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INTERVENTIONAL RADIOLOGY

ORIGINAL ARTICLE

Inversed albumin-to-globulin ratio and underlying liver disease severity as a prognostic factor for survival in hepatocellular carcinoma patients undergoing transarterial chemoembolization

Jinlong Li*
Zhi Li*
Shirui Hao*
Jitao Wang*
Wei Chen
Shoufang Dai
Zhenguo Hou
Borun Chen
Yewei Zhang
Dengxiang Liu

***Jinlong Li, Zhi Li, Shirui Hao, and Jitao Wang contributed equally to this work.**

From the Xingtai Institute of Cancer Control (J.L., S.H., J.W., W.C., S.D., Z.H., B.C., D.L. ✉ rmyy666@163.com), Xingtai People's Hospital, Hebei, China; Department of Infection Management (Z.L., Y.Z., ✉ zhangyewei@njmu.edu.cn), Xingtai General Hospital of North China Healthcare Group, Hebei, China; School of Medicine (J.W.), Southeast University Faculty of Medicine, Nanjing, China; Department of Hepatobiliary and Pancreatic Surgery (Y.Z.), The Second Affiliated Hospital of Nanjing Medical University, Nanjing, China.

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PURPOSE

Previous studies have shown that an inversed albumin-to-globulin ratio (IAGR) is a predictor of the prognosis of many cancers. However, the prognostic value of an IAGR for patients with hepatocellular carcinoma (HCC) who undergo transarterial chemoembolization (TACE) is still unclear. This study aims to evaluate the predictive value of an IAGR for the prognosis of those patients.

METHODS

This study retrospectively analyzed 396 patients with HCC who received TACE. Using a cut-off value of 1.0 for the albumin-to-globulin ratio, patients were divided into a normal albumin-to-globulin ratio (NAGR) (≥1) and an IAGR (<1) group. Univariate and multivariate analyses and time-dependent receiver operating characteristic analyses were performed to identify risk factors of overall survival (OS) and cancer-specific survival (CSS). Survival nomograms were constructed based on the multivariable analysis results and further evaluated using the consistency index (C-index) and calibration curve.

RESULTS

A total of 396 patients were included in the final analysis and were divided into the NAGR group (n = 298, 75.3%) and the IAGR (n = 98, 24.7%) group. The median OS and CSS were significantly worse in the IAGR group than in the NAGR group (OS: 8 vs. 26 months, CSS: 10 vs. 41 months, both $P < 0.001$). Multivariate analyses demonstrated that an IAGR was an independent risk factor for predicting worse OS [hazard ratio (HR), 2.024; 95% confidence interval (CI): 1.460–2.806] and CSS (HR: 2.439; 95% CI: 1.651–3.601). The nomogram-based model-related C-indexes for OS and CSS prediction were 0.715 (95% CI: 0.697–0.733) and 0.750 (95% CI: 0.729–0.771), and the calibration of the nomogram showed good consistency.

CONCLUSION

The IAGR along with underlying liver disease severity were the useful prognostic predictors of OS and CSS among patients with HCC undergoing TACE and might be useful to identify high-risk patients.

KEYWORDS

Hepatocellular carcinoma, transarterial chemoembolization, albumin-to-globulin ratio, overall survival, cancer-specific survival

Hepatocellular carcinoma (HCC) is the fourth most common cause of cancer-related death and ranks sixth in terms of incident cases worldwide.[1] However, most patients, when diagnosed with HCC, are ineligible for curative surgery.[2] Transarterial chemoembolization (TACE) is considered a first-line treatment for HCC patients with Barcelona Clinic Liver Cancer (BCLC) stage B[1,3] and has survival benefits comparable with other palliative treatments.[4,5] For HCC patients with BCLC stage C, TACE is also used as one of the critical treatment

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options and may provide survival benefits.[6-9] Successful initial treatment is critical for HCC patients; therefore, a simple and effective prognostic scoring system is needed for HCC patients undergoing TACE.

In numerous clinical studies on HCC that focused on patient prognosis, liver function was found to affect overall survival (OS).[10] Commonly used clinical liver function assessments include assessment of the levels of serum albumin, globulin, bilirubin, transaminases, and coagulation testing.[11] A low serum albumin level can indicate poor nutritional status or poor albumin synthesis in the liver; a high globulin level indicates excessive immune activation, which is common in patients with HCC.[12] The albumin-to-globulin ratio (AGR) is calculated as serum albumin/(total protein–albumin) and is often greater than 1.0 in healthy people. Severe inflammatory liver disease or cirrhosis frequently results in an inversed albumin-to-globulin ratio (IAGR) (<1.0).[13] The IAGR has been demonstrated to correlate with the prognosis of HCC patients.[14-16] Since the cohorts of previous studies[14-16] only included patients with early-stage HCC, no published study has focused on the prognostic value of the AGR in patients with intermediate and advanced HCC scheduled to undergo therapeutic TACE.

The present study aims to develop a nomogram model based on the AGR to predict the prognosis in patients undergoing TACE treatment for BCLC stage B/C HCC.

Methods

Patient enrollment

Patients who had HCC and underwent the first session of conventional TACE treatment between January 2016 and October 2020 at Xingtai People's Hospital were identified, and their clinical data were retrospectively analyzed. The inclusion criteria were as follows: [1] 18–75 years old, [2] a diagnosis of HCC confirmed by pathological examination or clinical feature criteria according to the European Association for the Study of the Liver guidelines,[2] [3] conventional TACE used for the first-line treatment of liver cancer, and [4] presence of BCLC stage B/C. The exclusion criteria included the following: [1] the presence of another cancer; [2] the presence of serious concomitant diseases, such as acute myocardial infarction, pulmonary embolism, or cerebral hemorrhage; or [3] missing data on important prognostic variables. This study was approved by the ethical committee of our institution [no. 2020(089)]. Written informed consent was obtained from each patient. Complete follow-up information was obtained through telephone interviews.

