Observational Study

Medicine

OPEN

Prognostic significance of systemic inflammatory parameters in high-grade glial tumor patients

Two center experience

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Abstract

We aimed to determine the prognostic values of the neutrophil-lymphocyte ratio, platelet-to-lymphocyte ratio, systemic immune-inflammation index, body mass index, and prognostic nutritional index scores in patients with high-grade glioma. This was a retrospective observational case series. Between 2015 and 2020, 79 patients with high-grade gliomas 2 oncology centers were included in our study. All patients ($n = 79$) had high-grade glial tumors and were treated with RT. Sixty-nine (87.3%) patients died, and the median 2 years overall survival was 12.7 months. Recurrence was observed in 25 (31.6%) patients at the end of the treatment. The median recurrence free survival was 24.4 months. There was no significant correlation between systemic inflammation indicators and survival parameters for OS and RFS. Only a marginally significant association between the neutrophil-lymphocyte ratio and RFS was found. Systemic inflammatory parameters and outcomes were not significantly correlated in patients with high-grade gliomas.

Abbreviations: BMI = body mass index, NLR = neutrophil-lymphocyte ratio, PLR = platelet-to-lymphocyte ratio, PNI = prognostic nutritional index, SII = systemic immune-inflammation index.

Keywords: Glial tumors, NLR, PLR, PNI

1. Introduction

Brain tumors account for only 2% of all cancers. In the United States, by 2022, an estimated 25,050 people will be diagnosed with malignant primary central nervous system (CNS) tumors. Overall prevalence rate of individuals with a brain tumor was estimated to be 209 per 100,000 in 2004 and 221.8 per 100,000 in 2010. However, their relationship with all cancers plays a significant role in morbidity and mortality, and these tumors cause approximately 18,280 deaths.[1] Brain tumors were classified according to their histopathological features. According to the World Health Organization classification, tumors are classified as low-grade or high-grade. High-grade brain tumors include anaplastic gliomas (anaplastic astrocytoma and anaplastic oligodendroglioma) and glioblastomas, which are aggressive and rapidly progressing. Treatment of high-grade brain tumors is more complex and difficult than low-grade ones.

Following maximum surgical resection, concomitant chemoradiotherapy (CRT) (with temozolomide) and adjuvant temozolomide are standard treatments for high-grade gliomas.[2,3] After standard treatment, high-grade tumors, in particular, have a poor prognosis and recurs.[4] Despite all the developments in oncological treatment modalities over the past 10 years, treatment options are limited for patients with recurrence. Prognostic and predictive molecular features based on molecular analysis are available for this group of patients. However, not all cancer centers can afford or implement molecular diagnostics. Consequently, there is a need for easier evaluation of the clinical and laboratory aspects. In this sense, prognostic information regarding glial tumors and many other malignancies is provided by systemic inflammatory indicators. There are limited studies in the literature showing the prognostic significance of systemic inflammation biomarkers for glioblastoma multiforme (GBM) patients.

Several studies have shown the predictive importance of systemic inflammatory biomarkers in patients with GBM. This study aimed to assess the predictive importance of clinicopathological characteristics and systemic inflammatory markers in patients with high-grade gliomas.

2. Methods

2.1. Patient selection

This study aimed to assess the predictive value of systemic inflammatory biomarkers in patients with high-grade gliomas.

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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How to cite this article: Oztep Eskici S, Yilmaz EB. Prognostic significance of systemic inflammatory parameters in high-grade glial tumor patients: Two center experience. Medicine 2024;103:16(e37726).

Received: 9 September 2023 / Received in final form: 27 February 2024 / Accepted: 5 March 2024

http://dx.doi.org/10.1097/MD.0000000000037726

This was a retrospective, observational study. Between 2015 and 2020, 79 patients from the radiation oncology departments of Mersin University and Mersin City Training and Research Hospital were included in this study. Those aged ≥18 years who underwent CRT due to histopathological diagnosis of GBM, those with adequate bone marrow reserve (Hemoglobin ≥ 10 g/dL, leukocyte ≥ 4,000 µL, platelet ≥ 100,000 µL), liver (aspartate amino transferase oralanine aminotransferase level < 5 below the upper limit), and 79 patients with kidney function (serum creatinine < 2 mg/dL), preoperative and postoperative brain magnetic resonance imaging (MRI) imaging, and postoperative surgery-CRT interval of 1 month were included. At the time of diagnosis, patients' laboratory findings and systemic inflammation biomarkers were recorded. Blood sample collection was timed after diagnosis in relation to treatment. The neutrophil-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), CLIGLI, body mass index (BMI), and prognostic nutritional index (PNI) were also calculated. Additionally, patients required adequate cerebral magnetic resonance imaging both before and after surgery. Patients who had previously (from diagnosis of glial tumor) received chemotherapy and/or cranial irradiation were excluded from this study. Before drawing blood samples from patients, corticosteroids were not administered.

