ORIGINAL ARTICLE

Systemic Inflammatory Markers for Prediction of Bevacizumab Benefit in Glioblastoma Multiforme

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ABSTRACT

Objective: To evaluate the predictive significance of systemic inflammation markers (SIMs) in patients with glioblastoma multiforme (GBM), who were treated with bevacizumab (Beva).

Study Design: Descriptive study.

Place and Duration of Study: The study was conducted at the Bezmialem Vakif University School of Medicine Hospital, Istanbul, Turkey, from January 2014 to September 2019.

Methodology: A total of 107 patients, 49 (45.8%) female and 58 (54.2%) male, were retrospectively included in the study. The cut-off values for the SIMs–C-reactive protein to albumin ratio (CAR), neutrophil to lymphocyte (NLR) platelet to lymphocyte ratio (PLR), and systemic immune-inflammatory index (SIII))–were defined by receiver operating characteristic (ROC) analysis. Overall survival (OS) was plotted using the Kaplan-Meier method and compared using the log-rank test. Cox regression analysis was performed for univariate and multivariate analyses.

Results: ROC analysis was performed to determine the optimal prognostic value of each parameter. CAR: 1.32, NLR: 2.9, PLR: 159, and SIII: 785 were determined as cut-off values for predicting OS based on the areas under the curve (AUC) in the ROC analysis. CAR at 0.626, had sensitivity of 67%, and specificity of 71% (p=0.129); NLR at 0.725 had sensitivity of 67%, and specificity of 79% (p=0.007); PLR at 0.675 had sensitivity of 67%, and specificity of 64% (p=0.036); and SIII at 0.685, had sensitivity of 56%, and specificity of 71% (p=0.026). A multivariate analysis demonstrated that CAR (p=0.006) and PLR (p=0.024) were independent prognostic factors for OS in patients with GBM, treated by Beva.

Conclusion: The present study's findings suggest that pretreatment CAR and PLR might be an independent predictive marker for patients with GBM, who are treated by Beva.

Key Words: *C-reactive protein-to-albumin ratio (AR), Glioblastoma multiforme, Neutrophil-to-lymphocyteratio (NLR), Platelet-to-lymphocyte ratio (PLR), Predictive score.*

INTRODUCTION

More than half of central nervous system (CNS) tumors consist of grade 4 gliomas (glioblastoma multiforme, GBM), and the five-year overall survival (OS) varies between 1% and 19%, depending on age.[1] The primary treatment of GBM patients is gross total resection and adjuvant radiotherapy (RT) plus temozolomide (TMZ).[2] In recurrent GBM patients, re-excision contributes to the survival of some patients.[3] However, the disease eventually recurs despite all local treatments.

Palliative systemic treatments are used in GBM patients for whom local treatments are not appropriate, but options are limited. TMZ is the only option in first-line systemic therapy, if the patient progresses after a long adjuvant interval. Options after TMZ are carmustine/lomustine, bevacizumab (Beva), and PVC.[4]

GBM is a tumor that shows high vascularity and expresses a very high rate of vascular endothelial growth factor (VEGF)-A. In addition, VEGF-A expression is associated with poor survival in GBM patients.[5] Beva is a recombinant, humanised monoclonal antibody against VEGF-A and inhibits its interaction with VEGFR 1/2 and neuropilins.[6] Despite this, although Beva improved the quality of life and progression-free survival (PFS) in GBM patients, it did not contribute to OS.[7] Many molecules and pathways related to the treatment resistance of Beva have been defined. Still, this issue has not yet been fully clarified, and, today, there is no established marker predicting Beva's response.[8] However, the detection of Beva's predictive markers is vital for optimising individualised therapy.