Main points

- An inversed albumin-to-globulin ratio (IAGR) before transarterial chemoembolization (TACE) treatment is an independent prognostic factor for worse overall survival and cancer-specific survival in hepatocellular carcinoma (HCC) patients.
- An IAGR and underlying liver disease severity can be used to identify high-risk HCC patients.
- The albumin-to-globulin-based nomograms showed good performance in predicting the prognosis of HCC patients who had undergone TACE.

Data collection

Clinical characteristics, including the demographic data and pathological results, were obtained from the medical record system. Laboratory features were measured within two days before TACE and included levels of albumin, globulin (total protein-albumin), total bilirubin, alanine aminotransferase (ALT), aspartate transaminase (AST), hemoglobin, platelets, international normalized ratio (INR), serum creatinine, and alpha-fetoprotein (AFP), as well as hepatitis B surface antigen (HBsAg) status. Data on tumor-related variables were obtained using computed tomography (CT) or magnetic resonance imaging (MRI) and included maximum tumor size, tumor numbers, vascular invasion, and distant metastasis. Vascular invasion was defined as the tumor involving the hepatic artery, portal vein, hepatic vein, or inferior vena cava as assessed by preoperative CT or MRI images.[17] The Child–Pugh grade[18] and albumin–bilirubin (ALBI) grade[10] were determined based on liver function and tumor-related variables. The AGR was calculated as serum albumin/(total protein-albumin). Patients with an AGR >1.0 and <1.0 were allocated to the normal AGR (NAGR) and IAGR groups, respectively.

TACE procedure

Conventional TACE was performed by three doctors with 15, 12, and 10 years of tumor interventional treatment experience, respectively, as described previously.[19,20] It was conducted by selective hepatic artery cannulation and superselection to the artery supplying the tumor, followed by an injection of a mixed emulsion of 5 mL of iodized oil (Lipiodol; Guerbet, Bloomington, IN, US) and 50 mg doxorubicin hydrochloride or cisplatin (2 mg/kg body weight). Finally, a gelatin sponge strip (Upjohn, Kalamazoo, MI, US) was used to embolize the tumor-supplying artery.

Follow-up

Periodic follow-ups were done on each patient until death or until the study was completed on October 15, 2021. OS was computed from the time of TACE treatment to the date of death. Cancer-specific survival (CSS) was defined as patients who died of liver cancer. All patients underwent laboratory testing and contrast-enhanced CT or MRI and were followed up with every three months for the first year. If the patient had an uneventful first year, the follow-up interval was thereafter changed to once every six months. Two independent clinicians completed the follow-up and review to reduce potential biases.

Statistical analysis

The variables were calculated as the mean ± standard deviation or median (interquartile range) for continuous data. Categorical data were expressed as numbers and percentages. The unpaired Student's t-test was used to compare continuous parametric variables, and the Mann–Whitney U test was used for continuous non-parametric variables. Pearson's chi-squared test and Fisher's exact test were used for categorical variables. To balance the baseline data, which consisted of maximum tumor size, hemoglobin, platelets, INR, ALT, AST, bilirubin, creatinine, and AFP, the two groups were compared by propensity-score matching (PSM) analysis at a 1:1 ratio to remove selection bias with a 1.0 caliper value. Kaplan–Meier curves were drafted to evaluate OS and CSS, and comparisons were performed using the log-rank test between the two groups. To identify the prognostic variables independently related to OS and CSS, a multivariable Cox regression analysis was performed using variables with a *P* value of <0.100 in the univariate analysis. Results of the regression analysis are shown as hazard ratios (HRs) and 95% confidence intervals (CIs). To compare the predictive ability among the clinical models (including the Child–Pugh and ALBI grades), the area under the time-dependent receiver operating characteristic (ROC) curves (AUC) (t = 1, 2, and 3 years) was calculated for OS and CSS.[21] Survival nomogram models were constructed based on the results of the multivariable analysis. The bootstrap resampling method was used for internal validation of the predictive models by selecting 1,000 repetitions

from the regression models for OS and CSS.[22] Statistical analyses were performed using R software version 4.0.5 (The R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org), with the "MatchIt," "survival," "timeROC," and "rms" packages. A *P* value of <0.05 was considered statistically significant.

Results

Patient characteristics

Using the predetermined inclusion and exclusion criteria, 396 patients (302 males, 94 females) were enrolled (Figure 1). The mean patient age was 61.1 ± 9.1 years. Using a cut-off value of 1.0 for the AGR (16), the patients were stratified into either the NAGR group (n = 298, 75.3%) or the IAGR group (n = 98, 24.7%) (mean AGR: 1.34 vs. 0.84, respectively). Patients in the IAGR group had a higher percentage of diabetes (18.4% vs. 9.4%), larger tumor size (mean: 6.9 vs. 6.0 cm), worse Child–Pugh grading (grade B: 43.9% vs. 13.1%), and worse ALBI grading (grades 2 and 3: 84.7% vs. 50.0%) than the NAGR group (Table 1). Several laboratory parameters, including albumin, globulin, AST, hemoglobin, platelets, serum creatinine, and INR, were significantly different between the two groups. No significant distribution differences were identified in the two groups for age, sex, HBsAg status, tumor number, or AFP level. After PSM, there was no significant difference except albumin and globulin in the baseline data between the two groups (Table 1).

