

Preoperative albumin-to-globulin ratio and prognostic nutrition index predict prognosis for glioblastoma

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Objective: Impaired immunonutritional status has disadvantageous effects on outcomes for cancer patients. Preoperative albumin-to-globulin ratio (AGR) and the prognostic nutrition index (PNI) have been used as prognostic factors in various cancers. We aimed to evaluate the clinical significance of the AGR and PNI in glioblastoma.

Materials and methods: This retrospective analysis involved 166 patients. Demographic, clinical, and laboratory data were collected. AGR and the PNI were calculated as $AGR = \text{albumin}/(\text{total serum protein} - \text{albumin})$ and $PNI = \text{albumin (g/L)} + 5 \times \text{total lymphocyte count (10}^9/\text{L)}$. Overall survival (OS) was estimated by Kaplan–Meier analysis. Receiver-operating characteristic analysis was used to assess the predictive ability of AGR and the PNI. Cox proportional-hazard models estimating hazard ratios (HRs) and 95% confidence intervals (CIs) were used for univariable and multivariable survival analyses.

Results: The cutoff values of AGR and PNI were 1.75 and 48. OS was enhanced, with high AGR (>1.75) and the PNI (>48) ($P < 0.001$ for both). Areas under the receiver-operating characteristic curve for AGR and the PNI were 0.68 and 0.631 for 1-year survival and 0.651 and 0.656 for 2-year survival ($P < 0.05$ for all), respectively. On multivariable analyses, both AGR and the PNI were independent predictors of OS (AGR, HR 0.785, 95% CI 0.357–0.979 [$P = 0.04$]; PNI, HR 0.757, 95% CI 0.378–0.985 [$P = 0.039$]). On subgroup analysis, AGR and the PNI were significant prognostic factors for OS in patients with adjuvant therapy (AGR $P < 0.001$; PNI $P = 0.001$).

Conclusion: Preoperative AGR and the PNI may be easy-to-perform and inexpensive indices for predicting OS with glioblastoma. AGR and the PNI could also help in developing good adjuvant-therapy schedules.

Keywords: glioblastoma, albumin-to-globulin ratio, prognostic nutrition index, prognosis

Introduction

The 5-year relative survival for glioblastoma (GB), the most commonly occurring glioma histological type (~45% of all gliomas), is ~5%.¹ The widely accepted therapy regimen for newly diagnosed GB includes maximal safe resection and concurrent chemotherapy with temozolomide and radiotherapy. The median survival of GB is only about 15 months, even with recent diagnostic and therapeutic advances.² Because of molecular and cellular heterogeneity, together with individual differences, the clinical outcomes of individual patients with similar diagnosis and treatment remain diverse.³ Moreover, a high incidence of local recurrence (~90%) is an important cause of low survival.⁴ Consequently, identifying prognostic biomarkers, such as in peripheral blood, could help in designing treatment strategies and stratifying patients with poor overall survival (OS) after surgery.

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Understanding the crucial biomarkers that play a part in GB malignant behavior might help clinicians educate patients about prognosis and monitor therapeutic efficacy. Laboratory markers found as prognostic factors for GB include *MGMT*, *IDH1*, *IDH2*, *EGFR*, telomerase reverse transcriptase, *p53*, *PDGF* and *PTEN*.^{5–9} Some clinical markers, such as histopathologic transformation, as well as geometric heterogeneity and/or spherical rim widths seen on magnetic resonance imaging, show high individual and combined prognostic value.^{10,11} However, the high cost of testing and the analytic subjectivity and instability of results limit the application of these markers in clinical practice. Novel and practical biomarkers for predicting outcomes with GB are needed.

