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Prognostic Significance of Albumin–Globulin Score in Patients with Operable Non-Small-Cell Lung Cancer

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ABSTRACT

Objective. This study was designed to evaluate the prognostic value of the preoperative albumin–globulin score (AGS) in the patients with non-small cell lung cancer (NSCLC) after pulmonary lobectomy.

Methods and Results. The optimal cutoff level was 40.00 and 27.05 g/L for Alb and Glb, respectively. Based on this and the previous study, patients with both an hypoalbuminemia (< 40.00 g/L) and an elevated Glb level (≥ 27.05 g/L) were assigned a score of 2, and patients with one or neither were assigned a score of 1 or 0, respectively. We investigated the correlations between the AGS and the clinicopathological characteristics of patients and found that AGS was significantly associated with TNM stage ($P = 0.016$). Multivariate Cox analyses indicated that the AGS was an independent prognostic indicator for NSCLC for disease-free survival (DFS) ($P = 0.001$) and overall survival (OS) ($P = 0.004$). Kaplan–Meier analysis and log-rank test demonstrated that there were significant differences in DFS ($P < 0.001$) and OS ($P < 0.001$) among the three AGS groups. Furthermore, our study showed that DFS and OS are significantly different in three groups of patients with different AGS, in both Squamous carcinoma ($P < 0.001$ for DFS; $P < 0.001$ for OS) or adenocarcinoma ($P = 0.034$ for DFS; $P = 0.035$ for OS). In addition, we enrolled 53 patients as an independent set of cases for the further validation of AGS. Multivariate analyses verified

AGS was an independent prognostic factor for NSCLC patients ($P = 0.020$ for DFS; $P = 0.018$ for OS).

Conclusions. Preoperative AGS is an independent prognostic factor for patients with operable NSCLC.

Lung cancer is the most common cause of cancer death worldwide, and its 5-year survival rates is less than 15%.[1] Non-small-cell lung cancer (NSCLC) accounts for more than 80% of lung cancer diagnoses.[2] Among all treatment of NSCLC, including surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy, the best choice for patients with early-stage disease is still surgery.[3–6] Plenty of indicators were proved to have prognostic value for NSCLC, especially the American Joint Committee on Cancer (AJCC), the Union for International Cancer Control (UICC) tumor-node- metastasis (TNM) staging system.[7,8] But it cannot be obtained preoperatively.

Recently, several host-based and inflammation-based indicators have been reported in the literature for patients with NSCLC, such as CRP/Alb ratio, neutrophil to lymphocyte ratio (NLR), and platelet to lymphocyte ratio (PLR).[9–13] Malnutrition and systemic inflammatory response were shown to promote tumor progression by destroying immune function, inducing angiogenesis and altering biological features of tumor cells.[14,15] Albumin (Alb) and globulin (Glb) are two major components of total proteins in serum human. Serum Alb is commonly used to evaluate the nutritional status and the severity of cancer patients.[16] The low level of Alb also is associated with systemic inflammatory response of the host.[17] So Alb has been reported to be an independent prognostic factor for NSCLC. The other important serum protein, globulin, plays an important role in immune and inflammation of the host through regulation of inflammatory cytokines.[18] Previous studies have shown that albumin to globulin ratio

Xiang Li, Sida Qin and Xin Sun contributed equally to this work.

TABLE 1 Baseline characteristics of 312 patients with NSCLC

Characteristics	No. of patients	Percentage (%)
Gender		
Male	223	71.5
Female	89	28.5
Age (year)		
≤ 60	170	54.5
> 60	142	45.5
Histological subtype		
Squamous carcinoma	116	37.2
Adenocarcinoma	160	51.3
Others (adenosquamous carcinoma, etc.)	36	11.5
Smoking		
Smoker	174	55.8
Never-smoker	138	44.2
Weight-loss		
≤ 5%	283	90.7
> 5%	29	9.3
ECOG-PS		
0	215	68.9
1	95	30.4
2	2	0.6
Differentiation		
Well	75	24.0
Intermediate	47	15.1
Poor or undifferentiated	190	60.9
T stage		
T1	58	18.6
T2	210	67.3
T3	29	9.3
T4	15	4.8
Lymph node metastasis		
Yes	134	42.9
No	178	57.1
TNM stage (AJCC, 7th)		
I	133	42.6
II	99	31.7
III	80	25.6
Neutrophil count (10^9/L)	4.13 ± 2.12	
Lymphocyte count (10^9/L)	1.69 ± 0.61	
Platelet count (10^9/L)	201.79 ± 73.39	
NLR	2.92 ± 2.83	
PLR	134.59 ± 72.17	
NSE (ng/ml)	16.25 ± 13.11	
CEA (ng/ml)	9.67 ± 22.82	
CYGRA21-1 (ng/ml)	6.06 ± 8.55	

TNM tumor-node-metastasis, *AJCC* American Joint Committee on Cancer, *ECOG-PS* Eastern Cooperative Oncology Group performance status, *NSE* neuron-specific enolase, *NLR* neutrophil/lymphocyte ratio, *PLR* platelet/lymphocyte ratio, *AGR* albumin/globulin ratio, *CEA* carcinoembryonic antigen, *CYGRA21-1* cytokeratin 19 fragment

TABLE 2 Correlation of AGS with the clinicopathological characteristics of the NSCLC patients