Many prognostic factors other than VEGF-A have been described in GBM patients, such as Karnofsky performance status (KPS) and age and genetic alterations including methylguanine-DNA methyltransferase (MGMT), isocitrate dehydrogenase (IDH), and telomerase reverse transcriptase (TERT).[9] It has been shown that systemic inflammation markers (SIMs) are associated with a bad prognosis in other cancer types.[10] However, prognosis studies of SIMs in GBM patients are inconsistent and have generally been investigated in patients receiving adjuvant therapy.[11] Due to the role of neutrophil in neoangiogenesis in GBM patients, SIMs may be an important prognostic and predictive factor.[12] Interestingly, the relationship between Beva treatment responses and SIMs in GBM patients has not been adequately studied.

In this study, the purpose was to evaluate the predictive importance of SIMs such as neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), C-reactive protein (CRP) to albumin ratio (CAR), and systemic immune-inflammatory index (SIII) in GBM patients receiving Beva treatment.

METHODOLOGY

In this descriptive study, archived records between January 2014 and September 2019 for all GBM patients in Bezmialem Vakif University Hospital, Turkey, were used. To be eligible, patients had to meet the criteria of having received two series of treatments including undergoing at least two months of Beva treatment, aged 18 to 80 years, having a histologically proven GBM (except anaplastic astrocytoma and anaplastic oligodendroglioma), having available contrast-enhanced pre- and post-operative magnetic resonance imaging (MRI) scans, and a pre-systemic treatment complete blood count and blood chemistry tests. The exclusion criteria were patients who were not in follow-up or who showed other inflammatory conditions including heart failure, liver cirrhosis, or end-stage renal disease before initiating systemic treatment.

All eligible patients initially underwent neurosurgical tumor extirpation with the end goal of maximal safe resection, if judged appropriate. Following the neurosurgical intervention, three-dimensional conformal RT or simultaneous integrated boost intensity-modulated RT to a total dose of 60 or 70 Gy (2.0 or 2.33 Gy/fx, five days a week) over six weeks was delivered by using linear accelerators. Concurrent TMZ (75 mg/m^2, seven days a week) was administered from the first until the last day of RT. All patients received standard pneumocystis jirovecii prophylaxis with trimethoprim-sulfamethoxazole during the concurrent chemoradiotherapy phase. In the adjuvant phase, patients received up to 12 cycles of maintenance TMZ (150 or 200 mg/m^2/d) for five days every 28 days. In the first-line treatment, TMZ (150 or 200 mg/m^2/d) for five days every 28 days treatment was continued until progression or intolerance in patients who were not suitable for surgery and RT after progression and who progressed six months after adjuvant therapy. Beva (10 mg/Kg) for every two weeks of treatment was continued until progression in the second-line treatment. If there were no symptoms, the patients were followed every three months with a gadolinium-enhanced MRI. Patients with symptoms were evaluated immediately.

Values for NLR, PLR, SIII, and CAR were calculated. Blood samples were obtained before the initial treatment to measure levels of CRP (mg/dL), albumin (g/L), and hemoglobin (Hb). White blood cells (WBC), neutrophil, lymphocyte, and platelet (Plt) counts were also determined. NLR and PLR were defined as absolute neutrophil count, and platelet counts were divided by the total lymphocyte count. SIII was calculated with the formula '(neutrophils × platelets)/lymphocytes.'

Statistical data were obtained using SPSS for Windows, Version 24.0 (SPSS Inc., Chicago, IL, USA). Qualitative variables were described by frequencies and percentages, continuous and ordinal variables by mean ±S.D., and median and interquartile ranges (IQRs). First, the Kolmogorov-Smirnov test was applied to determine whether the data were in the normal range of distribution. The Pearson χ^2 test was used to compare qualitative variables. The characteristics of patients were evaluated with descriptive analysis. ROC analysis was used to determine the cut-off values of inflammation markers. Survival analysis was performed by means of Kaplan-Meier survival curves and the log-rank test. Univariate and multivariate Cox proportional hazard models were used to identify predictors of overall survival. Hazard ratios (HRs) with 95% confidence intervals (CIs) were used to quantify the indexes estimating the survival. Hazard ratios of >1.0 indicated an increased likelihood of death. A two-sided p-value of <0.05 was deemed statistically significant.

