Original Article

Serum albumin levels and serum albumin-globulin ratio are associated with poor prognosis in glioblastoma

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Background: Serum albumin levels (ALB) and albumin-globulin ratio (AGR) are reliable and convenient markers of the nutritional status and inflammation of human body, and ALB has been identified as a prognostic factor in the patients of glioblastoma (GBM). However, no literature has reported the prediction value of AGR for GBM.

Methods: In this study we evaluate the serum ALB and AGR levels for GBM. A total of 126 patients with GBM who underwent surgical resection in our institution between 2013 and 2017 were analyzed retrospectively. Clinical information was obtained from electronic medical records. Multiple logistic regression and Cox proportional hazards models were used to assess the prediction value of preoperative ALB and AGR for GBM.

Results: Preoperative ALB (HR 0.342, 95% CI, 0.123–0.954, P=0.040) and postoperative adjuvant therapy (HR 0.042, 95% CI, 0.005–0.330, P=0.003) were significantly related to progression-free survival (PFS). Cox regression analysis showed the significance of adjuvant therapy (HR 3.579, 95% CI, 2.236–5.729, P<0.001). Preoperative AGR (HR 0.280, 95% CI, 0.103–0.763, P=0.013) and adjuvant therapy (HR 0.156, 95% CI, 0.047–0.513, P=0.002) were showed significance, and Cox regression analysis showed preoperative AGR (HR 1.810, 95% CI, 1.095–2.992, P=0.021) and adjuvant therapy (HR 4.702, 95% CI, 2.841–7.782, P<0.001) were independent predictors of overall survival (OS).

Conclusions: The ALB and AGR had significant predictive values for the prognosis of GBM; postoperative adjuvant treatment is also an independent predictor for the prognosis of GBM patients.

Keywords: Glioblastoma (GBM); albumin (ALB); albumin-globulin ratio (AGR); prognosis

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Introduction

Glioma is the most common type of invasive malignant tumor in central nervous system (CNS), accounting for 65% of primary intracranial tumors (1,2). In 2016, World Health Organization (WHO) classified glioma into grade I-IV histologically according to the degree of malignancy. Grade IV is glioblastoma (GBM), which is highly invasive with poor prognosis (3). Despite the complete resection of GBM plus postoperative radiotherapy and chemotherapy, the median PFS and OS is not optimistic (4). Although certain prognostic factors for GBM have been reported (5,6), the guiding function to the current treatment is limited, which warranted the new prognostic factors to be constantly

studied.

ALB and the albumin-globulin ratio (AGR) can reflect the nutritional status of the human body, which is closely associated with immunosuppression (7). Previous studies showed that ALB and AGR can predict the prognosis of neoplasm (8,9), besides, ALB can predict the prognosis of GBM (10-12), and there were few literatures had reported the prediction value of AGR on the prognosis of glioma (13). In this study, we aimed to evaluate the prognostic value of serum ALB and AGR in GBM by reviewing the relevant literatures.

Methods

Study population

The medical records of patients who underwent GBM resection at The First Affiliated Hospital of Xinjiang Medical University between January 2013 and December 2017 were reviewed. Patients were included on the basis of eligibility criteria, which were: (I) Diagnosis was confirmed by pathological examination after the first resection; (II) full pre-operative laboratory data were available (i.e., ALB, AGR); and (III) no hematological system disorders impaired liver function or primary tumor at other sites.

Data collection

Demographic information of patients, such as age, gender, nationality, pre-operative ABL, AGR, Karnofsky performance status (KPS), with or without any history of seizures, tumor site and maximum diameter of tumor, extent of surgical resection (total gross resection or incomplete resection), whether to receive postoperative adjuvant therapy, level of Ki-67 expression were collected from the medical records. Tumor characteristics were assessed using pre-operative magnetic resonance imaging (MRI). The extent of surgical resection was determined by the chief neurosurgeon during operation.