Characteristics	AGS = 0	AGS = 1	AGS = 2	P value
Gender				0.027
Male	52	106	65	
Female	26	50	13	
Age (year)				0.081
≤ 60	46	90	34	
> 60	32	66	44	
Histological subtype				0.003
Squamous carcinoma	24	53	39	
Adenocarcinoma	47	88	25	
Others (adenosquamous carcinoma, etc.)	7	15	14	
Smoking				0.266
Smoker	39	86	49	
Never-smoker	39	70	29	
Weight-loss				0.374
≤ 5%	69	145	69	
> 5%	9	11	9	
ECOG-PS				0.573
0	55	111	49	
1	23	44	28	
2	0	1	1	
Differentiation				0.014
Well	23	40	12	
Intermediate	17	23	7	
Poor or undifferentiated	38	93	59	
T stage				0.002
T1	18	31	9	
T2	52	110	48	
T3	4	8	17	
T4	4	7	4	
Lymph node metastasis				0.721
Yes	31	67	36	
No	47	89	42	
TNM stage (AJCC, 7th)				0.016
I	39	73	21	
II	23	42	34	
III	16	41	23	
Neutrophil count (10^9/L)	3.63 ± 1.72	4.15 ± 2.12	4.60 ± 2.36	0.035
Lymphocyte count (10^9/L)	1.71 ± 0.63	1.72 ± 0.61	1.62 ± 0.61	0.490
Platelet count (10^9/L)	181.13 ± 62.25	199.55 ± 67.68	224.10 ± 87.04	0.001
NLR	2.50 ± 1.81	2.93 ± 3.28	3.34 ± 2.65	0.010
PLR	119.09 ± 59.46	130.45 ± 69.28	158.35 ± 83.62	0.001
NSE (ng/ml)	13.85 ± 7.65	17.01 ± 13.40	17.1 ± 16.31	0.262
CEA (ng/ml)	8.76 ± 18.78	9.13 ± 20.99	11.65 ± 29.29	0.987
CYGRA21-1 (ng/ml)	4.80 ± 2.70	5.82 ± 5.62	7.82 ± 14.81	0.522

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TABLE 3 Prognostic factors for DFS identified by univariate and multivariate analyses

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Gender (male vs. female)	0.518	0.338–0.794	0.003	0.659	0.422–1.027	0.066
Age (year) (≤ 60 vs. > 60)	1.011	0.994–1.030	0.210			
Histological subtype	1.192	0.923–1.539	0.179			
Smoking (ever vs. never)	1.165	0.829–1.637	0.378			
Weight-loss (≤ 5 vs. > 5%)	1.734	0.995–3.023	0.052			
ECOG-PS (0/1/2)	1.422	1.008–2.006	0.045	1.019	0.694–1.495	0.924
Differentiation			< 0.001			< 0.001
Well	1	Reference		1	Reference	
Intermediate	1.076	0.475–2.439	0.861	1.026	0.448–2.350	0.951
Poor or undifferentiated	4.286	2.531–7.257	< 0.001	3.379	1.566–5.808	< 0.001
T stage (T1/T2/T3/T4)	1.570	1.252–1.971	< 0.001			
Lymph node metastasis (yes vs. no)	1.702	1.399–2.072	< 0.001			
TNM stage (AJCC 7th)			< 0.001			< 0.001
I	1	Reference		1	Reference	
II	1.761	1.158–2.680	0.008	1.298	0.845–1.995	0.224
III	3.620	2.391–5.480	< 0.001	2.642	1.631–4.279	< 0.001
Neutrophil count (10^9/L)	1.120	1.044–1.202	0.002			
Lymphocyte count (10^9/L)	0.798	0.597–1.066	0.127			
Platelet count (10^9/L)	1.003	1.000–1.005	0.017			
NLR (≤ 2.65 vs. > 2.65)	1.034	0.993–1.077	0.105			
PLR (≤ 119.73 vs. > 119.73)	1.003	1.001–1.005	0.005	1.002	0.999–1.004	0.181
CEA (ng/ml) (≤ 3.4 vs. > 3.4)	0.994	0.984–1.005	0.266			
CYGRA21-1 (ng/ml) (≤ 3.3 vs. > 3.3)	1.010	0.995–1.025	0.209			
NSE (ng/ml) (≤ 12.5 vs. > 12.5)	1.038	1.030–1.047	< 0.001	1.025	1.016–1.034	< 0.001
Alb (g/L) (< 40 vs. ≥ 40)	0.936	0.904–0.968	< 0.001			
Glb (g/L)	1.049	1.018–1.080	0.002			
AGR (≤ 1.47 vs. > 1.47)	0.282	0.168–0.474	< 0.001			
AGS	1.730	1.356–2.207	< 0.001	1.523	1.178–1.969	0.001

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(AGR) is an independent prognostic indicator for several cancers, such as breast cancer and gastric cancer.[19–22] Similarly, a recent study put forward a novel predictor, albumin–globulin score (AGS), which reflects the cumulative effect of both Alb and Glb on esophageal squamous cell carcinoma (ESCC) patients.[23] However, there is no report on the relationship between the AGS and the outcome in patients with operable NSCLC.