The prognostic outcomes of the IAGR and NAGR groups are compared in Table 2. The median and maximum follow-up periods were 13 and 62 months, respectively. During the observation period, 227 patients died, and 159 of them died of liver cancer. The death rate and the percentage of deaths due to liver cancer were significantly higher in the IAGR group than in the NAGR group (73.4% vs. 52.0% and 62.2% vs. 32.9%, respectively; both $P < 0.001$). The median OS and CSS were significantly worse in the IAGR group than in the NAGR group (8 vs. 26 months, and 10 vs. 41 months, respectively; both $P < 0.001$). The three-year OS and CSS rates were 41.2% and 21.9%, respectively, in the IAGR group, which were significantly worse than those of the NAGR group (65.0% and 29.5%, respectively, both $P < 0.001$). After PSM, the prognosis of patients in the IAGR group was significantly worse compared with the NAGR group, and the results were similar to those before PSM (Table 2). The comparison of the OS and CSS curves of the two groups are shown in Figure 2. As Figure 3 shows, although there was a difference in Child–Pugh grading between the NAGR and IAGR groups, the comparison of the OS curves of the Child–Pugh A and B showed no statistically significant difference ($P = 0.182$).

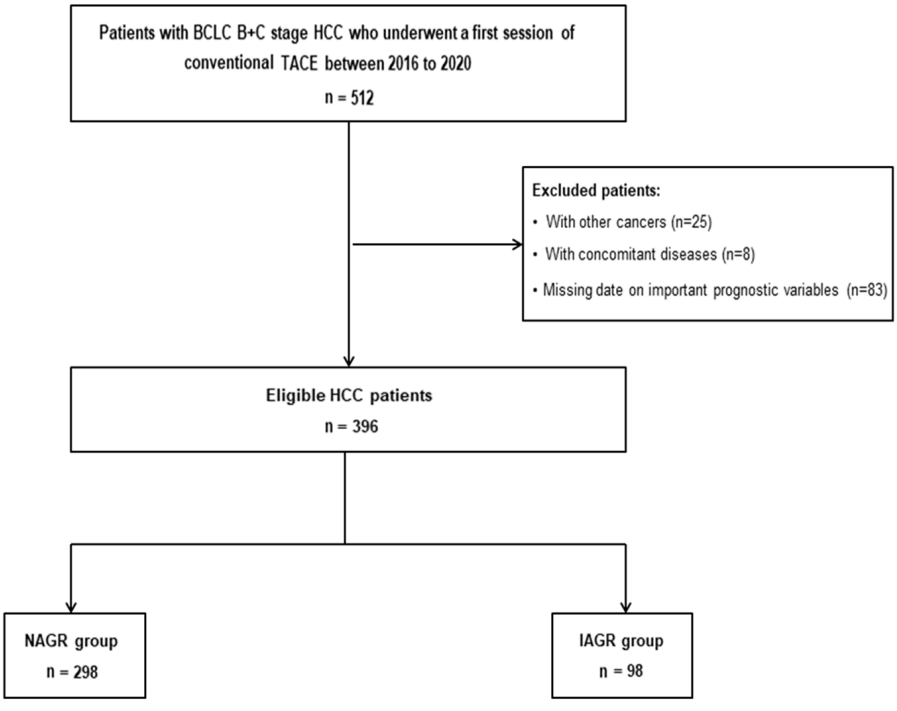

Figure 1. Flow chart of the study population. BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; IAGR, inversed albumin-to-globulin ratio; NAGR, normal albumin-to-globulin ratio; TACE, transarterial chemoembolization.

Univariate and multivariate analysis for OS and CSS

The results of the univariate and multivariate Cox regression analyses used to determine independent variables with OS and CSS after TACE treatment for HCC are shown in Tables 3 and 4. Multivariate analyses indicated that prognostic factors for worse OS and CSS [HR (95% CI)] were an IAGR [OS: 2.024 (1.460–2.806), CSS: 2.439 (1.651–3.601)], vascular invasion [OS: 2.089 (1.481–2.947), CSS: 1.869 (1.234–2.832)], distant metastasis [OS: 2.087 (1.427–3.053), CSS: 2.062 (1.311–3.243)], and maximum tumor size [OS: 1.683 (1.180–2.401), CSS: 1.768 (1.131–2.764)]. The AST level was also an independent risk factor for OS [1.488 (1.062–2.084)]. Nomograms for predicting OS and CSS were built based on the multivariate Cox regression model (Figure 4). The consistency indexes (C-indexes) for OS and CSS prediction were up to 0.715 (95% CI: 0.697–0.733) and 0.750 (95% CI: 0.729–0.771), respectively. The calibration of the nomogram for the probability of OS and CSS at one, two, and three years are shown in Figure 5. The results of the time-dependent ROC analysis comparing the values of various clinical scores in predicting OS and CSS are shown in Table 5. The AUC values of the AGR at one, two, and three years for OS were 66.4, 65.4, and 60.9, respectively; and 71.2, 70.4, and 62.9, respectively, for CSS. These values were better than the Child–Pugh grade at each timepoint ($P < 0.050$ for all) but similar to the ALBI grade ($P > 0.050$ for all).

Discussion

This study demonstrates that an IAGR could serve as an independent prognostic factor predicting unfavorable prognosis for OS and CSS in HCC patients who received TACE therapy. In addition, the AGR had a similar predictive value as the ALBI grade but a better predictive value than the Child–Pugh grade.