PFS was defined as the time interval between the date of surgery and the discovery of the first recurrence, or the time interval between the date of surgery and the death time of the patients without recurrence. Recurrence was defined as the appearance of new lesions at or outside the operative area during MRI scanning. OS was defined as the interval between date of the surgery and the date of death. Patients were censored at the end of follow-up, if the patient was still alive. The last follow-up was performed in December 2018. AGR was calculated as ALB count (g/L) divided by serum globulin count (g/L).

Statistical analysis

Descriptive analyses were used to describe patient demographics and clinical characteristics. Number of cases and percentages were calculated. We reported median PFS, 12-month PFS, also median OS, 18-month OS, and 95% confidence intervals (CI) for each subgroup. Log-rank tests were used to compare ALB, AGR and other factors, P values were calculated. P values of <0.05 were considered statistically significant. The multiple logistic regression analysis was used for multivariate analysis, survival between items of statistical significance for log-rank tests, Cox proportional hazards method for evaluate the impact on survival. All variables (preoperative ALB and AGR, with or without any postoperative seizure, tumor site, degree of surgical resection, whether to receive postoperative adjuvant therapy and Ki-67 expression) were included in the final multivariate model based on a prior identification. Data management and statistical analyses were conducted using SPSS 20 software.

Results

One hundred and twenty-six adult patients with primary GBM met the inclusion criteria for the study. Median OS and median PFS were 10.8 and 5.7 months (*Figure 1*). Most of the patients were male (59.5%), the median age was 55 years, (range, 19–80 years), and the mean age was 55.2 years; 12.7% of the patients experienced preoperative seizures and 13.2% of the patients experienced postoperative seizures. The complete surgical resection of GBM was performed in 60.3% of the patients and postoperative adjuvant therapy was performed in 60.5% of the patients; 43.7% of the tumors were located in the right hemisphere of the brain, 46% in the left and 10.3% was located in both hemispheres, and 53.2% was large (≥5 cm). We also reported Ki-67 level of the tumor, and have shown that the patients with the Ki-67 expression outreached 30% was 51.6% (*Table 1*).

The median PFS and 12-month PFS rate of the study sample were 5.7 months and 23.0%, respectively (*Figure 1A* and *Table 2*). Preoperative ALB, postoperative seizure, adjuvant therapy and Ki-67 level were found to be significant by log-rank analysis ($P<0.05$) (*Table 2*). But preoperative ALB (HR 0.342, 95% CI, 0.123–0.954, P=0.040) and accepting adjuvant therapy after surgery

