# Association of A Novel ADS Score and Overall Survival in Patients with Glioblastoma Multiforme

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**Article**

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# Abstract

**Background**: The purpose of this study is to investigate the effects of derived neutrophil-lymphocyte ratio (dNLR), albumin-fibrinogen ratio (AFR) and albumin-AFR-dNLR score (ADS) on the prognosis of glioblastoma multiforme (GBM) patients.

**Patients and Methods**: The clinical data of 142 GBM patients were retrospectively analyzed. Survival analyses were performed to assess the predictive role of ADS in GBM patients.

**Results**: There were 142 patients enrolled in the present study. Among these patients, 58 were female, and 84 were male. The mean age at diagnosis was 55±13.78 years. The mean fibrinogen, albumin, AFR, and dNLR were 2.95±0.93g/L, 42.48±3.78g/L, 15.84±5.14 and 3.09±3.90, respectively. Fifty patients had ADS of 0, 53 had ADS of 1, 27 had ADS of 2 and 12 had ADS of 3. In univariate analysis, patients age≥60 years (HR: 1.912;95%CI:1.217-2.878, p=0.002), albumin ≥41.7g/L(HR: 0.614; 95%CI: 0.417-0.905, p=0.014), AFR ≥13.9(HR: 0.649; 95%CI:0.440-0.958, p=0.029), dNLR ≥3.3(HR: 1.609;95%CI:1.024-2.529, p=0.039), ADS<1(HR: 0.378;95%CI:0.241-0.592), p<0.001 ), KPS<80(HR:1.826,95%CI:1.218-2.738,p=0.004), chemotherapy(HR: 0.455;95%CI:0.304-0.682, p<0.001) and gross total resection(HR: 0.380;95%CI:0.257-0.564, p<0.001) were correlated with the prognosis of GBM patients. In multivariate analysis (Table 5), AFR ≥13.9(HR:0.614; 95%CI:0.336-0.828), dNLR≥3.3(HR: 1.923; 95%CI: 1.115-3.316) and ADS<1(HR:0.301;95%CI:0.153-0.592) were associated with overall survival of GBM patients(all p<0.05). Furthermore, ADS, as continuous variable in multivariate analyses, maintained statistical significance after adjusted by confounding factors.

**Conclusion**: ADS, AFR, and dNLR are independent prognostic factors in patients with GBM.


# Background

Glioblastoma multiform (GBM) is a common fatal brain tumor in adults [1]. Although patients underwent standard radiotherapy + synchronous adjuvant temozolomide (TMZ) or even TTFields treatment after total gross resection, the clinical outcome of GBM patients was still poor [2, 3]. However, due to the heterogeneity of the tumor, the prognosis of patients is distinct. Currently, the common molecular markers such as isocitrate dehydrogenase (IDH) mutation, O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation, and telomerase reverse transcriptase (TERT) promoter region have been identified to stratify prognosis in different cohorts of GBM patients [4–6], while a simple and feasible model to predict survival of GBM patients has not been established yet.

As known to all, tumor-related inflammation plays a vital role in promoting angiogenesis and cell proliferation [7], which supports tumor progression. Serum inflammatory biomarkers such as platelet-to-lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR), and derived neutrophil-lymphocyte ratio (dNLR) have been reported to be associated with the diagnosis and clinical outcome of GBM patients [8, 9]. Besides, the nutritional status and prognostic nutritional indicator determined by serum albumin are the influencing factors for the prognosis of patients with GBM [10, 11]. Recently, a retrospective study

conducted by Gao et al. suggested that a new albumin-albumin-fibrinogen ratio (AFR)-dNLR score (ADS) can be used to predict survival in esophageal squamous cell carcinoma (ESCC) patients [12]. However, the effect of dNLR and ADS on the prognosis of GBM patients remains unclear. Therefore, this study aimed to evaluate the impact of dNLR, AFR, and ADS on the prognosis of patients with GBM.

