



# Prognostic values of preoperative albumin to globulin ratio for predicting clinical outcome in patients with high-grade gliomas

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**Background:** Gliomas was the most common primary central nervous system tumors which have an increased morbidity in recent years. And the clinical prognosis of high-grade gliomas (HGG, WHO grade III to IV) was most with an average survival rate of only dozens of months. Many researchers concluded that the level of preoperative albumin-to-globulin ratio (AGR) could predict the clinical outcome of patients with solid malignant tumors.

**Methods:** Two hundred and thirty-two cases of patients who were diagnosed HGG by pathology were enrolled in the study. The relevant data of the cohort included sex, age, preoperative Karnofsky performance score (KPS), extent of resection, albumin count and globulin count, isocitrate dehydrogenase (IDH) and survival time were collected. The survival rate was obtained by using the Kaplan-Meier method. The cut-off value of AGR was determined by X-tile software. Univariate survival analysis was performed by the log-rank method. Proportional hazards model (Cox model) was performed for multivariate analysis.

**Results:** The optimal cut-off value of AGR was 1.32. Results showed that the preoperative AGR was correlated with clinical prognosis of patients with HGG, and the survival time of the patients with high AGR (AGR >1.32) was significantly longer. Moreover, the prognosis of patients with high AGR was better in IDH wild-type HGG.

**Conclusions:** Preoperative AGR might predict the clinical prognosis of patients with HGG.

**Keywords:** High-grade glioma (HGG); albumin-to-globulin ratio (AGR); isocitrate dehydrogenase mutation (IDH mutation); prognosis

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## Introduction

Gliomas were one of the most common primary central nervous system tumors which have an increased morbidity in recent years. And the clinical prognosis of high-grade gliomas (HGG, WHO Grade III to IV) was most with an average survival rate of only dozens of months, even if patients received standardized treatment including

surgery, postoperative radiotherapy and chemotherapy (1). Therefore, forecasting for long-term prognosis of patients has a significant guiding for the treatment of patients.

Considerable researches have demonstrated that isocitrate dehydrogenase (IDH), phosphatase and tension homolog (PTEN), epidermal growth factor receptor (EGFR) were significant molecular markers for predicting

the prognosis of patients with glioma (2,3). In recent years, many researchers found that the level of preoperative neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR) and albumin-to-globulin ratio (AGR) could predict the clinical outcome of patients with solid malignant tumors such as hepatoma (4), renal cell carcinoma (5,6), lung cancer (7), etc. AGR could reflect the nutritional and systemic inflammation status in patients with tumor (8). For the moment there were limited studies focusing on the clinical prognosis of AGR in glioma patients, and the relationship between AGR level and the survival of patients with HGG was not investigated by far. The present study explored the prognostic significance of preoperative AGR for patients with HGG. And the relationship between AGR level and IDH mutation in HGG was also investigated.

## Methods

Two hundred and thirty-two cases of patients who were diagnosed HGG by pathology in The First Affiliated Hospital of Zhengzhou University from May 2011 to July 2015 were enrolled in the study. Within three months before glioma resection, all the patients did not receive additional surgery, radiotherapy and chemotherapy, and have no infection, hypertension, blood system diseases, autoimmune diseases and so on.

The relevant data of the cohort were collected through the medical record system, which included sex, age, preoperative Karnofsky performance score (KPS), extent of resection, hematology data (albumin count and globulin count within one week before surgery), postoperative molecular pathology such as IDH results, etc. The calculation of AGR was that AGR is the ratio of serum albumin and serum globulin.  $AGR = \text{albumin}/\text{globulin}$ .

The patients were followed-up regularly. Time from the operative date to the date of death was considered as overall survival (OS), and the interval from the operative date to the recurrence date was considered as progression-free-survival (PFS). This research was approved by the Ethics Committee of Zhengzhou University. All participants have written the informed consent.

The survival rate was calculated by using the Kaplan-Meier method. The cut-off score of AGR was determined by X-tile. Univariate survival analysis was performed by Log-rank method. Proportional hazards model (Cox model) was performed for multivariate analysis to determine independent prognostic factors. All statistical analyses were