METHODS

Patients

We retrospectively reviewed clinical data for 512 patients who were diagnosed with NSCLC and treated at the First Affiliated Hospital of Xi'an Jiaotong University between 2008 and 2013. The study was approved by the ethics committees at the First Affiliated Hospital of Xi'an Jiaotong University. All patients provided written, informed consent. The inclusion criteria of this study were: (1) pathologically diagnosed NSCLC, (2) surgery included radical resection, (3) preoperative testing included blood tests for liver function 1 week before surgery, and (4) a diagnosis without other malignancies, residual lung cancer or metastatic bronchogenic carcinoma. Patients who met the following criteria were excluded from the study: (1) died in the perioperative period or from non-cancer-related causes, (2) had incomplete medical records, (3) autoimmune disease and (4) severe liver or kidney malfunction. Moreover, the patients neither received neoadjuvant chemoradiation nor took nutritional supplements preoperatively. Based on the inclusion and exclusion criteria, a

TABLE 4 Prognostic factors for OS identified by univariate and multivariate analyses

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Gender (male vs. female)	0.455	0.281–0.736	0.001	0.679	0.412–1.121	0.130
Age (year) (≤ 60 vs. > 60)	1.004	0.985–1.023	0.696			
Histological subtype	1.174	0.893–1.544	0.251			
Smoking (ever vs. never)	1.200	0.832–1.732	0.329			
Weight-loss (≤ 5 vs. $> 5\%$)	1.700	0.954–3.027	0.072			
ECOG-PS (0/1/2)	1.407	0.972–2.036	0.070			
Differentiation			< 0.001			< 0.001
Well	1	Reference		1	Reference	
Intermediate	1.134	0.412–3.126	0.807	1.101	0.397–2.052	0.853
Poor or undifferentiated	6.064	3.161–11.631	< 0.001	4.692	2.417–9.109	< 0.001
T stage (T1/T2/T3/T4)	1.683	1.328–2.133	< 0.001			
Lymph node metastasis (yes vs. no)	1.722	1.400–2.119	< 0.001			
TNM stage (AJCC 7th)			< 0.001			< 0.001
I	1	Reference		1	Reference	
II	1.861	1.177–2.942	0.008	1.300	0.816–2.070	0.269
III	3.828	2.445–5.991	< 0.001	2.692	1.655–4.379	< 0.001
Neutrophil count (10^9/L)	1.141	1.060–1.227	< 0.001			
Lymphocyte count (10^9/L)	0.738	0.539–1.011	0.059			
Platelet count (10^9/L)	1.002	1.000–1.005	0.049			
NLR (≤ 2.65 vs. > 2.65)	1.043	1.002–1.086	0.040			
PLR (≤ 119.73 vs. > 119.73)	1.003	1.001–1.005	0.004	1.001	0.998–1.003	0.471
CEA (ng/ml) (≤ 3.4 vs. > 3.4)	0.995	0.985–1.006	0.371			
CYGRA21-1 (ng/ml) (≤ 3.3 vs. > 3.3)	1.010	0.995–1.026	0.178			
NSE (ng/ml) (≤ 12.5 vs. > 12.5)	1.039	1.031–1.047	< 0.001	1.025	1.016–1.034	< 0.001
Alb (g/L) (< 40 vs. ≥ 40)	0.932	0.899–0.967	< 0.001			
Glb (g/L)	1.048	1.016–1.081	0.003			
AGR (≤ 1.47 vs. > 1.47)	0.273	0.156–0.477	< 0.001			
AGS	1.806	1.389–2.350	< 0.001	1.513	1.142–2.004	0.004

TNM tumor-node-metastasis, *AJCC* American Joint Committee on Cancer, *ECOG-PS* Eastern Cooperative Oncology Group performance status, *NSE* neuron-specific enolase, *NLR* neutrophil/lymphocyte ratio, *PLR* platelet/lymphocyte ratio, *AGR* albumin/globulin ratio, *CEA* carcinoembryonic antigen, *CYGRA21-1* cytokeratin 19 fragment

total of 312 NSCLC patients were analyzed in this study. To further verify the value of AGS, we supplemented a validation group of 53 patients from April 2013 to May 2014.

Clinical Data Collection and Follow-Up

Patient information and laboratory data before surgery were retrieved from the patient records. All parameters were measured within 1 week before surgery to avoid any impacts of surgery, chemotherapy, or radiotherapy. We selected and evaluated the following clinicopathological factors: age, gender, smoking status, pathological type, tumor differentiation, adjuvant chemoradiation, and TNM stage (American Joint Committee on Cancer (AJCC) 7th edition). Smokers were defined as patients who had more than 100 cigarettes in their lifetime. The extent of weight loss and Eastern Cooperative Oncology Group performance status (ECOG-PS) were measured at the time of diagnosis. All patients enrolled in this study had complete blood counts and serum chemistry analysis, including white blood cell count, neutrophil count, lymphocyte count, and platelet count, measurements of Alb, Glb, as well as the serum tumor markers NSE, CEA, and cyfra21-1.