Several studies have reported that inflammation and malnutrition are closely related to the occurrence and development of cancer.[23,24] HCC often occurs at lesions caused by cirrhosis,[25] which induces local inflammatory responses and the release of inflammatory cytokines, thereby promoting an inflammatory microenvironment around the tumor.[26,27] The inflammatory microenvironment has the potential to induce deoxyribonucleic acid (DNA) damage and genomic instability, increase mutation rates, and enhance the proliferation of mutated cells.[28,29] Conversely, DNA damage could lead to inflammation

Table 1. Comparisons of characteristics between the IAGR and NAGR groups before and after PSM

Characteristics	Before PSM				After PSM			
	Total (n = 396)	IAGR (n = 98)	NAGR (n = 298)	*P* value	Total (n = 154)	IAGR (n = 77)	NAGR (n = 77)	*P* value
Age, years†	61.1 ± 9.1	61.4 ± 9.2	61.0 ± 9.0	0.704	60.6 ± 9.2	61.4 ± 8.9	59.8 ± 9.5	0.290
Male sex	302 (76.3)	77 (78.6)	225 (75.5)	0.630	119 (77.3)	64 (83.1)	55 (71.4)	0.123
BMI†	23.6 (21.4-25.9)	22.9 (21.0-25.9)	23.7 (21.5-25.9)	0.132	23.4 (21.1-25.9)	22.9 (20.9-25.6)	23.8 (21.4-26)	0.274
HBsAg (+)	282 (71.2)	73 (74.5)	209 (70.1)	0.485	106 (68.8)	58 (75.3)	48 (62.3)	0.117
Vascular invasion	56 (14.1)	20 (20.4)	36 (12.1)	0.059	27 (17.5)	17 (22.1)	10 (13)	0.203
Distant metastasis	56 (14.1)	17 (17.4)	39 (13.1)	0.377	30 (19.5)	13 (16.9)	17 (22.1)	0.542
Multiple tumors, ≥2	210/186 (53.0/47.0)	49/49 (50.0/50.0)	161/137 (54.0/46.0)	0.340	73/81 (48.1/52.9)	38/39 (49.4/51.6)	35/42 (45.5/54.5)	0.657
Maximum tumor size, cm†	6.0 (3.7-7.5)	6.0 (5.0-8.0)	5.9 (3.6-7.2)	0.003*	6.0 (5.0-7.5)	6.0 (3.9-7.5)	6.0 (5.0-7.5)	0.952
Hemoglobin, g/L†	128 (116-140)	119 (105-131)	131 (119-143)	<0.001*	120 (105-134)	120 (108-133)	119 (97-135)	0.932
Platelets, 109/L†	126 (87-179)	147 (94-222)	121 (83-167)	0.003*	141 (92-222)	133 (92-211)	155 (96-226)	0.569
INR†	1.11 (1.04-1.19)	1.15 (1.08-1.26)	1.09 (1.03-1.17)	<0.001*	1.13 (1.05-1.21)	1.14 (1.06-1.23)	1.11 (1.05-1.19)	0.126
ALT, U/L†	29.0 (19.9-43.7)	32.2 (22.2-46.8)	28.6 (18.5-41.8)	0.083	30.2 (21.5-47.8)	33.0 (23.0-49.5)	27.0 (19.9-44.5)	0.152
AST, U/L†	35.0 (25.0-54.1)	43.6 (29.0-74.1)	32.7 (24.5-48.6)	<0.001*	39.0 (27.1-67.0)	43.0 (29.0-77.1)	33.0 (25.0-56.0)	0.054
Albumin, g/L†	37.9 ± 6.4	31.8 ± 4.8	39.9 ± 5.6	<0.001*	35.4 ± 6.9	31.5 ± 4.8	39.3 ± 6.4	<0.001*
Globulin, g/L†	31.2 (27.5-35.8)	38.6 (35.5-41.9)	29.9 (26.5-32.6)	<0.001*	34.32 ± 6.59	38.29 ± 5.51	30.35 ± 5.02	<0.001*
Bilirubin, μmol/L†	19.2 (14.0-25.7)	22.3 (15.5-29.8)	18.7 (13.9-25.1)	0.049*	19.7 (14.1-26.7)	22.6 (14.0-29.8)	18.8 (14.7-24.8)	0.376
Creatinine, μmol/L†	62.1 (54.0-73.1)	59.1 (50.8-70.9)	63.5 (55.3-73.6)	0.027*	61.2 (51.4-76.8)	59.4 (50.8-71.5)	64.9 (55.0-79.0)	0.067
AFP, IU/mL†	4.92 (2.42-28.37)	4.92 (1.77-41.09)	4.92 (2.52-25.36)	0.960	4.9 (2.1-23.7)	4.9 (1.8-31.5)	4.1 (2.2-14.9)	0.447
Child–Pugh grade, A/B	314/82 (79.3/20.7)	55/43 (56.1/43.9)	259/39 (86.9/13.1)	<0.001*	104/50 (67.5/32.5)	42/35 (54.6/45.4)	62/15 (80.5/19.5)	<0.001*
ALBI grade†	-2.41 (-2.77-1.98)	-1.85 (-2.18-1.53)	-2.59 (-2.88-2.26)	<0.001*	-2.1 ± 0.6	-1.8 ± 0.4	-2.5 ± 0.6	<0.001*
Albumin-to-globulin ratio†	1.25 (1.01-1.48)	0.84 (0.77-0.91)	1.34 (1.19-1.52)	<0.001*	1.0 (0.9-1.3)	0.8 (0.8-0.9)	1.3 (1.1-1.5)	<0.001*

†values are mean ± standard deviation or median (interquartile range); **P* values <0.050. AFP, alpha-fetoprotein; ALBI, albumin–bilirubin; ALT, alanine aminotransferase; AST, aspartate transaminase; HBsAg, hepatitis B surface antigen; IAGR, inversed albumin-to-globulin ratio; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; NAGR, normal albumin-to-globulin ratio; PSM, propensity score matching.

