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The prognostic role of preoperative systemic immune-inflammation index and albumin/globulin ratio in patients with newly diagnosed high-grade glioma

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ABSTRACT

Objective: Preoperative systemic immune-inflammation index (SII) and the albumin/globulin ratio (AGR) have been used as prognostic markers in many malignancies. This study was conducted to evaluate the clinical significance of the preoperative SII and AGR in high-grade glioma (HGG) patients.

Patients and methods: A total of 169 patients with newly diagnosed HGG were enrolled in the current study. Overall survival (OS) of these patients was estimated by Kaplan-Meier analyses. Univariate and multivariate Cox regression analyses were performed to examine the relationships between OS and prognostic variables in patients with HGG.

Results: The cut-off values for SII and AGR were 324.38×10^9/L and 1.35, respectively. An inverse correlation was observed between SII and AGR. The Kaplan-Meier survival analyses demonstrated that high SII and low AGR were associated with poor OS of patients with HGG ($P = 0.002$ and $P = 0.012$, respectively). Multivariate analyses revealed that both SII (HR 1.641, 95% CI: 1.071–2.515; $P = 0.023$) and AGR (HR 0.566, 95% CI: 0.335-0.956; $P = 0.033$) were independent predictive indicators of OS of HGG patients.

Conclusions: In conclusion, this study demonstrated that high SII and low AGR values may serve as promising prognostic markers to identify HGG patients with poor prognosis.

1. Introduction

Glioma is the most common type of primary malignant tumor found in the central nervous system (CNS) [1]. According to the WHO classification of CNS tumors, gliomas are classified into four grades (grade I-IV) based on the degree of malignancy [2]. Despite aggressive treatment regimens, the outcomes of patients suffering from high-grade glioma (HGG, WHO grade III [anaplastic astrocytoma] and grade IV [glioblastoma]) have remained dismal, the median overall survival (OS) for patients with glioblastoma is 14.4 months, and 37.6 months for patients with anaplastic glioma [3]. Therefore, it is important to investigate reliable prognostic factors associated with this disease. Molecular biomarkers found as prognostic factors for glioma include telomerase reverse transcriptase (TERT) and isocitrate dehydrogenase (IDH) status [4]. Moreover, some studies found that MRI-based imaging markers could be used to assess the prognosis of glioma patients, such as the mean apparent diffusion coefficient value from the diffusion-weighted MRI and the relative cerebral volume value from the dynamic susceptibility contrast perfusion MRI [5,6]. However, the high cost of these test and the need of specialized diagnostic techniques limit the potential application of these markers in clinical practice. Therefore, novel and easily detectable biomarkers are needed for predicting survival outcomes of patients with HGG.

There is increasing evidence showing that patients' inflammatory and nutritional status before surgery can impact postoperative complications and survival outcomes after resection of malignant tumors [7,8]. A novel inflammatory marker, the systemic immune-inflammation index (SII), based on platelet, neutrophil, and lymphocyte counts [9], has recently been found to be a prognostic indicator for survival outcomes in many malignancies. Some studies have demonstrated that increased preoperative SII is associated with low survival rates of patients with in small cell lung cancer [9], hepatocellular carcinoma [10], and esophageal squamous cell carcinoma [11].

As two major components of the total serum protein, albumin and

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globulin have received increased attention as noninvasive prognostic markers for tumors [12,13]. Both albumin and globulin play important roles in the inflammatory processes, and serum albumin is also used as a tool to measure long-standing malnutrition in patients [14,15]. The albumin/globulin ratio (AGR) is an indicator of the inflammatory and nutritional status by combining these two factors in one measure [16]. Previous studies have confirmed the preoperative AGR as a prognostic marker in several types of tumors, including natural killer/T-cell lymphoma, colon cancer, hepatocellular carcinoma, and renal cell carcinoma [17–20]. Therefore, this study was designed to assess the prognostic values of the preoperative SII and AGR for OS of HGG patients.

