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Research Paper

Association Between Peripheral Blood Cell Parameters and Survival in Patients With Glioblastoma Undergoing Surgery

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ABSTRACT

Background and Aim: Glioblastoma (GBM) is the most aggressive primary malignancy of the central nervous system and continues to be associated with dismal survival outcomes despite advances in surgical and adjuvant therapies. In recent years, systemic inflammation has emerged as a potential contributor to tumor progression, prompting growing interest in readily accessible blood-based biomarkers. Among these, the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been proposed as simple and cost-effective prognostic indicators; however, their clinical utility in GBM remains uncertain.

Methods and Materials/Patients: This observational cohort study included 71 adult patients with histologically confirmed GBM. Pre-treatment hematological parameters were obtained within 24 hours before surgery, including leukocyte subsets and platelet counts, from which NLR and PLR were calculated. Overall survival (OS) was evaluated over a six-month follow-up period. Survival distributions were estimated using the Kaplan–Meier method, and associations between variables and survival were assessed using Cox proportional hazards models.

Results: At baseline, patients exhibited a systemic inflammatory profile, reflected by elevated median NLR and PLR values. During follow-up, 39.4% of patients died, with a median OS of 180 days. Despite this inflammatory pattern, neither NLR nor PLR was significantly associated with OS in either univariable or multivariable analyses. Similarly, no meaningful relationships were observed between survival and other hematological parameters or baseline clinical characteristics, including age, sex, and comorbidities.

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Conclusion: Our findings suggest that single pre-treatment measurements of commonly used inflammatory indices, such as NLR and PLR, may not reliably predict short-term survival in patients with GBM. These results highlight the complex and dynamic interplay between tumor biology and host immune response, which is unlikely to be captured by static peripheral blood markers alone. Future studies incorporating longitudinal biomarker assessment and integration with molecular tumor profiling may provide more robust and clinically meaningful prognostic models in GBM.

Highlights

- Pre-treatment NLR and PLR do not predict survival in GBM.
- Baseline inflammatory indices are not independent prognostic markers.
- Only single measurements limit the utility of blood-based biomarkers.
- Survival in GBM is not driven by static peripheral immune profiles.
- Dynamic immune monitoring is needed for better risk stratification.

Plain Language Summary

Glioblastoma (GBM) is a very aggressive and deadly type of brain cancer. Even with surgery, radiation, and chemotherapy, most patients do not survive long. Doctors are constantly searching for simple and cheap ways to predict how long a patient might live. One idea is to look at standard blood tests that measure different types of blood cells, such as white blood cells and platelets, which can show if the body has inflammation. Two common measures are the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR). This study was done to see if these simple blood tests could help predict the six-month survival of patients with GBM. We studied 71 patients with GBM. We found that while many of these patients had signs of inflammation in their blood, neither the NLR nor the PLR was linked to how long they survived. Patients with high or low levels of these markers had similar chances of survival. Our findings suggest that a single blood test taken before treatment may not be enough to predict a patient's outcome. This is important because it tells us that we need better and more complex methods for predicting survival in GBM. Instead of relying on a single test, future research should focus on tracking changes in these blood markers over time and combining them with other information about the patient's tumor. This could lead to more personalized care and better treatment decisions. This work contributes to the global effort to fight this difficult disease.

1. Introduction

Glioblastoma (GBM) is the most prevalent and aggressive primary malignant tumor of the central nervous system in adults and is classified as a grade IV astrocytoma according to the World Health Organization (WHO) classification. It constitutes nearly 60% of all primary brain tumors and approximately 45% of malignant primary brain and central nervous system neoplasms, with an annual incidence ranging from 3 to 5 cases per 100,000 individuals in Western populations. Despite decades of advances in neurosurgical techniques, radiotherapy planning, and systemic therapies, GBM continues to carry an extremely poor prognosis, with median overall survival (OS) rarely exceeding 14-16 months and a 5-year survival rate of less than 7% [1]. Large population-based studies indicate that long-term survival outcomes have shown only marginal improvement over the past two decades, emphasizing the persistent therapeutic limitations and the urgent need for more reliable prognostic markers [2]. The current standard treatment for GBM, established by the pivotal Stupp protocol, consists of maximal safe surgical resection followed by concurrent radiotherapy and temozolomide chemotherapy, with subsequent adjuvant temozolomide. However, several intrinsic biological characteristics of GBM, including diffuse infiltration into surrounding brain tissue, marked intratumoral heterogeneity, the presence of glioma

stem-like cells, and the restrictive role of the blood-brain barrier, significantly compromise treatment efficacy and contribute to inevitable tumor recurrence. These features also underlie substantial interindividual variability in treatment response and survival, suggesting that patient-related systemic factors may play an important role in disease progression and prognosis [3]. In recent years, molecular profiling has transformed the understanding of GBM biology. The updated 2021 WHO classification differentiates GBM into isocitrate dehydrogenase (IDH)-wildtype and IDH-mutant forms, with the former accounting for the majority of cases and exhibiting markedly worse clinical outcomes [4]. Additional molecular alterations, such as O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation, telomerase reverse transcriptase promoter mutations, epidermal growth factor receptor amplification, and phosphatase and tensin homolog loss, have been shown to influence prognosis and therapeutic responsiveness [5].

However, comprehensive molecular testing is not universally available due to financial, technical, and logistical constraints, particularly in resource-limited settings. Consequently, there is growing interest in identifying inexpensive, easily obtainable, and reproducible prognostic biomarkers derived from routine clinical assessments, including peripheral blood parameters [4]. The tumor microenvironment of GBM is profoundly immunosuppressive and is characterized by extensive infiltration of regulatory T cells, tumor-associated macrophages, and myeloid-derived suppressor cells, which collectively promote immune evasion and tumor progression [6]. Accumulating evidence suggests that systemic inflammation, as reflected by changes in circulating blood cell components, may mirror intratumoral immune dysregulation and influence clinical outcomes. In this context, hematological indices derived from complete blood count (CBC), such as absolute leukocyte subpopulations, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR), have attracted considerable attention as potential prognostic indicators across a wide range of solid tumors, including GBM [7, 8].

Neutrophils, which constitute the largest fraction of circulating leukocytes, exert dual effects in cancer. While they are essential components of innate immunity, tumor-associated neutrophils can facilitate tumor growth by promoting angiogenesis, remodeling the extracellular matrix, and suppressing adaptive immune responses by releasing cytokines, proteases, and reactive oxygen species (ROS) [9]. Elevated neutrophil counts and increased NLR have been consistently associated with poorer survival in patients with GBM, as demonstrated by several large-scale retrospective studies and meta-analyses [10]. In contrast, lymphocytes, particularly $CD8^+$ cytotoxic T cells, and $CD4^+$ helper T cells are central mediators of antitumor immunity [6]. Lymphopenia, frequently observed in patients with GBM due to both disease-related and treatment-induced immunosuppression, has been linked to reduced survival and diminished response to radiotherapy and emerging immunotherapeutic approaches [11].

