

# Prognostic significance of pretreatment albumin/globulin ratio in patients with hepatocellular carcinoma

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**Background:** Pretreatment nutritional and immunological statuses play an indispensable role in predicting the outcome of patients with various types of malignancies. The purpose of this study is to evaluate the predictive value of albumin/globulin ratio (AGR) in overall survival (OS) and recurrence in patients with hepatocellular carcinoma (HCC) following radical hepatic resection.

**Patients and methods:** This retrospective study included a total of 172 patients with HCC with complete medical and follow-up information between 2002 and 2012. AGR was calculated according to the following formula:  $AGR = \text{albumin} / \text{globulin}$ . Receiver operating characteristic curve analysis was performed to determine the optimal cutoff value. The associations of AGR with clinicopathological characteristics and prognosis were assessed. Further multivariate analysis using Cox regression model and subgroup analysis was performed to evaluate the predictive value.

**Results:** Receiver operating characteristic curve determined 37.65, 31.99, and 1.48 as the optimal cutoff values of albumin, globulin, and AGR in terms of 5-year OS or death, respectively. On the basis of the cutoff value of AGR, all the patients were divided, respectively, into low-AGR ( $n=105$ ) and high-AGR ( $n=67$ ) groups. AGR was found to be significantly correlated with age, cancer embolus, international normalized ratio, and postoperative outcome ( $P<0.05$ ). Hepatitis B virus infection (hazard ratio [HR]: 2.125; 95% confidence interval [CI]: 1.285–3.153), tumor node metastasis stage (HR: 1.656; 95% CI: 1.234–2.223), serum albumin (HR: 0.546; 95% CI: 0.347–0.857), and AGR (HR: 0.402; 95% CI: 0.233–0.691) were independent predictors of OS via univariate and multivariate survival analyses. However, alpha-fetoprotein (HR: 1.708; 95% CI: 1.027–2.838), tumor node metastasis stage (HR: 1.464; 95% CI: 1.078–1.989), and AGR (HR: 0.493; 95% CI: 0.293–0.828) functioned as independent risk variables for predicting recurrence. Moreover, AGR showed superior prognostic value for OS and recurrence in the subgroups with normal level of albumin or survival time beyond 6 months.

**Conclusion:** Pretreatment AGR might serve as an effective biomarker to evaluate the prognosis of patients with a diagnosis of HCC. Based on the results, AGR, characterized with easy accessibility, objectivity, and noninvasiveness, should be included in the routine assessment of HCC.

**Keywords:** hepatocellular carcinoma, albumin/globulin ratio, prognosis, survival, recurrence

## Introduction

Hepatocellular carcinoma (HCC) is one of the most prevalent malignancies, with increasing incidence and mortality worldwide.<sup>1,2</sup> Curative resection, which might significantly ameliorate the prognosis of patients with HCC, is a potentially effective

treatment strategy. However, the majority of persons have lost the chance of accepting curative surgery due to the clinical characteristics of HCC, including easy local invasion, lymph node, vascular, distant metastasis, and no symptom in the early days.<sup>2-4</sup> Despite improved diagnostic and treatment strategy, the prognosis of patients with HCC suffering from hepatic carcinectomy remains poor, which indicated that those patients had not benefited from the operation.<sup>5</sup> Hence, there is a need to further delineate prognostic determinants of predicting the risk of mortality and recurrence in order to better stratify those patients likely to benefit from surgical treatment and to assist with clinical decision-making in case of unnecessary toxicity and morbidity.

Of note, mounting evidence suggests that the presence of the systemic inflammatory response, reflected in routine hematology, has a decidedly protumor capacity leading to poor prognosis in a host of malignant neoplasms.<sup>6-9</sup> Albumin and globulin, the major constituents of serum proteins, have a vital effect on the systemic inflammatory response. Previous examinations had demonstrated that low serum albumin, a marker of nutrition state and chronic inflammation, is an independent predictor of mortality and recurrence rate in several types of malignancies.<sup>10</sup> Furthermore, globulin is of significant importance not only for host immunity and inflammation but also as a reaction for cumulative exposure of different cytokines. Studies even deemed that globulin might be an independent risk factor for predicting long-term mortality in colorectal or gastric cancer.<sup>11,12</sup> Pretreatment nutritional and immunological statuses play an equally indispensable role in predicting the outcome of patients with various types of malignancies. However, few reports have looked into the effect of albumin/globulin ratio (AGR) on patients with HCC suffering from hepatic carcinectomy. Hence, we conducted a retrospective analysis to investigate the relationship between preoperative AGR and clinicopathological features as well as outcome in patients with HCC.

## Patients and methods

### Study population

A cohort of 172 patients with a diagnosis of HCC presented to the First Affiliated Hospital of the Xi'an Jiaotong University College of Medicine between 2002 and 2012 were included in this retrospective study. All the patients underwent primary radical hepatic carcinectomy, and tissue specimens were pathologically proven to be HCC. Complete medical and follow-up information was obtained from records or telephone interviews. Patients with the following conditions were excluded: 1) multiple cancers; 2) incomplete laboratory test information such as serum albumin

or globulin; 3) concomitant diseases that affect the level of serum albumin or globulin such as lymphoblastic leukemia and autoimmune disease; and 4) rehepatectomy. Our study was approved by the ethical committee of the First Affiliated Hospital of the Xi'an Jiaotong University College of Medicine. Written informed patient consent was obtained. Patient records/information were anonymized and deidentified prior to analysis.

### Data collection

Clinicopathological variables, including demographic data (age, sex, smoking, and drinking), blood picture, hepatitis B, hepatitis C, serum albumin, globulins, alpha-fetoprotein (AFP), Child–Turcotte–Pugh (CTP) class, tumor node metastasis (TNM) stage, and pathological reports, were collected. Clinical, radiological criteria (computed tomography scan), and histological evidence were used to diagnose the presence of liver cirrhosis in all patients. Preoperative data were obtained before surgery, and the blood samples were collected from the first day of patients' admission. The earliest set of measurements was used if there were more than one set for a same patient. AGR was calculated using the equation:  $AGR = \text{albumin} / \text{total protein} - \text{albumin}$ . The TNM staging system for HCC is based on the American Joint Committee on Cancer (seventh edition).<sup>13</sup>

### Follow-up

All the patients received follow-up routinely until November 2013. Overall survival (OS) was computed from the time of surgery to our unit. The time to recurrence was defined as the interval between surgery and recurrence or the last observation without recurrence. All the cohort patients were followed up every 3 months for the first year, every 4 months for the second year, and every 6 months thereafter. The content embraces AFP, ultrasonic, and abdominal computed tomography. When postoperative serum AFP value of patients is  $>20$  ng/mL or ultrasonic/abdominal computed tomography finds new focus, we harbored the idea that they had suffered from tumor recurrence in the work. During the follow-up period, the relevant information, including death and recurrence time, AFP, and imaging result, was recorded in detail. For the sake of reducing the bias to maximum extent, there were two clinicians to complete the follow-up and review, respectively.