# Results

A total of 142 patients were included in the present study. Among them, 58 were female, and 84 were male. The mean age at the diagnosis was 55 ± 13.53 years. The median KPS was 80(range from 60 to 100). The most common tumor sites were the frontal lobe (44.37%), temporal lobe (32.39%), parietal lobe (17.61%), insular, thalamus and lateral ventricle (14.79%), and occipital lobe (6.34%). Twenty-five patients suffered a seizure before tumor resection. All patients underwent neoplasm resection. Total resection was performed in 64.79% of patients and incomplete resection in 35.21%. 66.9% of patients received temozolomide (TMZ) chemotherapy, and 60.56% of patients received radiotherapy after tumor resection. Forty-one patients received antiepileptic therapy due to the development of postoperative seizure or the presence of preoperative seizure. There were 57.04% patients harbored MGMT-promoter methylation and 17(11.97%) patients had IDH1 mutation(Table 1).

Table 1
The basic information of patients with GBM.

| Variable | Value | % |
|---|---|---|
| Sex | | |
| Male | 84 | 59.15% |
| Female | 58 | 40.86% |
| Age(y) | 55 ± 13.53 | |
| KPS | 80(60–100) | |
| Tumor involvement | | |
| Frontal | 63 | 44.37% |
| Temporal | 46 | 32.39% |
| Parietal | 25 | 17.61% |
| Occipital | 9 | 6.34% |
| Others | 21 | 14.79% |
| Preoperative seizure | 25 | 17.61% |
| Fibrinogen | 2.95 ± 0.93 | |
| Albumin | 42.48 ± 3.78 | |
| AFR | 15.84 ± 5.14 | |
| dNLR | 3.09 ± 3.90 | |
| ADS | | |
| 0 | 50 | 35.21% |
| 1 | 53 | 37.32% |
| 2 | 27 | 19.01% |
| 3 | 12 | 8.45% |
| MGMT methylation | 81 | 57.04% |
| IDH1 mutation | 17 | 11.97% |
| Extent of resection | | |
| Gross total resection | 92 | 64.79% |
| uncomplete resection | 50 | 35.21% |
| Adjuvant treatment | | |

| Variable | Value | % |
|---|---|---|
| Chemotherapy | 95 | 66.90% |
| Radiotherapy | 86 | 60.56% |
| Antiepileptic therapy | 41 | 28.87% |

The mean fibrinogen, albumin, AFR, and dNLR were 2.95 ± 0.93g/L, 42.48 ± 3.78g/L, 15.84 ± 5.14 and 3.09 ± 3.90, respectively. Fifty patients had ADS of 0, 53 had ADS of 1, 27 had ADS of 2 and 12 had ADS of 3(Table 1). Except for age, the distribution of other variables in ADS did not reach statistically significant (Table 2). Spearman test was also adopted to evaluate the correlation between ADS and age, and the result indicated that ADS was positively correlated with age ($r = 0.321$, $p < 0.001$). The optimal cut-off value of fibrinogen, albumin, AFR, dNLR for OS prediction measured by X-tile were 2.7g/L, 41.7g/L, 13.9, and 3.3, respectively (Table 3).

Table 2
The distribution of the baseline variables in ADS.

| | ADS | | | | p |
|---|---|---|---|---|---|
| Variable | 0 | 1 | 2 | 3 | |
| Sex | | | | | 0.518 |
| Male | 33 | 28 | 15 | 8 | |
| Female | 17 | 25 | 12 | 4 | |
| Age(year) | | | | | <0.001 |
| <60 | 46 | 34 | 12 | 8 | |
| ≥ 60 | 4 | 19 | 15 | 4 | |
| Tumor involvement | | | | | |
| Frontal | 28 | 20 | 11 | 4 | 0.219 |
| Temporal | 17 | 16 | 7 | 6 | 0.495 |
| Parietal | 6 | 11 | 5 | 3 | 0.591 |
| Occipital | 3 | 3 | 3 | 0 | 0.464 |
| Others | 6 | 8 | 5 | 2 | 0.594 |
| IDH1 mutation | 6 | 6 | 3 | 2 | 0.957 |
| Preoperative seizure | 10 | 13 | 3 | 0 | 0.215 |
| Extent of resection | | | | | 0.508 |
| gross total resection | 32 | 33 | 19 | 8 | |
| uncomplete resection | 18 | 20 | 8 | 4 | |
| Adjuvant treatment | | | | | |
| Chemotherapy | 37 | 38 | 16 | 6 | 0.112 |
| Radiotherapy | 33 | 34 | 15 | 4 | 0.178 |
| Antiepileptic therapy | 15 | 17 | 6 | 3 | 0.81 |