Among inflammatory markers, the NLR has emerged as one of the most practical and robust indicators of systemic immune imbalance. Its simplicity, low cost, and widespread availability make it an attractive prognostic tool in routine clinical practice. Meta-analytic evidence indicates that elevated pretreatment NLR is independently associated with poorer OS in patients with GBM, even after adjustment for established prognostic factors such as age, extent of resection, and molecular characteristics [12]. Nonetheless, optimal NLR cutoff values remain heterogeneous across studies, and recent data suggest that longitudinal changes in NLR during treatment may provide additional prognostic information beyond baseline measurements [13]. Platelets also play a critical role in cancer biology beyond their traditional function in hemostasis. They contribute to tumor progression by protecting circulating tumor cells from immune surveillance, facilitating tumor cell adhesion and extravasation, and releasing pro-angiogenic and growth-promoting factors, such as vascular endothelial growth factor, platelet-derived growth factor, and transforming growth factor-β [14]. Thrombocytosis and elevated PLR have been reported in patients with GBM and are often associated with more aggressive tumor behavior and unfavorable clinical outcomes [15]. Although the prognostic value of PLR appears less consistent than that of NLR, recent systematic reviews suggest that platelet-related indices may still provide complementary prognostic information [16]. In addition to leukocyte- and platelet-based indices, red blood cell distribution width (RDW) has recently emerged as a novel marker of systemic inflammation and physiological stress. Elevated RDW reflects increased heterogeneity in erythrocyte size and has been associated with adverse outcomes in cardiovascular disease and various malignancies [17]. RDW-based composite indices, including RDW-to-platelet ratio, have shown potential prognostic value in GBM, possibly reflecting chronic inflammation, nutritional status, and impaired hematopoiesis [18]. However, most existing studies are retrospective, involve relatively

small cohorts, and exhibit substantial methodological heterogeneity in cutoff definitions, timing of blood sampling, and adjustment for confounding factors such as corticosteroid use. Notably, data regarding the prognostic significance of hematological parameters in patients with GBM from northern Iran, particularly Guilan Province, are scarce. Given potential regional differences in genetic background, environmental exposures, lifestyle factors, and healthcare access, population-specific investigations are essential to determine the generalizability and clinical relevance of blood-based prognostic markers. Therefore, the present study aimed to evaluate the association between peripheral blood cell elements, with particular emphasis on leukocytes (neutrophils and lymphocytes) and platelets, and survival outcomes in patients with histologically confirmed GBM treated in Rasht City, Guilan Province, Iran. By focusing on readily available, cost-effective hematological parameters, this study aims to improve risk stratification and support more personalized prognostic assessment in patients with GBM.

2. Methods and Materials

Study design and setting

This retrospective observational cohort study was conducted at Poursina Hospital, a tertiary referral center affiliated with Guilan University of Medical Sciences, Rasht, Iran. The study protocol was approved by the institutional ethics committee and complied with the principles of the Declaration of Helsinki [19]. Written informed consent was obtained from all patients or their legal representatives. Reporting of this study adhered to the strengthening the reporting of observational studies in epidemiology (STROBE) guidelines [20].

Study population

Consecutive adult patients with a diagnosis of GBM who were admitted between January 2024 and June 2024 were screened for eligibility. Inclusion criteria were: (1) histopathological confirmation of GBM according to the 2020 WHO classification of tumors of the central nervous system [21]; (2) Availability of pre-treatment complete blood count (CBC) data; (3) Age ≥18 years; and (4) Complete clinical and follow-up records.

Patients were excluded if they had: (1) Non-GBM glioma histology or lower-grade gliomas; (2) concurrent or previous malignancies; (3) evidence of acute or chronic infection or inflammatory disease at baseline; (4) autoimmune disorders; or (5) corticosteroid administration before baseline blood sampling.

Additionally, patients receiving systemic immunosuppressive agents within four weeks before blood collection were excluded to minimize confounding effects on circulating leukocyte and platelet indices [22].

Data collection

Demographic and clinical variables were extracted from the hospital information system and medical records, including age, sex, comorbidities (hypertension, diabetes mellitus, cardiovascular disease, hyperlipidemia, asthma, and benign prostatic hyperplasia), tumor location, and treatment modalities. Tumor location was categorized based on cerebral lobe involvement. When available, the extent of surgical resection was classified as gross total resection, subtotal resection, or biopsy, consistent with previously established criteria [23].

Laboratory measurements

Peripheral venous blood samples were obtained within 24 hours before surgical intervention and before initiation of adjuvant therapy. CBC analyses were performed using automated hematology analyzers in a single institutional laboratory. The following parameters were recorded:

Total white blood cell (WBC) count ($\times 10^9$/L); Absolute neutrophil count ($\times 10^9$/L); Absolute lymphocyte count ($\times 10^9$/L); Platelet count ($\times 10^9$/L); Neutrophil percentage; Lymphocyte percentage

Inflammatory indices were calculated as follows (Equations 1 and 2):

1. NLR = Absolute neutrophil count / Absolute lymphocyte count

2. PLR= Platelet count / Absolute lymphocyte count

All laboratory procedures followed standardized internal quality-control protocols to ensure analytical reliability and minimize inter-assay variability [24].

Outcome definition

The primary outcome was OS, defined as the interval from the date of histopathological diagnosis to death from any cause or to the last follow-up. Survival status was assessed via structured telephone interviews at six months after diagnosis and cross-validated against

hospital records to reduce misclassification bias. Patients who were alive at the end of follow-up were censored [25].

Statistical analysis

Continuous variables were summarized as Mean±SD or median with interquartile range (IQR), depending on the data distribution, as assessed using the Shapiro-Wilk test, skewness, and kurtosis. Categorical variables were expressed as frequencies and percentages. Between-group comparisons were performed using the independent t-test or Mann-Whitney U test for continuous variables and the chi-square or Fisher's exact test for categorical variables.

OS was analyzed using Kaplan-Meier survival curves, and differences between groups were evaluated with the log-rank test. Associations between hematologic parameters and survival were examined using univariate and multivariate Cox proportional hazards regression models, with results reported as hazard ratios (HRs) and 95% confidence intervals (CIs). Variables with P<0.10 in univariate analyses were entered into the multivariate model. The proportional hazards assumption was verified using Schoenfeld residuals and log-minus-log plots [26]. Correlations between continuous variables were assessed using Spearman's rank correlation coefficient.

An NLR cutoff value of 4 was applied based on prior prognostic studies in the GBM population [27]. Statistical significance was defined as a two-tailed P<0.05. All analyses were performed using SPSS software, version 25.0; IBM Corp., Armonk, NY, USA).