### Statistical analysis

For continuous variables, the data were expressed as the mean value  $\pm$  standard deviation or median (minimum–maximum) based on whether they meet the distributed Kolmogorov–Smirnov test, ( $P < 0.05$ ) or not. Categorical

data were presented as frequency. Hence, the significance of difference between two groups was determined using the Student's *t*-test or Wilcoxon test for continuous variables and the Chi-squared test for categorical datum. The receiver operating characteristic (ROC) curve with 5-year OS was used to determine the ideal cutoff point, which allows the prediction for 5-year OS with the best sensitivity and specificity. Based on the cutoff point, patients were divided into two groups, namely the high-AGR group and the low-AGR group.

Survival curves for patients were estimated using the Kaplan–Meier method, and the difference among the curves was analyzed using the log-rank test. Factors showing significant prognostic value in the univariate analysis were further analyzed in the final multivariate Cox proportional hazards model. All statistical analyses were performed using PASW Statistics 22.0 software (IBM Corporation, Armonk, NY, USA). Finally, subgroup analysis was used to exclude confounding factors. Two-sided *P*-values of <0.05 were considered statistically significant.

## Results

### Patient characteristics

The baseline clinicopathological characteristics of 172 patients with a diagnosis of HCC, including 139 males and 33 females

(80.81% vs 19.19%), are summarized in Table 1. The median age of the patients was 53 years (range 24–80). The liver function of most patients was compensatory (Child A, 92.44%). Moreover, the majority of patients suffered from hepatitis B virus (HBV) infection (121/172, 70.35%), and they were classified, respectively, as TNM I (92/172, 53.49%), TNM II (42/172, 24.42%), or TNM III (38/172, 22.09%) according to TNM staging system. No TNM IV patients were included in the study because those patients had lost the chance of receiving operation based on Milan criteria. A minority of patients had a history of drinking, smoking, and hepatitis C virus infection and had been diagnosed with cirrhosis (34.30%). In addition, postoperative pathology confirmed that 15 patients with cancer embolus were included.

Among the 172 selected patients who were examined during the follow-up period, 81 patients (47.29%) died and 75 patients (43.60%) were diagnosed with tumor recurrence. Median time of OS and recurrence was 31 months (range 1–120) and 20 months (range 1–117), respectively.

### ROC curve analysis

ROC curve analysis was performed to determine the optimal cutoff values of AGR and albumin in terms of 5-year OS and

**Table 1** Associations between clinicopathological features and AGR

Parameters	Overall (n=172)	High-AGR group (AGR ≥ 1.48) (n=67)	Low-AGR group (AGR < 1.48) (n=105)	P-value
Age (years)	53 (24–80)	52 (24–80)	54 (28–75)	<b>0.002<sup>a</sup></b>
Sex (male/female)	139/33	58/9	81/24	0.126 <sup>b</sup>
Smoking (yes/no)	68/104	28/39	40/65	0.629 <sup>b</sup>
Drinking (yes/no)	40/132	16/51	24/81	0.877 <sup>b</sup>
AFP (ng/mL)	95.67 (1.31–69,677.00)	43.39 (1.31–69,677.00)	240.90 (1.87–65,898.00)	0.890 <sup>a</sup>
INR	1.06 (0.73–1.63)	1.03 (0.76–1.63)	1.09 (0.73–1.62)	0.002 <sup>a</sup>
Platelet (<100/≥100) (10 <sup>9</sup> /L)	58/114	22/45	36/69	0.845 <sup>b</sup>
CTP Class (A/B)	159/13	65/2	94/11	0.070 <sup>b</sup>
HBV infection (yes/no)	121/51	50/17	71/34	0.326 <sup>b</sup>
HCV infection (yes/no)	8/164	1/66	7/98	0.138 <sup>b</sup>
Cancer embolus (yes/no)	15/157	1/66	14/91	<b>0.007<sup>b</sup></b>
Tumor number (1/>1)	140/32	57/10	83/22	0.322 <sup>b</sup>
Tumor size (<5/≥5) (cm)	58/114	28/39	30/75	0.074 <sup>b</sup>
Vascular invasion (yes/no)	12/160	2/65	10/95	0.101 <sup>b</sup>
TNM I/II/III	92/42/38	42/16/9	50/26/29	0.065 <sup>b</sup>
BCLC stage A1+A2/A3+A4/B/C+D	58/15/79/20	27/9/25/6	31/6/54/14	0.084 <sup>b</sup>
Liver cirrhosis (yes/no)	59/113	18/49	41/64	0.101 <sup>b</sup>
Serum albumin (g/L)	38.21±0.41	42.27±4.98	37.07±4.97	<b>&lt;0.001<sup>c</sup></b>
Globulin	29.55 (15.56–50.20)	24.80 (15.56–32.00)	32.30 (21.30–50.20)	<b>&lt;0.001<sup>a</sup></b>
Lymphocytes (10 <sup>9</sup> /L)	1.36 (0.27–4.73)	1.34 (0.27–3.21)	1.32 (0.30–4.73)	0.713 <sup>a</sup>
Survival time (minutes)	31 (1–120)	39 (2–120)	25 (1–117)	<b>&lt;0.001<sup>a</sup></b>
Death (yes/no)	81/91	18/49	63/42	<b>&lt;0.001<sup>b</sup></b>
Recurrence time (minutes)	20 (1–117)	38 (2–115)	13 (1–117)	<b>&lt;0.001<sup>a</sup></b>
Relapse (yes/no)	75/97	21/46	54/51	<b>0.010<sup>b</sup></b>

