The prognostic value of the preoperative inflammatory index on the survival of glioblastoma patients

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Abstract
Objectives The growth and development of tumors are closely related to the initiation and amplification of the inflammatory response. Various inflammatory biomarkers had attained growing attention for nearly two decades and were discovered strongly associated with cancer patients’ prognosis, indicating that systemic inflammatory response is possibly essential to cancer progression. However, little was known about the sensitive biomarkers associated with the detection, persistence, treatment, and prognosis of GBM. Hence, the retrospective research endeavored to evaluate the prognostic value of preoperative inflammatory biomarkers in patients with GBM who initially received standardized treatment.

Methods The 232 glioblastoma patients eligible who were admitted to Qilu Hospitals in Shandong Province from January 2014 to January 2018 were collected for this analysis. Inflammatory markers, including the systemic immune-inflammation index (SII), systemic immune response index (SIRI), neutrophil–lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), monocyte-lymphocyte ratio (MLR), and albumin/globulin ratio (AGR), were designed. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan–Meier method, and we calculated the area under the ROC curve to determine the AUC value. Besides, we used the Cox proportional hazard model to estimate the relationship between variables and PFS and OS. The statistical differences between variables and PFS and OS were tested through the log-rank test. What is more, the LR method was used to perform Cox multiple regression analysis. The results were represented by hazard ratio (HR), 95% CI, any 2-tailed \( P < 0.01 \) was accepted as statistically different.

Results The multivariate Cox proportional hazard model presented that \( \text{SII} \geq 659.1 \) was an independent risk factor affecting OS (HR = 2.238, 95% CI = 1.471–3.406, \( P < 0.001 \)) and postoperative PFS (HR = 2.000, 95% CI = 1.472–2.716, \( P < 0.001 \)) in GBM patients. The 1-, 3-, and 5-year OS of the SII < 659.1 group was 70.8%, 26.9%, and 14.1%, respectively, while the 1- and 3-year OS of the SII \( \geq 659.1 \) group was 37.5% and 11.5% (\( P < 0.001 \)). The 1-, 3-, and 5-year PFS of the SII < 659.1 group was 36.3%, 19.6%, and 13%, respectively, while the 1-year PFS of the SII \( \geq 659.1 \) group was 11.3% (\( P < 0.001 \)). Results of patients’ clinical and pathological characteristics paraded that in comparison to the lower SII group, the higher SII group had significantly inferior Karnofsky Performance Scale (KPS) scores (\( P < 0.001 \)) and more frequent cystic changes of the tumors (\( P < 0.001 \)), whereas the values of SIRI, NLR, PLR, MLR, and AGR were low.

Conclusions SII is an independent inflammatory indicator for predicting the prognosis of GBM patients after receiving initially standardized treatments.

Keywords SII · Glioblastoma · Inflammatory index · Prognosis

Introduction

As the most common type of primary malignant brain tumor in adults, glioblastoma (GBM) is famous for high mortality and poor prognosis [1] in adult patients [2] which invades several brain lobes and deep structures. It has an estimated incidence of about 3.19 per 100,000 persons per year [3], and the 5-year survival rate is less than 10% [4, 5]. Despite standardized treatments including the maximum safe removal of the tumor, postoperative radiotherapy, and temozolomide (TMZ) chemotherapy, patients remain incurable and black with 12 to 15 months of median survival time [6]. In order to assess the progression of the tumors and adapt the treatment for GBM timely and properly, reliable
biomarkers that can quickly and conveniently evaluate the prognosis and treatment efficacy are necessary to be probed.

