Preoperative Inverse Albumin-to-Globulin Ratio Predicts Worse Oncologic Prognosis Following R0 Resection for Hilar Cholangiocarcinoma

Zhi-Peng Liu
Southwest Hospital, Third Military Medical University (Army Medical University)
Zheng-Jun Cheng
Chongqing Jiulongpo District Hospital of Integrated Traditional Chinese and Western Hospital
Hai-Su Dai
Southwest Hospital, Third Military Medical University (Army Medical University)
Wei-Yue Chen
Clinical Research Center of Oncology，Lishui Hospital of Zhejiang University
Xing-Chao Liu
Sichuan Provincial People's Hospital
Hai-Ning Fan
Affiliated Hospital of Qinghai University
Yu Pan
Southwest Hospital, Third Military Medical University (Army Medical University)
Jie Bai
Southwest Hospital, Third Military Medical University (Army Medical University)
Yan Jiang
Southwest Hospital, Third Military Medical University (Army Medical University)
Yan-Qi Zhang
Third Military Medical University (Army Medical University)
Shi-Quan Deng
Chongqing Jiulongpo District Hospital of Integrated Traditional Chinese and Western Hospital
Zhi-Yu Chen (chenzhiyu_umn@163.com)
Southwest Hospital, Third Military Medical University (Army Medical University)

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Abstract

Background & Aims: Inverse albumin-to-globulin ratio (IAGR) is defined as an AGR in serum of less than 1, which commonly indicates poor protein synthesis and severe inflammation. This study aimed to evaluate whether preoperative IAGR is associated with worse oncologic survival after R0 resection for hilar cholangiocarcinoma (HCCA).

Methods: Patients who underwent R0 resection for newly diagnosed HCCA from January 2011 to December 2018 were enrolled from a multicenter database. Based on their preoperative AGR levels, all patients were divided into the IAGR and NAGR groups. We compared their clinical characteristics and long-term oncologic prognosis. Univariate and multivariate Cox regression analyses were performed to identify risk factors for overall survival (OS) and recurrence-free survival (RFS). The time-dependent area under the curve (AUC) was compared to determine the predictive ability of AGR and other liver function indicators for long-term oncologic prognosis.

Results: Overall, 323 patients with R0 resection of HCCA were included; 58 (18.0%) were in the IAGR group. The 5-year OS and RFS rates in the IAGR group were 6.3% and 2.5%, which were significantly worse than those in the NAGR group (24.5% and 21.2%, $P < 0.05$). Multivariate Cox regression analyses identified IAGR an independent risk factor for predicting worse OS (HR: 1.619, 95% CI: 1.161-2.258, $P = 0.005$) and RFS (HR: 1.773, 95% CI: 1.289-2.438, $P < 0.001$). The time-dependent AUCs of AGR for OS and RFS were superior to those of other liver function indicators.

Conclusion: Preoperative IAGR is valuable for predicting worse OS and RFS in patients who underwent R0 resection for HCCA. AGR has ideal predictive ability for long-term oncological prognosis.

Introduction

Cholangiocarcinoma is the second most common hepatic malignancy after hepatocellular carcinoma (HCC) and has high morbidity and poor survival rates worldwide[1]. The overall incidence of hilar cholangiocarcinoma (HCCA) has increased in the past few years, requiring the attention of hepatobiliary surgeons[2]. At present, radical resection is the key treatment to cure HCCA[3]. However, a high postsurgery tumor recurrence rate limits the prognosis. Deep insight into preoperative independent risk factors related to recurrence and survival will aid in surgical decision-making.

Liver function level is associated with the long-term prognosis of hepatobiliary malignancies[4–6]. Albumin, globulin, albumin-to-globulin ratio (AGR), and alanine aminotransferase (ALT) are common clinical indicators used to evaluate liver function. ALT (normal range 0–40 U/L) mainly exists in liver tissue. Serum ALT levels are elevated due to pathological changes and injury in liver cells. Albumin (normal range 35–50 g/L) is synthesized by the liver. During poor protein synthesis, the serum level of albumin may decrease. In addition, a low serum level of albumin is commonly found in patients with malnutrition. Globulin (normal range 20–35 g/L) has an immune function. When the immune system is overactive, the serum level of globulin will increase. Moreover, a high serum level of globulin is commonly

found in patients with chronic hepatitis. AGR (normal range 1.0–2.0) is a surrogate marker that combines albumin with globulin[7]. The underproduction of albumin or overproduction of globulin may be the cause of the decrease in AGR. Many factors can lead to an inverse albumin-to-globulin ratio (IAGR, < 1.0), such as severe inflammatory liver diseases or cirrhosis. Furthermore, AGR can be used to assess the prognosis of patients with malignant gastrointestinal tumors, such as gastric cancer[8, 9], colorectal cancer[10, 11], and urothelial carcinoma[12, 13]. Based on the above studies, it is reasonable to speculate that AGR may have a potential impact on the prognosis of HCCA patients after R0 resection. The correlation between preoperative AGR and prognosis in patients who underwent surgery for cholangiocarcinoma has only been reported in a Chinese single-center study with a small sample size[6]. Regrettably, they only performed prognostic analyses on overall survival (OS) but not on recurrence-free survival (RFS), and they did not perform prognostic analyses for HCCA in the subgroups.

Using a multicenter database, this study aimed to identify whether preoperative AGR can independently predict the long-term oncologic prognosis of patients with HCCA following R0 resection and to compare the predictive ability of AGR and other liver function indicators for long-term oncologic prognosis.