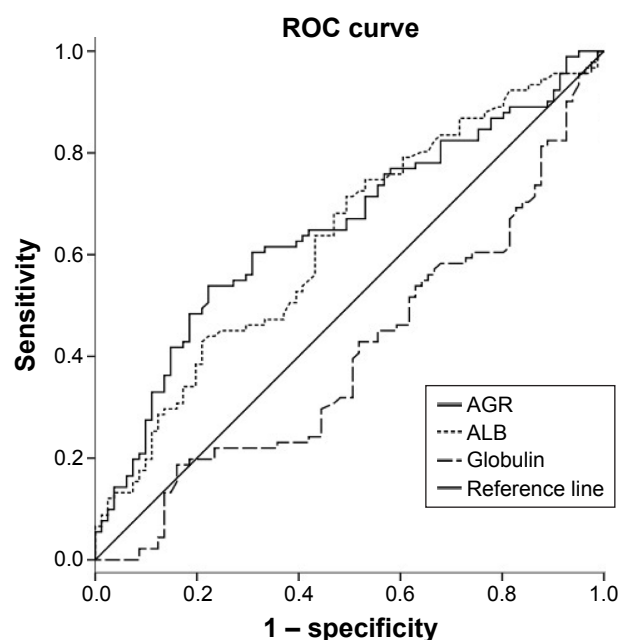
**Notes:** <sup>a</sup>Wilcoxon test; <sup>b</sup> $\chi^2$  test; and <sup>c</sup>Student's *t*-test. The values are expressed as the median (range), mean ± standard deviation, or number. Bold font represents *P*<0.05 and the relevant variables are statistically significant.

**Abbreviations:** AGR, albumin/globulin ratio; AFP, alpha-fetoprotein; INR, International Normalized Ratio; HBV, hepatitis B virus; HCV, hepatitis C virus; TNM, tumor node metastasis; BCLC, Barcelona clinical liver cancer; CTP, Child-Turcotte-Pugh.

globulin with 5-year death. When the Youden index was the maximum, the optimal cutoff point was obtained. As shown in Figure 1, the optimal cutoff values of albumin, globulin, and AGR were 37.65 (sensitivity of 71.4% and specificity of 49.4%, area under the curve (AUC) =0.627, 95% CI 0.570–0.735,  $P=0.004$ ), 31.98 (sensitivity of 44.4% and specificity of 75.8%, AUC =0.596, 95% CI: 0.511–0.681,  $P=0.030$ ), and 1.48 (sensitivity of 53.8% and specificity of 77.8%, AUC =0.652, 95% CI 0.544–0.711,  $P<0.001$ ), respectively. On the basis of the cutoff value of AGR, the whole cohort was divided into high-AGR group ( $n=67$ ) and low-AGR group ( $n=105$ ).

## Associations between AGR and clinicopathological features

The associations between AGR and various clinicopathological factors are shown in Table 1. Interestingly, compared with patients in the high-AGR group, participants in the low-AGR group were significantly associated with cancer embolus and high international normalized ratio. Additionally, it was not arduous to find that elderly patients were prone to appear in the low-AGR group. No significant distribution difference was found in sex, smoking, drinking, HBV and hepatitis C virus infections, CTP classification, low platelet, TNM stage, Barcelona clinical liver cancer (BCLC) stage, and level of AFP as well as the presence of liver cirrhosis between two groups.



**Figure 1** ROC analysis for optimal cutoff values of ALB, GLB, and AGR.

**Note:** The optimal cutoff values of ALB, GLB, and AGR were 37.65, 31.99, and 1.48, respectively.

**Abbreviations:** ROC, receiver operating characteristic; ALB, albumin; GLB, globulin; AGR, albumin/globulin ratio.

## Predictors of OS and recurrence

At the end of follow-up, 81 (47.09%) patients died and 75 (43.60%) patients experienced tumor recurrence, including local recurrence and distant metastasis. In the cohort, the 1-, 2-, and 5-year OS rates of postoperative patients were 76.7%, 64.9%, and 48.4%, respectively. The relationship between AGR and outcome is presented in Table 2. Low AGR value was associated with reduced OS and high recurrence rates. The 1-, 2-, and 5-year OS rates were 89.6%, 81.9%, and 71.9% in the high-AGR group and 68.6%, 54.1%, and 46.0% in the low-AGR group, respectively. Besides, patients in the high-AGR group had lower 1-year (15.5% vs 39.4%), 2-year (29.9% vs 55.2%), and 5-year (60.6% vs 65.6%) recurrence rates compared with those in the low-AGR group.

Using univariate analysis, AGR ( $P<0.001$ ), AFP  $\geq 400$  ng/mL ( $P=0.049$ ), albumin ( $P=0.002$ ), globulin ( $P=0.020$ ), HBV infection ( $P=0.048$ ), presence of cancer embolus ( $P=0.023$ ), and TNM stage ( $P<0.001$ ) were found to be significant predictors of cancer-specific OS. Kaplan–Meier survival analysis revealed that patients in the low-AGR group had worse OS than those in the high-AGR group (Figure 2A). Furthermore, multivariate analysis identified TNM stage (hazard ratio [HR]: 1.656; 95% CI: 1.234–2.223;  $P=0.001$ ), HBV infection (HR: 2.125; 95% CI: 1.285–3.513;  $P=0.003$ ), serum albumin (HR: 0.546; 95% CI: 0.347–0.857;  $P=0.009$ ), and AGR (HR: 0.402; 95% CI: 0.233–0.691;  $P=0.001$ ) as independent risk predictors of postoperative OS (Table 3).

In our study, higher risk of recurrence via individual Cox regression was noted in patients with albumin ( $P=0.033$ ), globulin ( $P=0.020$ ), AFP ( $P=0.005$ ), presence of cancer embolus ( $P=0.024$ ), and TNM stage ( $P=0.001$ ) as well as AGR ( $P=0.001$ ). As shown in Figure 2B, a lower AGR value was associated with shorter time to recurrence ( $P=0.001$ ). We further screened out independent risk variables including AFP (HR: 1.708; 95% CI: 1.027–2.838;  $P=0.039$ ), TNM stage (HR: 1.464; 95% CI: 1.078–1.989;  $P=0.0015$ ), and AGR (HR: 0.493; 95% CI: 0.293–0.828;  $P=0.008$ ) in Cox proportional hazard multivariate models (Table 4).