Preoperative albumin-to-globulin ratio (AGR) could reflect both malnutrition and systemic inflammation in cancer patients.¹² As a major component in serum protein, serum albumin is used to measure long-standing malnutrition and is also associated with systemic inflammation.¹³ Survival seems longer for patients with high than low preoperative serum albumin levels in adenocarcinoma of the gastric cardia and ovarian cancer.^{14,15} Globulin functions as a carrier of hormones, and plays an important role in immunity and inflammation.¹⁶ Recently, AGR was used to predict outcome with bladder urothelial carcinoma, small-cell lung cancer, and natural killer/T-cell lymphoma.^{12,17,18}

The prognostic nutrition index (PNI), based on albumin level and lymphocyte count, could reflect immunonutritional status and systemic inflammatory reaction with more accuracy than with each variable alone.^{19,20} Lymphocytes are key components of the immune system and are essential effector cells in antitumor immunity.^{21,22} Lymphocyte count (particularly CD4 cells) has been found to be decreased in GB and associated with poor survival time.^{23,24} The value of the PNI in predicting clinical outcomes has been verified in colorectal cancer, gastric cancer, and renal cell carcinoma, for example.^{25–27} However, no study has examined the prognostic role of AGR and the PNI in GB. In this study, we examined clinical data to analyze the prognostic value of the two immunonutritional factors AGR and PNI for OS in GB patients.

Materials and methods

Patients

We examined clinical data for 243 patients with a diagnosis of GB confirmed by postoperative pathological examination at Qilu Hospital of Shandong University from January 2010

to January 2015. Patients were followed every month for the first few years after surgery and thereafter every 2 months until death. The median follow-up time was 14 months (range 1–52 months). We excluded patients with metabolic syndrome, diabetes, heart disease, hypertension, autoimmune disease, and infection within 3 months.

We collected data on age, sex, smoking and drinking status, body mass index, Karnofsky performance status (KPS), tumor size, tumor localization (region of brain), extent of resection, preoperative lymphocyte count, preoperative albumin level, adjuvant radiotherapy and chemotherapy, and death. Tumor size was calculated from magnetic resonance-imaging data: longest \times widest diameter \times thickness (section thickness \times number of layers) \times 0.5.²⁸

Data for hematological variables were obtained for all enrolled patients within 1 week before surgery. The time from surgery to death was defined as OS. Data for patients alive at last follow-up were considered censored. The study protocol was approved by the ethics committee of Qilu Hospital. Patients all granted written informed consent for surgery and the use of clinical records.

Evaluation of AGR and PNI

We used the following formulas for calculating AGR and PNI:²⁹

$$\text{AGR} = \text{Albumin} / (\text{total serum protein} - \text{albumin}) \quad (1)$$

$$\text{PNI} = \text{Albumin (g/L)} + 5 \times \text{Total lymphocyte count (10}^9\text{/L)} \quad (2)$$

Statistical analysis

To determine differences between groups, continuous variables were analyzed by unpaired *t*-tests and categorical variables by χ^2 test. Data are shown as means (standard deviation) or median (interquartile range). We used the Kaplan–Meier method for estimating OS. Receiver-operating characteristic (ROC) curve analysis was applied to determine the best cutoff values for AGR and PNI, and area under the ROC curve estimation was used to assess the predictive ability of AGR and PNI. Univariable Cox analysis was used to analyze the prognostic significance of the variables. Multivariable analysis by Cox proportional-hazard model was used to determine the independence of the prognostic factors, estimating hazard ratios (HRs) and 95% confidence intervals (CIs). All statistical analyses involved the use of Statistical Package for the Social Sciences (SPSS) version 23.0 (IBM, Armonk, NY, USA). $P < 0.05$ was considered statistically

significant and the inclusion criterion to use a variable from univariable analysis in the multivariable analysis.