Inflammation is a complex cascade of defense-based reactions that the body produces in response to injury factors to remove and absorb necrotic tissue and repair damage. It has been asserted that inflammation as one key component of the tumor microenvironment contributes to promote tumor development (priming, proliferation, angiogenesis, and migration) [7], leading ultimately to adverse prognosis of various types of tumors [8–10]. Inflammatory factors including tumor-derived and host-derived cytokines, immune cells, and small inflammatory protein mediators are located in the tumor microenvironment and determined by neutrophils, lymphocytes, platelets, and acute phase proteins. The tumor microenvironment releases pro-inflammatory cytokines and growth factors which participate in every process of tumorigenesis through an intricate system. In the early stages of tumor development, inflammatory cytokines may alter the expression of tumor genes and induce gene mutations. During the development of tumors, tumor cells may overexpress pro-inflammatory mediators, producing cytokines and chemokines to attract immune cells, and convert some inflammatory stroma into mediators that support tumor spread and metastasis.

Hematological indicators such as neutrophils, lymphocytes, monocytes, and platelets count can reflect the inflammatory condition of the system and have potential value for prognostic prediction of many tumors [10–13]. Different combinations of these markers yielded various inflammatory markers, such as SII, SIRI, NLR, PLR, and MLR, which have been reported as important prognostic factors for malignancies including lung cancer, nasopharyngeal carcinoma, and COVID-19 cancer [14–16].

Recent studies have convincingly shown that infiltrating immune cells and other stromal components in the tumor microenvironment are associated with prognosis of glioma [17]. Accordingly, inflammation presumably also makes a difference to the survival of GBM patients and neutrophils, monocytes, lymphocytes, platelets, albumin, globulin, etc., also may play a crucial role in glioblastoma pathobiology [18]. Nonetheless, there are limited studies specially concentrating on GBM, and the explicit physiological and pathological conditions about the inflammatory factors involved in the glioblastoma are currently not fully understood [19]. Therefore, our study aims at investigating the associations between combined hematological inflammatory biomarkers and GBM patients’ prognosis, exploring the means for predicting the survival of GBM patients, and further to develop individualized treatment programs.

**Methods**

**Patients**

The data of 232 patients with glioblastoma admitted to Qilu hospitals in the Shandong Province were retrospectively collected from January 2014 to January 2018.

The inclusion criteria were as follows: (1) Patients were confirmed by pathological diagnosis with glioblastoma, all of whom had received surgical treatment, and no relevant anti-tumor treatment was performed before surgery. (2) All patients received standard treatment: 75 mg/(cm²·day) × 42 days of temozolomide was administered simultaneously during postoperative radiotherapy; temozolomide chemotherapy was given 1 month after the radiotherapy was completed, with a cycle of 28 days, and the medication lasted 5 days, once a day, with an interval of 23 days; 150 mg/(cm²·day) × 5 days in the first cycle, 200 mg/(cm²·day) × 5 days in the second to sixth cycles. (3) Clinical data should be complete. (4) There should be no inflammatory, blood system, or autoimmune system disease history. (5) There should be informed consent and voluntary participation.

The exclusion criteria are as follows: (1) concurrently suffering from other brain tumors; (2) combined with other serious complications; (3) incomplete and or absent follow-up; and (4) received steroid therapy or had infection and fever within 1 month before surgery.

**Data collection**

We accessed the information of patients from the electronic medical records, including cover gender, age, medical history, imaging data, laboratory examinations, radiological examinations, pathological results, drug treatments, surgical records, radiotherapy, and chemotherapy regimens and results. Among them, laboratory examinations such as platelet, neutrophil, and lymphocyte are recorded 1 day before the patient’s operation. Survival data was followed up by telephone and email to understand the patient’s survival status, tumor recurrence, or time to metastasis. In our research, all patients were followed up 3-monthly until January 2021. Overall survival (OS) was defined as the time from the first day after surgery to death due to GBM, and progression-free survival (PFS) was defined as the time from the first day after surgery to recurrence and deterioration or death due to GBM.
Definition of inflammation indicators

SII was calculated as platelet count \times \text{neutrophil count}/\text{lymphocyte count}; SIRI was calculated as neutrophil count/monocyte count/lymphocyte count; NLR was calculated as neutrophil count/lymphocyte count; PLR was calculated as platelet count/lymphocyte count; MLR was calculated as monocyte count/lymphocyte count; and AGR was calculated as albumin count/globulin count. With cancer-specific death as the endpoint, we determined the statistically optimum cutoff point which has the best sensitivity and specificity based on ROC analysis. Based on ROC curve results, the critical values of SII, SIRI, NLR, PLR, MLR, and AGR are defined as 659.1, 1.78, 2.54, 158.56, 0.36, and 1.94, respectively. The absolute value used for each indicator was not incremental, mainly because a non-linear relationship was observed between the incremental value and hazard ratio (HR).