Table 3
The definition of ADS (The cut-offs were identified by X-tile).

| Variable | Points | |
|---|---|---|
| | 0 | 1 |
| albumin(g/L) | ≥ 41.7 | < 41.7 |
| AFR | ≥ 13.9 | < 13.9 |
| dNLR | < 3.3 | ≥ 3.3 |

At the last follow-up, 103 patients died. The median OS of all patients was 496 days (95%CI:418.785-573.215 days). The median OS of the patients with ADS of0,1,2 and 3 were 679 days (95%:161.061-1196.939 days), 458 days (95%CI:388.762-527.238 days), 374 days (95%CI:321.416-426.514 days) and 151 days(95%CI:8.418-293.582days), respectively. Furthermore, the median OS of patients with ADS ≥ 1 was 320 days (95%CI:289.299-350.701days). In univariate analysis(Table 4), patients age ≥ 60 years old(HR: 1.912;95%CI:1.217–2.878, p = 0.002), albumin ≥ 41.7g/L(HR: 0.614; 95%CI: 0.417–0.905, p = 0.014), AFR ≥ 13.9(HR: 0.649; 95%CI:0.440–0.958, p = 0.029, Fig. 1), dNLR ≥ 3.3(HR: 1.609;95%CI:1.024–2.529,p = 0.039,Fig. 1), ADS < 1(HR: 0.378;95%CI:0.241–0.592, p < 0.001,Fig. 2), KPS < 80(HR:1.826,95%CI:1.218–2.738), chemotherapy(HR: 0.455;95%CI:0.304–0.682, p < 0.001) and gross total resection(HR: 0.380;95%CI:0.257–0.564, p < 0.001) were correlated with prognosis of GBM patients. In multivariate analysis (Table 5), AFR ≥ 13.9(HR:0.614; 95%CI:0.336–0.828), dNLR ≥ 3.3(HR: 1.923; 95%CI: 1.115–3.316) and ADS < 1(HR:0.301;95%CI:0.153–0.592) were associated with overall survival of GBM patients(all p < 0.05). Furthermore, ADS, as continuous variable in univariate and multivariate analyses, maintained statistical significance after adjusted by confounding factors. (Table 6 and Fig. 2).

Table 4
The univariate analysis for the prognostic role of ADS in GBM.

| Variable | Univariate analysis | |
|---|---|---|
| | HR(95%CI) | p |
| Sex | 0.945(0.638–1.401) | 0.779 |
| Age 60 | 1.912(1.217–2.878) | 0.002 |
| Tumor involvement | | |
| Frontal | 1.324(0.977–1.793) | 0.078 |
| Temporal | 0.997(0.661–1.504) | 0.988 |
| Parietal | 1.032(0.613–1.739) | 0.905 |
| Occipital | 2.089(0.768–5.680) | 0.149 |
| Others | 0.810(0.521–1.529) | 0.349 |
| Preoperative seizure | 1.442(0.856–2.429) | 0.169 |
| KPS < 80 | 1.826(1.218–2.738) | 0.004 |
| IDH1 mutation | 1.605(0.839–3.070) | 0.153 |
| MGMT methylation | 1.035(0.702–1.526) | 0.863 |
| Fibrinogen(≥2.7) | 1.399(0.947–2.066) | 0.092 |
| Albumin(≥41.7) | 0.614(0.417–0.905) | 0.014 |
| AFR(≥13.9) | 0.649(0.440–0.958) | 0.029 |
| dNLR(≥3.3) | 1.609(1.024–2.529) | 0.039 |
| ADS(<1) | 0.378(0.241–0.592) | <0.001 |
| Gross total resection | 0.380(0.257–0.564) | <0.001 |
| Chemotherapy | 0.455(0.304–0.682) | <0.001 |
| No-Radiation | 1.225(0.820–1.829) | 0.322 |
| Antiepileptic therapy | 1.058(0.694–1.613) | 0.794 |

Table 5
The multivariate analysis.

| Variable | Multivariate analysis | |
|---|---|---|
| | HR (95%CI) | p |
| Fibrinogen(≥2.7) | 1.047(0.827–1.326) | 0.701[a] |
| Albumin(≥41.7) | 0.910(0.450–1.839) | 0.792 [a] |
| AFR(≥13.9) | 0.614(0.336–0.828) | 0.004 [a] |
| dNLR(≥3.3) | 1.923(1.115–3.316) | 0.019 [a] |
| ADS(<1) | 0.301(0.153–0.592) | 0.001 [a] |

[a] adjusted by age, gender, tumor location, preoperative seizure status, KPS, MGMT promotor methylation, IDH1 mutation and treatment strategy.