Sample size estimation

Sample size calculation was based on previous studies reporting a HRs of approximately 1.6 for patients with NLR≥4 compared with NLR<4 [4]. Assuming survival proportions of 0.02 and 0.03, a group allocation ratio of 1.8, a significance level of α=0.05, and 80% statistical power, a minimum sample size of 68 patients was estimated. Allowing for a 10% attrition rate, a target enrollment of 75 patients was planned. Ultimately, 71 patients fulfilled all eligibility criteria and completed follow-up. Sample size estimation was conducted using PASS software, version 15.0; NCSS, USA [28].

3. Results

Patient demographics and clinical characteristics

A total of 71 patients with newly diagnosed GBM were included in the analysis. Table 1 presents baseline demographic and clinical characteristics. The cohort consisted of 46 men (64.8%) and 25 women (35.2%), yielding a male-to-female ratio of 1.84:1. The mean age at diagnosis was 50.5±17.6 years (range: 18-85 years), with the majority of patients (n=54, 76.1%) younger than 65 years.

Documented comorbidities were present in 23 patients (32.4%), with hypertension (14.1%) and diabetes mellitus (8.5%) being the most prevalent. The observed age distribution and male predominance are consistent with established epidemiological patterns reported in large population-based GBM cohorts, supporting the representativeness of the study population.

Baseline hematological profile

Table 2 presents baseline peripheral blood parameters. The median neutrophil proportion was 78% (IQR: 68-85), while the median lymphocyte proportion was 18% (IQR: 12-27), reflecting a neutrophil-skewed leukocyte profile. The median total WBC count was $8.8\times10^3/\mu L$ (IQR: 6.4-11.1×$10^3/\mu L$), and the median platelet count was $212\times10^3/\mu L$ (IQR: 176-278×$10^3/\mu L$).

The median NLR was 4.44 (IQR: 2.41-7.17), with more than half of the patients (53.5%) exhibiting NLR values ≥4. The median PLR was 138.92 (IQR: 100.45-192.03). Collectively, these findings indicate a systemic inflammatory and immunosuppressive peripheral blood phenotype at diagnosis, a feature increasingly recognized in GBM biology.

Survival outcomes

During the six-month follow-up period, 28 patients (39.4%; 95% CI, 28.7%, 51%) died. The mean OS was 127.2±68.4 days (95% CI, 111%, 143.4% days), and the median OS was 180 days (IQR: 36-180 days), extending beyond the predefined follow-up window.

OS outcomes are illustrated in Figure 1. The Kaplan-Meier curve demonstrates an estimated six-month survival probability of approximately 60%, with a non-uniform distribution of mortality events over time. Kaplan-Meier analysis for the entire cohort (Figure 1) demonstrated an estimated six-month survival

Table 1. Patient demographics and clinical characteristics (n=71)

Characteristic		No. (%)/Mean±SD
Age (y)		50.5±17.6
<65 (y)		54(76.1)
≥65 (y)		17(23.9)
Gender	Male	46(64.8)
	Female	25(35.2)
Comorbidities	Any comorbidity	23(32.4)
	Hypertension	10(14.1)
	Diabetes mellitus	6(8.5)
	Cardiovascular disease	2(2.8)
	Hyperlipidemia	2(2.8)
	Others	3(4.2)

probability of approximately 60%. These early survival outcomes align with previously reported short-term mortality rates in GBM patients receiving standard-of-care treatment.

Association between clinical variables and mortality

Table 3 presents associations between baseline clinical variables and six-month mortality. No statistically significant associations were observed for age ≥65 years (P=0.191), male sex (P=0.662), or the presence of any comorbidity (P=0.317).

Hematological parameters and survival status

As shown in Figures 2 and 3, substantial overlap was observed in the distributions of NLR and PLR between survivors and deceased patients, consistent with the lack of statistically significant group differences.

Table 4 presents comparative analyses of hematological parameters between survivors and deceased patients. No significant differences were observed in neutrophil or lymphocyte proportions, total WBC count, platelet count, NLR, or PLR (all P>0.05).

Table 2. Baseline hematological parameters (n=71)

Parameter	Median (IQR) / Mean±SD
Neutrophil (%)	78 (68-85)
Lymphocyte (%)	18 (12-27)
WBC count ($\times 10^2/\mu L$)	88 (64-111)
Lymphocyte count ($\times 10^2/\mu L$)	17.36 (11.7-21.28)
Platelet count ($\times 10^3/\mu L$)	212 (176-278)
NLR	4.44 (2.41-7.17)
PLR	138.92 (100.45-192.03)

Abbreviations: IQR: Interquartile range; WBC: White blood cell; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio.

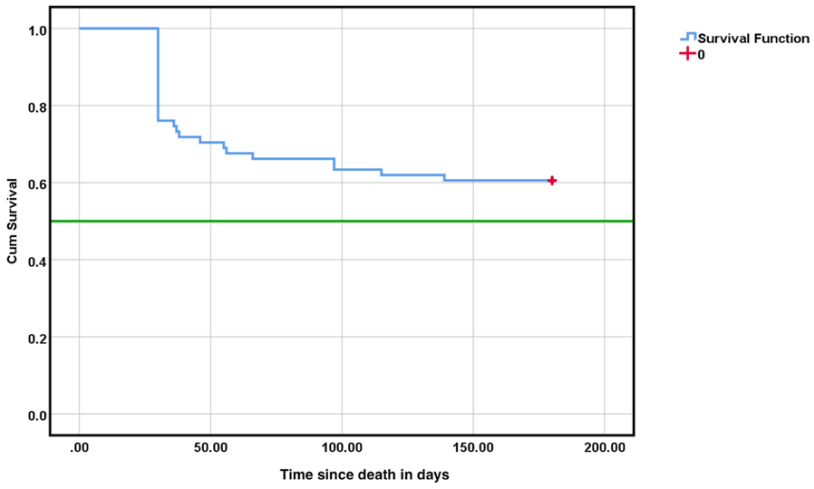

Figure 1. Kaplan-Meier survival curve for OS in the entire cohort of GBM multiforme patients (n=71)

Note: Median survival was 180 days.

Although these results contrast with some reports identifying NLR or PLR as prognostic markers, they are consistent with studies emphasizing substantial inter-patient heterogeneity and limited reproducibility of peripheral inflammatory markers in GBM prognosis. Multivariate projection of baseline hematological parameters did not reveal distinct clustering according to survival status (Figure 4), indicating limited prognostic separability at the systemic blood level.

Principal component analysis (PCA) of leukocyte- and platelet-related features reveals substantial overlap between survivors and deceased patients, with no distinct clustering observed.