Data analysis

The measurement data was expressed as mean (SD), and the counting data was described by the frequency and percentage. PFS and OS were estimated using the Kaplan–Meier method, and we calculated the area under the ROC curve to determine the AUC value. The relationships between variables and PFS and OS were estimated by the Cox proportional hazard model. The statistical differences between variables and PFS and OS were tested through the log-rank test. What is more, the LR method was used to perform Cox multiple regression analysis. The results were represented by hazard ratio (HR), 95% CI, and \( P \) values of 0.01 or less was accepted as statistically different. All statistical analysis was performed using SPSS 25.0.

Results

Patients and clinicopathologic features

In total, 232 cases were enrolled in this study, including 127 men (54.7%) and 105 women (45.3%), 39 patients aged \( \geq 65 \) years (16.8%), and 193 patients aged \(< 65 \) (83.2%) (Table 1); the study found that the 1-, 3-, and 5-year OS of GBM patients were 51.3%, 17.7%, and 9.8%, respectively (Fig. 1a), and the 1- and 3-year PFS were 24% and 13.4%, respectively (Fig. 1b).

Survival analyses of OS

The univariate Cox proportional hazard model showed that low Karnofsky Performance Scale (KPS), cystic change, partial tumor resection, right tumor site, Ki-67 expression \( \geq 30\% \), SII \( \geq 659.1 \), SIRI \( \geq 1.78 \), and NLR \( \geq 2.54 \) had a significant impact on poor OS (Table 2). A further observation among the factors presenting independent in multivariate analysis revealed that KPS \(< 60 \) (HR = 3.624, 95% CI = 2.525–5.203, \( P < 0.001 \)) and SII \( \geq 659.1 \) (HR = 2.238, 95% CI = 1.471–3.406, \( P < 0.001 \)) were statistically linked with poor OS in GBM.
patients. No statistically significant associations between SIRI, NLR, PLR, MLR, AGR, and OS were proved.

### Survival analyses of PFS

Results of the univariate Cox proportional hazard model revealed that age ≥ 65 years, cystic change, partial tumor resection, right tumor site, Ki-67 expression ≥ 30%, SII ≥ 659.1, SIRI ≥ 1.78, and NLR ≥ 2.54 as the factors manifested a meaningful association with poor PFS (Table 3). Among these variables, a further multivariate Cox proportional hazard model exhibited that three variables retained their independent discrepancies with PFS in GBM patients (Table 3), including age ≥ 65 years (HR = 3.965, 95% CI = 2.660–5.910, \( P < 0.001 \)), Ki-67 expression ≥ 30% (HR = 1.506, 95% CI = 1.119–2.033, \( P < 0.01 \)), and SII ≥ 659.1 (HR = 2.000, 95% CI = 1.472–2.716, \( P < 0.001 \)), respectively. No statistically significant associations between SIRI, NLR, PLR, MLR, AGR, and PFS were shown.

### Comparison of basic parameters for inflammatory biomarkers

The corresponding AUCs of SII, SIRI, NLR, PLR, MLR, and AGR were 0.656, 0.588, 0.615, 0.546, 0.516, and 0.519, respectively (Fig. 2), and the area under the ROC curve of SII was obviously better than those of SIRI, NLR, PLR, MLR, and AGR (\( P < 0.01 \)).