2.2. Statistical analysis

The normality of the distribution of continuous variables was tested using the Shapiro–Wilk test. The Mann–Whitney *U* test was used to compare 2 groups for nonnormal data, and the chi-square test was applied to investigate the relationship between categorical variables. Kaplan–Meier method was used to estimate survival times, and univariate hazard regression analysis was used to estimate hazard ratios and 95% confidence intervals. Categorical variables were presented as frequency and percentage (%), and numerical variables were presented as mean ± standard deviation (mean ± SD) or median and interquartile range. Statistical analysis was performed using SPSS for Windows version 24.0, and statistical significance was set at $P < .05$.

2.3. Ethics statement

Before collecting patient data, our institutional ethics committee evaluated and approved the study protocol (Project No. E78017789-050.01.04-1733364, Mersin University—September 7, 2021) according to the Declaration of Helsinki regarding biomedical research involving human subjects and the Guidelines for Good Clinical Practice. Written informed consent was obtained from all patients legal guardians.

3. Results

3.1. Study patients

A total of 96 patients were reviewed, and 79 patients were included in the study. The median age of the patients was 58 (range 25–80) years, and 50 (63.3%) patients were male. At a median follow-up time of 9 (range 1.1–56) months for the whole group, 69 patients (87.3%) were died. The 2-year and 3-year overall survival rates were, respectively, 26.5% and 0.8%, with a median 2-year overall survival of 12.7 months (Fig. 1). The majority of the patients' tumors were found in the temporal lobe (*n*: 31, 39.2%). The median tumor size was 5 cm.[2–11] Edema and shift were both present at the time of diagnosis in 52 (65.8%) and 33 (41.8%) individuals, respectively. The patient and tumor characteristics are shown in Table 1.

Surgical treatment was performed in 52 (65.8%), and all patients received CRT. Recurrence was observed in 25 (31.6%) patients at the end of the treatments. The median recurrence free survival was 24.4 months (Fig. 2). Median NLR rates was 1.93 (1.06–6.74), median PLR was 114.29 (20.37–306.71), median SII 787.39 (120.19–2733.75), median CLIGLI was 50.13 (14.2–137.32), median PNI was 40.01 (22.92–49.62), and median BMI was 25.73 (18.21–41.26). The values of systemic inflammation biomarkers are shown in Table 2.

3.2. Outcomes

We investigated the potential associations between several prognostic factors. The following variables were subjected to a univariate analysis: age, sex, tumor size, rest, surgery, BMI, NLR, PLR, SII, CLIGLI, and PNI scores. In univariate analysis, no statistically significant correlation was found between systemic inflammation indicators and OS. However, it has been demonstrated that surgery can lower HR by 42%, and there is a strong correlation between age and OS (HR = 1.03, 95% CI = 1.01–1.05, $P = .006$). In univariate analysis, no statistically significant correlation was found between systemic inflammatory markers and RFS. However, a statistically significant relationship was found between NLR and RFS was found (HR = 1.34, $P = .054$). In the multivariate analysis, no statistically significant relationship was found between systemic inflammation markers and survival parameters. The association between systemic inflammatory markers and PFS and OS is shown in Tables 3–5.

4. Discussion

In our study, OS and RFS were estimated 12.7 months (2 years) and 24.4 months, respectively. We investigated the association between survival parameters and the NLR, PLR, SII, BMI, and PNI. However, there was no statistically significant relationship between these variables and the survival parameters. Only a marginally significant relationship was found between NLR and RFS (HR = 1.34, $P = .054$). Patients who did not undergo surgical treatment and elderly patients had poorer outcomes.

Malignant tumor prognosis is crucial information that is being researched globally. The genetic features of cancers can

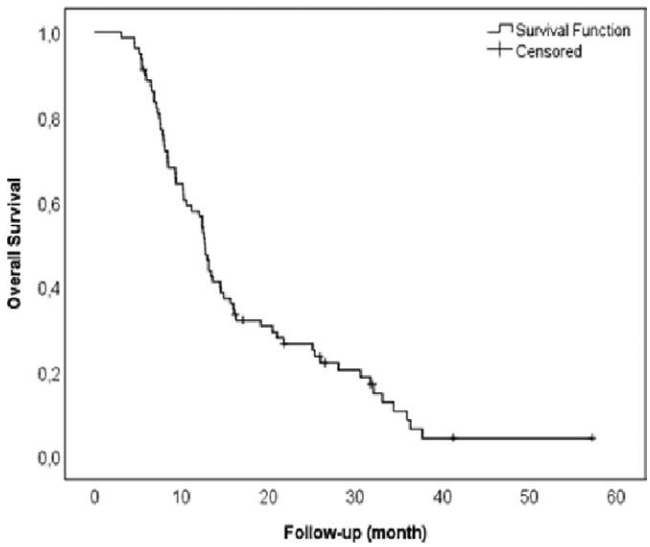

Figure 1. The 2- and 3-yr overall survival rates were, respectively, 26.5% and 0.8%, with a median 2-yr overall survival of 12.7 mo.