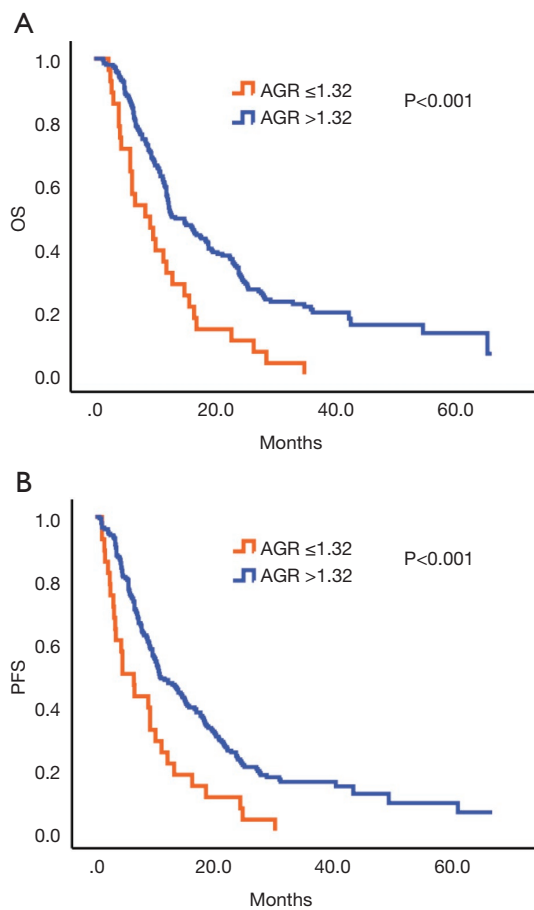
implemented to SPSS 25.0 software (IBM, USA) and X-tile software 3.6.1 (<http://x-tile.software.informer.com>).  $P < 0.05$  was considered as statistically significant.

## Results

The analysis of central tendency of AGR showed that the minimum was 0.69, the maximum was 2.78, the mean was 1.64 and the Std. Deviation was 0.31. According to the X-tile software, the optimal cut-off score of AGR was 1.32. Then the AGR queue was divided into two groups:  $AGR \leq 1.32$  and  $AGR > 1.32$ . Survival analysis showed that the 3-year survival rate of the two groups was 0.0% vs. 20.5%, respectively. And the difference between the two groups was statistically significant ( $P < 0.001$ ) (Figure 1A). Similarly, the median progression-free survival for the two groups was 0.0% vs. 15.6%, respectively and the difference was statistically significant, too ( $P < 0.001$ ) (Figure 1B).

Univariate analysis of general factors such as sex, age, KPS, extent of resection, radiotherapy, chemotherapy, tumor grade and IDH mutation revealed that degree of tumor resection (OS,  $P = 0.002$ , PFS,  $P = 0.006$ ), radiotherapy (OS,  $P < 0.001$ , PFS,  $P = 0.001$ ), chemotherapy (OS,  $P < 0.001$ , PFS,  $P < 0.001$ ), tumor grade (OS,  $P < 0.001$ , PFS,  $P < 0.001$ ), IDH mutation (OS,  $P < 0.001$ , PFS,  $P < 0.001$ ) were the factors which influenced the clinical outcome of patients with HGG. However, sex, age and KPS could not be factors in the clinical prognosis of patients with HGG ( $P > 0.05$ ) (Table 1). The above factors with statistical significance was included in a multivariate analysis. And the results showed that degree of resection (OS,  $P < 0.001$ , PFS,  $P = 0.002$ ), chemotherapy (OS,  $P = 0.037$ , PFS,  $P = 0.036$ ), tumor grade (OS,  $P < 0.001$ , PFS,  $P < 0.001$ ), preoperative AGR (OS,  $P = 0.003$ , PFS,  $P = 0.007$ ) were independent factors that affected the clinical prognosis of patients with HGG (Table 2). Result of multivariate analysis in IDH wild-type HGG revealed that AGR (OS,  $P = 0.005$ , PFS,  $P = 0.012$ ) was an independent risk factor that affected the clinical prognosis of patients (Table 3).

The cutoff values of AGR in IDH wild-type HGG and IDH mutation HGG were 1.32 and 1.77. Statistical analysis of mutation of IDH in sanger sequencing in patients showed that IDH mutation was noted in 27 cases of patients and IDH wild-type was found in 205 cases of patients. In IDH wild-type HGG, the high level of preoperative AGR revealed a considerable better clinical prognosis (3-year OS 0.0% vs. 15.6%,  $P = 0.002$ ) (Figure 2A), (3-year PFS 0.0% vs. 11.3%,  $P = 0.003$ ) (Figure 2B). There was no statistically



**Figure 1** Preoperative AGR was related with clinical outcome of patients with high-grade glioma. (A) Survival analysis showed that survival time (OS) of patients with high AGR were longer than patients with low AGR (P<0.001). (B) Survival analysis showed that survival time (PFS) of patients with high AGR were longer than patients with low AGR (P<0.001). AGR, albumin-to-globulin ratio; OS, overall survival; PFS, progression-free-survival.

significant between high AGR group and low AGR group of HGG patients with IDH mutation (OS, P=0.153, PFS, P=0.237) (Figure 2C,D).