## Additional analyses

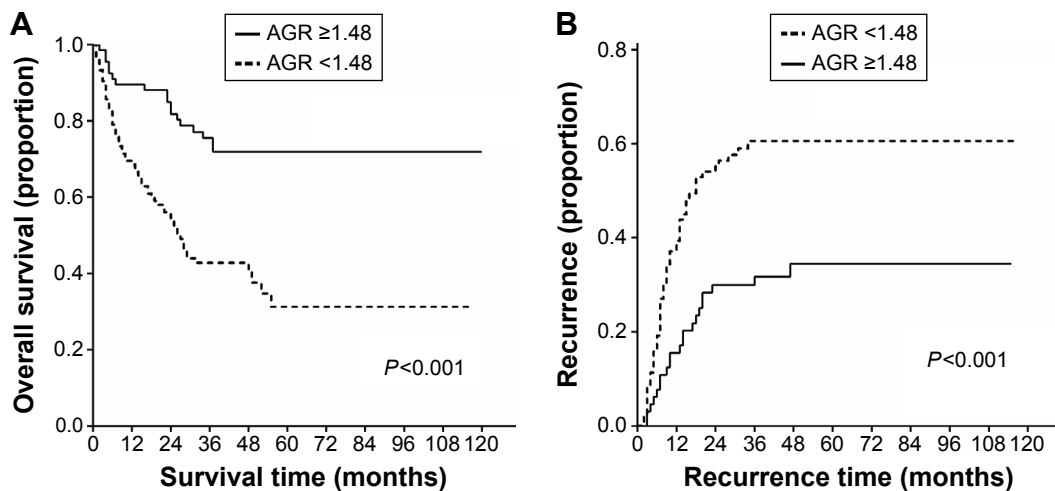
The TNM stage was considered to be a potent predictor of OS and recurrence for HCC, which was confirmed by our study (Figure 3A and B). All the patients were stratified according to the TNM staging system. Kaplan–Meier curves of patients with different TNM stages in terms of OS and recurrence are shown in Figure 4A–F. The difference was unfolded between two groups in Kaplan–Meier plots. In addition, a statistically significant difference in OS was confirmed

**Table 2** The overall survival and recurrence rate of patients between high and low groups based on cutoff point of albumin, globulin, and AGR, respectively

Rate	Time	Total (n=172)	Albumin			Globulin			AGR		
			Low group (n=66)	High group (n=106)	P-value	Low group (n=56)	High group (n=116)	P-value	Low group (n=105)	High group (n=67)	P-value
Overall survival (%)	1 year	76.7	70.1	81.0	0.084	79.3	71.4	0.326	68.6	89.6	<b>0.001</b>
	2 years	64.9	54.8	71.3	<b>0.022</b>	69.5	55.4	0.070	54.1	81.9	<b>&lt;0.001</b>
	5 years	48.4	32.4	63.0	<b>&lt;0.001</b>	61.1	31.3	<b>&lt;0.001</b>	46.0	71.9	<b>0.001</b>
Recurrence (%)	1 year	29.5	34.2	26.6	0.239	23.7	41.5	<b>0.020</b>	39.4	15.5	<b>&lt;0.001</b>
	2 years	44.7	55.9	38.1	<b>0.026</b>	39.4	55.6	0.051	55.2	29.9	0.457
	5 years	49.9	60.3	43.8	<b>0.028</b>	43.7	62.4	<b>0.017</b>	65.6	60.6	0.532

**Notes:** The P-values were calculated by Chi-squared test. Bold font represents  $P < 0.05$  and the relevant variables are statistically significant.

**Abbreviation:** AGR, albumin/globulin ratio.

**Figure 2** Kaplan-Meier curves for (A) OS and (B) recurrence between high-AGR ( $AGR \geq 1.48$ ) and low-AGR ( $AGR < 1.48$ ).

**Note:** The P-values were calculated by log-rank test.

**Abbreviations:** OS, overall survival; AGR, albumin/globulin ratio.

**Table 3** Univariate and multivariate analysis of factors associated with HCC overall survival

Parameters	Univariate analysis		Multivariate analysis	
	P-value	HR (95% CI)	P-value	HR (95% CI)
Age $>60$ years	0.053	1.556 (0.993–2.437)		
Sex (male/female)	0.849	1.055 (0.610–1.824)		
Smoking (yes/no)	0.376	0.812 (0.511–1.289)		
Drinking (yes/no)	0.054	0.547 (0.296–1.010)		
AFP $\geq 400$ ng/mL	<b>0.049</b>	1.600 (1.003–2.552)	0.087	1.534 (0.940–2.503)
Platelet $<100$ ( $10^9/L$ )	0.367	0.804 (0.501–1.290)		
CTP Class (A/B)	0.191	1.681 (0.772–3.660)		
HBV infection (yes/no)	<b>0.048</b>	1.583 (1.003–2.498)	<b>0.003</b>	2.125 (1.285–3.513)
HCV infection (yes/no)	0.728	0.815 (0.257–2.583)		
Cancer embolus (yes/no)	<b>0.023</b>	2.100 (1.110–3.971)	0.733	1.134 (0.550–2.340)
Tumor size ( $<5/\geq 5$ ) (cm)	<b>&lt;0.001</b>	5.114 (2.633–9.931)		
Tumor number ( $1/>1$ )	0.151	1.448 (0.874–2.401)		
TNM stage (per increase 1 stage)	<b>&lt;0.001</b>	1.658 (1.281–2.416)	<b>0.001</b>	1.656 (1.234–2.223)
BCLC stage (per increase 1 stage)	<b>&lt;0.001</b>	1.744 (1.343–2.344)		
Liver cirrhosis (yes/no)	0.490	0.847 (0.528–1.357)		
AGR (high/low)	<b>&lt;0.001</b>	0.323 (0.191–0.547)	<b>0.001<sup>a</sup></b>	0.402 (0.233–0.691)
Albumin $\geq 37.65$ g/L	<b>0.002</b>	0.500 (0.323–0.775)	<b>0.009<sup>a</sup></b>	0.546 (0.347–0.857)
Globulin $>32$ g/L	<b>0.020</b>	1.688 (1.085–2.628)	0.105 <sup>a</sup>	1.450 (0.925–2.272)

**Notes:** <sup>a</sup>Adjusting covariates including AFP, HBV infection, cancer embolus, and TNM stages. To avoid collinearity bias BCLC score and tumor, entered into the multivariate model but tested independently. Bold font represents  $P < 0.05$  and the relevant variables are statistically significant.

**Abbreviations:** HCC, hepatocellular carcinoma; HR, hazard ratio; AFP, alpha-fetoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus; TNM, tumor node metastasis; BCLC, Barcelona clinical liver cancer; AGR, albumin/globulin ratio; CI, confidence interval; CTP, Child-Turcotte-Pugh.