RESULTS

The clinicopathological characteristics of the patients are shown in Table I.

A total of 107 patients with GBM were identified in the institutional database. Fifty-eight (54.2%) patients were males, and 49 (45.8%) patients were females. The median age of the patients was 47.2 ± 12.1 years [<50 years patients (54/107, 50.5%)]. Eighty-two (76.6%) patients' ECOG PS was 0-1 at the time of diagnosis. The other patients' ECOGPS was 25 (23.4%). The most common localisations were the frontal lobe, 32 (29.9%); the temporal lobe, 30 (28.0%); the parietal lobe, 22 (20.6%); and others, 23 (21.5%). Primary GBM developed in 95 (88.8%) patients, and GBM secondary to low-grade glioma developed in 12 (11.2%) patients. Ki-67 was ≤20% in 61 patients (57%), and Ki-67 was> 20% in 46 patients (43%). P53 mutation was detected in 54 patients (50.5%). IDH mutation was detected in 23 patients (25%). Surgery was performed on 94 patients. Total excision was performed in 73 patients (77.7%) and subtotal excision in 21 patients (22.3%). All of the patients we evaluated received RT. While nine of these patients (8.4%) received RT alone, 98 patients (91.6%) received TMZ plus RT. One hundred five patients (98.1%) received adjuvant TMZ after chemoradiotherapy. The median duration of the use of TMZ was six months (IQR 25-75: 2-24). After progression, 16 of the patients (15%) received re-TMZ treatment and used it for a median of five months (IQR 25-75: 2 to 10).

Table I: Demographic features and tumor characteristics of the patients.

Gender
  Female
  Male
	49/107 (45.8%)
	58/107 (54.2%)
		Age (mean±sd)	47.2±12.1

Age
  ≤50
  >50
	54/107 (50.5%)
	53/107 (49.5%)
		ECOG PS
		  0-1
		  2+
			82/107 (76.6%)
			25/107 (23.4%)

Tumor localisation
  Frontal
  Temporal
  Parietal
  Others
	32/107 (29.9%)
	30/107 (28%)
	22/107 (20.6%)
	23/107 (21.5%)
		Type of surgery
		  Complete resection
		  Partial resection
			73/94 (77.7%)
			21/94 (22.3%)

Ki 67
  ≤20
  >20
	61/107 (57%)
	46/107 (43%)
		P53 status
		  Mutated
		  Non mutated
			54/107 (50.5%)
			53/107 (49.5%)

IDH-1 status
  Mutated
  Non-mutated
	23/92 (25%)
	69/92 (75%)
		First line treatment
		  RT
		  RT+Temozolamid
			9/107 (8.4%)
			98/107 (91.6%)

Origin
  Primer GBM
  Seconder GBM
	95/107 (88.8%)
	12/107 (11.2%)
		Second line Temozolamid
		  Present
		  Absent
			16/107 (15%)
			91/107 (85%)

Gamma knife
  Present
  Absent
	23/107 (21.5%)
	84/107 (78.5%)
		Adjuvant Temozolamid
		  Present
		  Absent
			105/107 (98.1%)
			2/107 (1.9%)

ECOGPS: Eastern cooperative oncology group performance status, TMZ: Temozolomide, IDH: İsocitrate dehydrogenase, HR: Hazard ratio, GBM: Glioblastoma multiforme.

Table II: Prognostic factors of overall survival with bevacizumab treatment.