Table 2. Comparisons of long-term oncologic outcomes between the IAGR and NAGR groups before and after PSM

	Before PSM				After PSM			
n (%)	Total (n = 396)	IAGR (n = 98)	NAGR (n = 298)	*P* value	Total (n = 154)	IAGR (n = 77)	NAGR (n = 77)	*P* value
Survival time, months†	13.0 (6.0-30.0)	6 (3.0-17.5)	16 (8.0-33.8)	<0.001*	11.0 (5.0-27.0)	8.0 (3.0-18.0)	12.0 (6.0-30.0)	0.007*
Death during the follow-up	227 (57.3)	72 (73.5)	155 (52.0)	<0.001*	103 (66.9)	55 (71.4)	48 (62.3)	0.304
Death due to liver cancer during the follow-up	159 (40.2)	61 (62.2)	98 (32.9)	<0.001*	70 (45.5)	44 (57.1)	26 (33.8)	0.006*
OS, months‡	19.0 (14.0-23.9)	8.0 (4.9-11.1)	26.0 (19.2-32.8)	<0.001*	12.0 (9.0-15.0)	10.0 (5.5-14.5)	17 (5.8-28.4)	0.040*
1-year OS rate, %	59.8	38.7	66.7		48.2	39.9	56.2	
2-year OS rate, %	45.8	27.8	51.2		36.8	29.4	43.9	
3-year OS rate, %	36.5	21.9	41.2		28.9	22.6	35.4	
CSS, months‡	37.0 (34.3-39.7)	10.0 (4.5-15.5)	41.0 (36.9-43.2)	<0.001*	35.0 (19.1-51.0)	12.0 (6.4-17.6)	38.0 (32.8-43.2)	0.002*
1-year DFS rate, %	70.3	43.9	78.8		62.2	46.5	78.1	
2-year DFS rate, %	61	37.5	68.7		54.3	40.1	68.8	
3-year DFS rate, %	50.3	29.5	57.1		45.1	32.8	58.1	

†values are mean ± standard deviation; ‡values are median and 95% confidence interval; **P* values<0.050. OS, overall survival; CSS, cancer-specific survival; PSM, promensity score matching; IAGR, inversed albumin-to-globulin ratio; NAGR, normal albumin-to-globulin ratio.

and subsequently promote tumorigenesis, similar to that in the diethylnitrosamine HCC model.[29,30] In addition to the development of cancer cachexia, chronic systemic inflammation contributes to progressive nutritional decline.[15,24] Malnutrition in patients with cancer cannot be reversed by simple nutritional supply alone, and it could eventually lead to a poor prognosis.[24]

Serum albumin, which is produced by the liver, is commonly used as a marker of liver function and nutritional status. Serum albumin has been reported to suppress HCC proliferation by decreasing the phosphorylation of the Rb protein and increasing the expression of p21 and p57 following an increase in the G0/G1-phase cell population.[31] Multiple studies have reported that hypoalbuminemia reflects liver dysfunction and malnutrition, which eventually impair immunity,[12] and that it affects the long-term OS and tumor recurrence.[31,32] Serum albumin assessment is one of the common components in the clinical models, such as the Child–Pugh grade and the ALBI grade, which are widely used to stratify HCC patients into prognostically distinct groups.[33]

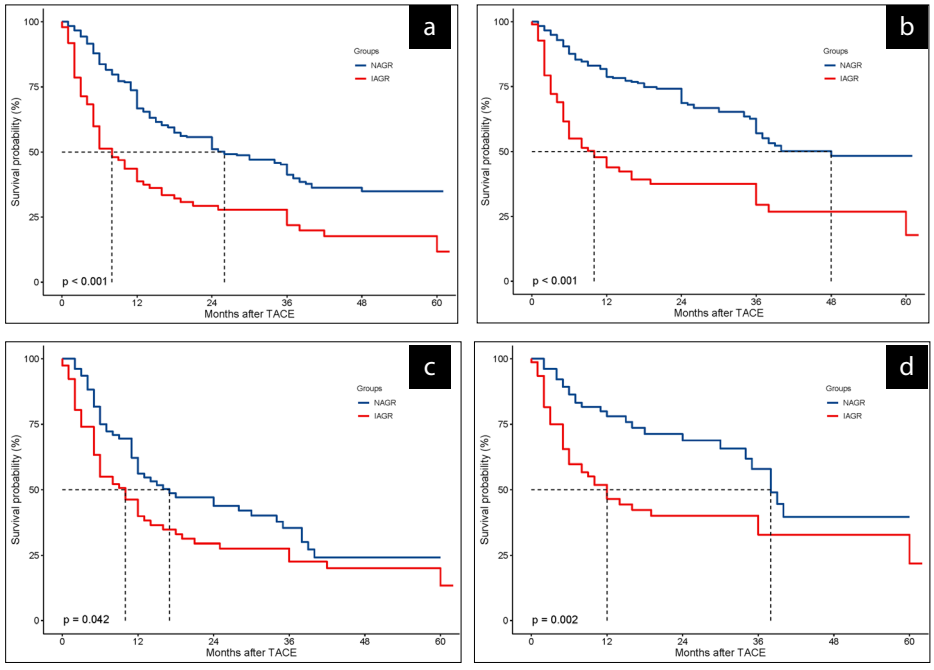

Figure 2. (a-d) Overall survival (OS) and cancer-specific survival (CSS) curves compar isons between the IAGR and NAGR groups before and after propensity score matching (PSM): **(a)**, OS before PSM; **(b)**, CSS before PSM; **(c)**, OS after PSM; **(d)**, CSS after PSM. IAGR, inversed albumin-to-globulin ratio; NAGR, normal albumin-to-globulin ratio; TACE, transarterial chemoembolization.