**Table 4** Univariate and multivariate analysis of factors associated with HCC recurrence

Parameters	Univariate analysis		Multivariate analysis	
	P-value	HR (95% CI)	P-value	HR (95% CI)
Age >60 years	0.557	1.157 (0.712–1.880)		
Sex (male/female)	0.757	0.917 (0.527–1.593)		
Smoking (yes/no)	0.551	0.866 (0.540–1.389)		
Drinking (yes/no)	0.610	0.866 (0.498–1.505)		
AFP $\geq 400$ ng/mL	<b>0.005</b>	2.057 (1.250–3.386)	<b>0.039</b>	1.708 (1.027–2.838)
Platelet <100 (10 <sup>9</sup> /L)	0.148	0.689 (0.416–1.141)		
CTP Class (A/B)	0.086	1.981 (0.908–4.322)		
HBV infection (yes/no)	0.134	1.444 (0.893–2.334)		
HCV infection (yes/no)	0.428	0.567 (0.139–2.311)		
Cancer embolus (yes/no)	<b>0.024</b>	2.237 (1.113–4.495)	0.857	1.074 (0.495–2.332)
Tumor size (<5/ $\geq 5$ ) (cm)	<b>&lt;0.001</b>	4.951 (2.604–9.415)		
Tumor number (1/ $>1$ )	0.133	1.501 (0.883–2.551)		
TNM stages (per increase 1 stage)	<b>0.001</b>	1.575 (1.199–2.068)	<b>0.015</b>	1.464 (1.078–1.989)
BCLC stage (per increase 1 stage)	<b>&lt;0.001</b>	1.761 (1.321–2.347)		
Liver cirrhosis (yes/no)	0.285	0.765 (0.468–1.251)		
AGR (high/low)	<b>0.001</b>	0.418 (0.252–0.694)	<b>0.008<sup>a</sup></b>	0.493 (0.293–0.828)
Albumin $\geq 37.65$ g/L	<b>0.033</b>	0.609 (0.386–0.960)	0.105 <sup>a</sup>	0.678 (0.425–1.084)
Globulin >32 g/L	<b>0.020</b>	1.729 (1.091–2.741)	0.066 <sup>a</sup>	1.545 (0.971–2.458)

**Notes:** <sup>a</sup>Adjusting covariates including AFP, cancer embolus, and TNM stages. To avoid collinearity bias BCLC score and tumor size were not entered into the multivariate model but tested independently. Bold font represents  $P < 0.05$  and the relevant variables are statistically significant.

**Abbreviations:** HCC, hepatocellular carcinoma; HR, hazard ratio; AFP, alpha-fetoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus; TNM, tumor node metastasis; BCLC, Barcelona clinical liver cancer; AGR, albumin/globulin ratio; CI, confidence interval; CTP, Child-Turcotte-Pugh.

at TNM II ( $P=0.043$ ) and TNM III ( $P=0.003$ ). Besides, a low AGR value might significantly increase recurrence probability in patients with TNM III ( $P=0.005$ ).

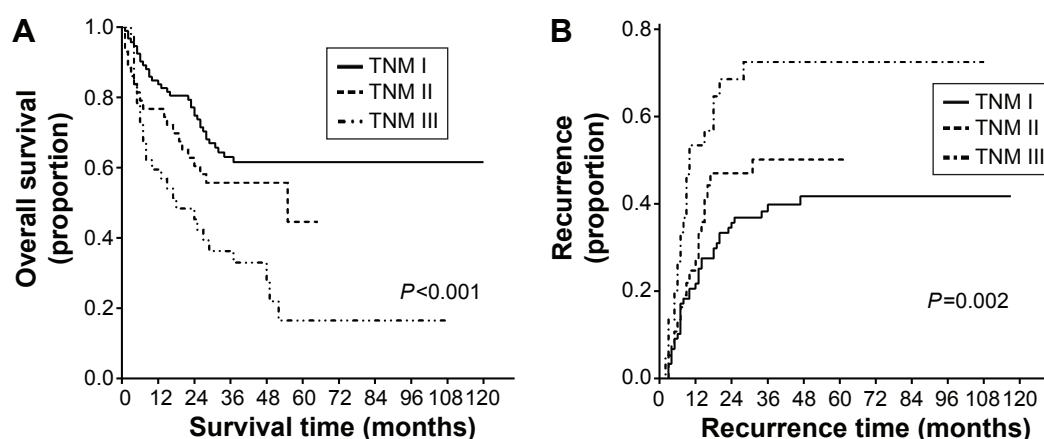
Previous reports suggested that hypoalbuminemia could function as an independent risk factor of predicting prognosis in malignancies. With the purpose of excluding the effect of hypoalbuminemia, Kaplan–Meier survival analysis was done among those patients who had albumin  $>35$  g/L. Whether predicting OS ( $P=0.002$ ) or recurrence ( $P=0.004$ ), AGR remained a significant predictor (Figure 5).

Surgical treatment might largely account for early death or recurrence. Hence, additional analysis was further conducted

among those patients who survived beyond 6 months to determine if the association between AGR and prognosis was merely secondary to the short-term mortality. Interestingly, AGR showed superior ability to predict OS and recurrence compared with albumin or globulin alone (Figure 6).