Table 6
The univariate and multivariate analysis to explore the predictive role of ADS as a continue parameter in patients with GBM.

| Variable | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | HR (95%CI) | p | HR (95%CI) | p [a] |
| ADS | | | | |
| 0 | Reference | 1 | Reference | 1 |
| 1 | 2.174(1.332–3.550) | 0.002 | 3.959(1.235–12.684) | 0.021 |
| 2 | 3.329(1.891–5.864) | <0.001 | 2.883(1.371–6.064) | 0.005 |
| 3 | 5.353(2.560-11.191) | <0.001 | 5.411(1.979–14.792) | 0.001 |

[a] adjusted by age, gender, tumor location, preoperative seizure status, KPS, MGMT promotor methylation, IDH1 mutation, and treatment strategy.

Stratification analysis based on IDH1 mutation status showed that AFR ≥ 13.9, dNLR ≥ 3.3 and ADS < 1 were independent predictors of prognosis for GBM patients with IDH1 wild type(Table S1 and Fig. 3). In addition, ADS, as continuous variable, was associated with survival of patients with IDH1 wild type(Table S2). Equally, whether ADS acted as a categorical or continue variable, it has an impact on the prognosis of IDH1 mutant GBM showed by univariate analysis(Fig. 3).

# Discussion

In this clinical research, a retrospective study was conducted with 142 GBM patients to assess the prognostic effects of ADS. The results indicated that high AFR (≥ 13.9) was associated with favorable prognosis and patients with high dNLR (≥ 3.3) or ADS (≥ 1) was correlated with poor clinical outcome. Furthermore, ADS is better than the individual markers dNLR or AFR in predicting prognosis of GBM patients. To our knowledge, this is the first study to explore the predictive role of ADS in patients with GBM.

There is growing evidence indicated that inflammatory response-associated with cancer may promote tumor progression [13]. Chemokines and cytokines of tumor cells or host cells regulate cellular communication in the tumor microenvironment, which leads to tumor invasion, metastatic spread, and angiogenesis [13]. It has been reported that inflammatory markers such as PLR and NLR are related to the survival of glioma patients [8, 9]. Also, nutritional status and blood coagulation affect the clinical outcome of GBM patients [10, 11, 14]. ADS represented the inflammation, nutritional information, and blood coagulation of patients, and can be used to assess the survival of GBM patients.

Although previous studies have suggested that dNLR is a noninvasive biomarker for differentiating GBM from low-grade gliomas [8], few studies have evaluated the role of dNLR in the survival of GBM patients. Unlike NLR, dNLR was calculated by neutrophil count/ (leukocyte count- neutrophil count). Many published studies have reported the prognostic effect of dNLR in cancer patients. Their findings have shown that high dNLR is associated with poor prognosis in patients with lymphoma, pancreatic cancer, gastric cancer, lung cancer, urothelial carcinoma, renal cell carcinoma, hepatocellular carcinoma and colorectal cancer [15–21], which is consistent with our results that GBM patients with increased dNLR have a poor prognosis. Neutrophils are the most abundant white blood cells and play a vital role in inflammatory responses. High dNLR may be due to increased neutrophils or decreased lymphocytes. During the development of GBM, tumor cells release a granulocyte colony-stimulating factor (CSF) to promote the growth of neutrophils[22], which may promote neutrophil aggregation in glioma[23]. Neutrophil activation associated with glioma may improve tumor growth, immunosuppression, and production of reactive oxygen species [24]. Lymphocyte counts and function were inhibited by tumor-related factors [25], which reduced lymphocyte resistance to glioma. Therefore, it is not difficult to understand that patients with low dNLR in GBM have a longer survival time than patients with high dNLR.