Table 1 Patient characteristics

Category	Study sample (N=126), N (%)	Preoperative ALB			Preoperative AGR		
		≥39.5 g/L (%)	<39.5 g/L (%)	P value	≥1.43 (%)	<1.43 (%)	P value
Sex				0.094			0.012*
Male	75 (59.5)	44 (58.7)	31 (41.3)		46 (61.3)	29 (38.7)	
Female	51 (40.5)	23 (45.1)	28 (54.9)		20 (39.2)	31 (60.8)	
Age				0.177			0.510
≥55	66 (52.4)	32 (48.5)	34 (51.5)		35 (53.0)	31 (47.0)	
<55	60 (47.6)	35 (58.3)	25 (41.7)		31 (51.7)	29 (48.3)	
National				0.383			0.289
Han Chinese	86 (68.3)	47 (54.7)	39 (45.3)		47 (54.7)	39 (45.3)	
Uyghur Chinese	40 (31.7)	20 (50.0)	20 (50.0)		19 (47.5)	21 (52.5)	
Preoperative KPS				0.292			0.385
≥70	62 (49.2)	35 (56.5)	27 (43.5)		34 (54.8)	28 (45.2)	
<70	64 (50.8)	32 (50.0)	32 (50.0)		32 (50.0)	32 (50.0)	
Preoperative seizure				0.497			0.061
Yes	16 (12.7)	8 (50.0)	8 (50.0)		5 (31.3)	11 (68.8)	
No	110 (87.3)	59 (53.6)	51 (46.4)		61 (55.5)	49 (44.5)	
Postoperative seizure†				0.136			0.563
Yes	16 (13.2)	11 (68.8)	5 (31.3)		8 (50.0)	8 (50.0)	
No	105 (86.8)	53 (50.5)	52 (49.5)		54 (51.4)	51 (48.6)	
Tumor site				0.811			0.710
Right	55 (43.7)	29 (52.7)	26 (47.3)		31 (56.4)	24 (43.6)	
Left	58 (46.0)	30 (51.7)	28 (48.3)		29 (50.0)	29 (50.0)	
Both	13 (10.3)	8 (61.5)	5 (38.5)		6 (46.2)	7 (53.8)	
Tumor size				0.482			0.442
≥5 cm	67 (53.2)	35 (52.2)	32 (47.8)		36 (53.7)	31 (46.3)	
<5 cm	59 (46.8)	32 (54.2)	27 (45.8)		30 (50.8)	29 (49.2)	
Degree of surgical resection				0.223			0.400
Total	76 (60.3)	43 (56.6)	33 (43.4)		41 (53.9)	35 (46.1)	
Subtotal	50 (39.7)	24 (48.0)	26 (52.0)		25 (50.0)	25 (50.0)	
Postoperative adjuvant therapy‡				0.094			0.211
Yes	75 (60.5)	44 (58.7)	31 (41.3)		42 (56.0)	33 (44.0)	
No	49 (39.5)	22 (44.9)	27 (55.1)		23 (46.9)	26 (53.1)	
Ki-67				0.491			0.056
≥30%	65 (51.6)	34 (52.3)	31 (47.7)		39 (60.0)	26 (40.0)	
<30%	61 (48.4)	33 (54.1)	28 (45.9)		27 (44.3)	34 (55.7)	

†, there were 5 case can't be confirmed whether seizure after surgery; ‡, there were 4 case can't be confirmed whether accept any adjuvant therapy after surgery. *, P<0.05 showed statistically significant. ALB, serum albumin levels; AGR, albumin-globulin ratio; KPS, Karnofsky performance status.

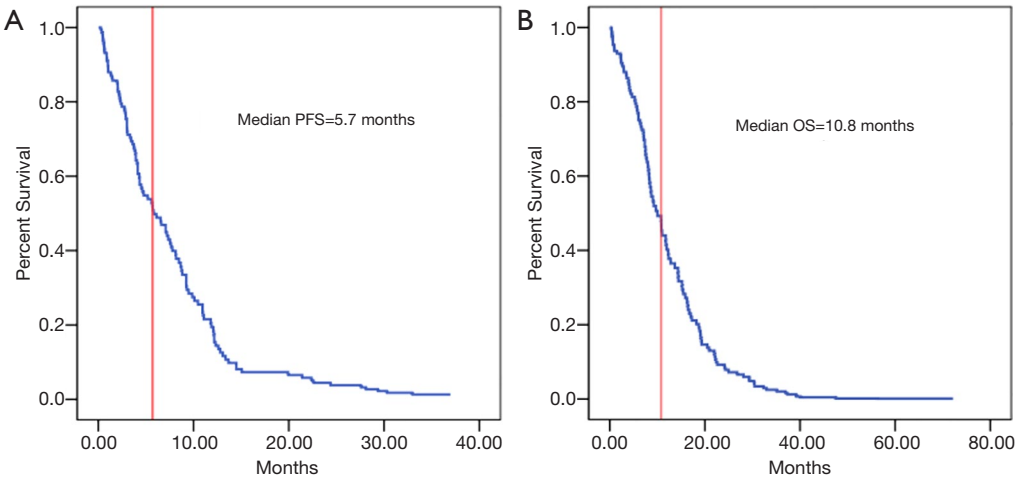

Figure 1 The percentage of PFS after the operation in the whole follow-up was showed in (A), and the median PFS was 5.7 months. While the percentage of OS after the operation in the whole follow-up was demonstrated in (B) with a median OS of 10.8 months. PFS, progression-free survival; OS, overall survival. The red line indicates the median.