**Discussion**

The immune and nutritional status of tumor patient was closely related to clinical prognosis (8). Numerous studies of solid tumor have shown that AGR could be a prognostic factor in cancer. Our study evaluated the clinical significance of preoperative AGR in 232 patients with HGG. Elevated preoperative AGR (AGR >1.32) indicated a better clinical

**Table 1** Univariate analysis of prognostic factors for OS and PFS in high grade glioma patients (n=232)

Factors	No. of cases	OS		PFS	
		3-year OS (%)	P value	3-year PFS (%)	P value
<b>Sex</b>					
Male	130	19.8	0.952	13.1	0.733
Female	102	15.0		14.2	
<b>Age</b>					
≤50	86	29.3	<0.001*	19.8	0.003*
>50	146	10.7		9.7	
<b>KPS</b>					
≤80	58	21.2	0.627	14.1	0.396
>80	174	16.2		13.2	
<b>Extent of resection</b>					
Gross total	176	17.9	0.002*	13.3	0.006*
Subtotal	56	18.2		14.1	
<b>RT</b>					
Yes	177	19.6	<0.001*	14.2	0.001*
No	55	11.3		11.8	
<b>CHT</b>					
Yes	167	21.9	<0.001*	16.5	<0.001*
No	65	5.9		4.8	
<b>AGR</b>					
≤1.32	28	0.0	<0.001*	0.0	<0.001*
>1.32	204	20.5		15.6	
<b>Grade</b>					
III	59	44.6	<0.001*	27.9	<0.001*
IV	173	7.8		8.0	
<b>IDH</b>					
IDH wt	205	13.0	<0.001*	9.5	<0.001*
IDH mut	27	51.3		41.3	

\*, P<0.05 showed statistically significant. AGR, albumin-to-globulin ratio; KPS, Karnofsky performance score; RT, postoperative primary radiation therapy; CHT, postoperative primary chemotherapy; IDH, isocitrate dehydrogenase.

prognosis and AGR was an independent prognostic factor for OS in patients with HGG. Moreover, in IDH wild-type HGG, higher preoperative AGR had a longer survival time

**Table 2** Multivariate analysis of prognostic factors for OS and PFS in patients with HGG (n=232)

Factors	OS		PFS	
	OR (95% CI)	P value	OR (95% CI)	P value
Complete resection (yes or no)	1.965 (1.375–2.807)	<0.001*	1.741 (1.229–2.466)	0.002*
Age ( $\leq 50$ or $>50$ )	1.184 (0.855–1.641)	0.310	1.167 (0.854–1.596)	0.333
RT (yes or no)	1.127 (0.745–1.705)	0.571	1.095 (0.729–1.644)	0.663
CHT (yes or no)	1.533 (1.026–2.291)	0.037*	1.521 (1.027–2.251)	0.036*
Grade (III or IV)	2.900 (1.899–4.429)	<0.001*	2.152 (1.468–3.154)	<0.001*
AGR ( $\leq 1.32$ or $>1.32$ )	0.528 (0.347–0.803)	0.003*	0.561 (0.369–0.851)	0.007*

\*,  $P < 0.05$  showed statistically significant. OR, odds ratio; CI, confidence interval; RT, postoperative primary radiation therapy; CHT, postoperative primary chemotherapy; AGR, albumin to globulin ratio; OS, overall survival; PFS, progression free survival; HGG, high-grade glioma.

**Table 3** Multivariate analysis of prognostic factors for OS and PFS in patients with IDH wild-type HGG (n=205)

Factors	OS		PFS	
	OR (95% CI)	P value	OR (95% CI)	P value
Complete resection (yes or no)	2.023 (1.399–2.925)	<0.001*	1.821 (1.271–2.610)	0.001*
Age ( $\leq 50$ or $>50$ )	1.259 (0.889–1.784)	0.195	1.213 (0.869–1.693)	0.256
RT (yes or no)	1.261 (0.820–1.939)	0.290	1.293 (0.846–1.976)	0.235
CHT (yes or no)	1.436 (0.952–2.167)	0.084	1.385 (0.923–2.077)	0.116
Grade (III or IV)	2.109 (1.313–3.387)	0.002*	1.524 (0.992–2.343)	0.055
AGR ( $\leq 1.32$ or $>1.32$ )	0.548 (0.359–0.838)	0.005*	0.582 (0.382–0.886)	0.012*