The optimal cutoff value was identified as 40.00 and 27.05 g/L for Alb and Glb using ROC curve analyses, respectively. Based on these cutoff values and the previous
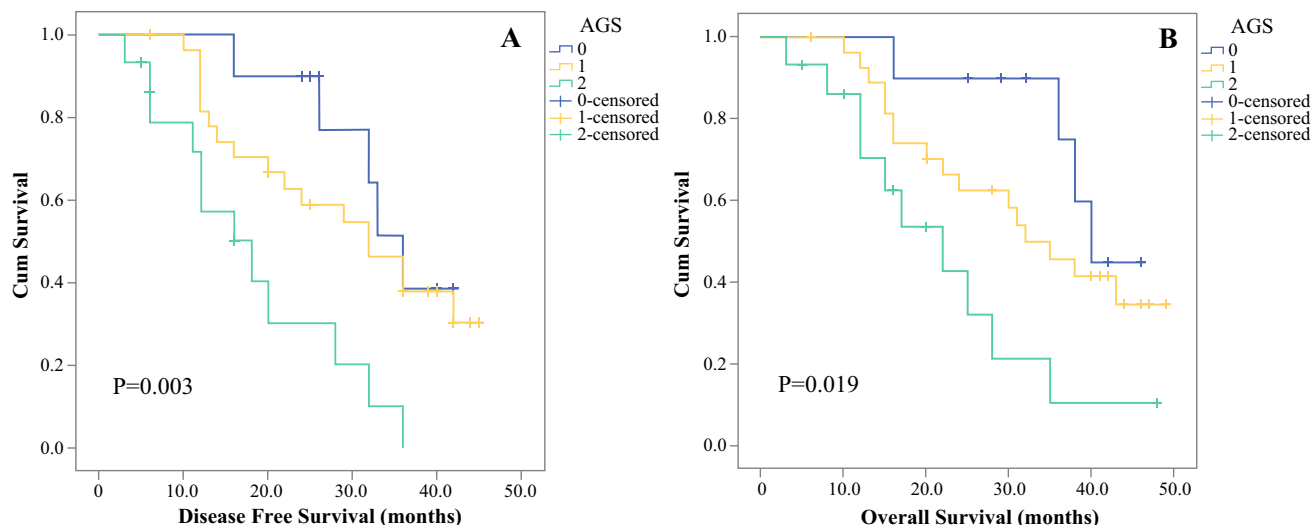
FIG. 1 Kaplan–Meier curves showing the differences in DFS and OS of 312 NSCLC patients. **a** Kaplan–Meier curve of DFS for NSCLC. **b** Kaplan–Meier curve of OS for NSCLC

study, we defined AGS as follows: patients with both an hypoalbuminemia (< 40.00 g/L) and an elevated Glb level (≥ 27.05 g/L) were assigned an AGS of 2, whereas those with only one of the two abnormalities were assigned an AGS of 1 and those with normal values for both parameters were assigned an AGS of 0. Weight loss was defined as loss of more than 5% pretreatment weight before operation. Other host-related and inflammation-related prognostic indicators used in this study were defined and calculated as follows: NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count, the PLR was defined as the absolute platelet count divided by the absolute lymphocyte count, and the AGR was defined as the ratio of serum Alb to Glb.

All patients were followed up for 3 years; the last date of follow-up was March 31, 2016 or death from any cause (the last date of follow-up in validated group was September 30, 2017). Patients were followed every 3 months for the first 2 years after radical resection and annually thereafter. The postoperative follow-up assessments included routine blood test, liver function, tumor biomarkers, whole body bone scan, computed tomography, and magnetic resonance imaging. The patient will receive a thorough examination when there is any evidence of recurrence and metastasis, including local relapse and distant metastasis, confirmed by computed tomography or magnetic resonance imaging.

Statistical Analysis

Disease-free survival (DFS) was defined as the duration of time between the date of surgery and the date of first recurrence or last follow-up. Data are presented as the

mean ± standard deviation (SD). To classify the patients into two groups, the optimal cutoff values of Alb and Glb were determined using ROC curve analyses. The significance of correlations between the preoperative AGS and clinicopathological characteristics was analyzed using the χ^2 test and Kruskal–Wallis test. The health status of all patients was provided by the hospital database or telephone interviews. Survival curve was estimated by Kaplan–Meier analysis, and the log-rank test was used to examine the significance of differences in survival distributions between groups. Univariate and multivariate Cox proportional hazards analyses were used to assess the relative effect of the AGS on DFS and OS. Hazard ratio (HR) and 95% confidence interval (95% CI) values were calculated by the Cox proportional hazards model. All statistical analyses were performed using the SPSS 20.0 statistical software (SPSS, Chicago, IL, USA). Generally, $P < 0.05$ was considered statistically significant for all analyses.