Results

Clinical characteristics of patients

After excluding data for 65 patients with the aforementioned diseases and 12 patients lost to follow-up, we examined data for 166 patients. Baseline characteristics are in Table 1. The median age at diagnosis was 50 (6–83) years, and 84 (50.6%) were male. The median body mass index was 22 (15.57–34.38). KPS was 80–100 in 91 patients (54.8%) and ≤ 70 in 75 patients (45.2%). The median tumor size was 40.1 (6.35–245.52) cm³. Most tumors were located in the frontal (38.6%), temporal (33.7%), and parieto-occipital

(20.5%) regions. Other locations, including ventricles, cerebellum, insular lobe, thalamus, and callosum, represented 7.2% of tumors. Total resection was performed to treat 109 patients (65.7%). The median preoperative albumin level, lymphocyte count, AGR, and PNI were 41.61 (33.91–52.11) g/L, $1.89 \times 10^9/L$ (0.73–3.67), 1.66 (1.19–2.58), and 51.1 (41.15–68.95), respectively. In all, 105 patients (63.3%) received adjuvant radiotherapy and 42 (25.3%) adjuvant chemotherapy.

Association of clinical characteristics with preoperative AGR and PNI

On ROC analysis, the cutoff values for AGR and PNI were 1.75 (sensitivity 0.554 and specificity 0.806) and 48 (sensitivity 0.782 and specificity 0.575). The high-AGR and -PNI groups had higher preoperative albumin levels than the low-AGR and -PNI groups ($P < 0.001$ for both) (Table 2). Similarly, preoperative lymphocyte counts in the high-AGR and -PNI groups were higher than those in the low-AGR and -PNI groups ($P = 0.013$ and $P < 0.001$).

Prognostic value of AGR and PNI

The median OS was 13 (range 1–52) months. Kaplan–Meier curves for OS based on preoperative AGR and PNI demonstrated that patients with AGR ≤ 1.75 or PNI ≤ 48 had significantly poorer OS than those with AGR > 1.75 or PNI > 48 ($P < 0.001$ for both) (Figure 1). For 1-year survival, the area under the ROC curve for AGR and PNI was 0.68 (sensitivity 0.67, specificity 0.774, 95% CI 0.577–0.783; $P = 0.038$), and 0.631 (sensitivity 0.834, specificity 0.429, 95% CI 0.523–0.739; $P = 0.045$), and for 2-year survival was 0.651 (sensitivity 0.524, specificity 0.786, 95% CI 0.55–0.752; $P = 0.024$) and 0.656 (sensitivity 0.766, specificity 0.55, 95% CI 0.548–0.765; $P = 0.041$) (Figure 2).

Univariable and multivariable analyses of prognostic factors for OS

We examined the functions of preoperative AGR and PNI in survival in our cohort (Table 3). On univariable Cox analysis, OS was associated with age ($P = 0.045$), KPS ($P = 0.009$), tumor size ($P = 0.022$), extent of resection ($P = 0.017$), preoperative albumin level ($P = 0.035$), lymphocyte count ($P = 0.028$), AGR ($P = 0.003$), PNI ($P < 0.001$), and adjuvant radiotherapy ($P = 0.004$) and chemotherapy ($P = 0.002$). On multivariable analysis, predictors of OS were KPS (HR 0.528, 95% CI 0.341–0.851; $P = 0.032$), tumor size (HR 1.343, 95% CI 1.014–1.726; $P = 0.037$), extent of resection (HR 0.416, 95% CI 0.334–0.885; $P = 0.026$), preoperative

Table 1 Clinical characteristics of 166 patients with glioblastoma

Age (years), mean \pm SD	50.41 \pm 14.5
Median (IQR)	50 (6–83)
Sex (male/female)	84/82
Preoperative BMI, mean \pm SD	22.4 \pm 3.52
Median (IQR)	22 (15.57–34.38)
KPS	
80–100	91 (54.8%)
≤ 70	75 (45.2%)
Smoking	
Never or light	115 (69.3%)
Heavy	51 (30.7%)
Drinking	
Never or light	122 (73.5%)
Heavy	44 (26.5%)
Tumor size (cm³), mean \pm SD	52.61 \pm 28.12
Median (IQR)	40.1 (6.35–245.52)
Tumor location, region	
Frontal	64 (38.6%)
Temporal	56 (33.7%)
Parieto-occipital	34 (20.5%)
Other	12 (7.2%)
Extent of resection	
Total	109 (65.7%)
Not total	57 (34.3%)
Preoperative	
Albumin level (g/L), mean \pm SD	42.21 \pm 4.07
Median (IQR)	41.61 (33.91–52.11)
Lymphocyte count (10⁹/L), mean \pm SD	1.97 \pm 0.64
Median (IQR)	1.89 (0.73–3.67)
AGR, mean \pm SD	1.65 \pm 0.41
Median (IQR)	1.66 (1.19–2.58)
PNI, mean \pm SD	51.92 \pm 5.23
Median (IQR)	51.1 (41.15–68.95)
Adjuvant radiotherapy	105 (63.3%)
Adjuvant chemotherapy	42 (25.3%)

