered: gender, age at diagnosis, KPS, NLR, and the extent of resection. With respect to NLR, receiving operating characteristics (ROC) curve analysis was performed in order to determine the cut-off value for predicting survival. A 2-sided P < 0.05 was considered as statistically significant.

RESULTS

Study population

Table 1 summarizes the patient data. Fifty-one patients (30 males, 21 females, mean age 59.2 ± 14.2)

Table 1: Patient data		
Patient characteristic	***n* (%)**	**OS P**
Gender		
Male	30 (58.8)	0.3
Female	21 (41.2)	
Age		
> 60	20 (39.2)	0.4
< 60	31 (60.8)	
KPS		
> 80	34 (66.7)	0.052
< 80	17 (33.3)	
NLR		
> 4.7	29 (56.8)	0.01
< 4.7	22 (43.2)	
Extent of resection		
GTR	32 (62.7)	0.036
STR	19 (37.2)	

KPS: Karnofsky performance status, GTR: gross total excision (> 95%), STR: subtotal excision (75-95%), OS: overall survival, NLR: neutrophil-to-lymphocyte ratio

met the inclusion criteria for the study. The majority of glioblastomas were lateralized, with 28 (54.9%) on the left and 21 (41.1%) on the right side. The most common tumor site was the temporal lobe (37.2%), followed by the occipital lobe (27.5%). The mean tumor volume was 32.1 ± 27.3 cm³. In 19 cases (37.2%), the tumor was located close to a ventricle. Thirty-four patients had a KPS over 80. In 32 cases, gross total excision was achieved, whereas in 19 cases there was subtotal tumor resection. One patient was lost to follow-up, and one patient died in the immediate postoperative period. After a mean follow-up period of 17 months (range: 3-39 months), 14 patients were alive.

Neutrophil-to-lymphocyte ratio

The mean NLR was 6.7 ± 4.6. Using ROC curve analysis, a cut-off NLR value of 4.7 was determined to best predict survival. Patients with an NLR exceeding 4.7 differed significantly from those with an NLR ≤ 4.7 and were associated with decreased survival time (11 *vs.* 18.7 months, P = 0.01) [Figure 1]. There was a significant increase in PFS for patients with an NLR lower than 4.73 (P = 0.03).

Extent of resection

Patients with gross total tumor excision had a median survival of 18 months, whereas in patients with subtotal tumor excision, the median survival time was 11 months. The difference was statistically significant (P = 0.036) [Figure 2].

Karnofsky performance status score

The median survival for patients with KPS over 80 was 17 months, whereas survival for patients with KPS under or equal to 80 was 11 months. However, the difference was marginally significant (P = 0.052). No significant difference in survival was observed with respect to patient age (P = 0.4) or gender (P = 0.3).

Tumor characteristics

In 19 cases, the tumor was located close to a ventricle. These patients were associated with reduced survival (P = 0.052). No prognostic significance was found for tumor location or laterality [Table 2]. No correlation was found between NLR and tumor volume.

Multivariate analysis

Using multivariate analysis, NLR (P = 0.011, 95% confidence intervals [CI]: 1.4-17.3) and extent of tumor resection (P = 0.025, 95% CI: 1.2-8.7) were identified as factors with independent prognostic power.