RESULTS

Patients' Baseline Characteristics

According to the inclusion and exclusion criteria, a total of 312 patients with histologically confirmed as NSCLC were enrolled in this study. In these patients, 223 (71.5%) of them were males and 89(28.5%) were females. The median age was 59 years, with an age range from 18 to 78 years. All patients were able to tolerate surgery, which included adenosquamous carcinoma and large cell carcinoma. There were 174 (55.8%) smokers and 138 (44.2%) nonsmokers. Twenty-nine (9.3%) patients had a loss of more than 5% pretreatment weight. A total of 215 (68.9%) patients were
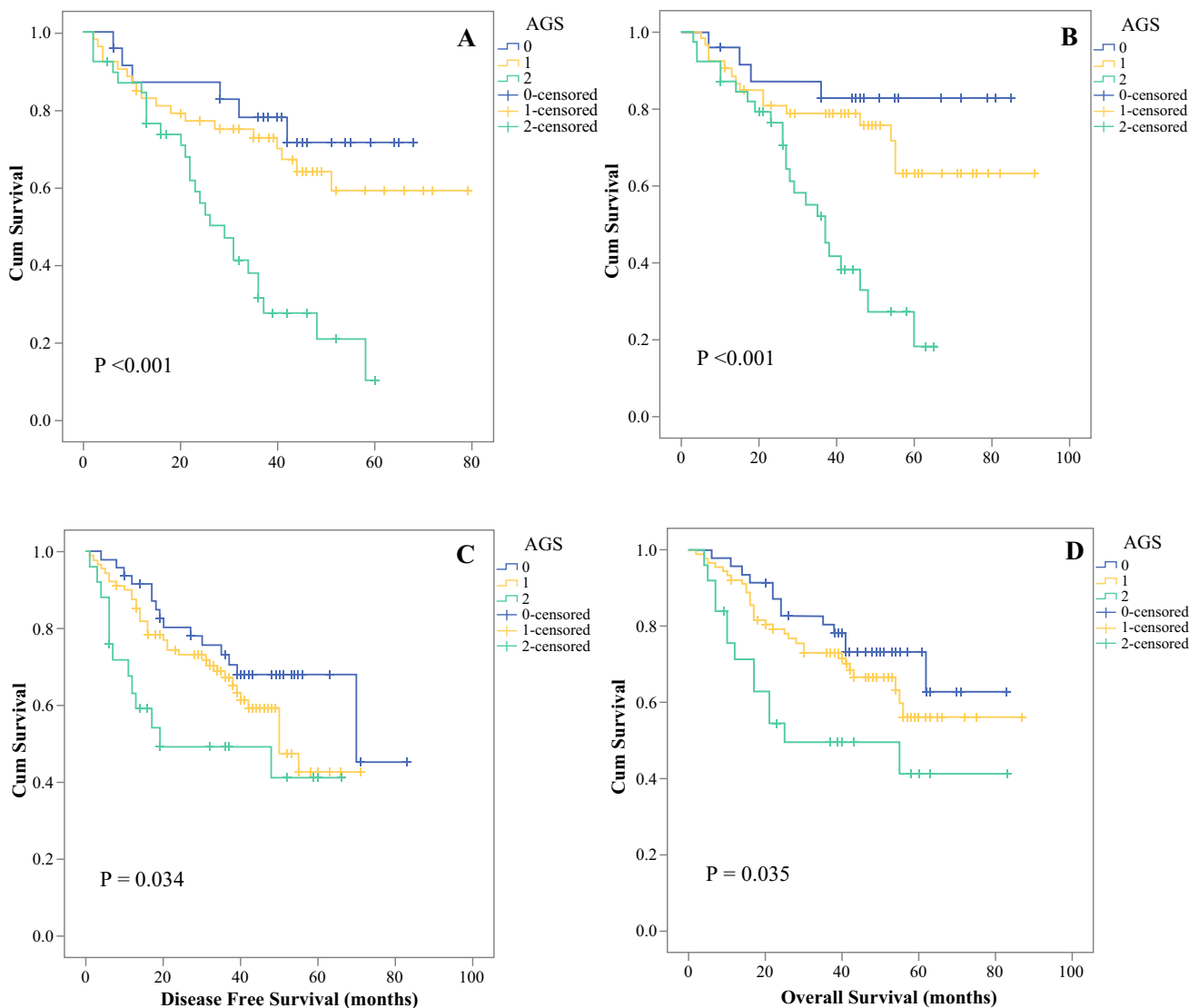
FIG. 2 Kaplan–Meier curves for SqCC and adenocarcinoma patients. **a** Kaplan–Meier curve of DFS for SqCC patients. **b** Kaplan–Meier curve of OS for SqCC patients. **c** Kaplan–Meier curve of DFS for adenocarcinoma patients. **d** Kaplan–Meier curve of OS for adenocarcinoma patients

classified into the ECOG-PS group of 0, whereas 95 (30.4%) of them were in the group of 1. The distribution of pathological stages was as follows: stage I, 133 (42.6%); stage II, 99 (31.7%); and stage III, 80 (25.6%; Table 1).

Correlation Between Preoperative AGS and Clinical Pathological Characteristics

The correlation between AGS and the clinicopathological characteristics is shown in Table 2. It was demonstrated that AGS has significant correlation with gender ($P = 0.027$), histological subtype ($P = 0.003$), differentiation ($P = 0.014$), adjuvant chemoradiation ($P = 0.013$), TNM stage ($P = 0.016$), neutrophil count ($P = 0.035$), platelet count ($P = 0.001$), NLR ($P = 0.010$), and PLR ($P = 0.001$).

Survival Analysis with the AGR

The follow-up period ranged from 2 to 91 (median: 41; mean: 39) months. At the end of the last follow-up, 119 of the total patients had died, and the ratio for loss to follow-up was 8.7% ($n = 27$). Survival analyses were performed in relation to AGS and patient prognosis. Univariate analyses of DFS revealed that gender ($P = 0.003$), ECOG-PS ($P = 0.045$), differentiation ($P < 0.001$), tumor stage ($P < 0.001$), node stage ($P < 0.001$), TNM stage ($P < 0.001$), neutrophil count ($P = 0.002$), PLR ($P = 0.005$), NSE ($P < 0.001$), Alb ($P < 0.001$), Glb ($P = 0.002$), AGR ($P < 0.001$), and AGS ($P < 0.001$) were significantly associated with DFS. Subsequent multivariate analyses revealed that AGS was an independent prognostic factor for NSCLC patients ($P = 0.001$); patients