Table 1

Patient and tumor characteristics.

		n	%
Median age		58 (range 25–80)	
Gender	Female	29	36.7
	Male	50	63.3
BMI	<25	36	45.6
	≥25	43	54.4
Size		5.41 ± 2.02	5 (2–11)
Rest (*n* = 40)		4.46 ± 1.85	4.5 (1–9)
Satellit (*n* = 9)		2.56 ± 0.53	3 (2–3)
Edema	Yes	52	65.8
	No	27	34.2
Shift	Yes	33	41.8
	No	46	58.2
Recurrence	Yes	25	31.6
	No	54	68.4
Final status	Died	69	87.3
	Alive	10	12.7
GPS	0	63	79.7
	1	15	19.0
	2	1	1.3
Tumor location	Temporal lobe	31	39.2
	Parietal lobe	18	22.8
	Frontal lobe	13	16.5
	Occipital lobe	9	11.4
	Other sites	8	10.1
Surgery	Yes	52	65.8
	No	27	34.2

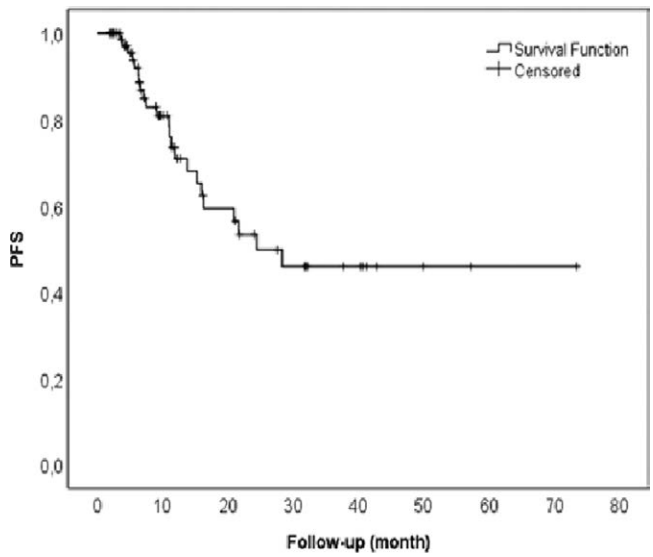

Figure 2. The median recurrence free survival was 24.4 mo.

be determined by molecular investigations and prognostic indicators can be established. However, given that not all facilities can employ these molecular tests and that they are expensive, it is imperative to identify prognostic markers based on clinical and laboratory results. As a result, research is being conducted using scoring techniques, including NLR, PLR, SII, BMI, PNI, and laboratory data, to determine the prognostic importance of systemic inflammatory markers in all cancers. According to several studies, higher levels of systemic inflammatory markers have been linked to a poor prognosis in a number of malignancies.[5] In several studies on glial tumors, systemic inflammatory markers have been found to be prognostic markers. These tests have the benefit of being reproducible and easy to identify.

Table 2

Values of systemic inflammation biomarkers.

	Descriptive statistics (*n* = 79)	
Variables	***n***	**%**
NLR	2.28 ± 1.02	1.93 (1.06–6.74)
PLR	117.96 ± 53.56	114.29 (20.37–306.71)
SII	844.56 ± 551.14	787.39 (120.19–2733.75)
CLIGLI	53 ± 22.25	50.13 (14.2–137.32)
BMI	26.26 ± 4.67	25.73 (18.21–41.26)
PNI	39.64 ± 4.59	40.01 (22.92–49.62)
Neutrophil	6.93 ± 2.95	5.9 (2.06–14.1)
Lymphocyte	3.14 ± 0.83	3.15 (1.15–5.4)
Platelets	347.8 ± 133.67	364 (108–810)

Wang et al found that NLR and PLR were prognostic factors in 141 GBM patients.[6] Similarly, Bambury et al[7] showed the prognostic significance of NLR in 137 patients with GBM. The results of the study by Kaya et al[8] in 90 glioblastoma patients in Turkey showed that NLR can be employed as a predictive factor. Han et al[9] showed the importance of the NLR for prognosis in 152 patients with GBM. Shi et al found that the SII had predictive relevance in 232 patients.[10] In a thorough meta-analysis, Peng et al showed that PNI and CONUT scores have predictive values in patients with glioblastoma.[11] In a meta-analysis involving 11 studies and 2928 patients with glial tumors, Liu et al found that serum albumin level, AGR, and PNI have predictive significance.[12] In contrast to these promising investigations, Lopes et al's[13] analysis of 139 GBM patients failed to demonstrate an association between a higher NRL and worse prognosis. Our study also examined broad systemic inflammatory markers; however, no statistically significant association was found. In addition, investigations of the significance of tumor localization in glial tumor prognosis have produced conflicting results. The most frequent tumor type in our analysis was temporal lobe cancer; however, no predictive differences were observed.