Note: Data are n (%), unless otherwise indicated.

Abbreviations: SD, standard deviation; IQR, interquartile range; BMI, body mass index; KPS, Karnofsky performance status; AGR, albumin-to-globulin ratio; PNI, prognostic nutrition index.

Table 2 Clinical characteristics of patients by AGR and PNI cutoffs

Characteristics	AGR		P-value	PNI		P-value
	≤1.75	>1.75		≤48	>48	
Age, years	50.5±14.94	50.39±11.68	0.958	52.74±14.06	49.29±14.59	0.134
Sex			0.496			0.391
Male	52	33		28	56	
Female	51	30		30	52	
Preoperative BMI	22.67±3.89	22.1±2.97	0.293	21.58±3.91	22.44±4.04	0.178
KPS			0.335			0.87
80–100	53	38		31	60	
≤70	50	25		27	48	
Smoking			0.145			0.542
Never or light	69	46		40	75	
Heavy	34	17		18	33	
Drinking			0.155			0.377
Never or light	79	43		44	78	
Heavy	24	20		14	30	
Tumor size (cm³)	54.25±44.37	50.13±37.55	0.528	53.83±36.97	51.92±46.37	0.77
Tumor location			0.522			0.191
Frontal	44	19		27	37	
Temporal	33	24		16	40	
Parieto-occipital	20	14		9	25	
Other	7	5		6	6	
Extent of resection			0.108			0.491
Total	63	46		35	74	
Not total	40	17		22	35	
Preoperative albumin level (g/L)	40.34±3.34	43.20±4.35	<0.001	41.09±3.28	43.69±4.41	<0.001
Preoperative lymphocyte count (10⁹/L)	1.91±0.55	2.10±0.61	0.013	1.87±0.46	2.22±0.48	<0.001
Adjuvant radiotherapy			0.192			0.093
No	24	37		34	27	
Yes	50	55		46	59	
Adjuvant chemotherapy			0.173			0.269
No	80	44		53	71	
Yes	23	19		15	27	

Note: Data are mean ± SD.

Abbreviations: AGR, albumin-to-globulin ratio; PNI, prognostic nutrition index; BMI, body mass index; KPS, Karnofsky performance status; SD, standard deviation.