2. Patients and methods

2.1. Study patients

This retrospective study enrolled 242 newly diagnosed HGG patients between October 2014 and May 2016 at West China Hospital (Chengdu, China). The HGG (WHO Grade III and IV gliomas) diagnosis was confirmed by pathological examination and graded according to the 2007 WHO classification of CNS tumors [21]. Of these 242 patients, 73 were excluded based on the following criteria: (1) tumor grade (Grade III or Grade IV) could not be confirmed at the time of diagnosis, (2) presence of active infection or autoimmune disorders, (3) presence of another malignant disease, (4) a history of anti-tumor therapy or received cortisol or antibiotics before blood tests, (5) age less than 18 years, (6) incomplete laboratory data before surgery, (7) death occurring shortly after surgery, owing to serious postoperative complications, and (8) loss to follow-up. The remaining 169 patients were included in this study. Clinicopathological data, including gender, age at surgery, pathological diagnosis, tumor size, tumor grade, tumor location, therapeutic information, postoperative Karnofsky performance status (KPS), and preoperative hematological variables (albumin, globulin, AGR, hemoglobin, neutrophil, lymphocyte, and platelet counts) were collected by review of the electronic medical records of the participating patients. The SII was calculated as follows: SII = (PxN)/L, with P = platelets, N = neutrophils, L = lymphocytes [9]. Tumor location was assigned as cerebral cortex and non-cerebral cortex areas [22]. In this study, tumors were categorized as small or large-size, based on a cut-off value of 3 cm for tumor size [23,24]. A serum albumin level below 40 g/L was defined as hypoalbuminemia [25], and hemoglobin level less than 120 g/L before surgery was defined as anemia [26]. OS was defined as the time from the date of surgery to date of death, or the date of last follow-up visit. The last follow-up visit was performed in August 2017.

2.2. Statistical analyses

Statistical analyses were performed using the Statistical Package for Social Science (SPSS for Windows, version 19.0) program. The cut-off values of preoperative hematological variables were obtained by X-tile software program (Version 3.6.1; Yale University, School of Medicine) as described previously [27]. A P-value < 0.05 was considered statistically significant. The chi-square test, with or without continuity correction, and the Fisher's exact test were used to analyze categorical variables. Correlation between continuous variables was tested using the Spearman's rank correlation coefficient (r). Survival curves were drawn with the Kaplan-Meier method and compared with the log-rank test. Univariate and multivariate Cox regression analyses were performed to estimate the prognostic variables. Only those variables significantly associated with OS in the univariate analyses ($P < 0.05$) were included into the multivariate analyses.

Table 1
Baseline patient characteristics.

Variables	N	%
Age (years)		
≥40/ < 40	137/32	81.07/18.93
gender		
Male/Female	99/70	58.58/41.42
Tumor size (cm)		
≥3/ < 3	157/12	92.90/7.10
Tumor location		
Cerebral cortex/Non cerebral cortex	149/20	88.17/11.83
Tumor grade		
WHO IV/WHO III	140/29	82.84/17.16
Extent of resection		
Gross total/Subtotal	111/58	65.68/34.32
Adjuvant radio/chemotherapy		
Yes/No	83/86	49.11/50.89
Hemoglobin (g/L)		
≥120/ < 120	150/19	88.76/11.24
Neutrophil ($\times 10^9$/L)		
≥2.82/ < 2.82	151/18	89.35/10.65
Lymphocyte ($\times 10^9$/L)		
≥1.33/ < 1.33	130/39	76.92/23.08
Platelet ($\times 10^9$/L)		
≥296/ < 296	13/156	7.69/92.31
Albumin (g/L)		
≥40/ < 40	130/39	76.92/23.08
Globulin (g/L)		
≥26.30/ < 26.30	103/66	60.95/39.05
AGR		
≥1.35/ < 1.35	150/19	88.76/11.24
SII ($\times 10^9$/L)		
≥324.38/ < 324.38	116/53	68.64/31.36
Postoperative KPS		
≥70/ < 70	105/64	62.13/37.87

AGR, albumin/globulin ratio; SII, systemic immune-inflammation index; KPS, Karnofsky performance status.