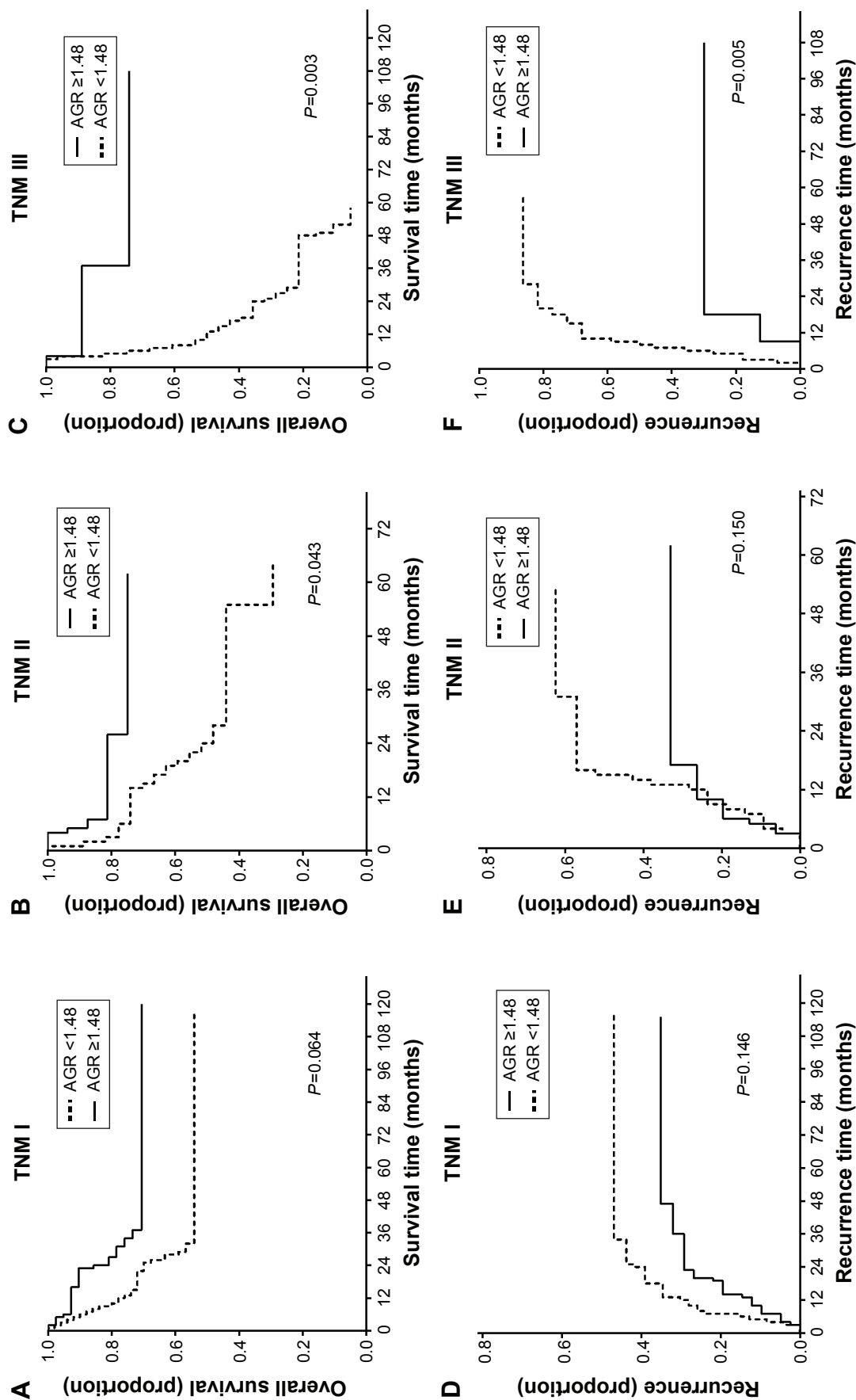
### Stratification of patients according to AGR and tumor size

Low AGR is the significant reflection of liver functional impairment of patients with HCC, while tumor size could well take into account the anatomical characteristics of liver tumor. As shown in Table 5, the combination of AGR and

**Figure 3** Kaplan–Meier curves for (A) OS and (B) recurrence among different TNM stages.

**Note:** The P-values were calculated by log-rank test.

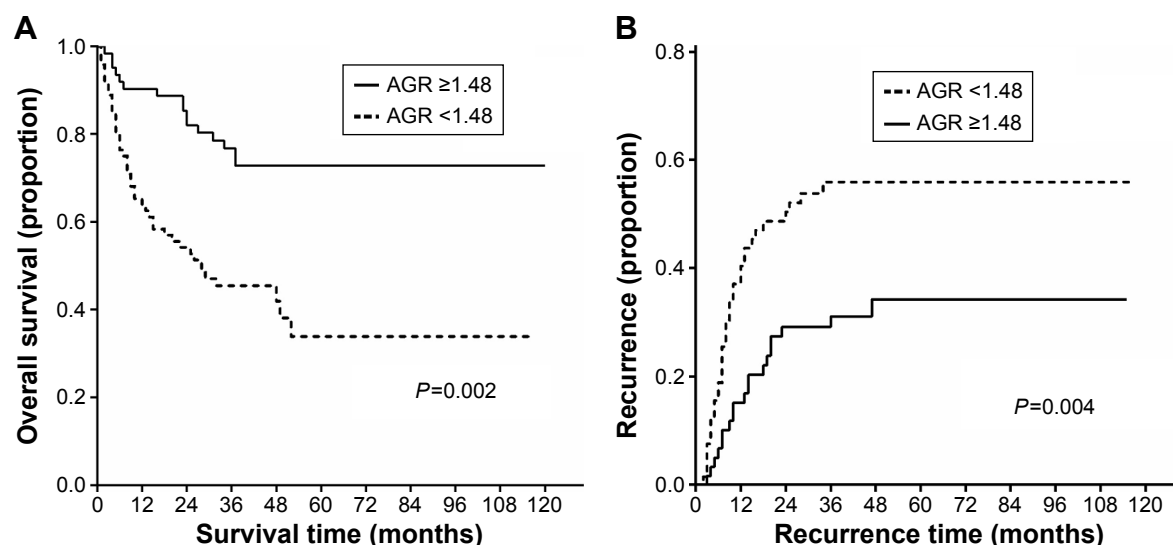
**Abbreviations:** TNM, tumor node metastasis; OS, overall survival.



**Figure 4** Kaplan-Meier curves for OS of patients stratified according to TNM stage including (A) TNM I, (B) TNM II, and (C) TNM III. Kaplan-Meier curves for recurrence of patients stratified according to TNM stage including (D) TNM I, (E) TNM II, and (F) TNM III.

**Note:** The P-values were calculated by log-rank test.

**Abbreviations:** TNM, tumor node metastasis; AGR, albumin/globulin ratio.



**Figure 5** Kaplan-Meier curves for OS (A) and recurrence (B) between high-AGR (AGR  $\geq 1.48$ ) and low-AGR (AGR  $< 1.48$ ) among patients with normal albumin.

**Note:** The P-values were calculated by log-rank test.

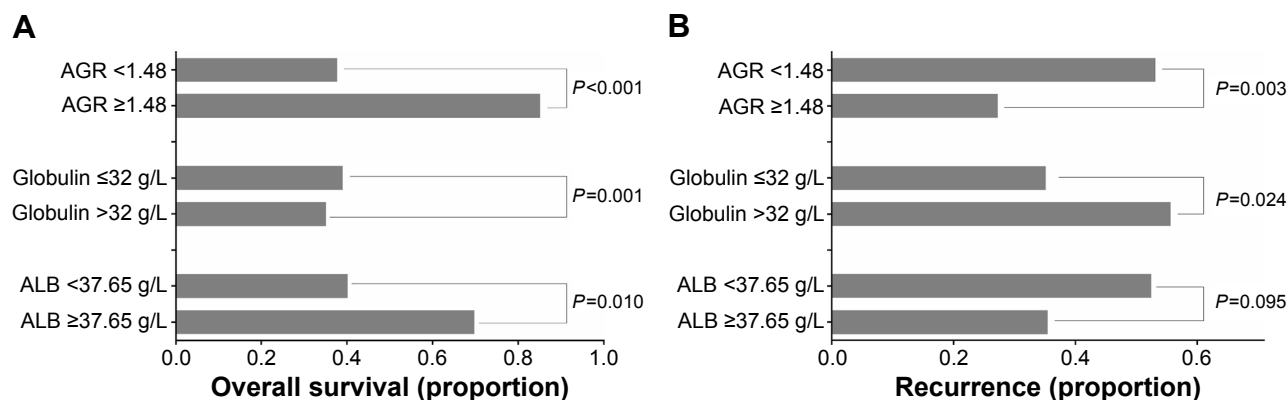
**Abbreviations:** OS, overall survival; AGR, albumin/globulin ratio.