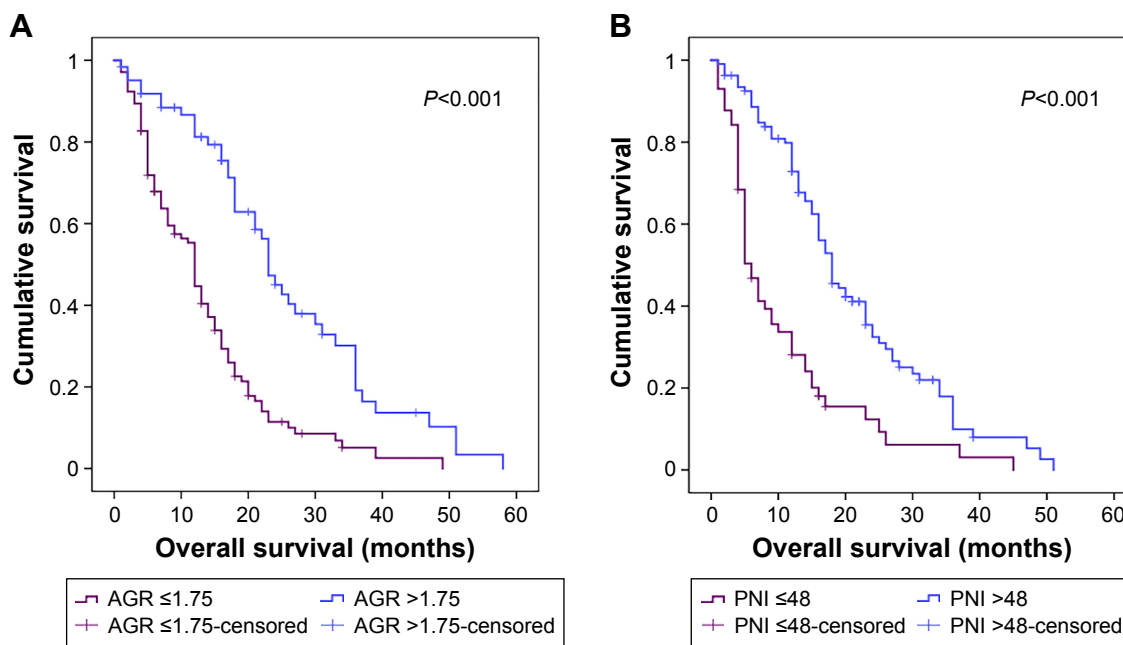


Figure 1 Prognosis of preoperative (A) AGR and (B) PNI in survival with glioblastoma.

Abbreviations: AGR, albumin-to-globulin ratio; PNI, prognostic nutrition index.

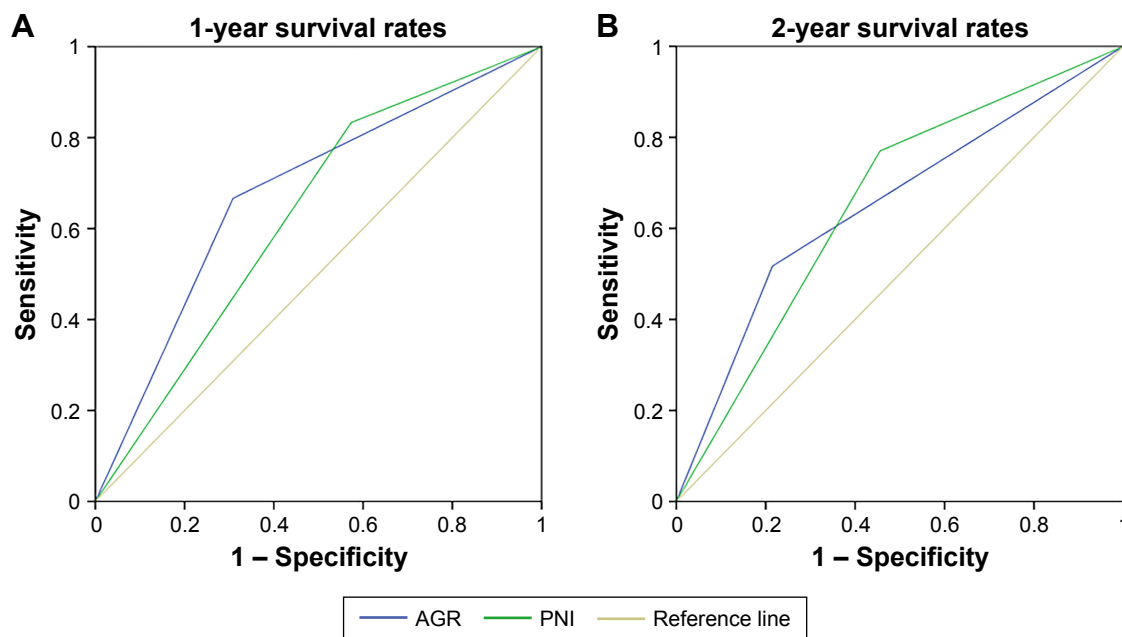


Figure 2 Predictive value of AGR and PNI for (A) 1-year and (B) 2-year survival. Receiver-operating characteristic curves for AGR and PNI. **Abbreviations:** AGR, albumin-to-globulin ratio; PNI, prognostic nutrition index.