3. Results

3.1. Patient characteristics

The clinicopathological characteristics of patients were shown in Table 1. A total of 169 patients (70 females and 99 males) newly diagnosed with HGG were included in this study. Within this group, 29 patients (17.16%) had WHO grade III (anaplastic astrocytoma) and 140 patients (82.84%) had WHO grade IV (glioblastoma) tumors. The median age of the patients was 53 years, ranging from 21 to 91 years. At their last follow-up visit, 48 (28.4%) patients were still alive and 121 (71.6%) patients had died. In this study, the cut-off values for neutrophil, lymphocyte, platelet, globulin, AGR, and SII were 2.82×10^9/L, 1.33×10^9/L, 296×10^9/L, 26.30 g/L, 1.35, and 324.38×10^9/L, respectively, as obtained by X-tile software program.

3.2. Associations of the SII and AGR with clinicopathological characteristics

In the current study, the SII had a significant relationship with the tumor grade ($P = 0.009$). The SII was also significantly associated with hematological variables, neutrophil counts ($P < 0.001$), lymphocyte counts ($P = 0.001$), and platelet counts ($P = 0.026$). Further, the AGR had a significant relationship with the platelet counts ($P < 0.001$), albumin and globulin levels ($P < 0.001$ and $P = 0.001$, respectively) (Table 2). In addition, we observed a trend towards an inverse correlation between SII and AGR ($r = -0.178$, $P = 0.021$) (Fig. 1).

3.3. Prognostic values of SII and AGR

The Kaplan-Meier survival analyses demonstrated that high SII and low AGR were associated with poor OS of patients with HGG ($P = 0.002$ and $P = 0.012$, respectively). The median OS was 17.0

Table 2
Associations of the variables SII and AGR with clinicopathological characteristics.

	SII			AGR		
Variables	≥324.38	< 324.38	P	≥1.35	< 1.35	P
Age (years)			0.210			0.192
≥40	97	40		119	18	
< 40	19	13		31	1	
Gender			0.748			0.576
Male	67	32		89	10	
Female	49	21		61	9	
Tumor size (cm)			0.262			0.275
≥3	110	47		141	16	
< 3	6	6		9	3	
Tumor location			0.375			0.187
Cerebral cortex	104	45		130	19	
Non cerebral cortex	12	8		20	0	
Tumor grade			0.009			0.866
WHO IV	102	38		124	16	
WHO III	14	15		26	3	
Hemoglobin (g/L)			0.304			0.068
≥120	101	49		136	14	
< 120	15	4		14	5	
Neutrophil ($\times 10^9$/L)			< 0.001			0.707
≥2.82	114	37		135	16	
< 2.82	2	16		15	3	
Lymphocyte($\times 10^9$/L)			0.001			0.221
≥1.33	81	49		118	12	
< 1.33	35	4		32	7	
Platelet ($\times 10^9$/L)			0.026			< 0.001
≥296	13	0		7	6	
< 296	103	53		143	13	
Albumin (g/L)			0.628			< 0.001
≥40	88	42		123	7	
< 40	28	11		27	12	
Globulin (g/L)			0.434			0.001
≥26.30	73	30		85	18	
< 26.30	43	23		65	1	

AGR, albumin/globulin ratio; SII, systemic immune-inflammation index.