In addition to nutritional status, serum albumin also represents an inflammatory response [26]. Accumulated evidence suggests that albumin can inhibit IL-6 through TNF-α, and they may be associated with a meditation on anti-cytotoxicity causing immune cells in GBM patients [27]. High albumin is associated with favorable prognosis in patients with GBM [11]. In this study, there was a correlation between albumin and OS in univariate analysis, but there was no statistical significance in the multivariate analysis after adjusting for other factors. The abnormalities of blood coagulation always developed in many cancers, including GBM [28, 29]. Fibrinogen reflects the coagulation status of blood, but the exact cause of the relationship between fibrinogen and tumor growth remained unknown. In recent years, many studies have shown that fibrinogen promotes cell adhesion and proliferation by combining growth factors such as vascular endothelial growth factor and fibroblast growth factor- 2 [30,

31]. Furthermore, fibrinogen can inhibit the natural killer cytotoxicity of tumor cells [32]. Studies have shown that fibrinogen is an independent predictor of survival in patients with non-small cell lung cancer, ovarian cancer and glioma [33–35], which is consistent with our findings that high fibrinogen is associated with poor prognosis. AFR base on the albumin/fibrinogen has also been reported as a prognostic factor associated with survival time of various malignancies [36]. In this study, we also observed that increased AFR is a predictor of favorable prognosis in GBM patients, which is an essential factor consistent with previously published researches [37].

ADS is a new inflammation-based prognostic score composed of serum albumin, fibrinogen, AFR, and dNLR, which was reported to be related to the survival of ESCC patients [12]. Recently, Gao and her colleagues conducted a clinical study of 153 patients with ESCC, which showed that low ADS was associated with favorable clinical outcomes. The author also suggested that ADS was superior to albumin, fibrinogen, AFR or dNLR in predicting OS in ESCC patients. In the present study, we found that ADS is positively correlated with age, but not with tumor size. The OS of patients with ADS of 1, 2 and 3 is shorter than patients with ADS of 0, which is consistent with previous studies [12]. In addition, ADS is better than the individual markers dNLR or AFR in predicting prognosis of GBM patients. Therefore, it is feasible and straightforward to apply ADS to predict the survival time of GBM patients in the clinic.

However, some limitations of the present study should be noted. On the one hand, some selection bias may be existed in this study due to the nature of the retrospective study. On the other hand, we were unable to assess the postoperative ADS dynamic in GBM patients and the relationship between these dynamics and clinical outcomes. Therefore, future large-samples prospective studies should expend our findings and evaluate the role of dynamic changes in postoperative ADS in GBM patients.

## Conclusion

ADS, AFR, and dNLR are independent factors for predicting the clinical prognosis of GBM patients. In addition, ADS is better than the individual markers dNLR or AFR in predicting the prognosis of GBM patients. As a result, it is feasible and straightforward to apply ADS to predict the survival of GBM patients.

## Patients And Methods

# Patients enrollment

Patients who underwent tumor resection in our hospital between November 2013 and December 2017 were identified. Furthermore, patients who met the following inclusion criteria were included in this study: (1) all patients were diagnosed as primary GBM by histopathological examination; (2) did not receive any treatment before tumor resection; (3) available survival information and hematological variables such as albumin, AFR, fibrinogen, and dNLR. Conversely, patients with acute and chronic inflammation, liver, autoimmune and hematological diseases, and any other malignant lesions were excluded. Also, patients

received treatment which may affect albumin, AFR, fibrinogen, dNLR, etc. were excluded, such as alkylating agent and corticosteroid. The data that support the findings of this study can be obtained from the corresponding author upon reasonable request. In addition, this study was approved by the ethics committee of West China Hospital of Sichuan University and obtained written informed consent from all patients, and all methods were performed in accordance with the relevant guidelines and regulations.

# Blood collection and detection

All the serum samples, peripheral blood, and plasma were collected between 6:30 and 8:00 a.m. within 3 days before operation. Purple, red, and blue tubes were used for complete blood count, blood biochemistry, and coagulation. The SYSMEX CA-7000 machine (Sysmex, Tokyo, Japan) and OLYMPUS AU5400 machine (Beckman Coulter, Tokyo, Japan) were employed to detect plasma fibrinogen and serum albumin via Clauss and bromocresol green methods, respectively.