AGR (HR 0.785, 95% CI 0.357–0.979; $P=0.04$), PNI (HR 0.757, 95% CI 0.378–0.985; $P=0.039$), and adjuvant radiotherapy (HR 0.599, 95% CI 0.32–0.983; $P=0.031$).

Prognostic impact of AGR and PNI with adjuvant therapy

Adjuvant therapy was defined as chemotherapy and/or radiotherapy. In our cohort, 123 (74.1%) patients received

adjuvant therapy. On subgroup analyses of patients with adjuvant therapy, survival differed with AGR ≤ 1.75 and > 1.75 ($P < 0.001$) (Figure 3A) and PNI ≤ 48 and > 48 ($P=0.001$) (Figure 3B).

Discussion

Impaired immunonutritional status has disadvantageous effects on outcomes for cancer patients. AGR and the PNI

Table 3 Prognostic factors for overall survival for 166 patients with glioblastoma

Characteristics	Univariable analysis		P-value	Multivariable analysis		P-value
	HR	95% CI		HR	95% CI	
Age (>50 vs ≤ 50 years)	1.423	1.001–2.145	0.045	1.017	0.996–2.286	0.371
Sex (female vs male)	1.014	0.718–1.434	0.935			
Preoperative BMI (>22 vs ≤ 22 kg/m ²)	1	0.859–1.142	0.993			
KPS (80–100 vs ≤ 70)	0.403	0.257–0.694	0.009	0.528	0.341–0.851	0.032
Smoking (heavy vs never or light)	1.096	0.761–1.577	0.623			
Drinking (heavy vs never or light)	0.944	0.645–1.383	0.769			
Tumor size (>40 vs ≤ 40 cm ³)	1.769	1.41–2.198	0.022	1.343	1.014–1.726	0.037
Tumor location						
Frontal		1	Ref			
Temporal	1.153	0.804–1.656	0.49			
Parieto-occipital	0.761	0.44–1.237	0.271			
Other	1.294	0.713–2.476	0.363			
Extent of resection (total vs not total)	0.315	0.244–0.762	0.017	0.416	0.334–0.885	0.026
Preoperative albumin level (>42 vs ≤ 42 g/L)	0.617	0.374–0.812	0.035	0.918	0.571–1.389	0.359
Preoperative lymphocyte count (>1.9 vs $\leq 1.9 \times 10^9/L$)	0.578	0.379–0.961	0.028	0.84	0.541–1.225	0.196
AGR (>1.75 vs ≤ 1.75)	0.456	0.244–0.608	0.003	0.785	0.357–0.979	0.04
PNI (>48 vs ≤ 48)	0.372	0.245–0.565	<0.001	0.757	0.378–0.985	0.039
Adjuvant radiotherapy (yes vs no)	0.554	0.402–0.721	0.004	0.599	0.320–0.983	0.031
Adjuvant chemotherapy (yes vs no)	0.542	0.357–0.822	0.002	0.866	0.494–1.298	0.226

Abbreviations: HR, hazard ratio; CI, confidence interval; BMI, body mass index; KPS, Karnofsky performance status; AGR, albumin-to-globulin ratio; PNI, prognostic nutrition index.