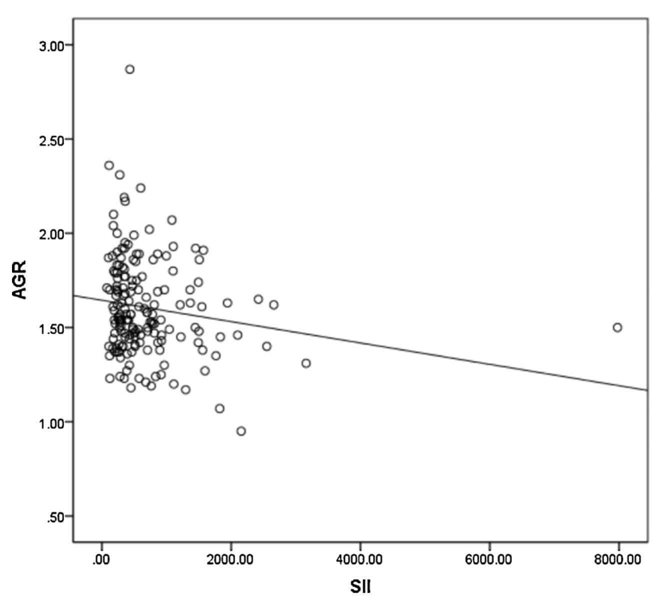

Fig. 1. Correlations between systemic immune-inflammation index (SII) and albumin/globulin ratio (AGR) (r = -0.178, P = 0.021).

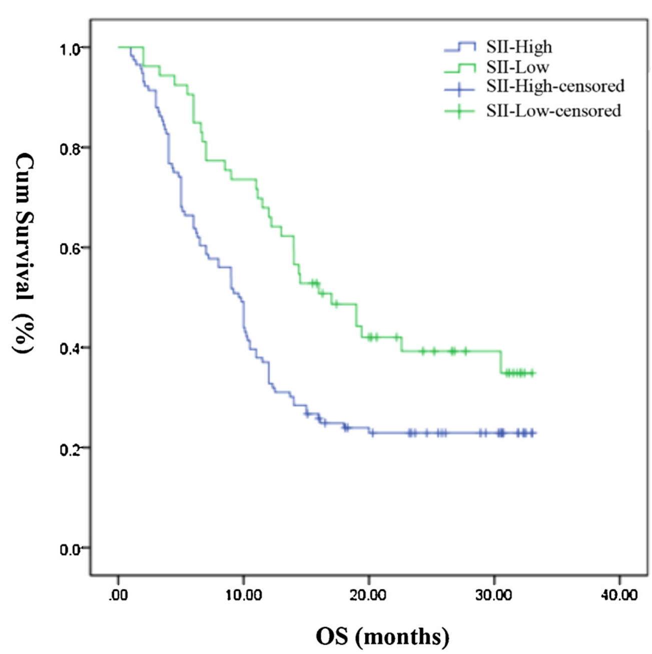

Fig. 2. Kaplan Meier survival curves according to systemic immune-inflammation index (SII) (log rank, P = 0.002).

months (95% CI: 11.5–22.5 months) for patients with SII < 324.38 × 10^9/L and 9.6 months (95% CI: 8.1–11.1 months) for those with SII ≥ 324.38 × 10^9/L (P = 0.002) (Fig. 2). In addition, patients with AGR < 1.35 had a median OS of 5.1 months (95% CI: 2.8–7.4 months), whereas patients with AGR ≥ 1.35 had a median OS of 11.1 months (95% CI: 9.7–12.5 months) (P = 0.012) (Fig. 3).

3.4. Univariate and multivariate analyses of prognostic factors for OS

We examined the prognostic values of the preoperative SII and AGR in predicting the survival of the patients participating in our study