Methods

Patient Selection

Enrolled patients with HCCA who underwent R0 resection for newly diagnosed HCCA from January 2011 to December 2018 from a multicenter database (Southwest Hospital, Sichuan Provincial People's Hospital, and Affiliated Hospital of Qinghai University) and their clinical and pathological data were analyzed. The exclusion criteria were as follows: (1) patients treated with neoadjuvant therapy; (2) patients who were unresectable at exploration; (3) patients who did not undergo hepatectomy; (4) patients who died within 30 days after resection; (5) patients with missing data on important variables; (6) patients who were lost to follow-up; and (7) patients with chronic renal dysfunction that could lead to abnormalities in serum globulin. The diagnosis of HCCA was confirmed by postoperative pathological examination. R0 resection was defined as complete resection of all macroscopic and microscopic HCCA tumors with microscopically clear resection margins in the surgical specimens. The study was conducted in accordance with the Declaration of Helsinki. The study was approved by the Institutional Review Board of the South West Hospital of Chongqing, China (No: KY2021129). Informed consent for clinical research was obtained from all the patients.

Patient Management

All patients underwent hepatectomy, extrahepatic bile duct resection and locoregional lymphadenectomy. To achieve radical resection, combined pancreaticoduodenectomy and/or combined vascular resection were aggressively performed based on preoperative system evaluation and radiological examinations. The type of hepatectomy was determined based on the location of the primary tumor, intraoperative ultrasound and intraoperative frozen-section histology examinations, as previously reported[14, 15].

Clinicopathological and Operative Variable **s**

The following clinical variables were reviewed: age, sex, American Society of Anesthesiologists (ASA) score, cirrhosis, preoperative hemoglobin, platelet, total bilirubin, AGR, ALT, aspartate aminotransferase (AST), international normalized ratio (INR), creatinine, carbohydrate antigen 19 – 9 (CA19-9), albumin, globulin, preoperative drainage, and Child–Pugh grade. All laboratory tests were performed within one week prior to radical resection. Cirrhosis was confirmed by postoperative histopathological examination. The following pathological variables were reviewed: maximum tumor size, tumor number, macrovascular invasion, microvascular invasion, peripheral nerve invasion, tumor differentiation, 8th American Joint Committee on Cancer (AJCC) stage, Bismuth classification, and lymph node metastasis. The following operative variables were reviewed: intraoperative blood loss, intraoperative blood transfusion, and extent of hepatectomy. Major hepatectomy was defined as the resection of three or more Chouinard liver segments, and minor hepatectomy was the resection of fewer than three segments.

Follow-up After Surgery

The patients were regularly (approximately 1–2 months) followed up after discharge from the hospital. Each of the follow-up visits used a standard protocol for the surveillance of HCCA recurrence. The standard protocol included clinical symptoms, physical examinations, laboratory tests (liver function and tumor biomarkers) and abdominal ultrasonography. Contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) was performed every 3–6 months after surgery or when tumor recurrence was highly suspected. Recurrence was confirmed by any new lesions detected by CT or MRI. The treatment for patients with tumor recurrence included reresection, targeted drug therapy or supportive therapy.

Study Endpoints

The primary endpoint of this study was OS. The secondary endpoint of this study was RFS. OS was defined as the time from the date of radical resection to the date of death or the date of the last follow-up. For patients with recurrence, RFS was defined as the time from the date of radical resection to the date of the diagnosis of tumor recurrence. For patients without recurrence, RFS was defined as the time from the date of radical resection to the date of death or the date of the last follow-up. All patients were followed up until death or loss to follow-up until this study was censored on August 31, 2021.

Statistical Analysis

The variables are presented as frequencies and percentages for categorical covariates and means ± standard deviations (SDs) or medians (ranges) for continuous covariates. Pearson's chi-square test was used for categorical covariates, while Student's t test or the Mann–Whitney U test was used for continuous covariates. For laboratory results, the upper and lower limits of the normal values were used to divide the patients into normal and abnormal groups, including 40 U/L for ALT and AST, 100 $\times 10^9$/L for PLT, 17.1 μmol/L for TB, and 1.17 for INR. This study used 150 U/L and 3 cm as the cutoff values for CA19-9 and maximum tumor size, respectively[16, 17]. The OS and RFS rates were compared between the

IAGR and NAGR groups using the Kaplan–Meier method and the log-rank test. Only significant variables with a *P value* < 0.1 in univariable analyses were included in multivariate analyses using the Cox proportional hazards model. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were estimated in the univariable and multivariable Cox regression analyses. Statistical analyses were performed using SPSS® version 26.0 (IBM, Armonk, New York, USA). The predictive ability of AGR and other liver function indicators was compared by the time-independent area under the receiver operating characteristic curve (AUROC) via the “survivalROC” package in R. *P* values were 2-sided, and a P value < 0.05 was considered statistically significant.