(HR 0.042, 95% CI, 0.005–0.330, P=0.003) were showed statistically significant by multivariate analysis (*Table 3*). Cox regression analysis showed that adjuvant therapy was statistically significant (HR 3.579, 95% CI, 2.236–5.729) (*Figure 2A*), but preoperative ALB (HR 1.218, 95% CI, 0.791–1.875, P=0.371) was not (*Figure 2B*).

The primary outcome of this study was death related to CNS tumor; deaths from other causes were considered as censored. Within this framework, the median OS and 18-month OS rate of the study sample were 10.8 months (*Figure 1B*), 29.4%, respectively (*Table 3*). Patients with different preoperative ALB and AGR levels experiencing seizure after surgery, tumor site and postoperative adjuvant therapy were found to be statistically significant (P<0.05) (*Table 4*). And those variables were included in a multivariate analysis, just the preoperative AGR (HR 0.280, 95% CI, 0.103–0.763, P=0.013) and adjuvant therapy (HR 0.156, 95% CI, 0.047–0.513, P=0.002) were found to be significant (*Table 5*). Cox regression analysis showed that preoperative AGR (HR 1.810, 95% CI, 1.095–2.992, P=0.021) (*Figure 3A*) and adjuvant therapy (HR 4.702, 95% CI, 2.841–7.782, P<0.001) (*Figure 3B*) were independent predictors of OS.

Discussion

GBM is the most common primary tumor of the CNS and its standard treatment is including surgical resection combined with radiotherapy and temozolomide (TMZ) chemotherapy (14). However, the survival of the patients with GBM varies and influenced by many factors. The five-year OS rate of patients is approximately 4.5% and the median survival of GBM is about 14.6 months, in spite of advanced diagnostic and therapeutic techniques (15).

In this study, we demonstrated that ALB and AGR are significantly independent prognostic factors in GBM. To our knowledge, ALB is one of the significant prognostic indicators of GBM, and the greater the ALB level is, the higher positive correlation with prognosis of GBM can be found, which indicates that elevated ALB serve as a protective role in survival of GBM patients. Our study showed ALB was an independent predictor of PFS in GBM (*Tables 2,3*), but it did not show statistical significances in the Cox analysis (*Figure 2A*). Univariate analysis showed ALB related with OS (*Table 4*), but multivariate analysis doesn't show any significance (*Table 5*). In oncology, nutrition supplies have focused great attention on cancer epidemiology, progression, and treatment outcomes (16). Several studies have suggested that nutrition condition is an essential factor for GBM patients' survival (17). Albumin and globulin are the main components of serum proteins, and albumin can reflect the nutrition status of the human body. Lower ALB has indicated poor nutrition status and had been reported to predict survival in various types of cancers (18-20). And increased ALB has been correlated with good clinical outcomes in GBM patients (11,12). These data of previous studies were consistent with our research, and prolonged OS in GBM patients is importantly

Table 2 Significant univariate predictors of progression-free survival in 126 patients with GBM

Items	N	Non-recurrence (n=29, 23.0%)	Recurrence (n=97, 77.0%)	χ^2 value	P value
Sex				0.031	0.910
Male	75	17 (22.7)	58 (77.3)		
Female	51	12 (23.5)	39 (76.5)		
Age				1.828	0.176
≥55	66	12 (18.2)	54 (81.8)		
<55	60	17 (28.3)	43 (71.7)		
National				1.006	0.316
Han Chinese	86	22 (25.6)	64 (74.4)		
Uyghur Chinese	40	7 (17.5)	33 (82.5)		
Preoperative ALB				5.600	0.018*
≥39.5 g/L	67	21 (31.3)	46 (68.7)		
<39.5 g/L	59	8 (13.6)	51 (86.4)		
Preoperative AGR				1.417	0.234
≥1.43	66	18 (27.3)	48 (72.7)		
<1.43	60	11 (18.3)	49 (81.7)		
Preoperative KPS				0.536	0.464
≥70	62	16 (25.8)	46 (74.2)		
<70	64	13 (20.3)	51 (79.7)		
Preoperative seizure				0.041	0.840
Yes	16	4 (25.0)	12 (75.0)		
No	110	25 (22.7)	85 (77.3)		
Postoperative seizure[†]				3.960	0.047*
Yes	16	7 (43.8)	9 (56.3)		
No	105	22 (21.0)	83 (79.0)		
Tumor site				4.553	0.103
Right	55	10 (18.2)	45 (81.8)		
Left	58	18 (31.0)	40 (69.0)		
Both	13	1 (7.7)	12 (92.3)		
Maximum tumor diameter				1.197	0.274
≥5 cm	67	18 (26.9)	49 (73.1)		
<5 cm	59	11 (18.6)	48 (81.4)		
Degree of surgical resection				2.303	0.129
Total	76	21 (27.6)	55 (72.4)		
Subtotal	50	8 (16.0)	42 (84.0)		
Postoperative adjuvant therapy[‡]				20.603	<0.001*
Yes	75	28 (37.3)	47 (62.7)		
No	49	1 (2.0)	48 (98.0)		
Ki-67				4.413	0.036*
≥30	65	10 (15.4)	55 (84.6)		
<30	61	19 (31.1)	42 (68.9)		