Cox proportional hazards regression analysis

Table 5 presents results of univariable and multivariable Cox regression analyses. In univariable models, none of the variables, including age ≥65 years, sex, comorbidities, NLR, or PLR, showed a significant association with OS.

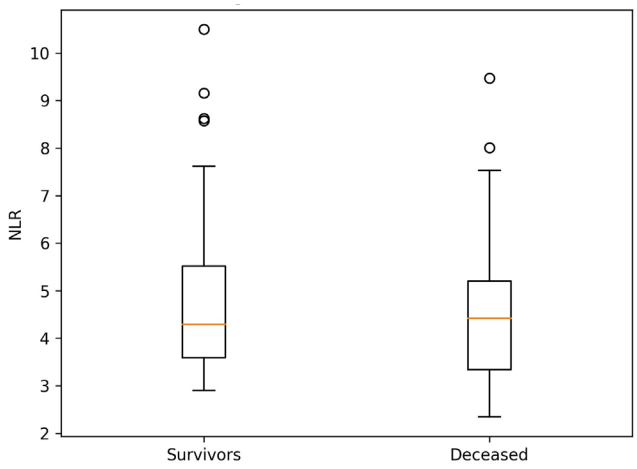

Figure 2. Distribution of systemic inflammatory indices according to survival status

Note: NLR stratified by survival outcome. Extensive overlap between groups indicates limited discriminative capacity of these indices.

Table 3. Association of clinical factors with 6-month mortality

Variables	No. (%)		P
	Survivors (n=43)	Deceased (n=28)	
Age ≥65 years	8(18.6)	9(32.1)	0.191
Male gender	27(62.8)	19(67.9)	0.662
Any comorbidity	12(27.9)	11(39.3)	0.317

Note: None of the individual comorbid conditions showed a significant relationship with mortality. These findings suggest that early survival in this cohort is unlikely to be primarily driven by baseline demographic or comorbidity profiles, highlighting the dominant influence of tumor-intrinsic and treatment-related factors.

After adjustment for age, sex, and comorbidities, NLR (adjusted HR: 0.86, 95% CI, 0.72%, 1.03%, P=0.094) and PLR (adjusted HR: 1, 95% CI, 0.99%, 1.01%, P=0.243) remained non-significant. The relatively wide confidence intervals likely reflect biological heterogeneity and underscore the limited prognostic resolution of single-parameter hematological indices. Figure 5 shows a forest plot visualization of univariate and multivariate Cox regression analyses, illustrating that all confidence intervals intersect the null effect line.

Kaplan-Meier survival analyses by subgroups

Figures 6, 7, 8, and 9 show stratified Kaplan-Meier survival curves. Although trends toward reduced survival were observed in patients aged ≥65 years, those with comorbidities, and patients with NLR ≥4, none of these differences reached statistical significance. Survival curves stratified by sex were nearly superimposable. Importantly, the directionality of these trends is concordant with previously described prognostic patterns, suggesting the presence of weak but consistent biological signals below conventional significance thresholds.

Correlation analyses

Spearman correlation analyses revealed no significant associations between survival duration and any hematological parameter, including neutrophil percentage, lymphocyte percentage, WBC count, platelet count, NLR, or PLR. Subgroup analysis restricted to deceased patients similarly failed to identify significant correlations. Pairwise correlation

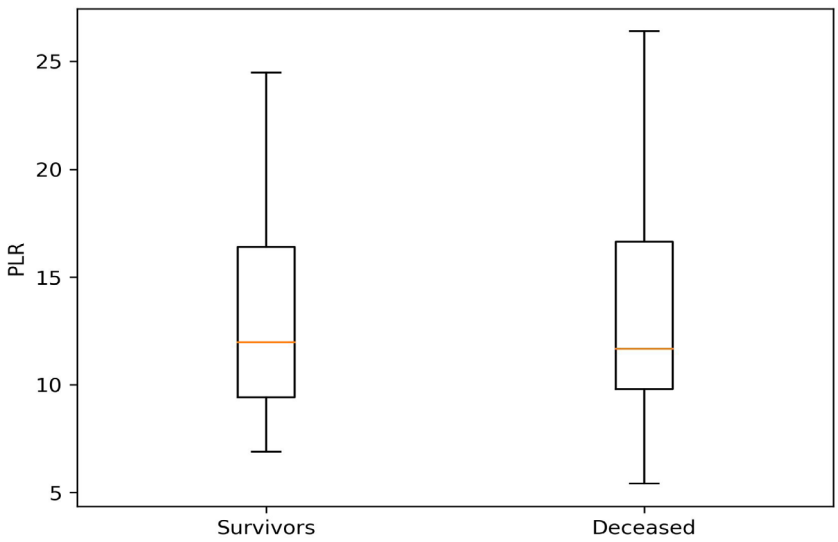

Figure 3. Distribution of systemic inflammatory indices according to survival status

Note: PLR stratified by survival outcome. Extensive overlap between groups indicates limited discriminative capacity of these indices.

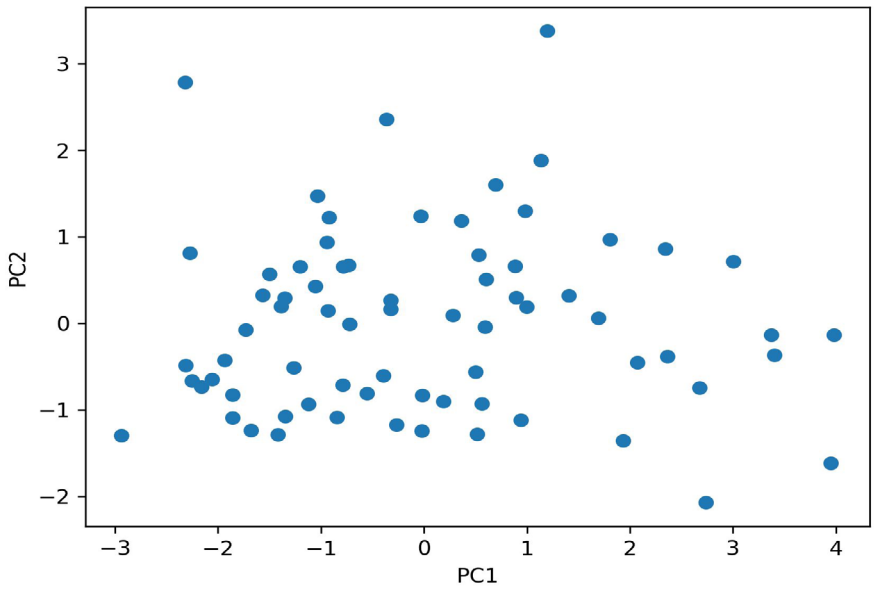

Figure 4. Multivariate projection of baseline hematological parameters

analysis further confirmed the absence of strong linear relationships between survival time and hematological parameters (Figure 10).