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**Table 2** Univariate and multivariate analyses of prognostic factors for overall survival

| Variable                              | Univariate analysis | Multivariate analysis |
|---------------------------------------|---------------------|-----------------------|
|                                       | \( HR \)            | \( 95\% CI \)         | \( P \)  | \( HR \)            | \( 95\% CI \)         | \( P \)  |
| Gender (female/male)                  | 0.876               | 0.376                 |       |                      |                      |       |
| Age (<65/≥ 65)                        | 0.704               | 0.487–1.017           | 0.061 |                      |                      |       |
| KPS (<60/≥ 60)                        | 0.315               | 0.227–0.438           | <0.001| 3.624               | 2.525–5.203          | <0.001|
| Cystic change (yes/no)                | 1.306               | 1.097–1.555           | 0.003 |                      |                      |       |
|Extent of tumor resection (part/complete) | 0.684               | 0.532–0.880           | 0.003 |                      |                      |       |
| Tumor location                        |                     |                       |       |                      |                      |       |
| Right/left                            | 0.687               | 0.519–0.909           | 0.009 |                      |                      |       |
| Bilateral/left                        | 0.885               | 0.668–1.171           | 0.392 |                      |                      |       |
| Ki67 (<30%/≥ 30%)                     | 1.594               | 1.183–2.149           | 0.002 |                      |                      |       |
| TP53 (mutation/no mutation)          | 1.329               | 0.994–1.775           | 0.055 |                      |                      |       |
| Reoperation (yes/no)                  | 1.118               | 0.899–1.391           | 0.316 |                      |                      |       |
| SII                                   | 2.24                | 1.651–3.040           | <0.001| 2.238               | 1.471–3.406          | <0.001|
| SIRI                                  | 0.652               | 0.484–0.879           | 0.005 |                      |                      |       |
| NLR                                   | 1.601               | 1.195–2.146           | 0.002 |                      |                      |       |
| PLR                                   | 1.201               | 0.890–1.611           | 0.222 |                      |                      |       |
| MLR                                   | 1.147               | 0.827–1.590           | 0.412 |                      |                      |       |
| AGR                                   | 1.14                | 0.798–1.629           | 0.472 |                      |                      |       |

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**Fig. 1** The overall survival (a) and progression-free survival (b) curves of this study
Association of patient characteristics with SII

Figure 3a displays that the 1-, 3-, and 5-year OS of the SII < 659.1 g group was 70.8%, 26.9%, and 14.1%, and the 1- and 3-year OS of the SII ≥ 659.1 g group was 37.5% and 11.5% (P < 0.001). As shown in Fig. 3b, the 1-, 3-, and 5-year PFS of the SII < 659.1 g group was 36.3%, 19.6%, and 13%, respectively; the 1-year PFS of patients with SII ≥ 659.1 g was 11.3% (P < 0.001). At the same time, we compared the clinicopathological features of patients with high SII (SII ≥ 659.1 g) and low SII (SII < 659.1 g). Our research showed that the high SII group had low KPS scores (P < 0.001) and cystic changes (P < 0.001), whereas SIRI, NLR, PLR, MLR, and AGR were all low in the high SII group (Table 4).

Discussion

In our research, we evaluated the prognostic values of SII, SIRI, NLR, PLR, MLR, and AGR for GBM, and discovered that the increase in SII was related to poor OS and PFS of GBM.

SII is a new inflammation marker, which serves as a comprehensive index based on the absolute value of peripheral

Table 3 Univariate and multivariate analyses of prognostic factors for progression-free survival