tumor size discovered a higher diagnostic accuracy in predicting postoperative clinical outcome of patients with HCC after surgery than BCLC stage score (concordance index: 0.769, 95% CI: 0.698–0.840 vs 0.712, 95% CI: 0.619–0.805). Therefore, all the patients were divided into three groups, namely Group A (AGR  $\geq 1.48$  and tumor size  $< 5$  cm,  $n=28$ ), Group B (AGR  $\geq 1.48$  but tumor size  $\geq 5$  cm, or tumor size  $< 5$  cm but AGR  $< 1.48$ ,  $n=69$ ), and Group C (AGR  $< 1.48$  and tumor size  $\geq 5$  cm,  $n=75$ ). The patients in Group A had a significantly better clinical outcome compared with patients in Group B or C ( $P<0.001$ ; Figure 7).

## Discussion

A group of patients with HCC suffering from radical hepatic carcinectomy still had high mortality and recurrence rate; consequently, factors associated with reduced OS or increased

recurrence should provide the ability to preselect those patients who would benefit most from more aggressive treatments.<sup>14</sup> Several studies stated that serum AFP, traditional tumor-related factors, and a number of molecular or gene biomarkers might function as independent parameters in predicting outcome. Nevertheless, it was becoming increasingly apparent that those factors had numerous limitations and deficiencies. The first and foremost, preoperative and postoperative levels of serum AFP have a negative detection rate of  $>20\%$ – $80\%$ .<sup>15</sup> In addition, the prognostic value of tumor-related factors such as the TNM staging system is inadequate just in terms of disease progression.<sup>16</sup> Besides, those molecular or gene biomarkers have an obvious heterogeneity in predicting prognosis.<sup>17</sup> The last but not the least, a slice of examinations are invasive or dispensable before operation, thus the clinical and practical value is largely limited. Therefore, the identification of



**Figure 6** Histograms compare the 5-year mortality (A) and recurrence rate (B) between high-AGR and low-AGR groups of ALB, GLB, and AGR based on the optimal cutoff values.

**Note:** The P-values were calculated by log-rank test.

**Abbreviations:** ALB, albumin; GLB, globulin; AGR, albumin/globulin ratio.



**Table 5** Ranking of discriminatory ability of the prognostic systems on the basis of C-index

Rank	Systems	C-index	95% CI
1	AGR + tumor size	0.769	0.698–0.840
2	BCLC	0.712	0.619–0.805
3	AGR	0.658	0.576–0.740

**Note:** C-index reflects the ability to predict survival: the greater the C-index, the more accurate the prognostic prediction.

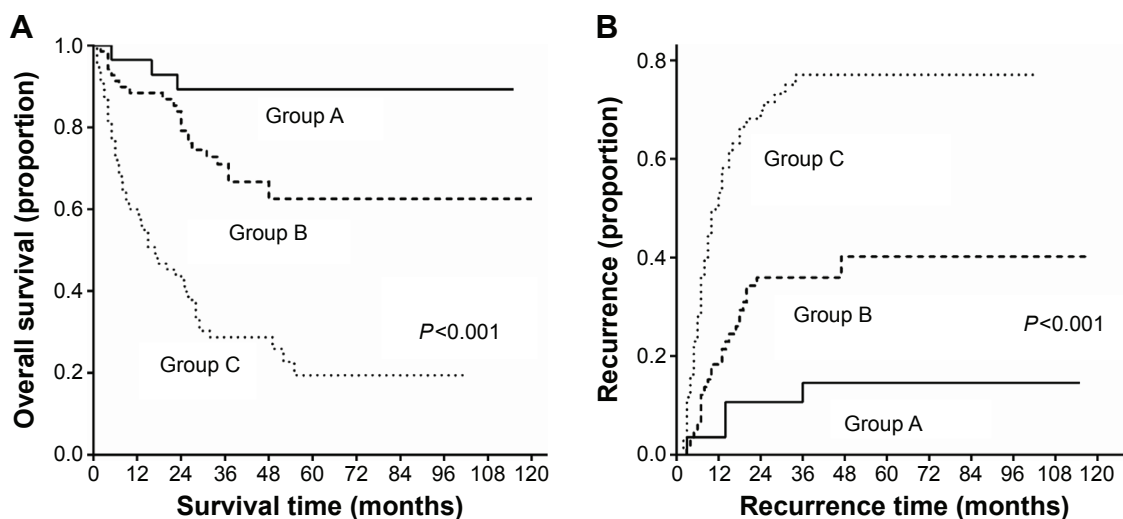
**Abbreviations:** C-index, concordance index; AGR, albumin/globulin ratio; BCLC, Barcelona clinical liver cancer; CI, confidence interval.

a simple, objective, and useful index to predict malignant patients' prognosis is of vital importance.

Nowadays, chronic inflammation is a critical contributor to tumor development, proliferation, and metastasis and is also related to the risk of death and recurrence among malignant patients after surgery.<sup>18</sup> The inflammation-based prognostic score such as Glasgow prognostic score,<sup>19</sup> neutrophil-to-lymphocyte ratio,<sup>20</sup> aspartate aminotransferase-to-platelet ratio,<sup>21</sup> and platelet-to-lymphocyte ratio<sup>22</sup> was proven to be independent prognostic parameters by previous studies. However, there are still some limitations for the use of these prognostic scores in patients with HCC. First, the effects of preoperative platelets level on the clinical outcomes of HCC remain contradictory and controversial. On the one hand, platelets contribute to liver regeneration and preoperative low platelets were associated with a high risk of death in patients with HCC.<sup>23</sup> On the other hand, high level of pretreatment platelets was verified as a significant predictive factor of an elevated risk of extrahepatic metastasis among patients with HCC.<sup>24</sup> Therefore, relevant models, including aminotransferase-to-platelet ratio and platelet-to-lymphocyte

ratio, have some limitations to predict survival in HCC. Second, unlike other cancers, clinical outcome in patients with HCC is prone to be influenced by the underlying liver function along with the extent of spread of primary tumor.<sup>25</sup> In the context of HCC, the neutrophil-to-lymphocyte ratio, just derived from circulating differential white blood cell count, might insufficiently reflect the liver function. Albumin, completely produced by liver, could commendably reveal the liver functions of patients with HCC, and globulin is composed of all kinds of proinflammatory proteins including acute-phase protein (CRP). Hence, we believe that AGR is superior to Glasgow prognostic score, which is calculated based on CRP and serum albumin, as a prognostic biomarker of systemic inflammation.