[†], there were 5 case can't be confirmed whether seizure after surgery; [‡], there were 4 case can't be confirmed whether accept any adjuvant therapy after surgery. *, P<0.05 showed statistically significant. GBM, glioblastoma; ALB, serum albumin levels; AGR, albumin-globulin ratio; KPS, Karnofsky performance status.

Table 3 Significant multivariate predictors of progression-free survival in 126 patients with GBM

Variable	B	P value	Exp(B)	95% CI
Preoperative ALB	−1.073	0.040*	0.342	0.123–0.954
Postoperative seizure	−0.669	0.285	0.512	0.150–1.748
Postoperative adjuvant therapy	−3.17	0.003*	0.042	0.005–0.330
Ki-67	−0.83	0.108	0.436	0.158–1.200

*, P<0.05 showed statistically significant. GBM, glioblastoma; ALB, serum albumin levels.

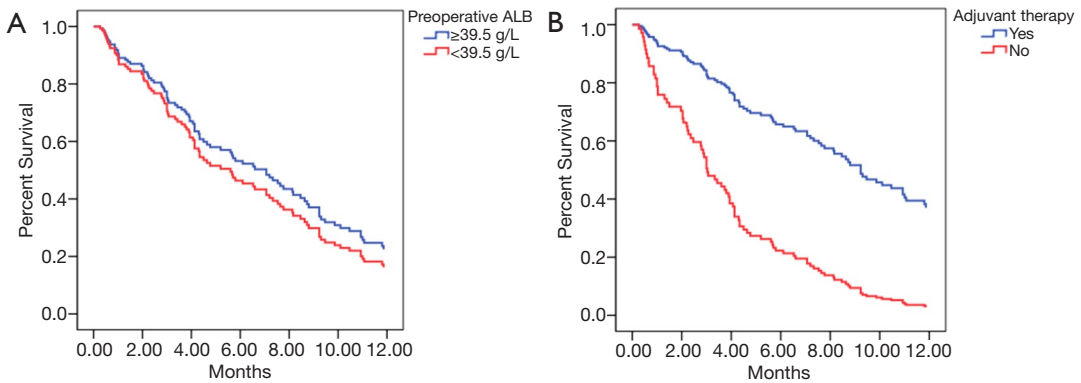

Figure 2 Cox regression analysis showed that the level of preoperative ALB was not related with PFS of patients with GBM (P=0.371) (A). Cox regression analysis showed that the PFS of patients with postoperative adjuvant therapy was longer than patients without postoperative adjuvant therapy (P<0.001) (B). PFS, progression-free survival; GBM, glioblastoma; ALB, Serum albumin levels.

due to high ALB level. Previous study has been proven ALB as a prognostic marker in GBM patients (11).