# Identification of hematological parameters

In the present study, preoperative serum albumin, white blood cell count (WBC), fibrinogen and absolute neutrophil counts were collected. AFR was defined as albumin divided by fibrinogen. The dNLR was calculated as follows: neutrophil/(WBC-neutrophil). The formula of ADS calculation was summarized in Table 1. In this study, patients with albumin $\geq$ 41.7 g/L or AFR $\geq$ 13.9 or dNLR $<$ 3.3 were identified as ADS of 0 points, while patients with albumin $<$ 41.7g/L or AFR $<$ 13.9 or dNLR $\geq$ 3.3 were split into 1 point. The sum points of the three parameters including albumin, AFR and dNLR were equivalent to the ADS, whose value range was from 0 to 3.

# Statistical analysis

Overall survival (OS) was defined as the duration from tumor resection to death, or the last follow up. All statistical analyses were performed on SPSS 19.0 version. Continuous and categorical variables were represented by mean ± SD and quantity, respectively. The t-test and Chi-square tests were used to compare continuous parameters and categorical parameters, respectively. The optimal cut-off for albumin, fibrinogen, AFR, and dNLR to predict OS was determined using X-tile. Additionally, Survival analyses including univariate and multivariate analysis were performed to assess the prognostic effect of ADS in GBM. $P \leq 0.05$ was considered statistically significant.

## Abbreviations

**GBM:** glioblastoma multiforme

**dNLR**: derived neutrophil-lymphocyte ratio

**AFR:** albumin-fibrinogen ratio

**ADS:** albumin- neutrophil-lymphocyte ratio- albumin-fibrinogen ratio score

**TMZ:** temozolomide

**IDH:** isocitrate dehydrogenase

**MGMT:** O6-methylguanine-DNA methyltransferase

**TERT:** telomerase reverse transcriptase

**WBC:** white blood cell count

**PLR:** platelet-to-lymphocyte ratio

**ESCC:** esophageal squamous cell carcinoma

**NLR:** neutrophil-lymphocyte ratio

**OS:** overall survival

**CSF:** colony-stimulating factor

# Declarations


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None.


### Author contributions

L.-Z.C. was involved in the validation, formal analysis, visualization, software, resources, writing - review & editing, supervision, and data curation.

L.-Z.C. and Y.-H.L. were responsible for the conceptualization, methodology, software, investigation, writing - original draft, validation, formal analysis, and visualization.

L.-Z.C., H.Y., Y.-H.L., Z.-J. Z., J.-X.L. and X.-W.Z. were involved in the resources, writing - review & editing, supervision, and data curation.

L.-Z.C., H.Y., X.-W. Z., Z.-J.Z., , J.-X.L. and H.P. were responsible for the writing: review & editing.

All authors have read and agreed to the final version of the manuscript.

### Data Availability Statement

The data used in this article can be obtained from the corresponding author by email.

### Competing interests

The authors declare that they have no competing interests.