Table 1
Comparisons of clinicopathological and operative variables between the IAGR and NAGR groups

Variables	Total (N = 323)	NAGR (N = 265)	IAGR (N = 58)	*P* value
Age, years*	55.8 ± 9.0	56.1 ± 8.7	54.3 ± 9.5	0.156
Male sex	187 (57.9)	156 (58.9)	31 (53.4)	0.449
ASA score > 2	34 (10.5)	25 (9.4)	9 (15.5)	0.172
Cirrhosis	27 (8.4)	22 (8.3)	5 (8.6)	0.937
Preoperative drainage	95 (29.4)	80 (30.2)	15 (25.9)	0.512
Child–Pugh grade B	36 (11.1)	27 (10.2)	9 (15.5)	0.243
Hemoglobin, g/L*	121.7 ± 24.8	123.4 ± 25.7	113.7 ± 18.7	0.007
Platelet, $\times 10^9$/L*	220 (172, 280)	217 (179, 267)	217 (179, 267)	0.151
Total bilirubin, μmol/L*	167.2 (70.7, 263.9)	177.6 (72.4, 281.8)	177.6 (72.4, 281.8)	0.027
Albumin, g/L*	36.7 ± 4.7	37.5 ± 4.4	33.3 ± 4.3	< 0.001
Globulin, g/L*	29.8 ± 5.8	28.1 ± 4.4	37.4 ± 5.2	< 0.001
AGR*	1.27 ± 0.25	1.35 ± 0.20	0.89 ± 0.07	< 0.001
ALT, U/L*	74.5 (35.9, 163.0)	73.5 (39.5, 157.8)	106.0 (45.9, 183.0)	0.412
AST, U/L*	64.7 (34.0, 123.0)	65.0 (37.0, 123.3)	63.5 (41.0, 131.0)	0.747
INR*	0.964 ± 0.105	0.957 ± 0.099	0.996 ± 0.125	0.018
Creatinine, μmol/L*	60.99 ± 19.4	61.39 ± 19.40	59.13 ± 19.62	0.385
CA 19 − 9, U/L*	178.0 (94.9, 353.9)	150.1 (81.9, 333.0)	249.5 (117.8, 746.5)	0.010
Maximum tumor size, cm *	2.89 ± 1.30	2.88 ± 1.28	2.94 ± 1.40	0.748
Macrovascular invasion	194 (60.1)	154 (58.1)	40 (69.0)	0.126
Microvascular invasion	63 (19.5)	51 (19.2)	12 (20.7)	0.801
Peripheral nerve invasion	110 (34.1)	87 (32.8)	23 (39.7)	0.320

Note: *Values are the mean ± standard deviation or median (interquartile range) unless otherwise indicated.

Variables	Total (N = 323)	NAGR (N = 265)	IAGR (N = 58)	*P* value
Poor tumor differentiation	69 (21.4)	57 (21.5)	12 (20.7)	0.890
Lymph node metastasis	101 (31.3)	80 (30.2)	21 (36.2)	0.371
Bismuth type, III-IV	122 (37.8)	98 (37.0)	24 (41.4)	0.531
8th AJCC stage, III-IV	117 (36.2)	92 (34.7)	25 (43.1)	0.229
Intraoperative blood loss, ml*	650 (400, 1000)	600 (400, 1000)	700 (400, 1050)	0.630
Intraoperative blood transfusion	203 (62.8)	165 (62.3)	38 (65.5)	0.642
Major hepatectomy	238 (73.3)	191 (72.1)	47 (81.0)	0.160

Note: *Values are the mean ± standard deviation or median (interquartile range) unless otherwise indicated.

Results

Patient Characteristics

A total of 323 patients with R0 resection of HCCA were included based on the abovementioned inclusion criteria, as shown in Fig. 1. There were 187 (57.9%) males and 136 (42.1%) females. We collected the AGR of patients within one week of surgery and used 1.0 as the cutoff value. All patients were divided into the NAGR (AGR ≥ 1, n = 265, 82.0%) group and the IAGR (AGR < 1, n = 58, 18.0%) group (mean AGR: 1.35 *vs.* 0.89). The clinicopathological and operative characteristics are summarized in Table 1. The baseline characteristics showed significant differences in some variables between the two groups, including hemoglobin, albumin, globulin, INR, and CA 19 − 9.

Oncological Outcomes

The long-term oncological outcomes between the IAGR and NAGR groups are shown in Table 2. The death rate and recurrence rate were both significantly higher in the IAGR group than in the NAGR group (79.3% *vs.* 65.3%, $P = 0.038$; 87.9% *vs.* 69.4%, $P = 0.001$). The OS and RFS curves of the two groups are shown in Fig. 2A and Fig. 2B, respectively. The median OS and RFS in the IAGR group were 17.7 and 13.0 months, respectively. The median OS and RFS in the NAGR group were 24.0 and 19.0 months, respectively. The 1-, 3-, and 5-year OS rates in the IAGR group were 64.9%, 15.7%, and 6.3%, respectively, which were significantly worse than those in the NAGR group (76.5%, 37.0%, and 24.5%, respectively, $P = 0.001$). The 1-, 3-, and 5-year RFS rates in the IAGR group were 54.2%, 9.9%, and 2.5%, respectively, which were significantly poorer than those in the NAGR group (68.9%, 33.4%, and 21.2%, respectively, $P < 0.001$).