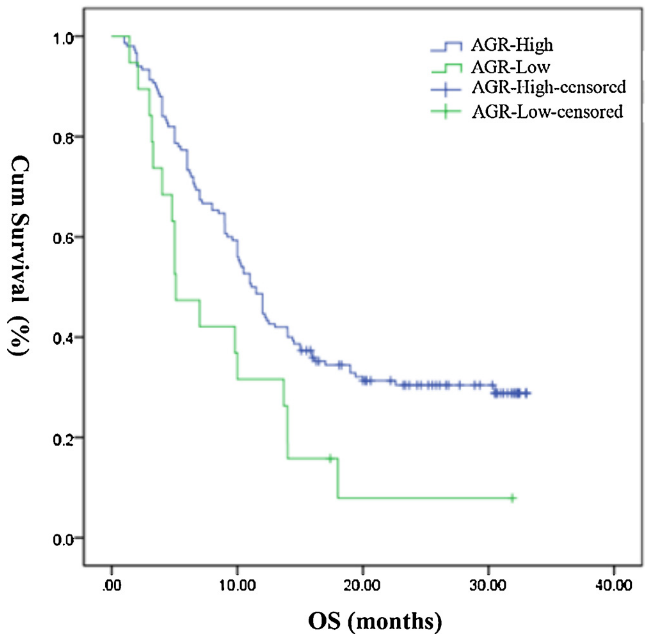

Fig. 3. Kaplan Meier survival curves according to albumin/globulin ratio (AGR) (log rank, P = 0.012).

(Table 3). A univariate analysis revealed that age (P = 0.015), tumor location (P = 0.016), tumor grade (P < 0.001), extent of resection (P < 0.001), adjuvant treatment (P < 0.001), neutrophil counts (P = 0.024), lymphocyte counts (P = 0.001), SII (P = 0.003), AGR (P = 0.015) and postoperative KPS (P = 0.011) were significant predictors of OS. In multivariate analysis, predictors of OS were tumor grade (HR 4.092, 95% CI: 2.133–7.848; P < 0.001), extent of resection (HR 0.233, 95% CI: 0.152–0.357; P < 0.001), adjuvant treatment (HR 0.481, 95% CI: 0.328–0.705; P < 0.001), SII (HR 1.641, 95% CI: 1.071–2.515; P = 0.023), AGR (HR 0.566, 95% CI: 0.335–0.956; P = 0.033), and postoperative KPS (HR 0.466, 95% CI: 0.319–0.680; P < 0.001).

4. Discussion

Inflammation and malnutrition induced by cancer are crucial host-related factors that may have adverse effects on the clinical outcomes of cancer patients [28]. SII and AGR have been proposed as prognostic factors in various malignant tumors [9–11,17–19]. In the current study, we investigated the prognostic role of preoperative SII and AGR in 169 patients with newly diagnosed HGG. In our study, univariate and multivariate Cox analyses showed that SII and AGR were significant prognostic factors for OS in patients with HGG. These findings were also confirmed by Kaplan-Meier method using log-rank test.

As an integrated marker that is based on platelet, neutrophil, and lymphocyte counts, the prognostic predictive value of the preoperative SII in patients with HGG might be explained by the varied functions of these three types of cells. Nolte et al. found that growth of glioblastoma was paralleled by an elevation of platelet counts [29]. In addition, there have been recent reports showing that platelet-derived growth factor plays a key role in glial tumorigenesis [30]. Previously, it has been shown that neutrophils could affect tumor angiogenesis [31]. Teramukai et al. found that elevated pretreatment neutrophil counts were associated with adverse clinical outcomes in patients with advanced non-small-cell lung cancer [32]. Moreover, a positive correlation was found between the extent of the neutrophil infiltration into the glioma and peripheral blood neutrophil counts; further, the high peripheral blood neutrophil counts indicated that glioma-derived factors might affect bone marrow production of neutrophils [33]. Furthermore, Liang et al. found that neutrophils may promote glioma angiogenesis by inducing a shift of tumor from proneural to mesenchymal subtype [34]. In addition, lymphocyte count is an indicator of cell-mediated immunity, which is very important in host defense against tumors [35]. Han et al. reported that a low count of CD8 (+) tumor-infiltrating lymphocytes (TILs) combined with a high count of CD4 (+) TILs is associated with poor prognosis in patients with glioblastoma [36]. Therefore, increased neutrophil counts or decreased lymphocyte counts may confer a poor prognosis. In this study, we showed that a high preoperative SII was an independent predictor of poor OS in patients with HGG. Similar results have been reported in previous studies of other malignant tumors [9–11]. Lv et al demonstrated that high SII was associated with poor OS in patients with glioblastoma, but it was not an independent prognostic factor [37].

Table 3
Univariate and Multivariate Cox proportional analyses regarding overall survival.