TABLE 5 Baseline characteristics of 53 patients with NSCLC

Characteristics	No. of patients	Percentage (%)
Gender		
Male	40	75.5
Female	13	24.5
Age (year)		
≤ 60	28	52.8
> 60	25	47.2
Histological subtype		
Squamous carcinoma	24	45.3
Adenocarcinoma	26	49.1
Others (adenosquamous carcinoma, etc.)	3	5.6
Smoking		
Smoker	30	56.6
Never-smoker	23	43.4
Weight-loss		
$\leq 5\%$	51	96.2
$> 5\%$	2	3.8
ECOG-PS		
0	38	71.7
1	15	28.3
Differentiation		
Well	6	11.3
Intermediate	22	41.5
Poor or undifferentiated	25	47.2
T stage		
T1	4	7.5
T2	26	49.1
T3	23	43.4
Lymph node metastasis		
Yes	22	41.5
No	31	58.5
TNM stage (AJCC 7th)		
I	14	26.4
II	26	49.1
III	13	24.5
Neutrophil count (10^9/L)	5.14 ± 3.47	
Lymphocyte count (10^9/L)	1.63 ± 0.43	
Platelet count (10^9/L)	226.45 ± 93.03	
NLR	3.63 ± 3.10	
PLR	149.08 ± 68.04	
NSE (ng/ml)	16.37 ± 7.32	
CEA (ng/ml)	5.85 ± 9.53	
CYGRA21-1 (ng/ml)	10.71 ± 21.84	

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with AGS = 0 had better prognosis than patients with AGS = 1 or AGS = 2 (hazard ration [HR]: 1.523; 95% confidence interval [CI]: 1.178–1.969). In addition, differentiation (HR: 3.379; 95% CI 1.566–5.808; $P < 0.001$) and TNM stage (HR: 2.642; 95% CI

TABLE 6 Prognostic factors for DFS identified by univariate and multivariate analyses

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Gender (male vs. female)	0.554	0.240–1.278	0.166			
Age (year) ($\leq$ 60 vs. > 60)	1.004	0.965–1.044	0.855			
Histological subtype	0.797	0.451–1.409	0.436			
Smoking (ever versus never)	0.898	0.455–1.772	0.756			
Weight-loss ($\leq$ 5 vs. > 5%)	0.642	0.087–4.727	0.664			
ECOG-PS (0 vs. 1)	1.390	0.675–2.862	0.372			
Differentiation (well/intermediate/poor)	0.828	0.498–1.377	0.468			
T stage (T1/T2/T3)	1.363	0.775–2.396	0.282			
Lymph node metastasis (yes vs. no)	2.565	1.655–3.976	< 0.001			
TNM stage (AJCC 7th)			< 0.001			< 0.001
I	1	Reference		1	Reference	
II	1.194	0.463–3.080	0.713	0.916	0.325–2.581	0.869
III	7.882	2.776–22.375	< 0.001	10.204	3.270–31.847	< 0.001
Neutrophil count (10^9/L)	1.107	0.920–1.124	0.743			
Lymphocyte count (10^9/L)	0.743	0.358–1.540	0.424			
Platelet count (10^9/L)	1.004	1.001–1.007	0.006			
NLR ($\leq$ 2.65 vs. > 2.65)	0.997	0.881–1.129	0.964			
PLR ($\leq$ 119.73 vs. > 119.73)	1.006	1.001–1.011	0.016	1.004	0.997–1.011	0.242
CEA (ng/ml) ($\leq$ 3.4 vs. > 3.4)	1.042	1.006–1.080	0.052			
CYGRA21-1 (ng/ml) ($\leq$ 3.3 vs. > 3.3)	1.005	0.992–1.019	0.456			
NSE (ng/ml) ($\leq$ 12.5 vs. > 12.5)	1.062	1.014–1.113	0.011	1.040	0.969–1.118	0.278
Alb (g/L) (< 40 vs. $\geq$ 40)	1.000	0.940–1.064	0.996			
Glb (g/L)	1.093	1.032–1.157	0.002			
AGR ($\leq$ 1.47 vs. > 1.47)	0.118	0.033–0.415	0.001			
AGS	2.236	1.279–3.909	0.005	2.061	1.120–3.795	0.020

TNM tumor-node-metastasis, *AJCC* American Joint Committee on Cancer, *ECOG-PS* Eastern Cooperative Oncology Group performance status, *NSE* neuron-specific enolase, *NLR* neutrophil/lymphocyte ratio, *PLR* platelet/lymphocyte ratio, *AGR* albumin/globulin ratio, *CEA* carcinoembryonic antigen, *CYGRA21-1* cytokeratin 19 fragment

1.631–4.279; P < 0.001) were significant independent predictors of DFS (Table 3).

For OS, multivariate analysis using the 12 clinicopathological characteristics selected by univariate analyses (excluding Alb and Glb) demonstrated that preoperative AGS was significantly associated with OS (HR: 1.513, 95% CI 1.142–2.004, P = 0.004) along with TNM stage (HR: 2.692; 95% CI 1.655–4.379; P < 0.001) and differentiation (HR: 4.692; 95% CI 2.417–9.109; P < 0.001; Table 4).