Table 2
Comparisons of long-term oncologic outcomes between the IAGR and NAGR groups

Oncologic outcomes	Total (N = 323)	NAGR (N = 265)	IAGR (N = 58)	*P* value
Period of follow-up, months*	20.0 (12.0, 34.0)	21.0 (12.0, 36.0)	16.0 (7.5, 26.0)	0.005
Death during the follow-up	219 (67.8)	173 (65.3)	46 (79.3)	0.038
Recurrence during the follow-up	235 (72.8)	184 (69.4)	51 (87.9)	0.004
OS, months**	24.0 (21.5–26.5)	24.0 (19.1–28.9)	17.5 (10.1–23.9)	0.001
1-year OS rate, %	74.4	76.5	64.9	
3-year OS rate, %	33.4	37.0	15.7	
5-year OS rate, %	21.5	24.5	6.3	
RFS, months**	19.0 (16.6–21.4)	19.0 (13.9–24.1)	13.0 (7.0–19.0)	< 0.001
1-year RFS rate, %	66.3	68.9	54.2	
3-year RFS rate, %	28.3	33.4	9.9	
5-year RFS rate, %	17.7	21.2	2.5	

Prognostic Analyses for OS and RFS

The results of univariable and multivariable Cox regression analyses for predicting OS and RFS after R0 resection for HCCA are listed in Table 3 and Table 4, respectively. Multivariate Cox regression analyses demonstrated that IAGR was an independent risk factor for predicting worse OS (HR: 1.619, 95% CI: 1.161–2.258, $P = 0.005$) and RFS (HR: 1.773, 95% CI: 1.289–2.438, $P < 0.001$). Furthermore, CA19-9 > 150 U/L, maximum tumor size > 3 cm, macrovascular invasion, microvascular invasion, poor tumor differentiation, and lymph node metastasis were independent risk factors for both OS and RFS, as expected.

Table 3
Univariable and multivariable Cox regression analyses for predicting overall survival

Variables	HR Comparison	Univariable analyses		Multivariable analyses*	
		P	HR (95% CI)	*P*	HR (95% CI)
Age	> 60 *vs.* ≤ 60 years	0.518	1.107 (0.814–1.505)		
Sex	Male *vs.* Female	0.622	1.070 (0.817–1.401)		
ASA score	> 2 *vs.* ≤ 2	0.285	1.279 (0.815–2.006)		
Cirrhosis	Yes *vs.* No	0.341	1.257 (0.785–2.014)		
Preoperative drainage	Yes *vs.* No	0.943	0.989 (0.742–1.320)		
Hemoglobin	< 110 *vs.* ≥ 110 g/L	0.097	1.296 (0.954–1.760)	0.941	NA
Platelet	< 100 *vs.* ≥ 100 $\times 10^9$/L	0.671	1.113 (0.678–1.830)		
Total bilirubin	> 17.1 *vs.* ≤ 17.1 μmol/L	0.287	1.330 (0.787–2.247)		
AGR	IAGR (< 1) *vs.* NAGR (≥ 1)	0.012	1.534 (1.099–2.142)	0.005	1.619 (1.161–2.258)
ALT	> 40 *vs.* ≤ 40 U/L	0.120	1.261 (0.941–1.690)		
AST	> 40 *vs.* ≤ 40 U/L	0.105	1.288 (0.949–1.748)		
INR	< 1.17 *vs.* ≥ 1.17	0.781	1.099 (0.563–2.147)		
Creatinine	> 80 *vs.* ≤ 80 μmol/L	0.572	1.150 (0.709–1.864)		
CA19-9	> 150 *vs.* ≤ 150 U/L	0.001	1.590 (1.214–2.082)	0.001	1.567 (1.188–2.067)
Maximum tumor size	> 3 *vs.* ≤ 3 cm	< 0.001	1.688 (1.268–2.249)	< 0.001	1.728 (1.291–2.313)
Macrovascular invasion	Yes *vs.* No	0.001	1.597 (1.207–2.113)	0.001	1.617 (1.213–2.156)

Note: *Variables identified as significant at $P < 0.100$ in univariable analyses were entered into multivariable Cox regression analyses.

Variables	HR Comparison	Univariable analyses		Multivariable analyses*	
		P	HR (95% CI)	*P*	HR (95% CI)
Microvascular invasion	Yes *vs.* No	0.004	1.625 (1.173–2.252)	0.003	1.658 (1.181–2.328)
Peripheral nerve invasion	Yes *vs.* No	0.152	1.222 (0.929–1.607)		
Tumor differentiation	Poor *vs.* Well/Moderate	0.004	1.566 (1.150–2.133)	0.001	1.706 (1.239–2.348)
Lymph node metastasis	Yes *vs.* No	< 0.001	1.999 (1.513–2.640)	< 0.001	1.998 (1.508–2.649)
Intraoperative blood loss	> 1500 *vs.* ≤ 1500 ml	0.379	1.176 (0.819–1.689)		
Intraoperative blood transfusion	Yes *vs.* No	0.465	1.107 (0.843–1.453)		
Extent of hepatectomy	Major *vs.* Minor	0.291	1.177 (0.870–1.583)		

Note: *Variables identified as significant at $P < 0.100$ in univariable analyses were entered into multivariable Cox regression analyses.