| Variable                              | Univariate analysis | Multivariate analysis |
|---------------------------------------|---------------------|-----------------------|
|                                       | HR                  | 95% CI                | P        | HR                  | 95% CI                | P        |
| Gender (female/male)                  | 0.916               | 0.684–1.228           | 0.558    |                     |                      |          |
| Age (<65/≥65)                         | 3.782               | 2.563–5.580           | <0.001   | 3.965               | 2.660–5.910           | <0.001   |
| KPS (<60/≥60)                         | 0.989               | 0.973–1.005           | 0.170    |                     |                      |          |
| Cystic change (yes/no)                | 1.265               | 1.063–1.506           | 0.008    |                     |                      |          |
| Extent of tumor resection (part/complete) | 0.605               | 0.469–0.780           | <0.001   |                     |                      |          |
| Tumor location                        |                     |                       |          |                     |                      |          |
| Right/left                            | 0.358               | 0.172–0.746           | 0.006    |                     |                      |          |
| Bilateral/left                        | 0.475               | 0.228–0.989           | 0.047    |                     |                      |          |
| Ki67 (<30%/≥30%)                      | 1.571               | 1.168–2.113           | 0.003    | 1.506               | 1.119–2.033           | 0.007    |
| TP53 (mutation/wild)                  | 1.237               | 0.926–1.653           | 0.150    |                     |                      |          |
| Reoperation (yes/no)                  | 1.165               | 0.936–1.449           | 0.172    |                     |                      |          |
| SII                                   | 2.13                | 1.568–2.893           | <0.001   | 2.000               | 1.472–2.716           | <0.001   |
| SIRI                                  | 0.704               | 0.522–0.948           | 0.021    |                     |                      |          |
| NLR                                   | 1.638               | 1.221–2.197           | 0.001    |                     |                      |          |
| PLR                                   | 1.266               | 0.943–1.699           | 0.122    |                     |                      |          |
| MLR                                   | 1.268               | 0.914–1.768           | 0.155    |                     |                      |          |
| AGR                                   | 1.108               | 0.775–1.583           | 0.573    |                     |                      |          |

Fig. 2 Receiver operating curve analysis of overall survival
blood neutrophils, platelets, and lymphocytes, comprehensively reflecting the immunological status. SII was proved to be closely linked to the prognosis of various diseases such as metastatic renal cell carcinoma [20], non-small cell lung cancer [13], and colorectal cancer [21] [22–24]. But studies rarely focused on identifying the prognostic value of SII for GBM.

The higher SII may reflect the imbalance of the tumor’s immune response. SII potentially affects the prognosis of GBM with the following mechanisms: first, neutrophils inhibit the immune cytolytic activity (monocytes and macrophages) [25] mainly concentrated in the peritumoral matrix of glioma tissues. With increasing neutrophils, more and more pro-angiogenic factors including vascular endothelial growth factor (VEGF) and matrix metalloproteinases will be produced and enhance angiogenesis to stimulate the development of GBM. In addition, neutrophil elastase (NE) secreted by neutrophils has a direct promotion effect on tumor growth [26], which has been confirmed in esophageal cancer [27]. A large number of researches have suggested that the increase in lymphocyte infiltration in tumors is associated with the improvement of patient prognosis [28]. The second mechanism is that lymphocytes participate in cell-mediated antitumor immune responses [29, 30], and their decrease leads to a decrease in cytolytic activity, while lymphopenia allows tumor cells to evade immune surveillance and prevents cytotoxic T cells from autoimmune response. Thirdly, platelets support tumor cells in escaping from the immune system, protecting cancer cells from natural killer-mediated lysis, accordingly accelerating metastasis [31]. VEGF and platelet-derived growth factor (PDGF) secreted by platelets are also prominent contributors to cell proliferation and tumor metastasis [32, 33]. Therefore, we believed that increased platelet levels promote the progression of brain tumors.

However, based on our research, the values of SIRI, NLR, PLR, MLR, and AGR in predicting survival, except for SII, were not proved. Although the SIRI (M×N/L) formula is similar to the SII (P×N/L) formula, where simply the monocytes in the SIRI substitute the platelets of the SII, a relationship between SIRI and GBM survival results was not found. According to Erkan Topkan’s conclusions, SIRI played a crucial role in survival prediction in glioblastoma multiforme patients treated with standard protocol [34]. We speculated that the causes presumably were that SIRI served as a dynamic indicator, and its value fluctuates during treatment, affecting final results. However, it could not rule out that the SIRI prediction effect was unable to appear on account of insufficient sample size. Therefore, we need to prudently interpret that the platelets potentially played a preferable role in promoting

