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-lymphocyte ratio (NLR), Platelet-to-lymphocyte ratio (PLR), Predictive score.

How to cite this article: Besiroglu M, Shbair AT, Yasin AI, Topcu A, Turk HM, Demir T. Systemic Inflammatory Markers for Prediction of Bevacizumab Benefit in Glioblastoma Multiforme. J Coll Physicians Surg Pak 2021; 31(01):39-44.

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.

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.⁴ Beva is a recombinant, humanised monoclonal antibody against VEGF-A and inhibits its interaction with VEGFR 1/2 and neuropilins.⁵ 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). It has been shown that systemic inflammation markers (SIMs) are associated with a bad prognosis in other cancer types. However, prognosis studies of SIMs in GBM patients are inconsistent and have generally been investigated in patients receiving adjuvant therapy. Due to the role of neutrophil in neoangiogenesis in GBM patients, SIMs may be an important prognostic and predictive factor. Interestingly, the relationship between Bevacizumab (Beva) treatment 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, archival 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 preoperative magnetic resonance imaging (MRI) scan was used to quantify the indexes estimating the survival. 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 124 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 | Age (mean±sd) | ECOG PS | Type of surgery |
|--------|--------|------|---------------|---------|-----------------|
|        | 49/107 (45.8%) | 58/107 (54.2%) | 47.2±12.1 | 0-1 | Complete resection |
| Age ≤50 | 54/107 (50.5%) | 53/107 (49.5%) | 82/107 (76.6%) | 2+ | Partial resection |
| Age >50 | 25/107 (23.4%) | | |

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

| Ki 67 | ≤20 | >20 |
|-------|-----|-----|
|       | 61/107 (57%) | 46/107 (43%) | 54/107 (50.5%) | 53/107 (49.5%) |

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

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

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

| P53 status | Mutated | Non mutated |
|------------|---------|-------------|
|            | 54/107 (50.5%) | 53/107 (49.5%) |

| Type of surgery | Total excision | Partial excision |
|----------------|---------------|------------------|
|                | 1.39 (0.83-2.33) | 1.39 (0.83-2.33) |

| Re TMZ | Present | Absent |
|-------|---------|--------|
|       | 1.04 (0.59-1.85) | 1.04 (0.59-1.85) |

| Gamma knife | Present | Absent |
|-------------|---------|--------|
|             | 1.48 (0.87-2.51) | 1.48 (0.87-2.51) |

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

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

| Gender | Male | Female | p-value | p-value |
|--------|------|--------|---------|---------|
|        | Reference | 1.25 (0.83-1.88) | p=0.289 |
| Age    | ≤50 | Reference | 0.78 (0.51-1.19) | p=0.246 |
|        | >50 | Reference | 0.78 (0.51-1.19) | p=0.246 |

| ECOGPS | 0-1 | 2+ | p<0.001 | Reference | 3.74 (2.20-6.38) | p<0.001 |
|--------|-----|----|---------|---------|-----------------|---------|
|        | Reference | 4.54 (2.71-7.59) | p=0.001 |

| Localisation | Frontal | Parietal | Temporal | Others | p=0.384 | p=0.249 | p=0.926 |
|--------------|---------|----------|---------|--------|---------|---------|---------|
|              | Reference | 0.77 (0.42-1.39) | 0.73 (0.42-1.25) | 1.03 (0.59-1.80) | p=0.384 |
|              | Reference | 0.77 (0.42-1.39) | 0.73 (0.42-1.25) | 1.03 (0.59-1.80) | p=0.249 |
|              | Reference | 0.77 (0.42-1.39) | 0.73 (0.42-1.25) | 1.03 (0.59-1.80) | p=0.926 |

| Origin | Primer GBM | Seconder GBM | p=0.075 |
|--------|------------|--------------|---------|
|        | Reference | 1.78 (0.94-3.36) | p=0.075 |

| Ki 67 | ≤20% | >20% | p=0.655 | p=0.655 |
|-------|------|------|---------|---------|
|       | Reference | 1.10 (0.73-1.65) | p=0.655 |
|       | Reference | 1.10 (0.73-1.65) | p=0.655 |

| PS3 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 | p=0.210 |
|---------|----------------|------------------|---------|
|         | Reference | 1.39 (0.83-2.33) | p=0.210 |

| Re TMZ | Present | Absent | p=0.890 |
|-------|---------|--------|---------|
|       | Reference | 1.04 (0.59-1.85) | p=0.890 |

| Gamma knife | Present | Absent | p=0.149 |
|-------------|---------|--------|---------|
|             | Reference | 1.48 (0.87-2.51) | p=0.149 |

| CAR | ≤1.32 | >1.32 | p<0.001 | Reference | 1.92 (1.21-3.05) | p=0.006 |
|-----|-------|-------|---------|-----------|-----------------|---------|
|     | Reference | 2.27 (1.45-3.55) | p<0.001 |

| NLR | ≤2.9 | >2.9 | p=0.009 | Reference | 1.38 (0.87-2.17) | p=0.170 |
|-----|------|------|---------|-----------|-----------------|---------|
|     | Reference | 1.78 (1.15-2.75) | p=0.009 |

| PLR | ≤159 | >159 | p=0.010 | Reference | 1.66 (1.07-2.59) | p=0.024 |
|-----|------|------|---------|-----------|-----------------|---------|
|     | Reference | 1.78 (1.15-2.76) | p=0.010 |

| SII | ≤785 | >785 | p=0.020 | Reference | 0.96 (0.53-1.73) | p=0.898 |
|-----|------|------|---------|-----------|-----------------|---------|
|     | Reference | 1.65 (1.08-2.50) | p=0.020 |

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, SII: 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, SII, and CAR values) were recorded. ROC analysis was performed to determine the optimal predictive value of each parameter. Accordingly, NLR: 2.9, PLR: 159, SII: 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 SII 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 SII >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: SII ≤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. SII >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 SII (≤785 and >785) of overall survival.

CAR: C-reactive protein albumin ratio, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, SII: Systemic immune inflammation index, OS: Overall survival, CI: Confidence interval.

The ECOGPS level of ≥2 HR: 4.54 (2.71-7.59) p<0.001 was 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 SII >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 = 0.056, 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 SII 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 SII 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 approximately unacceptable levels, approximately 10%. Although Beva contributed to PFS and quality of life in GBM patients, who progressed under TMZ treatment, it did not improve OS. 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. 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. Because of the decrease in albumin, while CRP increases, CAR is accepted as a rational method in cancer studies. 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.
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. The prognostic significance of the Glasgow prognostic score (GPS), which uses both CRP and albumin levels in GBM patients, has been demonstrated. A study showing the prognostic significance of CAR in GBM patients treated with adjuvant CRT was recently published.

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. The authors could not show the prognostic and predictive importance of SII. Unlike this study, Topkan et al. showed that SII is a prognostic factor in patients with GBM who received adjuvant therapy.

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. Bertaut et al. showed that an increase in the pre-treatment neutrophil count in GBM patients improved the Beva treatment response. Conversely, studies show that the increase in NLR is a poor prognostic factor. 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 importance 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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