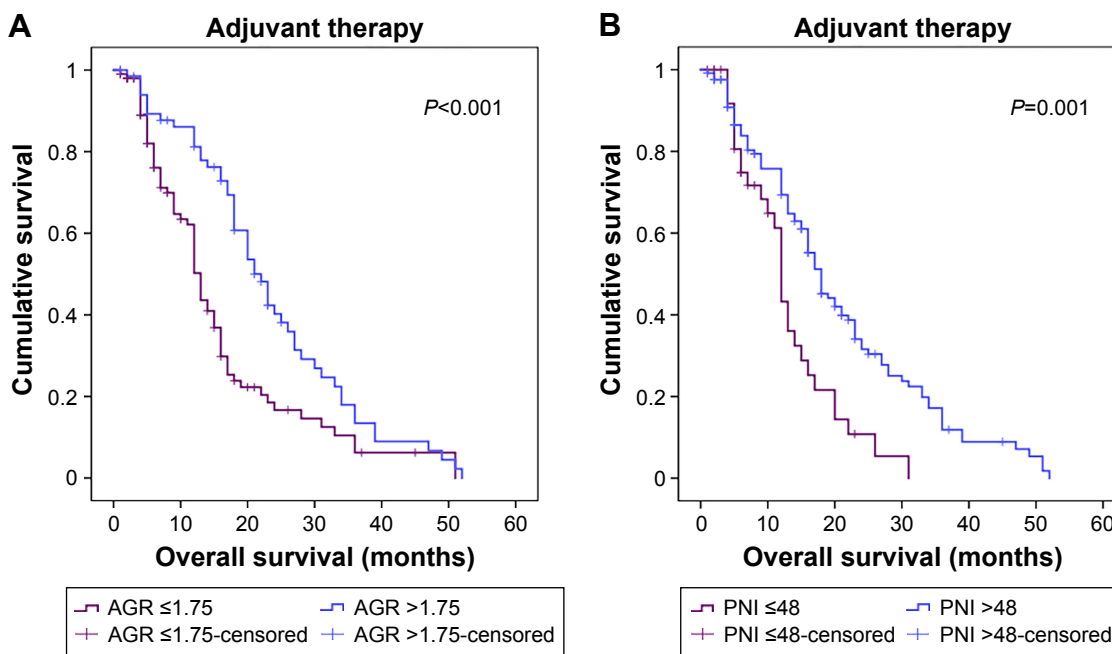


Figure 3 Subgroup analyses of the prognostic impact of (A) AGR and (B) PNI for patients with adjuvant therapy by Kaplan–Meier survival curves. **Abbreviations:** AGR, albumin-to-globulin ratio; PNI, prognostic nutrition index.

have been used as prognostic factors in various cancers. We evaluated the clinical significance of AGR and the PNI in 166 patients with GB. OS was enhanced with high AGR (>1.75) and PNI (>48). Both were independent predictors of OS, and significant prognostic factors for OS in patients with adjuvant therapy. Preoperative AGR and PNI may be easy-to-perform and inexpensive indices for predicting OS in GB patients.

Cancer patients frequently show malnutrition, which is responsible for decreased capacity for treatment tolerance, increased mortality, and worse quality of life in the post-operative period.³⁰ Moreover, malnutrition has been found to be associated with an immunosuppressed condition,³¹ which suggests inadequate antitumor immunity.²¹ Chronic inflammation has been identified as a hallmark of cancer, and most neoplastic tissues contain an inflammatory component, even those not causally associated with an obvious inflammatory reaction.³² Cell inflammatory mediators promote tumorigenesis by increasing tumor proliferation and metastasis, and can also exert an immunosuppressive effect, with resulting impaired lymphocyte function and reduced lymphocyte count, which enables the escape of cancer cells from immunosurveillance.^{33–35} Meanwhile, inflammation was found to be closely related to the genesis and development of GB.^{23,24,28,36} In view of the relationship between nutrition and immunocompetence, as well as the influence of inflammation on GB, patients’ nutritional status and immunocompetence should be evaluated in the management of GB.

In this study, we evaluated AGR and the PNI, two integrated immunonutritional indices, for their prognostic values for GB patients, and found cutoff values of 1.75 and 48, respectively. Preoperative AGR and the PNI were significantly associated with OS in GB, which agrees with findings for other malignancies.^{12,17,18,25–27} Although AGR and PNI were associated with preoperative albumin level and lymphocyte count, the predictive value of both remained significant after adjustment for other clinical characteristics on multi-variable analysis. According to the ROC analysis, AGR had better specificity than the PNI, and the PNI had better sensitivity than AGR. The two factors may accurately predict OS with GB. Based on indicators of preoperative inflammation, immunity, and nutritional status, AGR and the PNI could provide important prognostic information in GB.