Kaplan–Meier analysis and log-rank test demonstrated that there were significant differences in DFS and OS among three groups of patients with different AGS (P < 0.001 and P < 0.001, respectively). Patients with higher AGS had better prognosis (Fig. 1). Therefore, the preoperative AGS was able to divide the patients into three independent groups. Furthermore, we performed another Kaplan–Meier analysis to evaluate the prognostic value of AGS in NSCLC patients with different histological subtype. We found that DFS and OS are significantly different in three groups of patients with different AGS in both squamous carcinoma (SqCC) (P < 0.001 for DFS; P < 0.001 for OS) and adenocarcinoma (P = 0.034 for DFS; P = 0.035 for OS). However, these differences are more significant in squamous carcinoma patients (Fig. 2). Therefore, the preoperative AGS was able predict the prognosis for patients with NSCLC, especially for squamous carcinoma (SqCC) or adenocarcinoma.

FURTHER VALIDATION IN AN INDEPENDENT SET OF CASES

The baseline characteristics of the validation group of 53 patients are listed in Table 5. We performed survival analyses to identify the correlation between AGS and

TABLE 7 Prognostic factors for OS identified by univariate and multivariate analyses

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Gender (male vs. female)	0.629	0.267–1.480	0.288			
Age (yr) ($\leq$ 60 vs. > 60)	1.009	0.968–1.052	0.673			
Histological subtype	0.642	0.341–1.205	0.168			
Smoking (ever vs. never)	0.955	0.465–1.961	0.900			
Weight-loss ($\leq$ 5 vs. > 5%)	0.803	0.109–5.943	0.830			
ECOG-PS (0 vs. 1)	1.623	0.771–3.416	0.202			
Differentiation (well/intermediate/poor)	0.711	0.407–1.240	0.229			
T stage (T1/T2/T3)	1.355	0.740–2.481	0.325			
Lymph node metastasis (yes vs. no)	2.457	1.584–3.812	< 0.001			
TNM stage (AJCC.7th)			< 0.001			< 0.001
I	1	Reference		1	Reference	
II	0.941	0.353–2.511	0.903	0.802	0.269–2.389	0.691
III	6.089	2.199–16.863	0.001	9.383	2.965–29.696	< 0.001
Neutrophil count (10^9/L)	1.022	0.923–1.131	0.679			
Lymphocyte count (10^9/L)	0.702	0.324–1.521	0.370			
Platelet count (10^9/L)	1.004	1.001–1.007	0.010			
NLR ($\leq$ 2.65 vs. > 2.65)	1.007	0.887–1.143	0.914			
PLR ($\leq$ 119.73 vs. > 119.73)	1.006	1.001–1.011	0.016	1.004	0.997–1.011	0.261
CEA (ng/ml) ($\leq$ 3.4 vs. > 3.4)	1.032	0.992–1.074	0.121			
CYGRA21-1 (ng/ml) ($\leq$ 3.3 vs. > 3.3)	1.002	0.985–1.019	0.815			
NSE (ng/ml) ($\leq$ 12.5 vs. > 12.5)	1.069	1.021–1.120	0.005	1.044	0.969–1.124	0.259
Alb (g/L) (< 40 vs. $\geq$ 40)	1.022	0.955–1.094	0.529			
Glb (g/L)	1.091	1.027–1.159	0.005			
AGR ($\leq$ 1.47 vs. > 1.47)	0.158	0.042–0.597	0.007			
AGS	2.134	1.192–3.821	0.011	2.143	1.137–4.040	0.018

TNM tumor-node-metastasis, *AJCC* American Joint Committee on Cancer, *ECOG-PS* Eastern Cooperative Oncology Group performance status, *NSE* neuron-specific enolase, *NLR* neutrophil/lymphocyte ratio, *PLR* platelet/lymphocyte ratio, *AGR* albumin/globulin ratio, *CEA* carcinoembryonic antigen, *CYGRA21-1* cytokeratin 19 fragment

patient prognosis. Multivariate analyses verified that AGS was an independent prognostic factor for NSCLC patients (*P* = 0.020 for DFS; *P* = 0.018 for OS; Tables 6 and 7).

Kaplan–Meier analysis and log-rank test also validated that there were significant differences in DFS and OS among the three AGS groups (*P* = 0.003 and *P* = 0.019, respectively; Fig. 3).

DISCUSSION

It is now widely accepted that systemic inflammation is associated with the poor prognosis in cancer patients. In previous studies, some indicators, such as NLR, PLR, CRP/Alb ratio, and AGR, showed their prognostic value for several tumors.[9–13] NLR and PLR are useful prognostic markers for patients with NSCLC. The CRP/Alb ratio is an inflammation-based independent prognostic factor for patients with esophageal squamous cell carcinoma, SCLC, and hepatocellular carcinoma.[24–26] AGR predicts the

outcome of patients with upper tract urothelial carcinoma, esophageal squamous cell carcinoma, or metastatic colorectal cancer.[22,23,27] Based on this, a recent study calculated a novel index, AGS, to predict the outcome of patients with esophageal squamous cell carcinoma. They compared the prognostic value of preoperative AGR and AGS in a cohort study of 458 ESCC patients from a statistical point of view and concluded that AGS outperformed AGR as a prognostic factor in ESCC.[23] To the best of our knowledge, this is the first study to demonstrate the prognostic significance of preoperative AGS in patients with NSCLC.