Table 4
Univariable and Multivariable Cox regression analyses for predicting recurrence-free survival

Variables	HR Comparison	Univariable analyses		Multivariable analyses*	
		P	HR (95% CI)	*P*	HR (95% CI)
Age	> 60 *vs.* ≤ 60 years	0.425	1.128 (1.838–1.519)		
Sex	Male *vs.* Female	0.790	1.036 (0.799–1.343)		
ASA score	> 2 *vs.* ≤ 2	0.401	1.121 (0.774–1.899)		
Cirrhosis	Yes *vs.* No	0.386	1.225 (0.774–1.939)		
Preoperative drainage	Yes *vs.* No	0.707	0.948 (0.716–1.254)		
Hemoglobin	< 110 *vs.* ≥ 110 g/L	0.056	1.333 (0.993–1.790)	0.866	NA
Platelet	< 100 *vs.* ≥ 100 $\times 10^9$/L	0.984	1.005 (0.612–1.650)		
Total bilirubin	> 17.1 *vs.* ≤ 17.1 μmol/L	0.175	1.437 (0.851–2.425)		
AGR	IAGR (< 1) *vs.* NAGR (≥ 1)	0.002	1.642 (1.197–2.251)	0.001	1.739 (1.261–2.397)
ALT	> 40 *vs.* ≤ 40 U/L	0.045	1.340 (1.007–1.784)	0.186	NA
AST	> 40 *vs.* ≤ 40 U/L	0.032	1.389 (1.028–1.875)	0.125	NA
INR	< 1.17 *vs.* ≥ 1.17	0.746	1.111 (0.588–2.099)		
Creatinine	> 80 *vs.* ≤ 80 μmol/L	0.808	1.061 (0.656–1.719)		
CA19-9	> 150 *vs.* ≤ 150 U/L	0.001	1.577 (1.216–2.046)	0.003	1.500 (1.149–1.957)
Maximum tumor size	> 3 *vs.* ≤ 3 cm	0.002	1.567 (1.183–2.075)	0.002	1.574 (1.184–2.093)
Macrovascular invasion	Yes *vs.* No	0.001	1.576 (1.204–2.063)	0.002	1.562 (1.185–2.058)

Note: *Variables identified as significant at $P < 0.100$ in univariable analyses were entered into multivariable Cox regression analyses.

Variables	HR Comparison	Univariable analyses		Multivariable analyses*	
		P	HR (95% CI)	*P*	HR (95% CI)
Microvascular invasion	Yes *vs.* No	0.004	1.593 (1.158–2.192)	0.007	1.578 (1.135–2.192)
Peripheral nerve invasion	Yes *vs.* No	0.178	1.201 (0.920–1.567)		
Tumor differentiation	Poor *vs.* Well/Moderate	0.005	1.548 (1.144–2.094)	0.001	1.658 (1.214–2.266)
Lymph node metastasis	Yes *vs.* No	< 0.001	1.968 (1.502–2.578)	< 0.001	1.938 (1.475–2.548)
Intraoperative blood loss	> 1500 *vs.* ≤ 1500 ml	0.282	0.210 (0.855–1.714)		
Intraoperative blood transfusion	Yes *vs.* No	0.627	1.067 (0.821–1.386)		
Extent of hepatectomy	Major *vs.* Minor	0.401	0.132 (0.848–1.512)		

Note: *Variables identified as significant at $P < 0.100$ in univariable analyses were entered into multivariable Cox regression analyses.

Moreover, AGR was found to surpass albumin and ALT in predicting OS and RFS according to the results of time-dependent AUROC analysis, as shown in Figs. 3A and 3B.

Discussion

This study aimed to assess the association between AGR and long-term oncologic survival in patients who underwent R0 resection for HCCA. AGR is calculated by dividing the concentration of albumin by the concentration of globulin and has been used as an effective tool for evaluating liver function. In clinical practice, the normal AGR of patients is > 1.0. Consequently, this value was considered a threshold to divide all patients into the IAGR and NAGR groups in our study. A retrospective study of 123 patients with cholangiocarcinoma from China demonstrated the prognostic value of the preoperative AGR for OS. They found that it is superior to measuring globulin or albumin alone for predicting mortality in cholangiocarcinoma patients[6]. However, compared with our research, they lacked research on RFS, had only a small sample size, and did not analyze the various types of cholangiocarcinoma in subgroups. We used a multicenter database and only selected patients with HCCA to compensate for the abovementioned deficiencies. Notably, for the first time, preoperative IAGR was confirmed to be an independent risk factor for predicting long-term oncologic survival in patients with HCCA. Although the incidence of HCCA is less than 1% of systemic tumors, the long-term prognosis is poor. Therefore, we enrolled as many patients as possible with adequately long periods of follow-up. In addition, we carried

out an analysis of multiple prognostic risk factors, including clinical, pathological, biochemical, and operative variables.

As a carrier of sex hormones, globulin is commonly used to reflect the inflammatory status of patients, along with most proinflammatory proteins (including complement components, high-sensitivity C-reactive protein, immunoglobulins, etc.). Chronic inflammation may produce chronic oxidative stress and generate oxygen-free radicals[18]. Oxygen-free radical signaling can activate HIF-1, which in turn upregulates gene expression for glycolysis, angiogenesis, and other cellular metabolisms[19]. This facilitates the transformation of ordinary cells into cancer cells and tumor growth. Based on the above reasons, many scholars believe that chronic inflammation plays a crucial role in various aspects of tumor progression and development, including proliferation, metastasis, and survival, in patients with malignant tumors[20, 21]. In previous studies, serum globulin was suggested to be an independent predictor of long-term outcomes in some diseases, such as lung cancer, gastric cancer, and esophageal squamous carcinoma[22–25]. A Japanese research team found that elevated serum non-albumin proteins and immunoglobulins were strongly related to common variants of tumor necrosis factor receptor superfamily member 13B (TNFRSF13B)[26]. TNFRSF13B is closely associated with tumor progression[27]. This finding suggested a potential relationship between the development of malignant tumors and serum globulin.