		Univariate analysis HR (%95 CI)	p-value	Multivariate analysis HR (%95 CI)	p-value
Gender	Male Female	Reference 1.25 (0.83-1.88)	p=0.289		
Age	≤50 >50	Reference 0.78 (0.51-1.19)	P=0.246		
ECOGPS	0-1 2+	Reference 4.54 (2.71-7.59)	P<0.001	Reference 3.74 (2.20-6.38)	p<0.001
Localisation	Frontal Parietal Temporal Others	Reference 0.77 (0.42-1.39) 0.73 (0.42-1.25) 1.03 (0.59-1.80)	p=0.384 p=0.249 p=0.926		
Origin	Primer GBM Seconder GBM	Reference 1.78 (0.94-3.36)	p=0.075		
Ki 67	≤20% >20%	Reference 1.10 (0.73-1.65)	p=0.655		
P53 mutation	Absent Present	Reference 1.02 (0.68-1.54)	p=0.913		
IDH mutation	Present Absent	Reference 1.14 (0.68-1.90)	p=0.629		
Surgery	Total excision Partial excision	Reference 1.39 (0.83-2.33)	p=0.210		
Re TMZ	Present Absent	Reference 1.04 (0.59-1.85)	p=0.890		
Gamma knife	Present Absent	Reference 1.48 (0.87-2.51)	p=0.149		
CAR	≤1.32 >1.32	Reference 2.27 (1.45-3.55)	P<0.001	Reference 1.92 (1.21-3.05)	p=0.006
NLR	≤2.9 >2.9	Reference 1.78 (1.15-2.75)	P=0.009	Reference 1.38 (0.87-2.17)	p=0.170
PLR	≤159 >159	Reference 1.78 (1.15-2.76)	P=0.010	Reference 1.66 (1.07-2.59)	p=0.024
SIII	≤785 >785	Reference 1.65 (1.08-2.50)	P=0.020	Reference 0.96 (0.53-1.73)	p=0.898

ECOGPS: Eastern cooperative oncology group performance status, HR: Hazard ratio, CI: confidence interval, CAR: C-reactive protein albumin ratio, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, SIII: Systemic immune inflammation index.

All patients who progressed after TMZ received Beva treatment. After the first progression, 23 (21.5%) patients received gamma knife treatment.

Patients' inflammation parameters (NLR, PLR, SIII, and CAR values) were recorded. ROC analysis was performed to determine the optimal predictive value of each parameter. Accord-

ingly, NLR: 2.9, PLR: 159, SIII: 785, and CAR:1.32 were determined as cut-off values for predicting OS based on the areas under the curve (AUC) in the ROC analysis. CAR at 0.626, had sensitivity of 67%, and specificity of 71% (p=0.129); NLR at 0.725 had sensitivity of 67%, and specificity of 79% (p=0.007); PLR at 0.675 had sensitivity of 67%, and specificity of 64% (p=0.036); and SIII at 0.685, had sensitivity of 56%, and specificity of 71% (p=0.026). NLR >2.9 (ORR: 51.4% *vs.*48.6%, p = 0.007), PLR >159 (ORR: 54.3% *vs.* 45.7%, p = 0.014), and SIII >785 (ORR: 42.9% *vs.* 57.1%, p = 0.007) were associated with a worse objective response rate (ORR). CAR >1.32 (ORR: 58.6% *vs.* 41.4%, p = 0.363) could not be demonstrated with ORR.

Survival analysis of patients treated with first line TMZ and second line Beva as systemic therapy was performed after Beva treatment started. All these patients were followed up with the best supportive care after Beva. The median follow-up after initiation of Beva was 8.4 (2.2-60.1 months) months. Patients' median OS after Beva initiation was 8.4 months (7.2-9.6, CI 95%), One-year OS was 29%, and two-year OS was 12%, respectively.