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# Figures

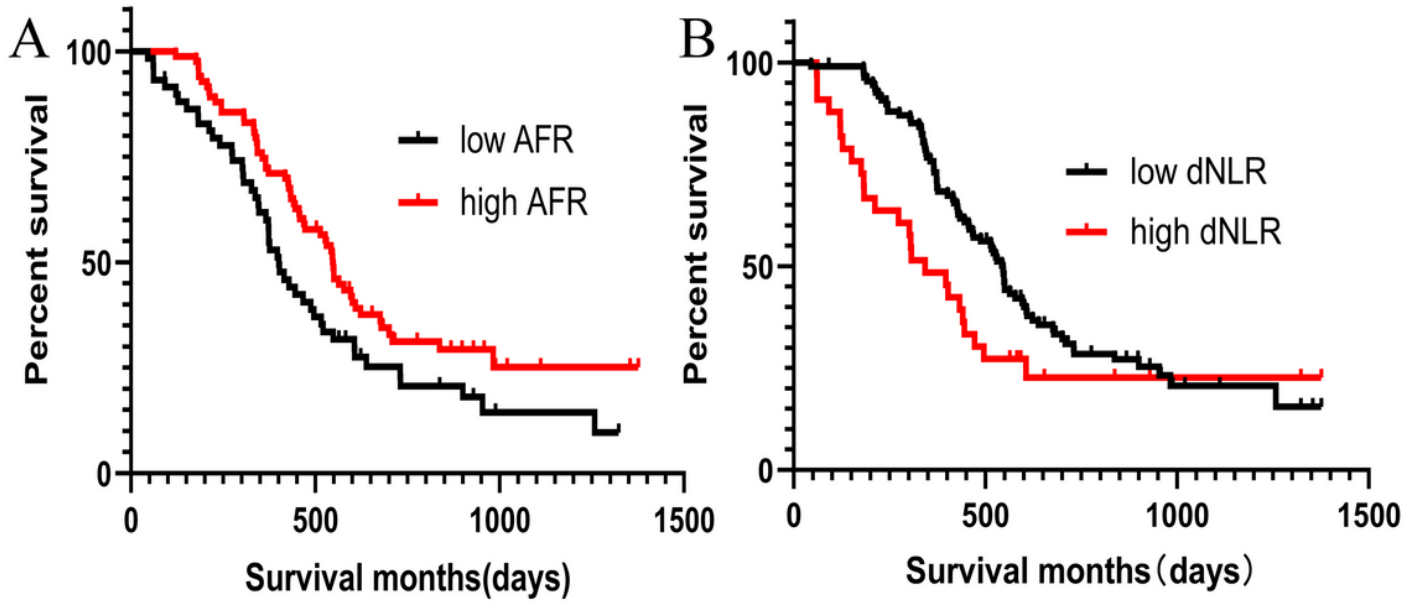


**Figure 1**

The survival graphs of AFR(A) and dNLR(B) in GBM.

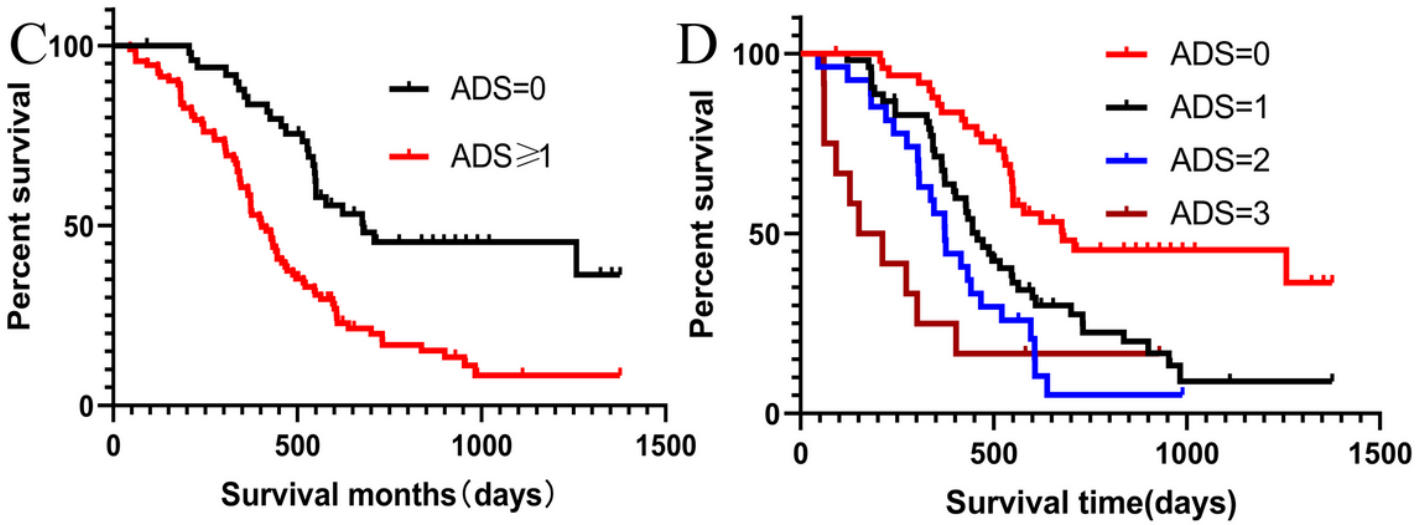


**Figure 2**

The survival graphs of ADS as categorical(C) and continue(D) variable.