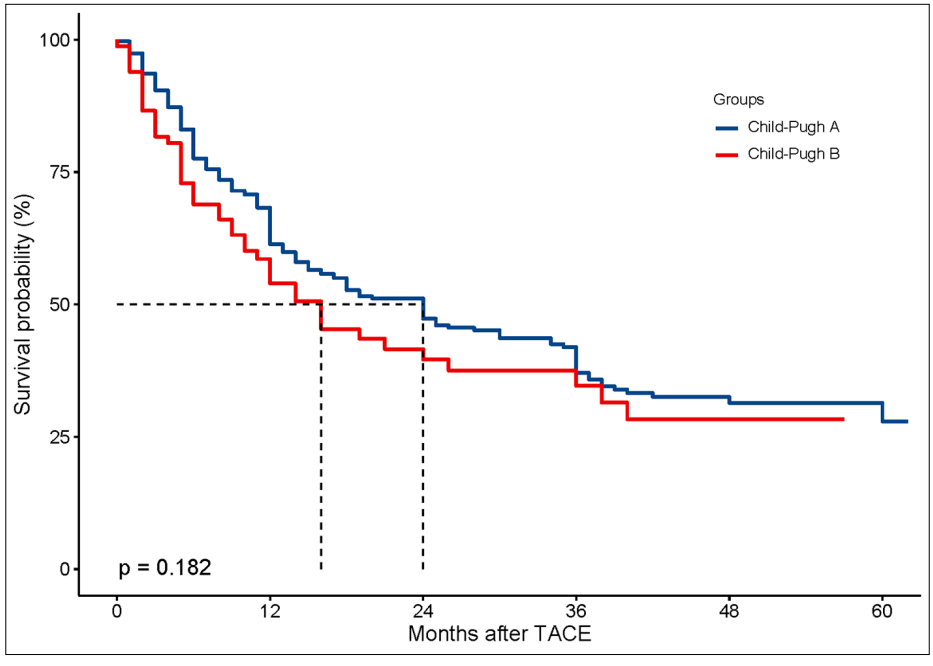

Figure 3. Overall survival curves comparisons between the Child–Pugh score A and B.

TACE, transarterial chemoembolization.

Globulins consist of several pro-inflammatory proteins,[14] including C-reactive protein, α2-macroglobulin, fibrinogen, prothrombin, and serum amyloid A.[34] Since immunoglobulins in humans are mainly metabolized by the liver, the ability to clear immunoglobulins in patients with severe hepatic dysfunction may be reduced, resulting in hyperglobulinemia.[35,36] Tumor-related inflammation stimulates the production of various cytokines, such as interleukin (IL)-1, IL-6, and tumor necrosis factor,[37] which can act on the liver and induce the synthesis of positive acute-phase reactants.[34] This might explain the increased serum globulin levels observed in this study. Moreover, several studies have reported that pro-inflammatory factors are associated with the prognosis of HCC patients.[38,39]

The AGR reflects the relative levels of albumin and globulin, which indicate hepatic nutritional and inflammatory states as well as the degree of hepatic functional impairment.[15] These may contribute to the observed correlation with HCC prognosis.[14-16] In addition, Suh et al.[40] demonstrated that a low AGR was a risk indicator for both short- and long-term cancer development in the general population.

The study results show that patients with intermediate- and advanced-stage HCC who have a low AGR are predicted to have poor prognosis after TACE. Therefore, if there is a high risk of adverse effects from TACE therapy, or limited potential benefits, clinicians should be cautious when selecting the therapeutic method. In the present study, vascular invasion and distant metastasis were identified as the independent risk factors for worse OS and CSS; AST was an independent risk for only OS. Each of these risk factors has been reported previously.[16,41] Based on the results of multivariate analysis, an AGR-based nomogram model for predicting OS and CSS was constructed, which can be used to predict the prognosis of HCC patients receiving TACE and to screen high-risk prognostic subgroups. This AGR-based nomogram model performs well in predicting the prognosis OS and CSS, and the C-indexes and calibration curves support survival prediction.

Table 3. Univariable and multivariable Cox regression analyses in predicting overall survival

Characteristics	UV HR (95% CI)	UV *P* value	MV HR (95% CI)2	MV *P* value*
Age, >60 years	0.832 (0.640-1.082)	0.170		
Male sex	0.909 (0.676-1.223)	0.529		
Hypertension	1.273 (0.939-1.725)	0.120		
HBsAg (+)	0.906 (0.686-1.197)	0.488		
Vascular invasion	2.846 (2.064-3.924)	**<0.001**	2.089 (1.481-2.947)	**<0.001**
Distant metastasis	2.477 (1.786-3.435)	**<0.001**	2.087 (1.427-3.053)	**<0.001**
Maximum tumor size, >5 cm	2.655 (1.945-3.625)	**<0.001**	1.683 (1.180-2.401)	**0.004**
Multiple tumors	1.804 (1.386-2.348)	**<0.001**	NS	0.387
Child–Pugh grade B	1.237 (0.897-1.706)	0.194		
IAGR	2.151 (1.625-2.847)	**<0.001**	2.024 (1.460-2.806)	**<0.001**
ALBI grade 2 + 3	1.503 (1.144-1.974)	**0.003**	NS	0.689
ALT, >40 U/L	1.345 (1.019-1.775)	**0.036**	NS	0.731
AST, >40 U/L	2.099 (1.616-2.727)	**<0.001**	1.488 (1.062-2.084)	**0.021**
Bilirubin, >17.1 µmol/L	0.967 (0.739-1.263)	0.803		
Creatinine, >80 µmol/L	1.109 (0.782-1.571)	0.562		
Hemoglobin, <110 g/L	1.512 (1.111-2.057)	**0.008**	NS	0.403
Platelet, <100 10^9/L	0.717 (0.540-0.953)	0.022	NS	0.538
INR, >1.17	1.213 (0.911-1.615)	0.187		
AFP, >200 IU/mL	1.754 (1.236-2.488)	**0.002**	NS	0.246

Those variables found significant at *$P < 0.100$ in univariable analyses were entered into multivariable Cox regression analyses. AFP, alpha-fetoprotein; ALBI, albumin–bilirubin; ALT, alanine aminotransferase; AST, aspartate transaminase; CI, confidence interval; HBsAg, hepatitis B surface antigen; HR, hazard ratio; IAGR, inversed albumin-to-globulin ratio; INR, international normalized ratio; MV, multivariable; NS, not significant; UV, univariable.