The effect of SIMs on the survival of patients treated with Beva was evaluated. The patients were divided into two groups: CAR ≤1.32 and >1.32. Median survival was 11.9 months (9.0-14.8 months, 95% CI) in the first group and 7.7 months (6.4-8.9 months, 95% CI) in the second group. At the time of diagnosis, survival was significantly worse in patients with CAR> 1.32 (p <0.001, Figure 1). The patients were divided into two groups: NLR ≤2.9 and> 2.9. The median OS was 9.8 months (6.8-12.7 months, CI 95%) in the first group and 8.1 months (7.2-9.0 months, CI 95%) in the second group. NLR> 2.9 was found to be associated with a worse prognosis. (p = 0.008, Figure 1). The patients were divided into two groups: PLR ≤159 and> 159. Median survival was 9.5 months (6.0-13.0 months, 95% CI) in the first group and 8.0 months (6.5-9.5 months, 95% CI) in the second group. PLR> 159 was found to be associated with a worse prognosis (p = 0.009, Figure 1). The patients were divided into two groups: SIII ≤785 and >785. Median survival was 9.4 months (6.9-11.9 months, 95% CI) in the first group and eight months (6.9-9.1 months, 95% CI) in the second group. SIII >785 was associated with a significantly poor prognosis, p = 0.018, Figure 1).

Univariate and multivariate analyses were performed to assess the predictive value for OS in all patients. Univariate and multivariate Cox regression analyses are summarized in Table II.
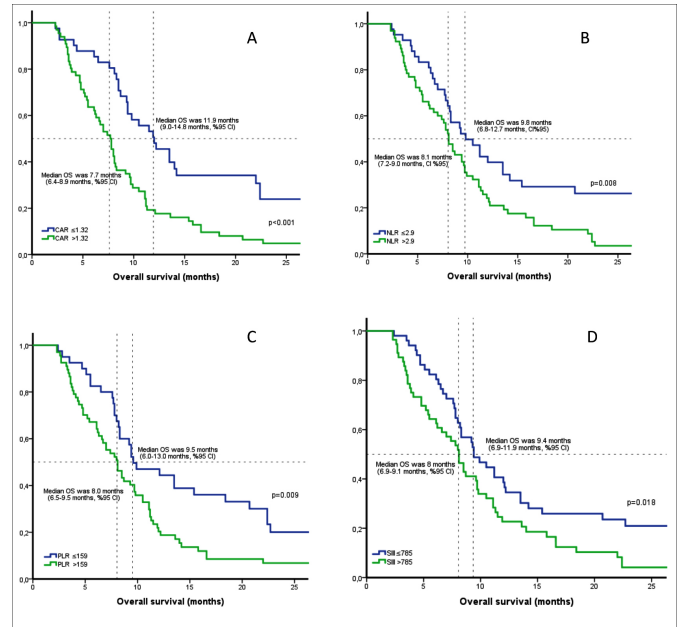

Figure 1: Kaplan-Meier curves according to SIMs of overall survival. (A) Kaplan-Meier curves according to CAR (≤1.32 and >1.32), (B) Kaplan-Meier curves according to NLR (≤2.9 and >2.9) of overall survival, (C) Kaplan-Meier curves according to PLR (≤159 and >159) of overall survival, (D) Kaplan-Meier curves according to SIII (≤785 and >785) of overall survival.
CAR: C-reactive protein albumin ratio, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, SIII: Systemic immune inflammation index, OS: Overall survival, CI: Confidence interval).

The ECOGPS level of ≥2 HR: 4.54 (2.71-7.59) p<0.001was found to be associated with worse survival. Among the systemic inflammation parameters, CAR >1.32: HR: 2.27 (1.45-3.55) p <0.001, NLR >2.9: HR: 1.78 (1.15-2.75) p = 0.009, PLR >137: HR of 1.78 (1.15-2.76), p = 0.010, and SIII >785 HR: 1.65 (1.08-2.50) p = 0.020 were significantly associated with an increased risk of death. In multivariate Cox regression analysis, CAR >1.32 HR: 1.92 (1.21-3.05, p = 0.006, PS ≥2 HR: 3.74 (2.20-6.38) p <0.001 and PLR >159 HR: 1.66 (1.07-2.59) p = 0.024 showed an increased risk of death.

DISCUSSION

In the present study, the predictive value of pretreatment CAR, PLR, NLR, and SIII was assessed in patients with GBM, who were treated by Beva. It was demonstrated that elevation in all of the inflammatory markers was correlated with poor OS, but only elevated CAR and PLR was found to be an independent predictive factor compared to NLR and SIII by multivariate analysis. The results consistently showed that increased CAR and PLR are significantly associated with a shorter OS and serves as an independent predictive factor for patients with GBM, who were treated by Beva.