Albumin may affect the survival of patients with malignant tumors through several mechanisms. Serum albumin is commonly used as a biomarker of liver function and nutritional status. Moreover, in the clinical setting, serum albumin forms an important component in many scores that are designed to reflect liver function, such as Child–Pugh grading and ALBI grading. A low serum albumin level may be related to liver dysfunction[28]. Poor liver function and malnutrition are common reasons for the worse long-term prognosis of patients with hepatobiliary tumors. Furthermore, chronic inflammation may lead to a low level of serum albumin. Mantovani et al. indicated that tumor cells and immune cells stimulate the release of various growth factors and cytokines (including interleukin-6, tumor necrosis factor, etc.) during the process of tumor-associated systemic inflammation[29]. These growth factors and cytokines inhibit serum albumin production and stimulate tumor growth and progression through the stimulation of the migration and subversion of the host immune response[29–31]. In addition, Laursen et al. found several anticancer mechanisms of serum albumin, such as antioxidant function[32]. Previous studies reported that the development and progression of tumor cell lines in vitro, such as human breast cancer cell lines, were regulated by high serum albumin concentrations[33].

Multivariable Cox regression analyses revealed that preoperative IAGR was the only indicator of liver function that was significantly associated with worse OS and RFS in patients with HCCA who underwent R0 resection. This result should remind hepatic surgeons of the importance of preoperative AGR in predicting survival and recurrence following HCCA R0 resection. A retrospective study of lung adenocarcinoma indicated that serum albumin and globulin concentrations were severely affected by blood volume, which may reduce their predictive value[34]. The hydration status of patients commonly influences the serum levels of albumin and globulin. However, AGR is not easily affected by the hydration

status of the patient. Azab et al. found that serum albumin and serum globulin levels are increased or decreased proportionately in conditions such as dehydration and fluid retention[35]. A multicenter study from China observed that the preoperative IAGR was associated with worse survival and recurrence conditions in patients with HCC after surgery and that the performance of AGR in predicting prognosis after liver resection was the best among the key indexes reflecting liver function[36]. In addition, it is worth noting that in this study, AGR was found to surpass other indicators of liver function, such as albumin and ALT, in predicting OS and RFS according to the result of time-dependent AUROC analysis. Considering that AGR is a valuable biomarker reflecting liver function and that AGR is not influenced by hydration status, we concluded that it can serve as a more advantageous biomarker for HCCA prognosis than other liver function indicators alone.

In this study, laboratory parameters, including hemoglobin, albumin, globulin, INR, and CA 19 – 9, showed significant differences between the IAGR and NAGR groups. However, it was not appropriate to use propensity score matching to balance the baseline characteristics between the two groups to examine the association between the preoperative AGR and prognosis, as it may lead to more selection biases between the IAGR and NAGR groups. Consequently, in our study, we used classical statistical approaches (univariable and multivariable Cox regression analyses) to determine the relationship between the preoperative IAGR and poor prognostic outcomes in patients following R0 resection for HCCA while adjusting for the other risk factors.

In addition to the preoperative IAGR, a few other independent risk factors that lead to worse OS and RFS were identified in our study. These independent risk factors included CA19-9 > 150 U/L, maximum tumor size > 3 cm, macrovascular invasion, microvascular invasion, poor tumor differentiation, and lymph node metastasis. All these independent risk factors have been reported in a previous study[37–42].

There are several limitations to this study. First, this study was a retrospective study, which may lead to biases, including selection, confounding, and information biases. Nonetheless, this study used a large sample from a multicenter database to improve the accuracy of the results. Second, this study did not measure specific inflammatory and nutritional indicators, such as neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, sarcopenia, and C-reactive protein. Inflammatory and nutritional indicators may reflect liver function. This study compared the predictive ability of different liver function indicators, including AGR, albumin, and ALT, in predicting long-term oncologic survival. Third, this study used 1.0 as the cutoff value in normal clinical practice to divide all patients into the INGR and NAGR groups. Identifying the best cutoff value for AGR to determine prognosis will be our focus of future research.

Conclusion

Using a multicenter database, preoperative IAGR was found to be independently associated with worse OS and RFS following R0 resection for HCCA in this study. In addition, AGR was found to surpass albumin and ALT in predicting OS and RFS. This finding may allow hepatic surgeons to obtain a preoperative prediction of the prognosis of patients with HCCA. With its low cost, easy application and

broad availability, AGR can be used as a biomarker for the prognostication of patients with HCCA who underwent R0 resection.

Abbreviations

ALB, albumin; ALT, alanine aminotranferase; AJCC, American Joint Committee on Cancer; ASA, American Society of Anesthesiologists; AST, aspartate transaminase; AUC, area under the curve; AUROC: area under receiver operating characteristic curves; CA19-9, Carbohydrate antigen 19-9; CI, confidence interval; CT, computed tomography; HCCA, hilar cholangiocarcinoma; NAGR: normal albumin-to-globulin ratio; HR, hazard ratio; IAGR: inversed albumin-to-globulin ratio; INR, international normalized ratio; MRI, magnetic resonance imaging; OS, overall survival; RFS, recurrence-free survival; SD: standard deviation.

Declarations

Ethics approval and consent to participate: The study was approved by the Institutional Review Board of the South West Hospital of Chongqing, China (No: KY2021129). Informed consent for clinical research was obtained from all the patients. All methods in this study were confirmed to be performed in accordance with the relevant guidelines and regulations

Consent for publication: Not applicable.