Spearman correlation coefficients indicate weak, non-significant associations, highlighting the absence of dominant linear relationships.

These findings indicate that baseline peripheral blood indices, when considered in isolation, may be insufficient to capture the complex, multi-layered determinants of survival in GBM.

4. Discussion

This prospective cohort study evaluated the prognostic relevance of routinely available hematological parameters, with a particular focus on NLR and PLR, in patients with newly diagnosed GBM. An important consideration in interpreting these findings is that the lack of statistically significant associations does not necessarily indicate the absence of a biological relationship. Rather, it may reflect the limited sensitivity of single-time-point peripheral blood measurements in capturing the complex and dynamic interactions between tumor biology and the

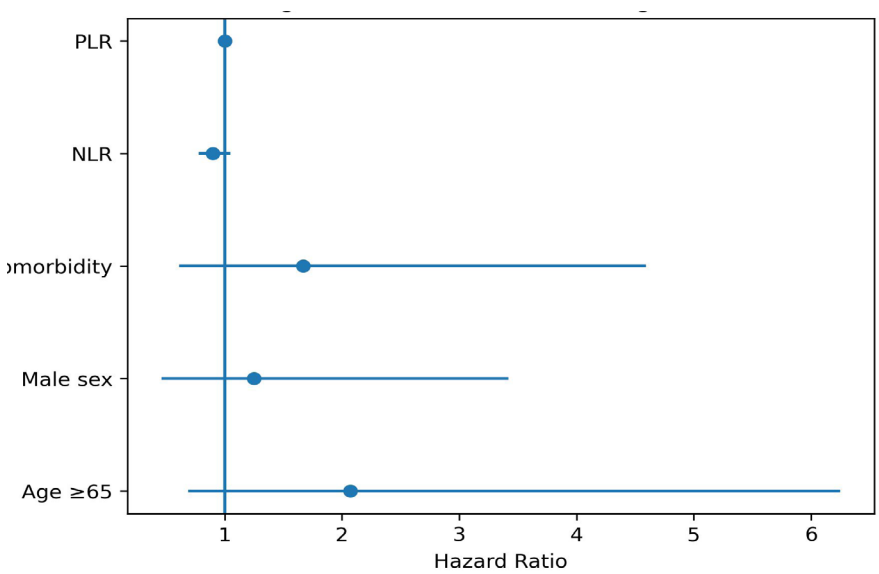

Figure 5. Forest plot of univariate and multivariate Cox proportional hazards regression analyses

Note: HRs and 95% CIs are shown for clinical and hematological variables. All estimates cross the null value, indicating no independent association with OS.

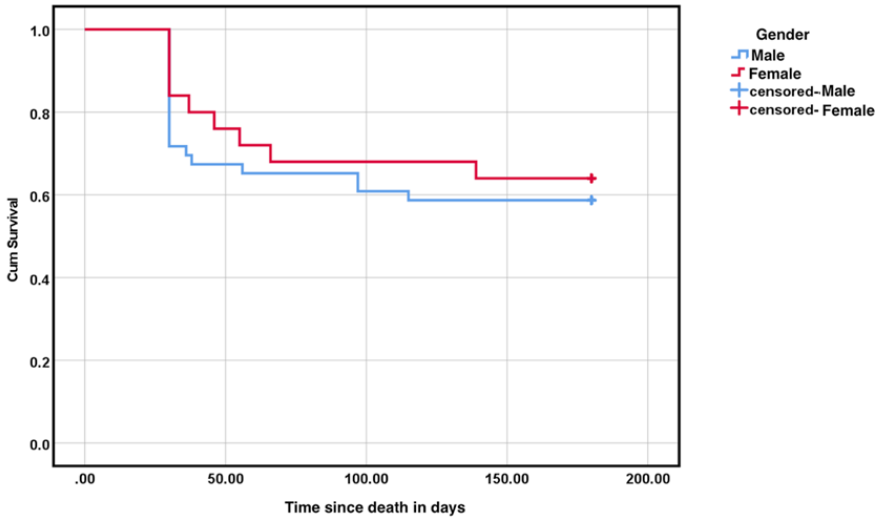

Figure 6. Kaplan-Meier survival curves stratified by gender

Note: No significant difference was observed (log-rank P=0.491).

host immune response. In GBM, systemic inflammation is highly heterogeneous and temporally variable, which may reduce the prognostic resolution of static indices, such as NLR and PLR, when assessed before surgical intervention. Contrary to a substantial body of retrospective literature, our findings demonstrated that neither baseline leukocyte-derived indices nor platelet-related parameters were independently associated with six-month OS. These results remained consistent across univariable and multivariable Cox regression models, as well as across Kaplan-Meier subgroup analyses stratified by demographic, clinical, and inflammatory variables. Collectively, these findings suggest that single pre-treatment measurements of systemic inflammatory markers may have limited prognostic utility in predicting short-term survival in GBM [29-32].

The discrepancy between our findings and those of prior studies reporting significant associations between inflammatory indices and survival outcomes may be attributed to several methodological and biological factors. First, variations in the timing of biomarker assessment (preoperative versus longitudinal measurements) may substantially influence prognostic performance. Second, differences in patient selection, including treatment protocols, extent of surgical resection, and use of corticosteroids, may contribute to inconsistent results across studies. Third, heterogeneity in cutoff values for NLR and PLR further complicates direct comparisons. These factors collectively highlight the need for standardized approaches in future investigations. Systemic inflammation has emerged as a fundamental component of GBM pathophysiology, extending beyond

Table 4. Hematological parameters by survival status

Parameter	Median (IQR)		P
	Survivors (n=43)	Deceased (n=28)	
Neutrophil (%)	78 (68-86)	78 (69-82)	0.337
Lymphocyte (%)	16 (12-27)	18 (14.5-28)	0.340
WBC ($\times 10^2/\mu L$),	95 (68-116)	79 (56.5-98)	0.180
Platelets ($\times 10^3/\mu L$)	208 (170-277)	227.5 (202-280)	0.148
NLR	5 (2.41-7.33)	4.19 (2.50-5.77)	0.332
PLR	135 (95.6-180.9)	141.6 (105.7-196.4)	0.525

Abbreviations: NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; IQR: Interquartile range.