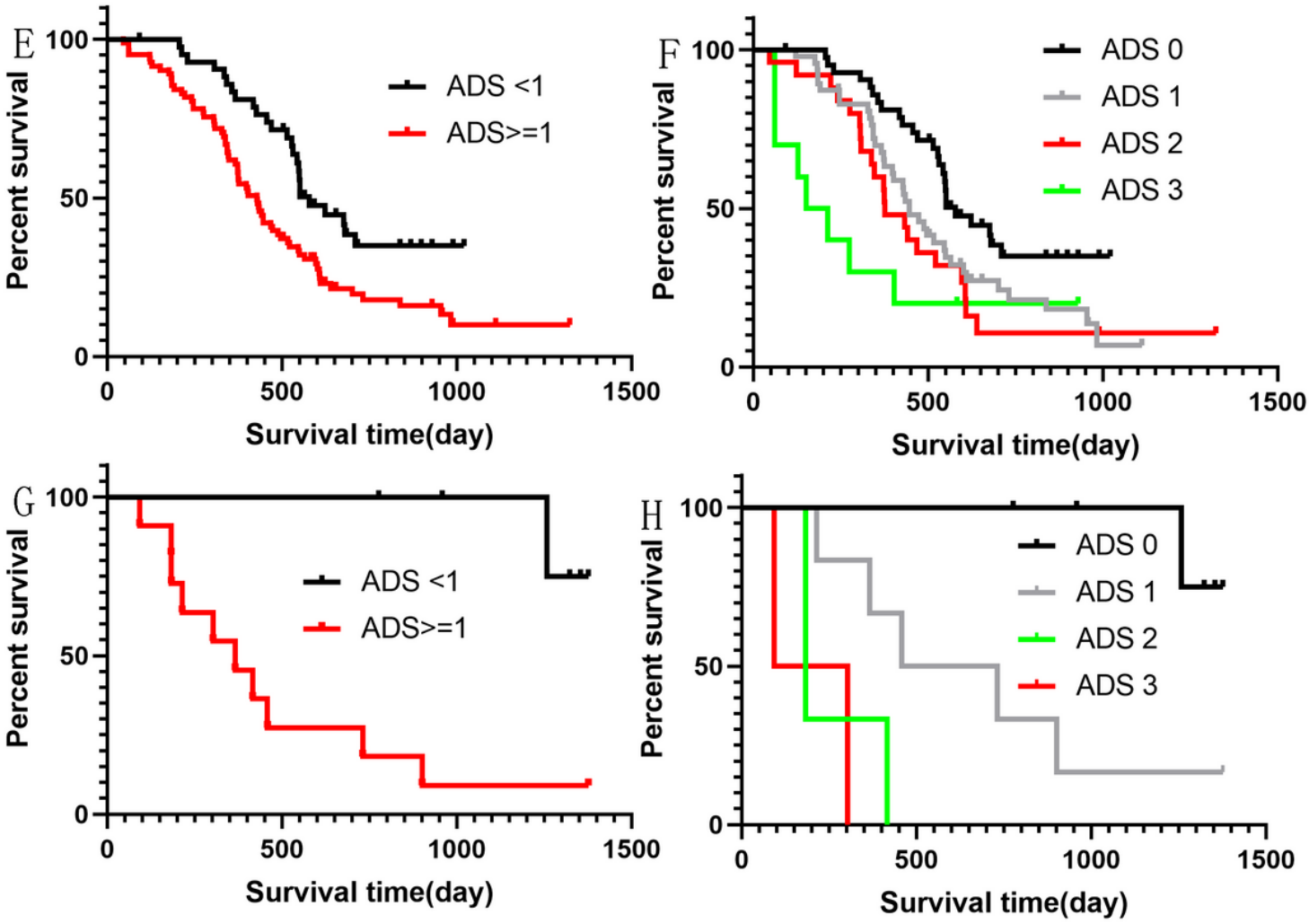


**Figure 3**

The prognostic role of ADS in GBM patients based on IDH1 wild type(E and F) and IDH1 mutation(G and H).

# Supplementary Files

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