Availability of data and materials: All data generated or analysed during this study are included in this published article and its supplementary information files.

Authors' Disclosures of Potential Conflicts of Interest: The author(s) indicated no potential conflicts of interest.

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Author's Contribution: ZY Chen and SQ Deng designed the research. ZP Liu, ZJ Cheng, and HS Dai performed the research. ZP Liu, ZJ Cheng, HS Dai, WY Chen, XC Liu, HN Fan, Y Pan, J Bai, Y Jiang, and YQ Zhang analyzed the data. ZP liu, ZJ Cheng, and HS Dai wrote the paper. YQ Zhang, SQ Deng and ZY Chen reviewed the manuscript. ZY Chen integrated the entire study. All authors read and approved the final manuscript. ZP liu, ZJ Cheng, and HS Dai contributed equally to this work.

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Figures

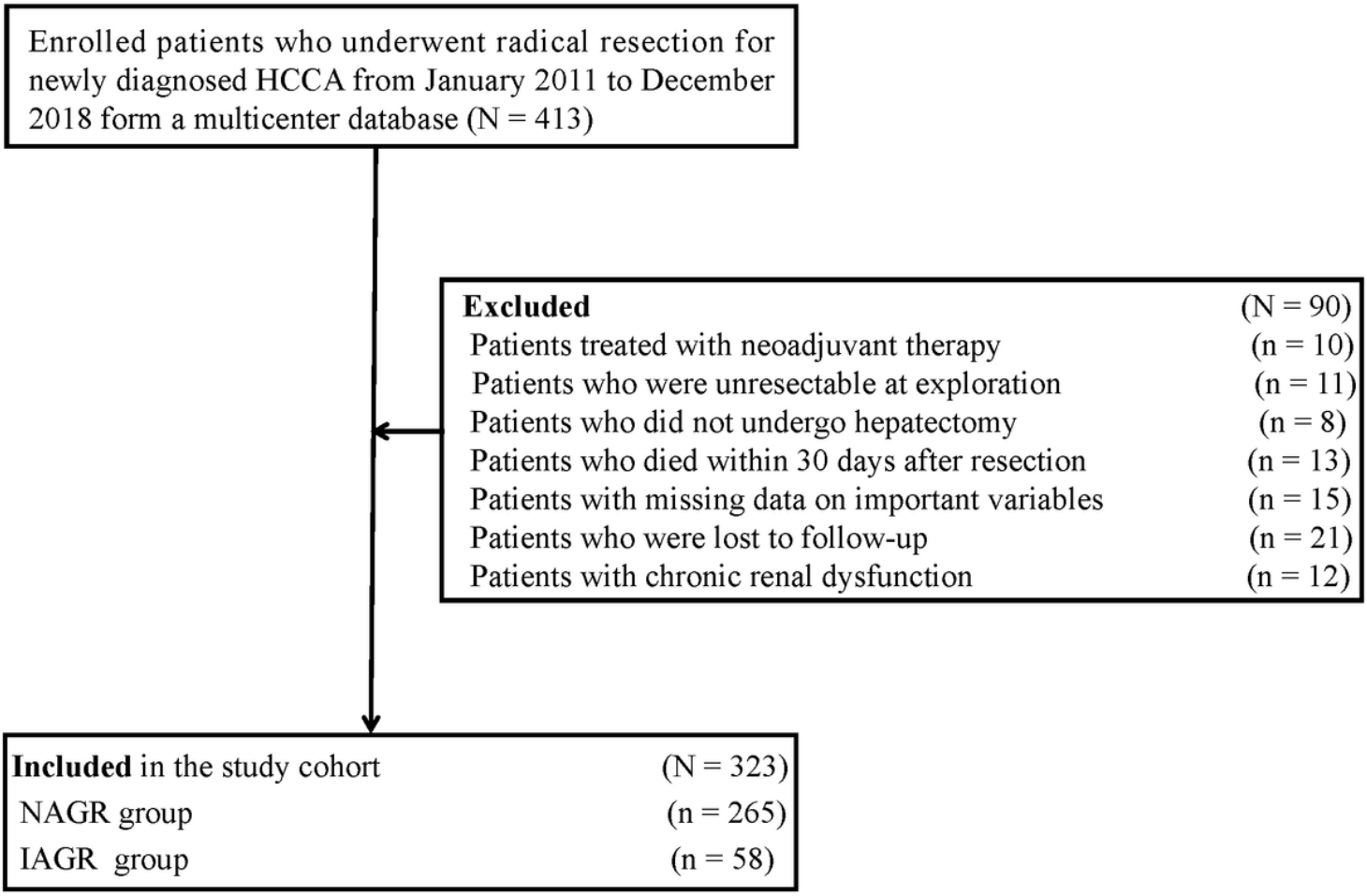

Figure 1

Selection of the study population.

Abbreviations: HCCA, Hilar cholangiocarcinoma; NAGR, normal albumin-to-globulin ratio; IAGR, inversed albumin-to-globulin ratio.