The good prognosis with high AGR and PNI values might be explained by the functions of albumin, globulin, and lymphocytes. Albumin has antioxidative effects against some of the most common carcinogens, including nitrosamines and aflatoxins. Also, it can stabilize cell growth and DNA replication and buffer sex-hormone homeostasis to prevent sex hormone-induced cancers.³⁷ Albumin can inhibit the proliferation of human breast cancer cells by regulating the activities of autocrine growth-regulatory factors in vitro.³⁸ However, the inflammatory response was reported to play an independent role in decreasing albumin level apart from malnutrition.¹³ In cancer-related

inflammation, the proinflammatory cytokines released by tumor and immune cells modulate albumin production and help in cancer progression, angiogenesis, and malignant transformation.^{32,39} Serum globulin, including immunoglobulins, CRP, complements, and other acute-phase proteins are upregulated with inflammation and play a crucial role in immunity and inflammation.^{40,41} As a component of the innate immune system, high CRP levels can induce the production of inflammatory cytokines and tissue factor in monocytes.⁴² Complement activation can initiate or sustain the inflammatory process by leading to chemotaxis, plasma protein exudation at inflammatory sites, and opsonization of infectious agents and damaged cells.⁴¹ High levels of globulin reflect an inflammatory state, believed to play a major role in cancer progression and metastasis.³³ Lymphocytes play a key role in host defense against cancer by inhibiting the proliferation and invasion of tumor cells via inducing cytotoxic cell death and production of cytokines.³² Cytotoxic T lymphocytes inhibit tumor growth by inducing apoptosis of cancer cells, whereas CD8⁺ T-lymphocyte infiltration is associated with overall good outcome.⁴³ Lymphocytopenia, reflecting insufficient anti-tumor immunocompetence, can be induced by a systemic inflammatory reaction.²⁰

We performed a subgroup analysis of OS for patients with adjuvant therapy (radiotherapy and/or chemotherapy). For GB patients receiving adjuvant therapy after surgery, low AGR or PNI value was significantly associated with short OS, so these patients acquired less benefit from adjuvant therapy. Patients with poor immune and nutrition status showed inferior tolerance to adjuvant therapy, and the adverse effects of adjuvant therapy were more prominent in patients with immunosuppression and malnutrition, thus affecting the long-term outcomes.^{30,44} Albumin could protect tissues against most forms of radiation,³⁷ thereby protecting against the adverse effects of radiotherapy. Moreover, systemic inflammation might impair the activity of CYP3A4, a crucial drug-metabolizing enzyme.⁴⁵ Decreased activity of CYP3A4 has been found to be related to reduced hepatic drug clearance and increased drug toxicity.⁴⁶ Therefore, it is important to maximize the curative effects of adjuvant therapy and diminish its adverse effects.

AGR and the PNI may be appropriate factors for survival in stratifying patients who acquire more benefit from adjuvant therapy, and immunonutritional intervention and anti-inflammation therapy could be considered efficient therapeutic strategies for GB patients who have received radiotherapy and/or chemotherapy.

The present study has several limitations. First, the retrospective design and limited number of patients might indicate bias. Second, unknown physiological and pathophysiological factors might have had an unavoidable impact on AGR and the PNI. Furthermore, although serum CRP and cytokine levels were important indicators of cancer-related inflammation, these factors were not routinely examined in our hospital, which prevents us from acquiring a better understanding of the mechanism of tumor progression caused by inflammation. In this study, AGR and the PNI were assessed only once before surgery. The predictive significance of the kinetics of AGR and the PNI remains to be investigated.

Conclusion

This study demonstrated that low AGR and PNI values could be promising immunonutritional markers to identify GB patients with poor prognostic potential. The application of AGR and the PNI in evaluating preoperative immunonutritional status might facilitate the formulation of more effective preoperative regulation strategies and better adjuvant-therapy schedules.

Acknowledgments

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Disclosure

The authors report no conflicts of interest in this work.

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