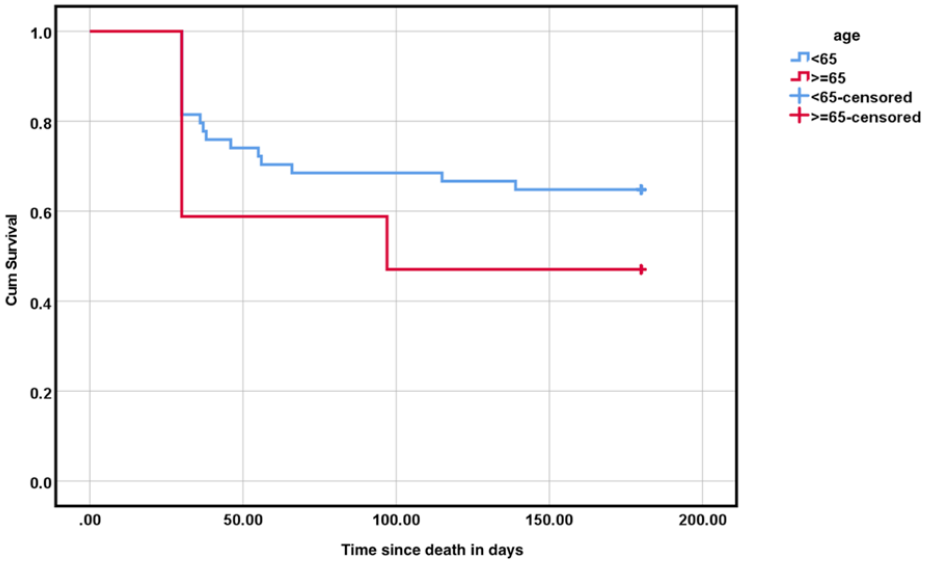

Figure 7. Kaplan-Meier survival curves stratified by age (<65 vs ≥65 years)

Note: Patients ≥65 years showed a trend toward reduced survival (median: 97 vs 180 days), but this did not reach statistical significance (log-rank P=0.131).

the tumor microenvironment to induce widespread immune dysregulation at the peripheral level. GBM is characterized by profound lymphopenia, expansion of myeloid-derived suppressor cells, and functional exhaustion of cytotoxic T lymphocytes, resulting in a paradoxical state of chronic inflammation coexisting with systemic immunosuppression. Recent integrative analyses have further demonstrated that circulating immune signatures may reflect tumor-intrinsic molecular programs associated with angiogenesis, mesenchymal transition, and resistance to therapy. Within this framework, elevated neutrophil and platelet counts are often interpreted as surrogate markers of a pro-tumor inflammatory milieu. From a mechanistic perspective, the limited prognostic value of peripheral inflammatory indices in GBM may be explained by the unique immunological characteristics of the central nervous system. The blood–brain barrier, although often disrupted in GBM, still imposes selective constraints on immune cell trafficking. Furthermore, key components of the tumor microenvironment, including tumor-associated macrophages and regulatory T cells, are not directly reflected in routine peripheral blood counts. Consequently, circulating leukocyte and platelet indices may provide only a partial and indirect representation of the intratumoral immune landscape. However, this biologically complex and dynamic immune landscape may not be adequately captured by static, single-time-point peripheral blood measurements [33, 34].

Previous studies and meta-analyses have frequently reported associations between elevated NLR or PLR and inferior survival outcomes in GBM. Pooled analyses have suggested HRs ranging from approximately 1.3 to 1.6 for

Table 5. Cox regression analysis for OS

Variables	Univariate HR (95% CI)	P	Multivariate HR (95% CI)	P
Age ≥65 years	2.07 (0.69-6.25)	0.196	1.54 (0.46-5.2)	0.489
Male gender	1.25 (0.46-3.42)	0.662	1.32 (0.46-3.84)	0.606
Any comorbidity	1.67 (0.61-4.59)	0.319	1.42 (0.46-4.36)	0.538
NLR (continuous)	0.9 (0.78-1.05)	0.175	0.86 (0.72-1.03)	0.094
PLR (continuous)	1 (0.99-1.01)	0.441	1 (0.99-1.01)	0.243

Abbreviations: NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; HR: Hazard ratio.

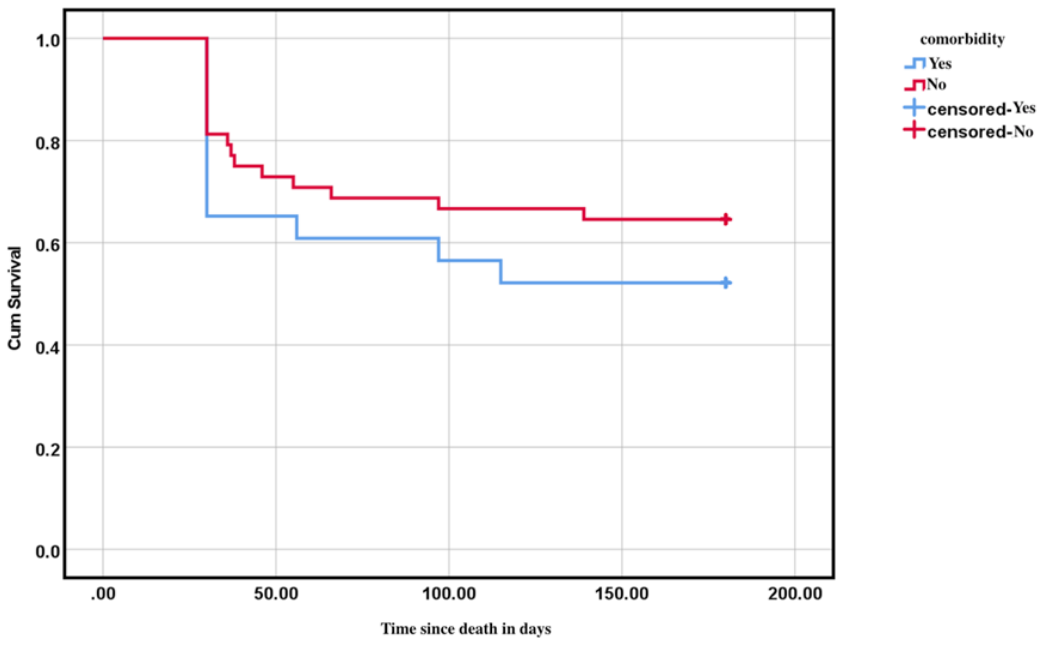

Figure 8. Kaplan-Meier survival curves stratified by presence of comorbidities

Note: No significant association was observed (log-rank P=0.258).

elevated inflammatory ratios, supporting their potential role as adverse prognostic indicators. Additionally, recent machine-learning and multivariable prognostic models incorporating NLR, PLR, and composite systemic inflammation indices have demonstrated improved predictive performance in selected cohorts. Importantly, our findings support an emerging conceptual shift in GBM prognostication, whereby single baseline biomarkers are increasingly recognized as insufficient for accurate risk stratification. Instead, integrative approaches that combine dynamic inflammatory markers with molecular and genomic tumor features may offer superior predictive performance. This paradigm aligns with the principles of precision oncology, emphasizing the need to move beyond isolated parameters toward multidimensional prognostic models. Nevertheless, the reproducibility of these associations has been inconsistent across studies, likely reflecting heterogeneity in patient populations, treatment protocols, steroid exposure, biomarker cut-off definitions, and timing of blood sampling. Our findings align with reports that failed to demonstrate the independent prognostic value of baseline inflammatory markers, reinforcing the notion that their clinical utility may be context-dependent rather than universal [31, 35, 36].