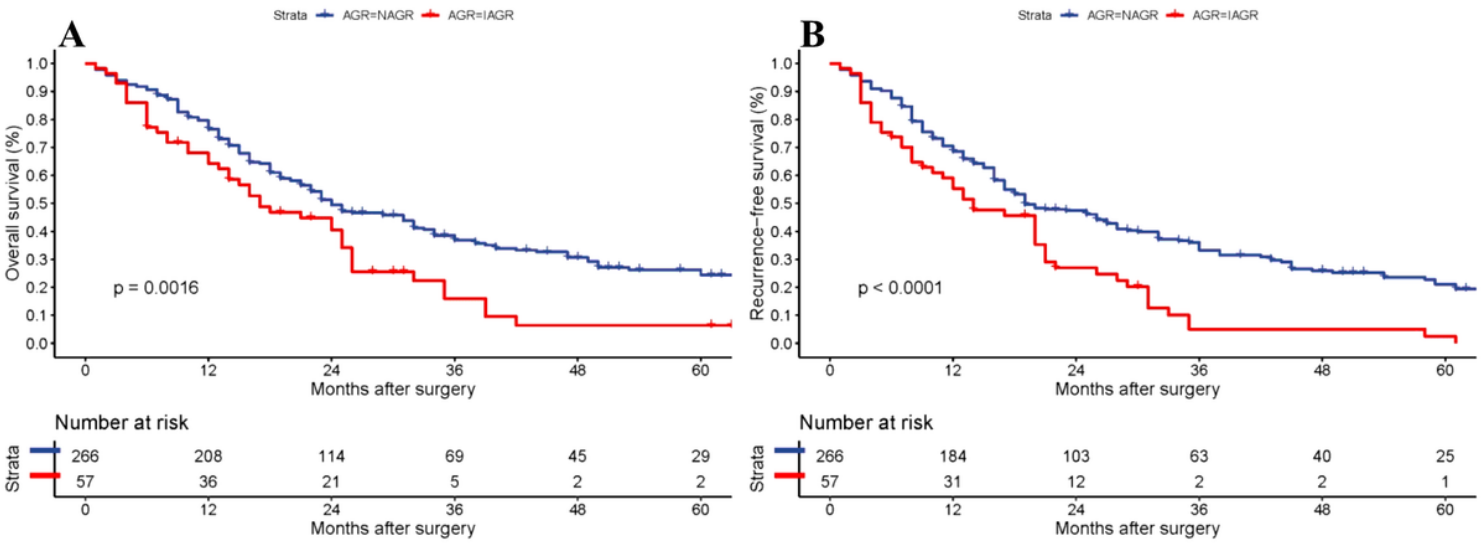

Figure 2

Overall survival (A) and recurrence-free survival (B) curve comparisons between the IAGR and NAGR groups.

Abbreviations: NAGR, normal albumin-to-globulin ratio; IAGR, inversed albumin-to-globulin ratio.

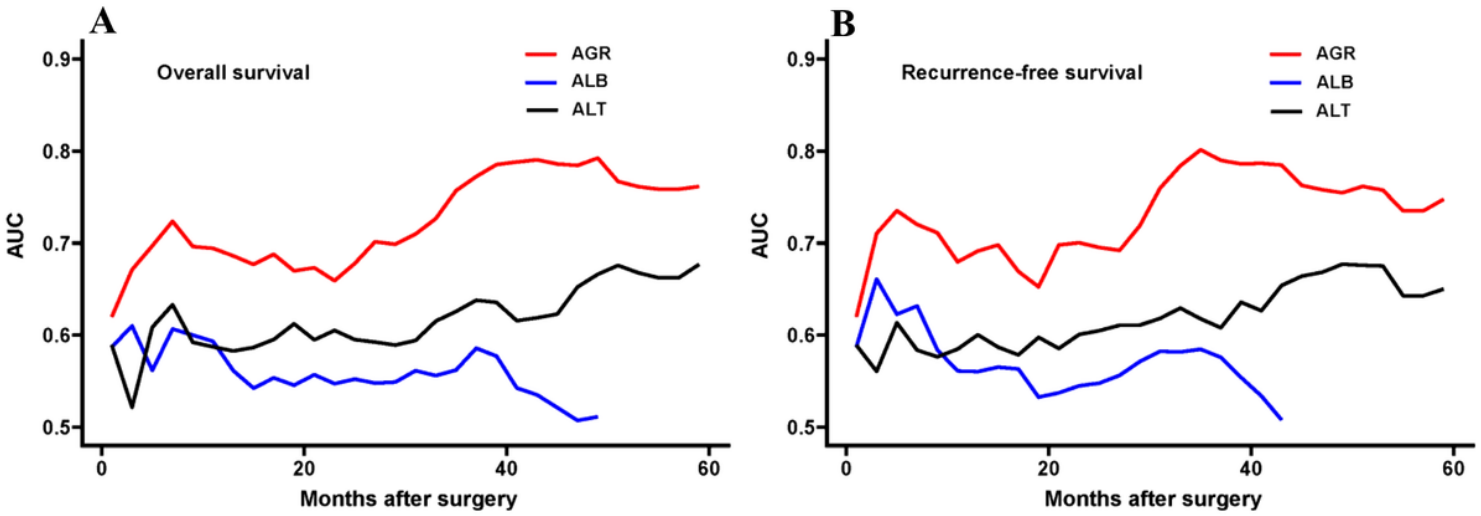

Figure 3

Predictive ability of AGR and ALB for overall survival (A) and recurrence-free survival (B).

Abbreviations: AGR, albumin-to-globulin ratio; ALB, albumin; ALT, alanine aminotranferase.

Supplementary Files

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- Data.xlsx