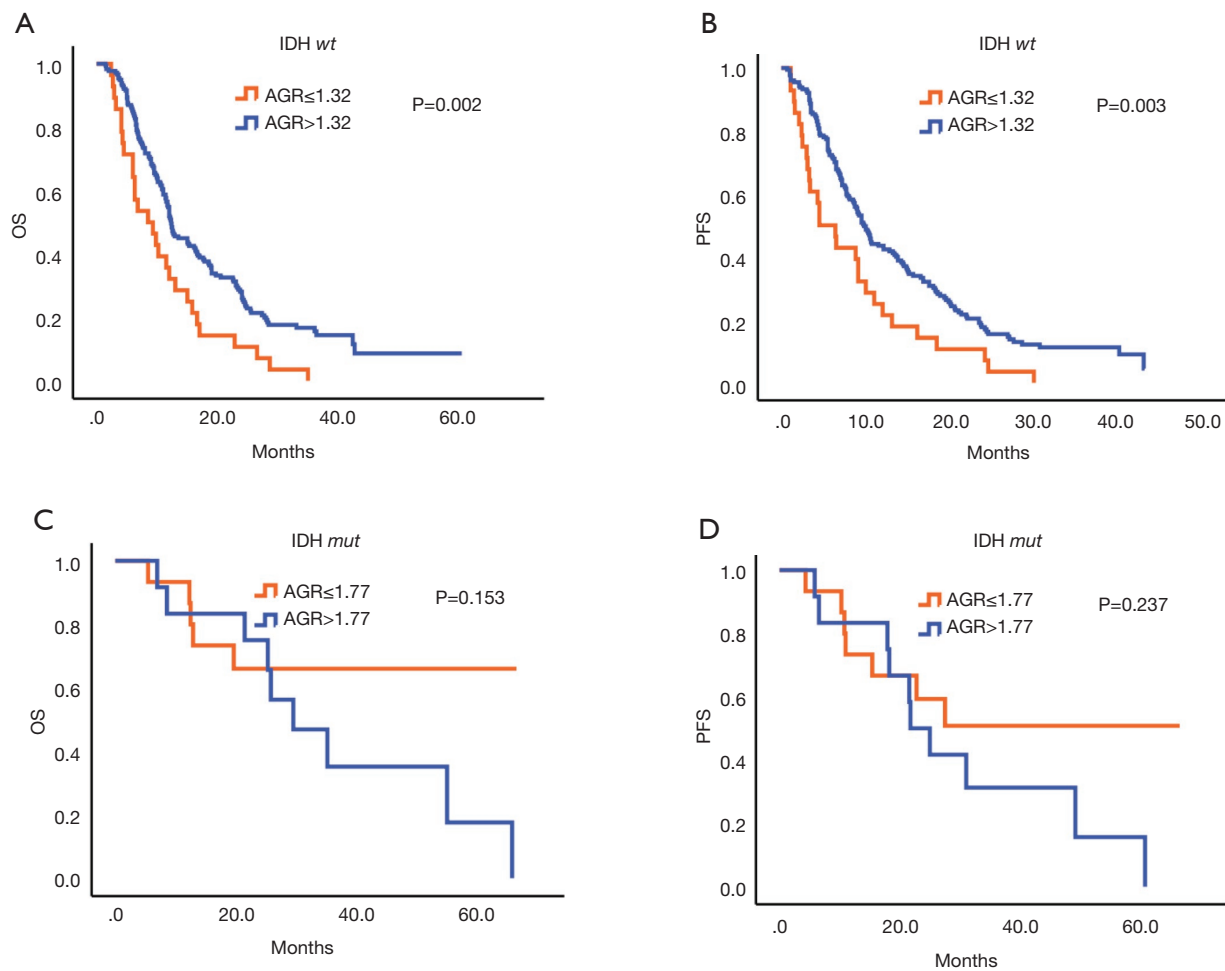
\*,  $P < 0.05$  showed statistically significant. OR, odds ratio; CI, confidence interval; RT, postoperative primary radiation therapy; CHT, postoperative primary chemotherapy; AGR, albumin to globulin ratio; IDH, isocitrate dehydrogenase; OS, overall survival; PFS, progression free survival; HGG, high-grade glioma.

and could further predict the clinical outcome.