This is the first study to show the predictive importance of traditional SIMs in the Beva treatment of GBM patients. Surgery and adjuvant radiotherapy plus TMZ have improved survival in GBM patients, but five-year OS is still at approxi-

mately unacceptable levels, approximately 10%.[1] Although Beva contributed to PFS and quality of life in GBM patients, who progressed under TMZ treatment, it did not improve OS.[7] However, as seen in this study, there may be patients who benefit from Beva treatment for a long time in some patient subgroups. Therefore, the markers that predict the treatment of Beva will contribute to individualized treatment.

The relationship between inflammation and the development of carcinogenesis in glioma patients was shown.[13] Positive phase reactants (*e.g.,* CRP, sedimentation, neutrophil, platelet) increase; while negative phase reactants, such as albumin, decrease using mediators released from necrotic cells in cancer tissue.[14] Because of the decrease in albumin, while CRP increases, CAR is accepted as a rational method in cancer studies.[15]

CRP is an essential parameter for evaluating inflammation, but it may increase for many other reasons. Because of this, it is difficult to show its real importance in GBM patients.[16] Although the decrease in albumin is associated with inflammation, it is also affected by the patient's nutritional state. Therefore, it is questionable to associate albumin's prognostic significance with inflammation only in GBM patients.[17] The prognostic significance of the Glasgow prognostic score (GPS), which uses both CRP and albumin levels in GBM patients, has been demonstrated.[18] A study showing the prognostic significance of CAR in GBM patients treated with adjuvant CRT was recently published.[19]

The prognostic and predictive significance of PLR could not be demonstrated in studies conducted with GBM patients. However, in this study, PLR was predictive and prognostic in GBM patients treated with Beva.[20] The authors could not show the prognostic and predictive importance of SIII. Unlike this study, Topkan *et al.* showed that SIII is a prognostic factor in patients with GBM who received adjuvant therapy.[21]

NLR's predictive and prognostic significance could not be demonstrated while the studies that inspired this study showed the predictive importance of NLR in cancer types other than GBM treated with Beva.[22,23] Bertaut *et al.* showed that an increase in the pre-treatment neutrophil count in GBM patients improved the Beva treatment response.[24] Conversely, studies show that the increase in NLR is a poor prognostic factor.[25] However, contrary to all these contradictory studies, the prognostic or predictive significance of the increase in NLR in GBM patients in this study could not be shown. More studies are needed in GBM patients treated with Beva to elucidate the importance of NLR.

The limitations of this study are its retrospective, single--centre design, the lack of MGMT result, and the relatively small number of patients.

CONCLUSION

The prognostic significance of SIMs and predictive impor-

tance of CAR and PLR in GBM patients receiving second-line Beva treatment was demonstrated. If confirmed in larger prospective patient groups, CAR and PLR may contribute to the individualised treatment decision of GBM patients as an objective, cheap, and easy predictive tool.

ETHICAL APPROVAL:
The Clinical Research Ethics Committee of Bezmialem Vakif University approved the study, prior to initiation of the research work.

PATIENTS' CONSENT:
This study was retrospective and covered the years 2014-2019. It was often difficult to reach patients from the previous seven to eight years, because some of these patients did not have contact information, and some of them have died. For these reasons, informed consent could not be obtained from patients.

CONFLICTS OF INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
MB: Conception, design, supervision, resources, materials, data collection and processing, analysis and interpretation, literature search, writing manuscript, and critical review.
ATMS: Design, supervision, resources, materials, data collection and processing, literature search, writing manuscript, and critical review.
AIY, AT, HMT: Resources, materials, data collection, and processing.
TD: Conception, design, supervision, resources, materials, data collection and processing, literature search, writing manuscript, and critical review.

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