Alb, produced by the liver, is a major protein in blood. It is one of the most commonly used markers for assessing patients' nutritional status.[28] In patients with various cancers, low baseline serum Alb predicted shorter survival. When patients are well nourished and their hepatocytes are generating Alb normally, they are more resistant to disease and tumor growth.[16,29,30] Thus, Alb levels reflect the ability
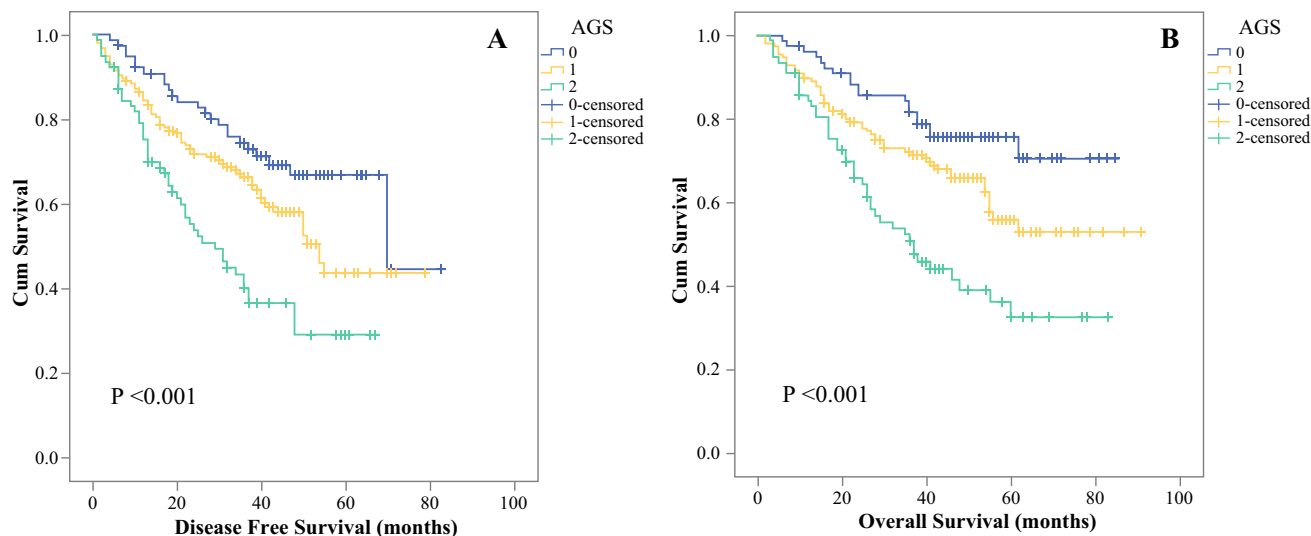
FIG. 3 Kaplan–Meier curves showing the differences in DFS and OS of 53 NSCLC patients. **a** Kaplan–Meier curve of DFS for NSCLC. **b** Kaplan–Meier curve of OS for NSCLC

of the host to fight the tumor to a certain degree. On the other hand, the production of Alb by hepatocytes is suppressed by the activation of proinflammatory cytokines, such as interleukin-1, interleukin-6, and tumor necrosis factor-α. These proinflammatory cytokines can promote tumor development.[17,30] Furthermore, albumin acts as a free-radical scavenger, stabilizes cell growth and replication of DNA, and maintains the homeostasis of sex hormones in the body; thereby, it inhibits the development of hormone-related cancer.[17,31–33] Therefore, albumin can be regarded as a both nutritional and inflammation-related factor.

Glb (total protein-Alb) includes various acute-phase proteins, such as C-reactive protein (CRP), serum amyloid A, complement components, fibrinogen, ceruloplasmin, and immunoglobulins.[18,34] A higher level of CRP predicts poor survival in patients with several cancers.[35,36] Increased complement 3 and IgA predict poorer prognosis in patients with colorectal cancer.[19,20] When these proteins are produced in inflammatory conditions, the level of the globulin increases to reflect systemic inflammation in cancer patients.

Derived from Alb and Glb, AGS could expand the predictive value for prognosis of patients with cancer, comprehensively evaluating both the nutritional condition and systemic inflammation of the host. This was reflected in its prominent value in prognosis of NSCLC patients. By investigating correlations between the AGS and the clinicopathological characteristics of patients, we found that AGS was significantly associated with TNM stage, gender, histological subtype, differentiation, adjuvant chemoradiation, NLR, and PLR. The Kaplan–Meier analysis and log-rank test demonstrated that there were significant differences in DFS and OS among three groups of patients with different AGS. Moreover, our study also showed that AGS remained an independent marker in SqCC or adenocarcinoma. Besides, multivariate Cox analyses indicated that the AGS was an independent prognostic indicator for NSCLC. Furthermore, a validation group for the validation of AGS's prognostic value proved that there were significant differences in DFS and OS among the three AGS groups.

CONCLUSIONS

Preoperative AGS is an independent prognostic factor for patients with operable NSCLC and is able to divide these patients into three independent groups before surgery. Also, higher-risk patients based on the preoperative AGS indicate a poorer prognosis.

This study was limited by the inclusion of a single center, a relatively small number of patients, and its retrospective design. In addition, the biological mechanisms underlying the prognostic roles are yet to be elucidated. Therefore, our results require confirmation by a multicenter, prospective study with a large number of patients and basic research in cell and animal models to provide a better conclusion and integrate with other noninvasive testing of biomarkers into more comprehensive clinical practice.[37,38]

ETHICAL APPROVAL All clinical studies were conducted in accordance with the protocol approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University.

DISCLOSURE The authors declare no conflict of interest.

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