Table 4. Univariable and multivariable Cox regression analyses in predicting cancer-specific survival

Characteristics	UV HR (95% CI)	UV *P* value	MV HR (95% CI)2	MV *P* value*
Age, >60 years	0.935 (0.682-1.283)	0.679		
Male sex	0.876 (0.615-1.247)	0.462		
Hypertension	0.879 (0.588-1.315)	0.531		
HBsAg (+)	1.127 (0.796-1.594)	0.501		
Vascular invasion	2.687 (1.820-3.966)	**<0.001**	1.869 (1.234-2.832)	**0.003**
Distant metastasis	2.468 (1.675-3.638)	**<0.001**	2.062 (1.311-3.243)	**0.002**
Maximum tumor size, >5 cm	2.977 (2.024-4.378)	**<0.001**	1.768 (1.131-2.764)	**0.012**
Multiple tumors	1.963 (1.429-2.696)	**<0.001**	NS	0.168
Child–Pugh grade B	1.412 (0.977-2.041)	0.066	NS	0.164
IAGR	2.769 (2.010-3.815)	**<0.001**	2.439 (1.651-3.601)	**<0.001**
ALBI grade 2 + 3	1.910 (1.357-2.687)	**<0.001**	NS	0.496
ALT, >40 U/L	1.357 (0.976-1.887)	0.069	NS	0.764
AST, >40 U/L	2.128 (1.556-2.910)	**<0.001**	NS	0.116
Bilirubin, >17.1 µmol/L	1.185 (0.853-1.645)	0.312		
Creatinine, >80 µmol/L	1.188 (0.789-1.787)	0.409		
Hemoglobin, <110 g/L	1.539 (1.068-2.216)	**0.021**	NS	0.759
Platelet, <100 10^9/L	0.572 (0.400-0.819)	**0.002**	NS	0.087
INR, >1.17	1.328 (0.948-1.859)	0.099	NS	0.161
AFP, >200 IU/mL	2.014 (1.351-3.002)	**0.001**	NS	0.074

Those variables found significant at *$P < 0.100$ in univariable analyses were entered into multivariable Cox regression analyses. AFP, alpha-fetoprotein; ALBI, albumin–bilirubin; ALT, alanine aminotransferase; AST, aspartate transaminase; CI, confidence interval; HBsAg, hepatitis B surface antigen; HR, hazard ratio; IAGR, inversed albumin-to-globulin ratio; INR, international normalized ratio; MV, multivariable; NS, not significant; UV, univariable.

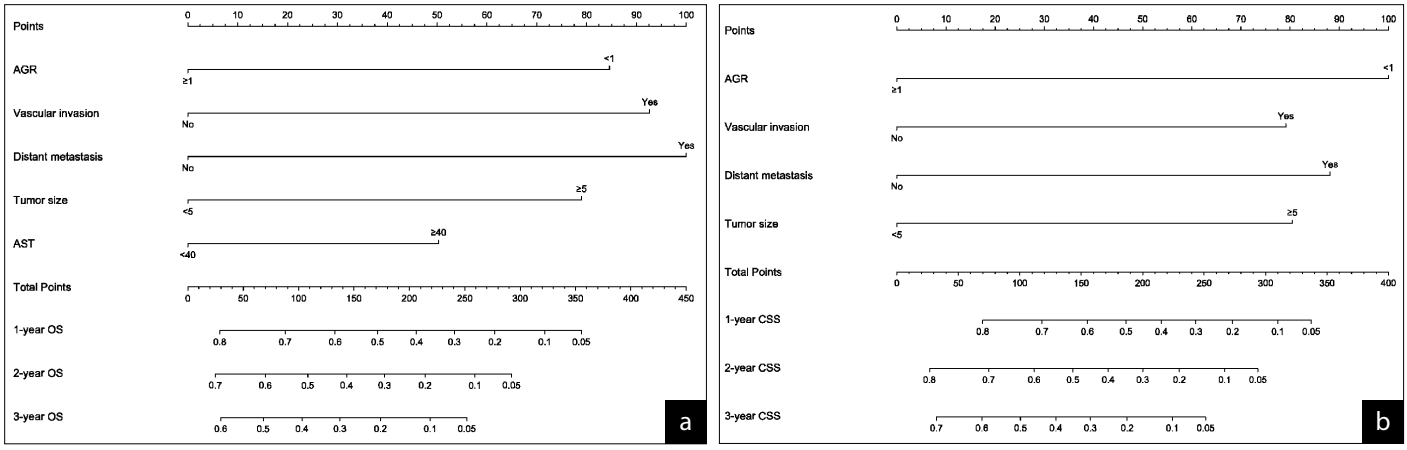

Figure 4. (a-b) Nomogram for predicting 1-, 2-, and 3-year overall survival (OS) and cancer-specific survival (CSS): **(a)**, nomogram for OS; **(b)**, nomogram for CSS. AGR, albumin-to-globulin ratio; AST, aspartate transaminase; CSS, cancer-specific survival; OS, overall survival.