Serum albumin, produced by liver, maintains osmotic pressure and functions as a carrier to transport various kinds of metabolic substances. Increasing evidence showed that hypoalbuminemia indicated persons' malnutrition, which was associated with poor OS and high recurrence in patients with gastric, colorectal, pancreatic, lung, ovarian, breast, and liver cancer.<sup>8,26,27</sup> Even though the mechanism by which low albumin may impact on OS or recurrence is not completely discovered, there are several reasons to explain it. Albumin is an antioxidant, which has the ability to buffer some biochemical changes, stabilize cell growth and DNA replication, and maintain sex hormone homeostasis.<sup>28</sup> In addition, high level of serum albumin could function as antiproliferative reagent in human cancer cells in vitro.<sup>29,30</sup> Besides, hypoalbuminemia is not only a syndrome of poor nutritional status but also associated with chronic inflammation.<sup>31,32</sup> Low serum albumin could weaken human defense system, thus

**Figure 7** Kaplan–Meier curves for OS (A) and recurrence (B) of the subgroup study stratification of patients according to AGR and tumor size.

**Notes:** Group A (AGR  $\geq 1.48$  and tumor size  $< 5$  cm,  $n=28$ ). Group B (AGR  $\geq 1.48$  but tumor size  $\geq 5$  cm, or tumor size  $< 5$  cm but AGR  $< 1.48$ ,  $n=69$ ), and Group C (AGR  $< 1.48$  and tumor size  $\geq 5$  cm,  $n=75$ ). The P-values were calculated by log-rank test.

**Abbreviations:** OS, overall survival; AGR, albumin/globulin ratio.

increasing susceptibility to infect and resulting in cytokine-induced suppression, which affect long-term OS and recurrence.<sup>33,34</sup> Prognostic value of albumin was also proven among those HCC patients following the surgical treatment in current investigation.

Globulin (total protein – albumin) consists of all kinds of proinflammatory proteins. High level of globulin indicated a systematic inflammatory response.<sup>14</sup> With the development of tumor biology, growing evidence suggested that a systematic inflammatory response played an indispensable role in proliferation, progression, development, and metastasis of tumor cells by altering its biological features and destroying host immune function.<sup>35</sup> Convincing evidence supported the concept that inflammatory pathways can be redirected into a tumor-promoting path by the peritumoral stroma through the activation of innate immunity in HCC.<sup>36–38</sup> In addition, patients with malignancy might largely benefit from taking regular nonsteroidal anti-inflammatory drugs such as aspirin.<sup>39,40</sup> Additionally, HBV infection is closely related to HCC occurring in the East and mediate the consistent expression of HBV immunogenic proteins, resulting in a potent systematic inflammatory.<sup>2</sup> Similar to previous results in our study, we observed that the patients with HBV infection had significantly worse OS compared with counterparts with no HBV infection. Finally, chronic oxidative stress and oxygen-free radicals from a systematic inflammatory response had been manifested to stimulate tumor initiation, promotion, and progression.<sup>41</sup>

Systematic inflammatory responses could inhibit synthetic function of liver leading to hypoalbuminemia.<sup>3,10</sup> When it comes to malignancy, malnutrition and systematic inflammatory are inseparable in predicting the oncological outcome. AGR, a combination of the two earlier mentioned predictors, reflects nutrition and systemic inflammatory states at the same time. Our study, consistent with previous reports,<sup>11,14,42–46</sup> concluded that patients with high-AGR had better OS and lower recurrence rate compared with those with low-AGR, especially in normal serum albumin and the cohort whose survival time was beyond 6 months. Furthermore, there was no difficulty to find that AGR was a superior predictive index compared with albumin or globulin alone. Besides, AGR is less sensitive and susceptible to measurement variability such as dehydration or fluid retention, as it is a ratio instead of absolute value alone.<sup>11</sup> Nowadays, several prognostic stage models, including BCLC,<sup>47</sup> the Japan Integrated Staging,<sup>48</sup> Cancer of the Liver Italian Program,<sup>49</sup> and Chinese University Prognostic Index,<sup>50</sup> are subsequently used to stratify HCC. Among the earlier mentioned models,

the BCLC stage has been proven to be an independent prognostic biomarker by numerous investigations and has been used in the clinical setting worldwide.<sup>51</sup> In our study, the combination of AGR and tumor size showed a higher diagnostic accuracy in predicting postoperative OS compared with BCLC stage.

In the course of our investigation, AGR was also found to correlate significantly with age and the presence of cancer embolus. Elderly patients tend to develop poor immunological status and malnutrition due to physical function and appetite loss.<sup>52,53</sup> Hence, AGR does tend to be lower in elderly patients than the other patients. Although it has been suggested that patients with liver cirrhosis tend to have poor outcomes, the relationship was not seen in this study.<sup>54,55</sup> This may be due to various postoperative factors that were not identified in the study and exceed the impact of liver cirrhosis in terms of the effect on the prognosis.

As far as we know, our study is the first to demonstrate the relation between ARG and outcome of patients following the surgical treatment of HCC. Nevertheless, there are some limitations or weaknesses in our study, inevitably. To begin with, the study is a retrospective analysis, some preoperative medical cases or follow-up data were incomplete, which may lead to a negative impact on the survival outcome. Besides, as CRP, an important indicator of cancer-related inflammation, was not routinely measured in the past, the correlation between CRP and AGR was not analyzed. Therefore, the function of AGR still needs to be confirmed via multicenter clinical study.

Despite these limitations, pretreatment AGR is an independent predictor of long-term mortality and recurrence. As a result, this biomarker, characterized with easy accessibility, objectivity, and noninvasiveness, might provide the ability to preselect patients who would benefit most from more aggressive treatments in the clinical setting.

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## Disclosure

The authors report no conflicts of interest in this work.

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