An important explanation for the absence of significant associations in our cohort relates to the timing of biomarker assessment. All hematological parameters were obtained before surgical intervention, within a narrow pre-treatment window. Emerging evidence suggests that dynamic changes in systemic inflammatory markers during the disease course, particularly during chemoradiotherapy or at progression, may carry greater prognostic relevance than baseline values alone. Longitudinal studies have shown that increases in NLR, PLR, or red cell distribution width during treatment correlate more strongly with unfavorable outcomes than preoperative measurements. These observations support the hypothesis that systemic inflammatory indices may serve more effectively as disease-monitoring or treatment-response biomarkers than as static baseline prognostic tools [30, 32].

Several biological mechanisms may further explain why baseline leukocyte and platelet indices failed to demonstrate prognostic significance in this study. First, disruption of the blood-brain barrier in GBM facilitates bidirectional exchange of cytokines, immune mediators, and circulating cells, resulting in fluctuating peripheral immune profiles that may not accurately reflect intratumoral immune activity at a single time point. Second, key immunosuppressive components of the GBM microenvironment, including tumor-associated macrophages, regulatory T cells, and myeloid-derived suppressor cells, are not directly quantified by routine CBC-derived markers. Third, even limited perioperative corticosteroid exposure can alter leukocyte distribution and obscure biologically meaningful differences

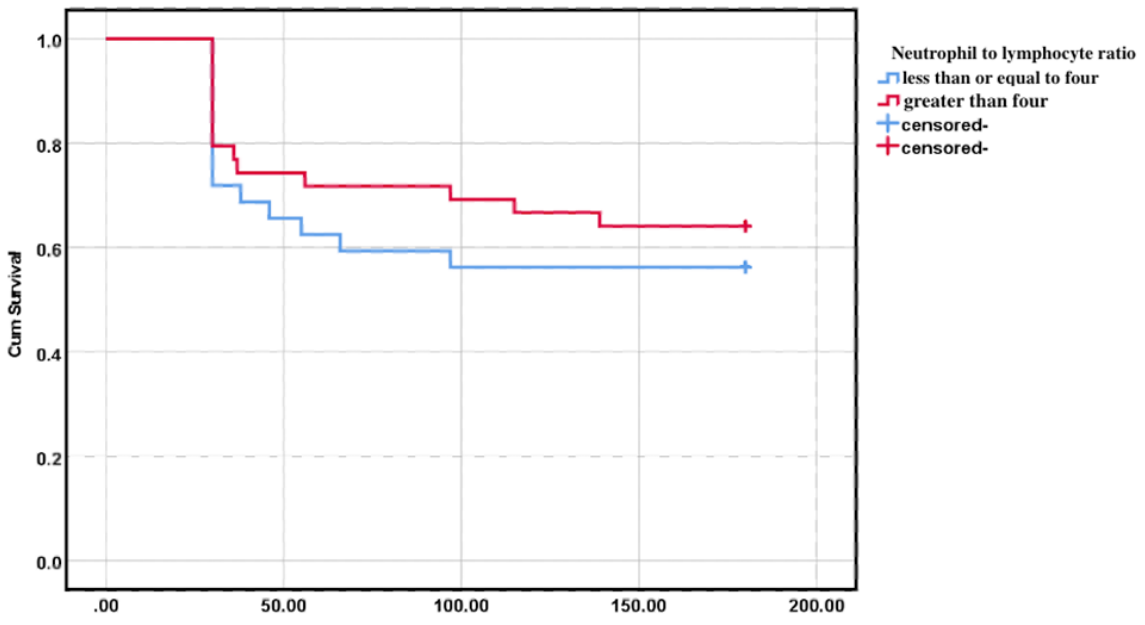

Figure 9. Kaplan-Meier survival curves stratified by NLR (<4 vs ≥4)

Note: No significant difference was detected (log-rank P=0.439).

between patients [29, 33]. The lack of statistically significant associations between age, sex, comorbidities, and short-term survival in our cohort is also noteworthy. Although advanced age is traditionally considered a strong prognostic factor in GBM, increasing evidence suggests that molecular tumor characteristics, extent of resection, and treatment-related variables may exert a greater influence on early survival outcomes than demographic factors alone. This observation may be particularly relevant in cohorts with a relatively younger age distribution, such as the present study, where the majority of patients were under 65 years of age [33]. Our findings further underscore the growing recognition that systemic inflammatory biomarkers may require integration with molecular and genomic tumor features to achieve clinically meaningful prognostic performance. Recent studies have demonstrated that combining peripheral immune indices with molecular subtype classification, IDH mutation status, MGMT promoter methylation, or radiogenomic features significantly improves survival prediction accuracy. Such integrative, multilayer biomarker models align with contemporary precision oncology paradigms that emphasize the interplay among tumor biology, the host immune response, and therapeutic context [37].

Several limitations merit consideration. Despite prospective data collection, the study was conducted at a single center with a relatively modest sample size and limited follow-up duration. Although previously reported effect sizes informed sample size calculations, the wide CIs observed in multivariable analyses indicate residual uncertainty and raise the possibility of type II error. These constraints are common in GBM research and highlight the need for larger, multicenter validation studies [29]. From a clinical standpoint, our results suggest that baseline CBC-derived inflammatory indices should not be used in isolation for risk stratification in patients with newly diagnosed GBM. Nonetheless, given their low cost, universal availability, and biological plausibility, these markers remain attractive candidates for incorporation into composite prognostic algorithms or longitudinal monitoring frameworks. Future studies should prioritize standardized longitudinal sampling, rigorous control of steroid exposure, and integration with molecular tumor profiling to better define the role of systemic inflammatory markers in GBM prognostication [30, 33]. Future research should prioritize longitudinal monitoring of inflammatory markers throughout the disease course, as well as their integration with radiomic and molecular data. Advanced analytical approaches, including machine learning–based models, may further enhance the predictive value of these biomarkers and facilitate individualized prognostic assessment in patients with GBM. In conclusion, this study demonstrates that baseline leukocyte- and platelet-derived inflammatory indices, including NLR and PLR, are not independently associated with short-