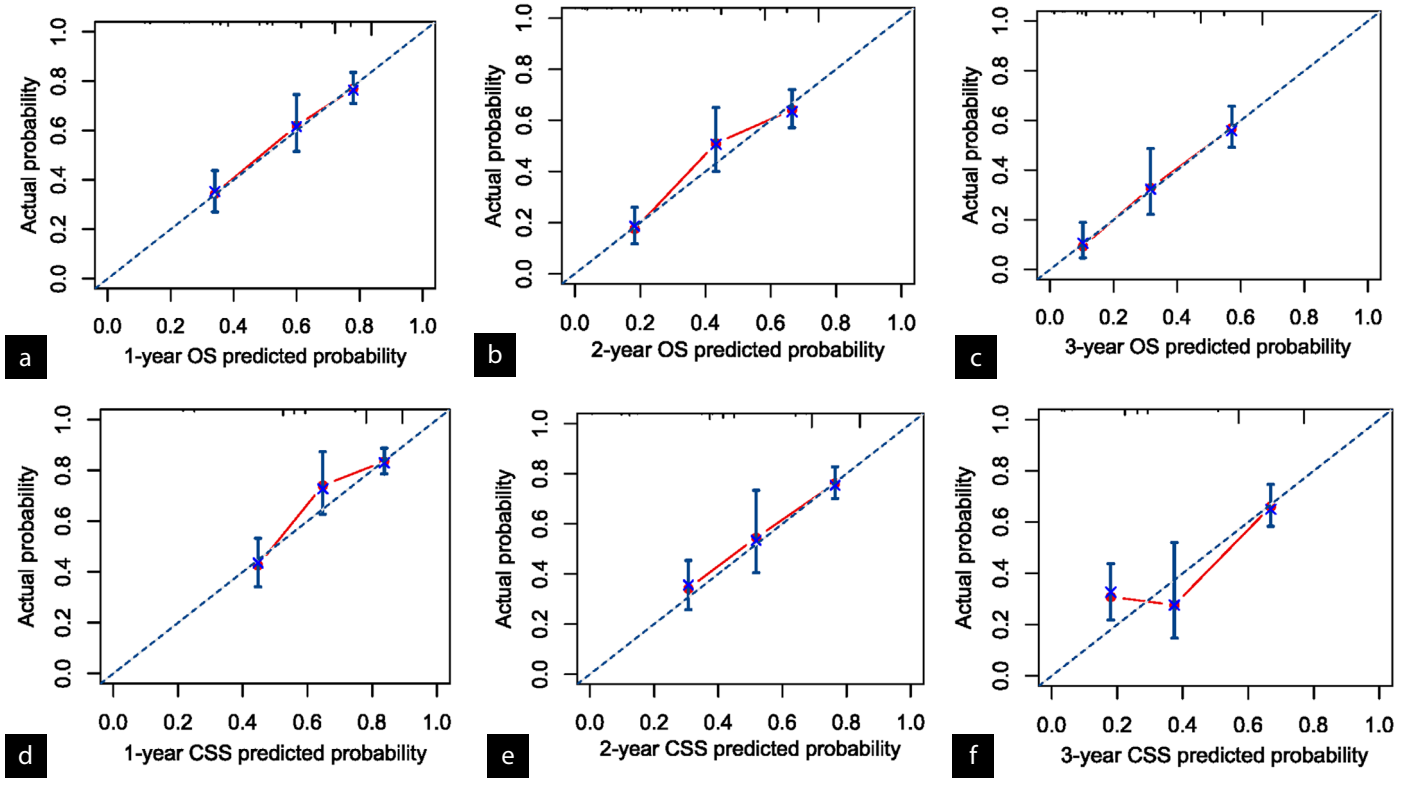

Figure 5. (a-f) Calibration curves for 1-, 2-, and 3-year overall survival (OS) and cancer-specific survival (CSS): **(a)**, 1-year OS; **(b)**, 2-year OS; **(c)**, 3-yer OS; **(d)**, 1-year CSS; **(e)**, 2-year CSS; **(f)**, 3-year CSS.

Table 5. Comparisons of time-dependent ROC analysis for the prediction of overall survival and disease-specific survival

Time-dependent AUC (95% CI)	1-year	2-year	3-year
Overall survival			
AGR	66.4 (60.3-72.6)	65.4 (59.3-71.5)	60.9 (53.7-68.2)
Child–Pugh grade	57.0 (51.2-62.8)*	57.2 (51.6-62.9)*	57.6 (50.9-64.3)*
ALBI grade	64.4 (58.3-70.6)	64.1 (58.0-70.3)	63.5 (56.3-70.6)
Disease-specific survival			
AGR	71.2 (65.0-77.4)	70.4 (63.8-77.0)	62.9 (55.0-70.9)
Child–Pugh grade	54.0 (49.0-59.0)*	55.9 (50.9-60.9)*	53.9 (48.4-59.4)*
ALBI grade	67.5 (61.1-73.9)	69.1 (62.5-75.7)	65.9 (58.1-73.8)

*P values <0.050 for statistical difference in the AUC values compared with AGR. AGR, albumin-to-globulin ratio; ALBI, albumin–bilirubin; AUC, area under the receiver operating characteristic curve; CI, confidence interval; ROC, receiver operating characteristic.

The present study has several limitations. First, it has the limitations inherent in a retrospective study. Some patients may have received other anti-tumor treatments during the follow-up period. Second, all patients were recruited from one hospital in China, and most of them had chronic hepatitis B virus infection; therefore, these results may not apply to other populations. Third, the cut-off AGR value used was 1.0, which is commonly used in clinical practice, but the cut-off threshold might need further optimization. In addition, further prospective studies are necessary to examine how the AGR could influence treatment options for HCC patients.

In conclusion, this study demonstrated that an IAGR before TACE treatment for HCC is an independent prognostic factor for worse OS and CSS. The AGR-based nomograms showed good performance in predicting patient prognoses and could be used to identify HCC patients with BCLC stage B/C who are at high risk when undergoing TACE treatment.

Conflict of interest disclosure

The authors declare no conflicts of interest.

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