In recent years, several studies showed that AGR could be used to predict long-term mortality in various type of cancers (21,22). And there is a small amount of studies on AGR in gliomas (13), while in our study, AGR is strongly correlated with prognosis of GBM, serum AGR <1.43 was associated with short OS of GBM (*Table 5*, *Figure 3A*) but no significance in PFS (*Table 2*). Recent Meta-analysis reported the outcomes of 4,136 patients from 14 available studies concluded that low AGR was significantly correlated with poor OS (HR 1.87, 95% CI, 1.50–2.34, P<0.001) (23). Zhou *et al.* (24) suggested that small cell lung cancer patients with serum AGR <1.29 was 1.35 times more likely to die than those with AGR >1.29. Mao *et al.* (25) showed that patients with gastric cancer with AGR <1.50 had poor OS rate compared to those AGR >1.50. Wang *et al.* (26) reported that AGR <1.51 was associated with a significant deterioration of OS in the patients with early stage non-small cell lung cancer. In the study of Wang *et al.* (27), serum AGR <1.45 was an independent prognostic factor for poor PFS in patients with prostate cancer. For glioma, Liu *et al.* (13) suggested that preoperative AGR (AGR >1.32) indicated a better clinical prognosis and AGR was an independent prognostic factor for OS in patients with high-grade glioma. These results are strongly consistent with our retrospective data of GBM study.

The good prognosis with high ALB and AGR might be elucidated by the functions of nutrition factors including albumin and globulin. In our study, we analyzed the clinical outcomes of ALB and AGR in 126 patients with GBM, while among the several variables, low levels of ALB and AGR could reflect poor outcome of GBM patients. PFS and OS were extended with high ALB and AGR, indicating both are independent predictors of OS and PFS, besides, postoperative adjuvant therapy is significant prognostic factor for OS and PFS in GBM patients. So, ALB and AGR are convenient and inexpensive indices for predicting OS and PFS in GBM patients. Albumin has antioxidative effects anti-carcinogens and in cancer related inflammation, the albumin production also could be modulated by the pro-inflammatory cytokines released by tumor and immune cells

Table 4 Significant univariate predictors in 126 patients with GBM during 18 months follow up

Items	N	Survived (n=37, 29.4%)	Died (n=89, 70.6%)	χ^2 value	P value
Sex				1.407	0.236
Male	75	25 (33.3)	50 (66.7)		
Female	51	12 (23.5)	39 (76.5)		
Age				0.293	0.589
≥55	60	19 (31.7)	41 (68.3)		
<55	66	18 (27.3)	48 (72.7)		
National				2.478	0.115
Han Chinese	86	29 (33.7)	57 (66.3)		
Uyghur Chinese	40	8 (20.0)	32 (80.0)		
Preoperative ALB				4.358	0.037*
≥39.5g/L	67	25 (37.3)	42 (62.7)		
<39.5g/L	59	12 (20.3)	47 (79.7)		
Preoperative A/G				8.905	0.003*
≥1.43	66	27 (40.9)	39 (59.1)		
<1.43	60	10 (16.7)	50 (83.3)		
Preoperative KPS				0.493	0.483
≥70	62	20 (32.3)	42 (67.7)		
<70	64	17 (26.6)	47 (73.4)		
Preoperative seizure				0.585	0.444
Yes	16	6 (37.5)	10 (62.5)		
No	110	31 (28.2)	79 (71.8)		
Postoperative seizure[†]				5.724	0.017*
Yes	16	9 (56.2)	7 (43.8)		
No	105	28 (26.7)	77 (73.3)		
Tumor laterality				6.200	0.045*
Right	55	17 (30.9)	38 (69.1)		
Left	58	20 (34.5)	38 (65.5)		
Both	13	0 (0.0)	13 (100.0)		
Tumor size				0.070	0.791
≥5cm	67	19 (28.4)	48 (71.6)		
<5cm	59	18 (30.5)	41 (69.5)		
Degree of surgical resection				3.505	0.061
Total	76	27 (35.5)	49 (64.5)		
Subtotal	50	10 (20.0)	40 (80.0)		
Postoperative adjuvant therapy[‡]				18.181	<0.001*
Yes	75	33 (44.0)	42 (56.0)		
No	49	4 (8.2)	45 (91.8)		
Ki-67				0.128	0.721
≥30	65	20 (30.8)	45 (69.2)		
<30	61	17 (27.9)	44 (72.1)		

[†], there were 5 case can't be confirmed whether seizure after surgery; [‡], there were 4 case can't be confirmed whether accept any adjuvant therapy after surgery. *, P<0.05 showed statistically significant. GBM, glioblastoma; ALB, serum albumin levels; AGR, albumin-globulin ratio; KPS, Karnofsky performance status.