### Table 4 Comparison of clinicopathological characteristics of patients with different SII scores

| Variable                  | SII < 659.10 (n=96) | SII ≥ 659.10 (n=136) | P     |
|---------------------------|----------------------|----------------------|-------|
| Age < 65                  | 84 (87.5%)           | 109 (80.1%)          | 0.140 |
| Male                      | 54 (56.3%)           | 75 (55.1%)           | 0.868 |
| KPS < 60                  | 8 (8.3%)             | 45 (33.1%)           | <0.001|
| Cystic change             | 36 (37.5%)           | 24 (17.6%)           | 0.001 |
| Tumor location (left)     | 52 (54.2%)           | 70 (51.5%)           | 0.911 |
| TP53 (mutation)           | 51 (53.1%)           | 61 (44.9%)           | 0.214 |
| Ki67 (0–20%)              | 50 (52.1%)           | 52 (38.2%)           | 0.062 |
| SIRI < 1.78               | 94 (94.9%)           | 56 (42.1%)           | <0.001|
| NLR < 2.54                | 84 (87.5%)           | 28 (20.6%)           | <0.001|
| PLR < 158.56              | 82 (85.4%)           | 60 (44.1%)           | <0.001|
| MLR < 0.36                | 88 (91.7%)           | 86 (63.2%)           | <0.001|
| AGR < 1.94                | 78 (81.3%)           | 109 (80.1%)          | 0.834 |

Fig. 3 Comparison of overall (a) and progression-free (b) survival of patients with different SII scores

![Graph](image-url)
glioblastoma growth, immune escape, and cell survival than monocytes.

Some previous studies [34–38] have investigated the role of NLR, PLR, MLR, and AGR in GBM, but there was no consistent conclusion. In our study, we did not find the prognostic values of NLR, PLR, MLR, and AGR for the survival of GBM. It may be because the inflammatory indicator only involves two parameters, which are affected by many factors, and the predictive effect is unstable. In addition, the cutoff value of the inflammation index in this study was obtained through the ROC curve. Compared with other studies, the cutoff value was slightly higher, which may also affect the results. Therefore, we need to interpret the results of the study carefully and carry out large-scale prospective studies to verify the results.

At the same time, this study explored the relationships between SII and clinicopathological characteristics. We revealed that SII was related to KPS and cystic tumor, which suggested that the inflammatory mediators released by necrotic tissue cells [39] might contribute to tumor proliferation, development, and metastasis and affect the prognosis of patients.

This study, to our best information, presented the first exploration of a meaningful correlation between higher SII value and poorer survival outcomes in GBM. In addition, our findings were not only harmonious with the outcomes of accessible literatures of SII, but also have other novel results in GBM as follows: (1) realized neutrophils, lymphocytes, and platelets could be considered as inexpensive and clinically pertinent biomarkers in GBM occurrence and progression; (2) found that SII emerged to satisfy the criteria for predicting the prognosis of GBM patients undergoing standardized treatment, further to formulate suitable treatment plans; and (3) further revealed a strong immune and inflammatory response in GBM, providing reference for the establishment of prognostic approaches for GBM patients.

Of course, our review also has some certain limitations. First, this study is a single-institutional retrospective analysis enrolling a small GBM cohort and further evaluation in prospective studies is warranted to validate these results and provide a basis for multidimensional physical and physiological individual treatment. Second, thresholds of inflammation markers have considerable heterogeneity, and the most common thresholds should be considered in clinical work. Third, we only analyzed the inflammatory indicators in the period of time before surgery, and comprehensive analysis of data at multiple time points before and after radiotherapy and chemotherapy should be added in the follow-up.

Conclusion

SII has a good prognostic value for GBM patients. In brief, dynamic SII monitoring of patients before and after surgery is essential and can be valid for predicting the prognosis of GBM. At the same time, a large-scale prospective study should be carried out to confirm the best tipping point for SII.

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Declarations

Ethics approval The Ethics Committee of the School of Nursing and Rehabilitation, Shandong University, approved all procedures, and performed under the guidelines outlined in the Declaration of Helsinki. Researchers have obtained informed consent in research involving human, and have adopted the principle of confidentiality.

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