DISCUSSION

In the present study, we found that patients with an NLR over 4.7 were associated with reduced median overall survival. Patients with subtotal tumor excision
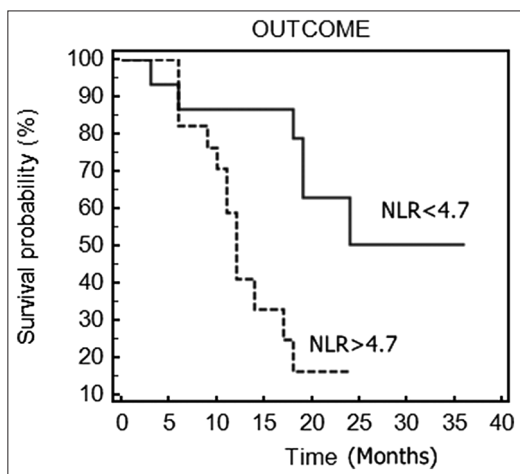
Figure 1: Relationship between neutrophil-to-lymphocyte ratio (NLR) index (cut-off = 4.7%) and survival in glioblastoma patients. NLR: neutrophil-to-lymphocyte ratio
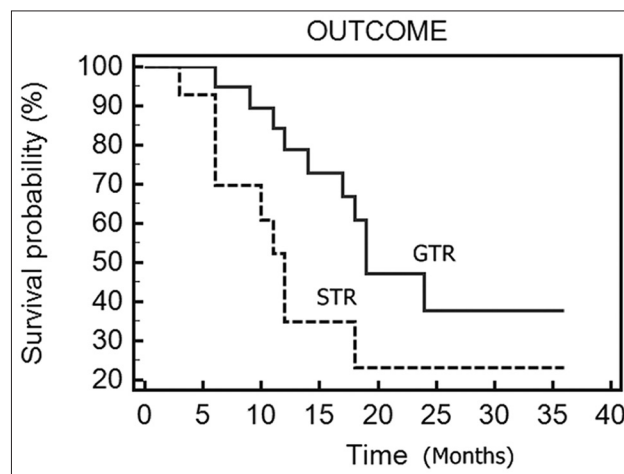

Figure 2: Representative Kaplan-Meier survival curve of patients grouped according to the extent of resection. GTR: gross total excision (> 95%); STR: subtotal excision (75-95%)

had reduced median overall survival compared with patients with gross total tumor excision. There was a trend toward increased survival for patients with KPS over 80 and tumors not related to the ventricular system.

In addition to genetic factors, systemic inflammatory response has also been implicated in carcinogenesis. Bambury *et al.* also studied the prognostic impact of the NLR in a cohort of patients with glioblastoma.[1] The authors studied 84 patients that had full blood count results available at first presentation with symptoms of glioblastoma, and the NLR was calculated. The results of this study showed that age over 65 years, gender, eastern cooperative oncology group performance status ≥ 2, frontal tumor, extent of surgical resection, completion of the adjuvant chemoradiation protocol, and NLR > 4 were significantly correlated with overall survival. The present study verified the above findings. Furthermore, we found no correlation between NLR and tumor volume. Patients with tumors not related to the ventricular system had a better prognosis.

In other cancer studies, a prognostic significance of NLR was found. A recent meta-analysis of 26 studies in primary liver cancer demonstrated that the high NLR can strongly predict poor survival in these patients, indicating the predictive value of the NLR as a new biomarker in primary liver cancer.[6] Furthermore, high NLR was associated with vascular invasion and correlated with alpha-fetoprotein levels. Proctor *et al.*[12] studied 12,118 patients who had been sampled within 2 years of their cancer diagnosis and found that NLR was independently associated with survival in all cancers studied.

Apart from NLR, other inflammatory markers have also been associated with patient prognosis. Steffens *et al.*[17]

Table 2: Tumor characteristics	
Parameter	**Proportion**
Tumor location (%)	
Frontal	15.7
Temporal	37.2
Parietal	13.7
Occipital	27.5
Multifocal	5.8
Laterality (%)	
Right	41.1
Left	54.9
Midline	4
Located near ventricle (%)	37.2
Tumor volume (cm³)	32.1 ± 27.3

have reported that a high preoperative serum C-reactive protein level is an independent predictor of poor survival in patients with renal cell carcinoma. In the present study, we verified the prognostic significance of gross total tumor excision. This is a well-established prognostic factor.[18] Karnofsky performance scale and age have been also associated with glioblastoma prognosis.[14,18] In the present study, there was a trend towards increased survival for patients with KPS over 80. Glioblastomas adjacent to the lateral ventricles have been suggested to harbor a dismal prognosis.[19,20] Neural and cancer stem cells have been found in the subventricular zone that lines the lateral ventricles.[20] Thus, tumors in this region may be more invasive with higher potential to recruit migratory progenitor cells.[20] In the present study, we verified the prognostic significance of tumors located adjacent to the ventricles.

In conclusion, our results are in agreement with Bambury *et al.*, as well as other reports of the prognostic significance of NLR in a variety of cancers.[2,3] NLR is an inexpensive and widely available biomarker of glioblastoma aggressiveness, and thus should be used alongside current glioblastoma prognostic factors. Nevertheless, there is obviously a need for future studies

with larger numbers of patients in order to confirm our preliminary observations.

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