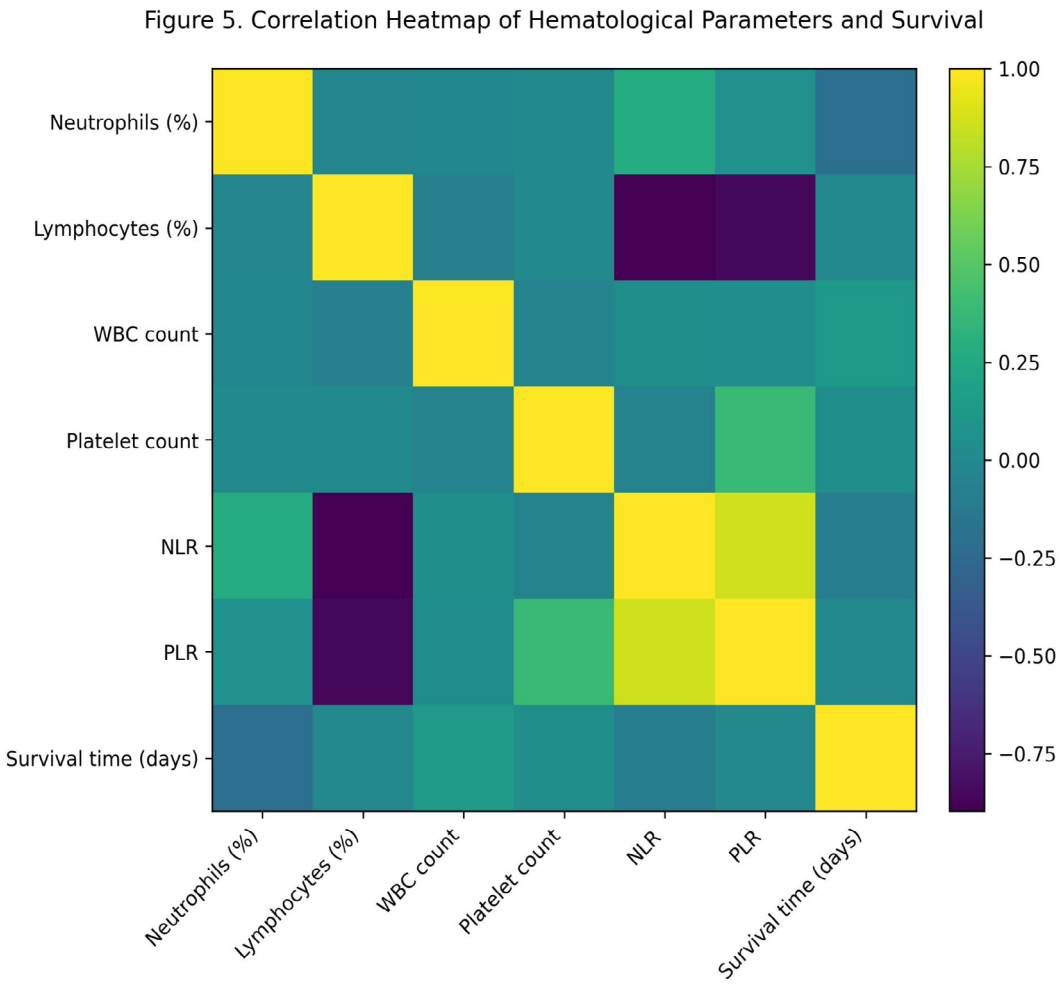

Figure 10. Correlation heatmap of hematological parameters and survival duration

term survival in patients with GBM. These findings highlight the complexity of systemic immune-tumor interactions and support the emerging concept that dynamic immune monitoring and multi-parameter biomarker integration, rather than single baseline measurements, may be required to achieve clinically meaningful prognostic stratification in GBM [30, 33].

5. Conclusion

In this prospective cohort of patients with newly diagnosed GBM, routinely measured peripheral blood parameters, including neutrophil, lymphocyte, and platelet counts, as well as derived inflammatory ratios such as NLR and PLR, were not independently associated with six-month OS. Although non-significant trends toward poorer outcomes were observed among older patients and those with higher baseline NLR values, these associations did not achieve statistical significance in univariable or multivariable analyses. These findings indicate that single baseline measurements of systemic inflammatory markers may have limited utility as standalone prognostic tools for short-term survival assessment in patients with GBM. The results of this study reinforce the concept that GBM prognosis is governed by complex, dynamic interactions among tumor molecular characteristics, host immune responses, and treatment-related factors, rather than by isolated systemic biomarkers alone. While peripheral inflammatory indices offer biological plausibility and practical advantages, their prognostic value appears insufficient when applied in isolation, particularly at a single pre-treatment time point. Accordingly, reliance on conventional hematological markers alone for risk stratification in GBM should be approached with caution. Importantly, these findings do not negate the potential clinical relevance of systemic inflammatory markers; rather, they highlight the need to integrate them into broader, multidimensional prognostic models. Emerging evidence supports incorporating

inflammatory indices alongside molecular tumor profiling, radiomic features, and advanced analytical approaches, such as machine learning, to enhance prognostic accuracy and support personalized treatment strategies. Longitudinal monitoring of inflammatory markers during treatment may further improve their clinical value by capturing dynamic changes in tumor-host immune interactions. In summary, this study provides population-specific evidence that baseline CBC-derived inflammatory markers, including NLR and PLR, do not independently predict short-term survival in GBM. These findings contribute to the growing body of literature emphasizing the limitations of static prognostic biomarkers in GBM and support a shift toward integrated, dynamic, and multi-parameter prognostic frameworks. Future prospective multicenter studies with larger sample sizes, extended follow-up, standardized biomarker assessment, and comprehensive molecular characterization are required to validate these observations and to define the optimal role of systemic inflammatory markers within precision prognostication models for GBM.

Limitations

Several limitations should be acknowledged. The relatively small sample size and single-center design may limit the generalizability of our findings and increase the risk of type II error. Additionally, the absence of key molecular and clinical variables, such as MGMT promoter methylation, IDH mutation status, extent of resection, and performance status, may have introduced residual confounding. The relatively short follow-up period further restricts the assessment of long-term survival outcomes. These limitations underscore the need for larger, multicenter studies with comprehensive data integration.

Ethical Considerations

Compliance with ethical guidelines

This study was conducted in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments. The research protocol was approved by the Research Ethics Committee of Guilan University of Medical Sciences, Rasht, Iran (Code: IR.GUMS.REC.1403.284). Written informed consent was obtained from all individual participants or their legal representatives included in the study.

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Authors' contributions

Conceptualization, study design, review and editing: Ali Akbar Samadani; Data collection: Reza Hatami, Seyedeh Elham Norollahi, Paridokht Karimiyan, Zahra Abedi, Delaram Nazari, and Fatemeh Afsha; Data analysis and interpretation: Ali Ashraf, Shahrokh Yousefzadeh-Chabok, and Ali Akbar Samadani; Writing the original draft: Reza Hatami, Zahra Abedi, and Ali Akbar Samadani; Final approval: All authors.

Conflict of interest

The authors declared no conflict of interest.

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