Table 5 Significant multivariate predictors in 126 patients with GBM during 18months follow up

Characteristic	B	P value	Exp(B)	95% CI
Preoperative ALB	−0.375	0.449	0.687	0.260–1.817
Preoperative AGR	−1.273	0.013*	0.280	0.103–0.763
Postoperative seizure	−0.872	0.155	0.418	0.126–1.391
Tumor site	–	0.896	–	–
Postoperative adjuvant therapy	−1.860	0.002*	0.156	0.047–0.513

*, P<0.05 showed statistically significant. GBM, glioblastoma; ALB, serum albumin levels; AGR, albumin-globulin ratio.

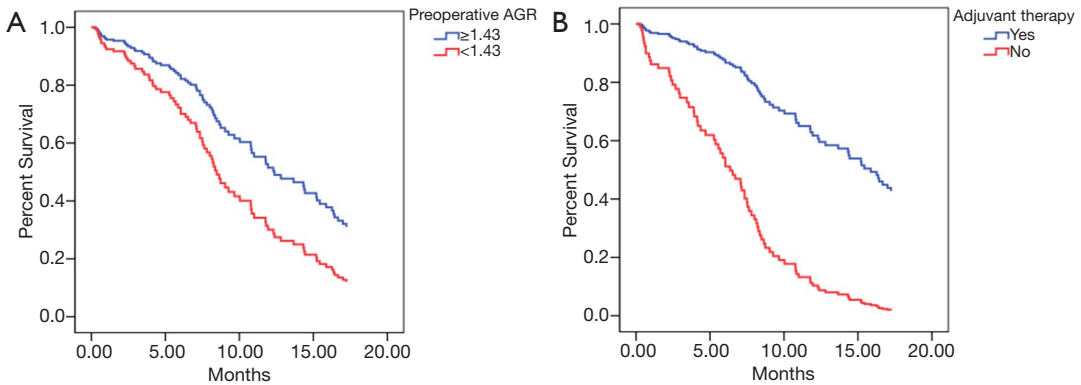

Figure 3 Cox regression analysis showed that the OS of patients with high preoperative AGR (AGR ≥1.43) was longer than patients with low preoperative AGR (AGR <1.43) (P=0.021) (A). Cox regression analysis showed that the OS of patients with postoperative adjuvant therapy was longer than patients without postoperative adjuvant therapy (P<0.001) (B). PFS, progression-free survival; ALB, serum albumin levels.

and serve as a role in cancer progression and angiogenesis (28,29). In several analyses, all these nutritional indicators were associated with OS, and the prognostic effect of ALB can be attributed to its role as a nutritional indicator. Consistent with previous studies, our data showed that ALB has a good predictive value than other nutritional indicators in GBM (30,31). According to the results ALB and AGR are not only strong indicators of nutritional status, but also responsible for specific pathophysiological process such as inflammatory responses. The ALB and AGR may indicate the patients' general condition, nutritional statues and the severity of the inflammatory reactions.

Admittedly, there were some limitations in the present study. Our single center study had a small sample size with its retrospective nature, which may lead to some systematic bias.

Conclusions

Taken together, serum ALB and AGR are associated with poor prognosis in GBM, those are important nutritional factors of the human body, and however, the specific mechanism is still unclear and needs to be further investigated.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2020.01.57). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All procedures were approved by the ethics committees of The First Affiliated Hospital of Xinjiang Medical University based on the consent information of all families (No. 20180223-13) and informed consent was taken from all individual participants.

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