	Univariate			Multivariate		
Variables	HR	95%CI	P	HR	95%CI	P
Age (years) (≥40 vs. < 40)	1.895	1.132–3.171	0.015	1.419	0.825–2.439	0.206
Gender (male vs. female)	1.315	0.911–1.899	0.144			NI
Tumor size(≥3 vs. < 3)	1.395	0.681–2.861	0.363			NI
Tumor location (Cerebral cortex vs. Non cerebral cortex)	0.523	0.308–0.887	0.016	0.864	0.476–1.567	0.630
Tumor grade (WHO IV vs. WHO III)	3.452	1.852–6.434	< 0.001	4.092	2.133–7.848	< 0.001
Extent of resection (Gross total vs. Subtotal)	0.248	0.169–0.363	< 0.001	0.233	0.152–0.357	< 0.001
Adjuvant radio/chemotherapy (yes vs. no)	0.352	0.243–0.510	< 0.001	0.481	0.328–0.705	< 0.001
Hemoglobin (≥120 vs. < 120)	0.689	0.407–1.168	0.167			NI
Neutrophil (≥2.82 vs. < 2.82)	2.291	1.117–4.700	0.024	1.561	0.656–3.717	0.314
Lymphocyte (≥1.33 vs. < 1.33)	0.523	0.352–0.777	0.001	0.784	0.513–1.198	0.261
Platelet (≥296 vs. < 296)	1.395	0.730–2.666	0.314			NI
Albumin (≥40 vs. < 40)	0.675	0.452–1.009	0.055			NI
Globulin (≥26.30 vs. < 26.30)	0.705	0.491–1.012	0.058			NI
AGR (≥1.35 vs. < 1.35)	0.527	0.315–0.882	0.015	0.566	0.335–0.956	0.033
SII (≥324.38 vs. < 324.38)	1.848	1.231–2.773	0.003	1.641	1.071–2.515	0.023
Postoperative KPS (≥70 vs. < 70)	0.624	0.434–0.897	0.011	0.466	0.319–0.680	< 0.001

NI, not included in multivariate survival analysis; AGR, albumin/globulin ratio; SII, systemic immune-inflammation index; KPS, Karnofsky performance status.

Hypoalbuminemia might be caused by systemtic inflammation and malnutrition, resulting in impairment of immune functions [20]. As part of cancer-associated systemic inflammation, activation of cytokines, such as IL-6 and tumor necrotic factor-α, can lower albumin concentration [38]. The level of globulins is elevated mainly due to accumulation of acute-phase proteins and immunoglobulins, which is induced by inflammation [28]. The AGR, as a combined measure of two indicators (i.e., albumin and globulin), more accurately reflects the nutritional and inflammatory status of our body; thus, it may be particularly useful as a prognostic biomarker for predicting clinical outcomes in cancer patients [16]. Previous studies have shown that low AGR is correlated with poor prognosis in various malignant tumors, including glioblastoma [16–20,28,39,40]. In accordance with previous studies, our findings clearly demonstrated that preoperative low AGR was correlated with poor clinical outcome in patients with HGG. Furthermore, an inverse correlation was observed between the preoperative AGR and SII. Several studies have observed that preoperative nutritional intervention could reduce the length of postoperative hospital stay and improve prognosis in patients with cancer [41,42]. Based on our results, it is speculated that survival could be improved by reducing inflammation and improving nutritional status of patients with HGG.

We acknowledge that there are several potential limitations of our study. First, this is a single-center retrospective study, which may introduce selection bias. Second, as West China Hospital is a large tertiary referral center in southwest China and mainly serves patients with large or complex lesions. It is therefore possible that our samples do not accurately represent the entire HGG population. Third, data related to glioma-associated pathological factors, TERT and IDH, were unavailable [4]. Therefore, our findings need to be further validated in larger multi-center prospective studies.

5. Conclusion

In conclusion, this study demonstrated that high SII and low AGR values could be promising prognostic markers to identify HGG patients with poor prognosis. The mechanism underlying the prognostic value of SII and AGR in patients with HGG should be clarified.

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