Our study's limitations include being retrospective, being limited to a small sample, and not considering additional molecular and clinical prognostic variables. Studies that will address these limitations will be more enlightening.

5. Conclusion

No significant correlation was observed between systemic inflammatory indicators and survival parameters in our study. However, studies using larger case series have shown the importance of these characteristics. Before making treatment decisions, it is critical to investigate these inexpensive and simple tests.

Acknowledgments

The authors thank the reviewers for their valuable comments on this manuscript.

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Table 3

Univariate hazard regression analysis results for overall survival and relapse free survival time.

	OS		RFS	
Variable	**HR (95% CI)**	***P***	**HR [95% CI]**	***P***
Gender	1.47 (0.89–2.43)	.129	1.11 (0.48–2.57)	.805
Age	1.03 (1.01–1.05)	.006	1 (0.96–1.03)	.867
Tumor size	0.96 (0.85–1.09)	.506	1.02 (0.84–1.23)	.863
Rest	1.15 (0.96–1.38)	.130	1.11 (0.87–1.41)	.408
Surgery	0.58 (0.35–0.96)	.033	0.53 (0.23–1.25)	.146
BMI	1.05 (0.66–1.69)	.828	1.3 (0.55–3.08)	.548
NLR	1.05 (0.85–1.29)	.667	1.34 (0.99–1.81)	.054
PLR	1 (0.99–1)	.784	1.01 (1–1.01)	.174
SII	1 (1–1)	.476	1 (1–1)	.496
CLIGLI	1 (0.99–1.01)	.555	0.99 (0.97–1.02)	.560
PNI	0.99 (0.94–1.03)	.594	1.02 (0.94–1.11)	.651

Table 4

Relationship between OS and systemic inflammatory parameters and clinical features.

	Final status		
Variables	**Exits (*n* = 69)**	**Alive (*n* = 10)**	***P***
Gender			
Female	24 (34.8)	5 (50.0)	.358
Male	45 (65.2)	5 (50.0)	
Age	59 (52–67)	49 (38–62)	.021*
Tumor size	5 (4–6.5)	5 (4.5–7.5)	.363
Rest	5 (3–5)	4 (3.5–5)	.843
BMI			
<25	31 (44.9)	5 (50.0)	.764
≥25	38 (55.1)	5 (50.0)	
Surgery	44 (63.8)	6 (80.0)	.312
NLR	1.94 (1.63–2.82)	1.9 (1.54–2.1)	.282
PLR	115.71 (87.39–141.85)	106.06 (76.23–127.46)	.658
SII	790.28 (383.14–1263.91)	709.26 (395.38–926.21)	.461
CLIGLI	50 (35.9–62)	64.3 (44.3–80.9)	.200
PNI	40 (37–42.7)	39.8 (38.9–43.4)	.417

*Significant at .05; Mann–Whitney *U* test for numerical, chi-square test for categorical variables.

Table 5

Relationship between RFS and systemic inflammatory parameters and clinical features.

	Recurrence		
Variables	**Yes (*n* = 25)**	**No (*n* = 54)**	***P***
Gender			.681
Female	10 (40)	19 (35.5)	
Male	15 (60)	35 (64.8)	
Age	53 (49–61)	59 (52–67)	.058
Tumor size	5 (4–7.5)	5 (4–6.5)	.635
Rest	5 (3–6)	4 (3.5–5)	.319
BMI			.243
<25	9 (36)	27 (50)	
>=25	16 (64)	27 (50)	
Surgery	14 (56)	38 (70.4)	.210
NLR	2 (1.63–3.15)	1.9 (1.59–2.61)	.337
PLR	127.46 (76.23–152.8)	110.91 (89.05–133.68)	.210
SII	837.88 (411.67–1249.13)	762.58 (383.14–1140.95)	.584
CLIGLI	49.95 (33.25–72.62)	50.17 (37.71–62.17)	.704
PNI	39.81 (38.81–40.81)	40.02 (37.01–43.42)	.658

Supervision: Sukran Oztep Eskici, Eda Bengi Yilmaz.
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