Albumin was the most abundant serum protein and normal level of albumin maintained the normal physiological activity. Albumin was produced by the liver, as a biological marker for assessing liver function (9). We are aware that patients with cancer always experience malnutrition which leads to an increased postoperative mortality. And studies have found that malnutrition was involved in immunosuppression (10,11). The level of albumin was not only related to nutritional status, but also one of the clinical prognostic indices of various malignancies. Study finding showed that low serum albumin level could be risk factors of severe postoperative complications in elderly gastric cancer patients (12). Hypoalbuminemia might ultimately be correlated with biochemical recurrence of prostate cancer (13) and was a predictor of poor surgical outcomes

of colon cancer (14). Serum globulin mainly refers to the immune-related proteins which including immunoglobulin, complement, C-reactive protein (CRP), interleukin and so on. Studies have shown that these inflammatory proteins were involved in tumor prognosis. Elevated levels of complement 3 and IgA indicated poor prognosis of patients with lung cancer (15) and elevated levels of CRP was related to survival rate of patients with esophageal carcinoma (16).

Research showed that the level of immunoglobulin in serum was reacted with the inflammatory state of the organism. Almost all the primary tumors existed persistent chronic inflammation, and high levels of immunoglobulin played a major role in the progression and metastasis of cancer (17). A study in nasopharyngeal carcinoma showed that low AGR had a significant correlation to high neutrophil counts (18). Neutrophil could help tumors



**Figure 2** Preoperative AGR was related with IDH wild-type HGG. (A,B) Survival analyses showed that among the patients with IDH wild-type HGG, high level of preoperative AGR revealed a better clinical prognosis (OS,  $P=0.002$ ; PFS,  $P=0.003$ ). (C,D) There was no statistically significant in HGG patients with IDH mutation in different level of AGR (OS,  $P=0.153$ ; PFS,  $P=0.237$ ). AGR, albumin-to-globulin ratio; OS, overall survival; PFS, progression-free-survival; IDH, isocitrate dehydrogenase; HGG, high-grade glioma.

invade by producing angiogenesis factors (19) and the high NLR indicated a poor prognosis of multiple tumors (20,21). Preoperative AGR reflected the body's nutritional status and inflammatory response. AGR could reduce the influencing factor of body dehydration or water retention which might cause the count change of albumin or globulin and could better reflect the impact of patient's outcome. A meta-analysis of pretreatment albumin to globulin ratio in cancers revealed that low pretreatment AGR is associated with poor prognosis in human cancers, and AGR should be used as a prognostic marker during cancer therapy (22). For patients with glioblastoma, AGR ( $>1.75$ ) (23) and AGR ( $1.87 \pm 0.36$ ) (24) have high predictive

values for glioblastoma. In hepatoma carcinoma patients, low pretreatment AGR ( $<1.18$ ) was significantly related to shorter OS (25). In patients with colorectal cancer, a low pretreatment serum AGR ( $<1.4$ ) was an independent predictor of poor OS (18) and the AGR higher than the cut-off values ranging from 1.15–1.75 was related to better OS (26). Not only in cancer patients, low AGR is a risk factor for cancer incidence and mortality, both short- and long terms, in a generally healthy screened population (27). In our research, the cut-off values of AGR were 1.32. It's similar to these results above-mentioned.

IDH, TERT and 1p/19q were important molecular pathological index in gliomas. They had important

clinical significance to differentiate tumor types and predict prognosis and the prognosis of patients with IDH mutation was better (28-30). In our study, we analyzed the mutation of IDH and showed that the survival time of patients with high AGR was longer in the patients with IDH wild-type. It's essential to direct the treatment of glioma patients. In the future, we will require more basic medical experimentation to further elucidate the molecular mechanism.

Compared with previous study of AGR in glioblastoma (23), our sample number of this study was larger and covered the HGG (WHO Grade III to IV). So, the results were more representative. In this study, we confirmed the preoperative AGR was correlated with clinical prognosis of patients with HGG, the survival time of patients with high AGR was longer. And the prognosis of patients with high AGR was better in IDH wild type. Therefore, the inexpensive preoperative AGR might predict the clinical prognosis of patients with HGG and then aid the decision-making process in clinical treatment.

Admittedly, some limitations existed in the present study. Our research was a retrospective study. The accuracy of the results might be influenced by systematic bias. Patients of our research only proceed in one medical center.

## Conclusions

In conclusion, high preoperative AGR indicated a better clinical prognosis and AGR was an independent prognostic factor for OS in patients with HGG. Moreover, in IDH wild-type HGG, higher preoperative AGR had a longer survival time and could further predict the clinical outcome.

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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.2019.08.16>). 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). This research was approved by the Ethics Committee of Zhengzhou University. All participants have written the informed consent.

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