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Preoperative albumin-alkaline phosphatase ratio affects the prognosis of patients undergoing hepatocellular carcinoma surgery

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Abstract.

BACKGROUND: The correlation between the preoperative albuminalkaline phosphatase ratio (AAPR) and the prognosis of hepatocellular carcinoma (HCC) patients after radical resection is still not comprehensive.

OBJECTIVE: This study aims to observe the correlation between preoperative AAPR and the prognosis of HCC patients after radical resection.

METHODS: We constructed a retrospective cohort study and included 656 HCC patients who underwent radical resection. The patients were grouped after determining an optimum AAPR cut-off value. We used the Cox proportional regression model to assess the correlation between preoperative AAPR and the prognosis of HCC patients after radical resection.

RESULTS: The optimal cut-off value of AAPR for assessing the prognosis of HCC patients after radical resection was 0.52 which was acquired by using X-tile software. Kaplan-Meier analysis curves showed that a low AAPR ($\leqslant 0.52$) had a significantly lower rate of overall survival (OS) and recurrence-free survival (RFS) ($P < 0.05$). Multiple Cox proportional regression showed that an AAPR > 0.52 was a protective factor for OS (HR $= 0.66$, 95%CI 0.45-0.97, $p = 0.036$) and RFS (HR $= 0.70$, 95% CI 0.53–0.92, $p = 0.011$).

CONCLUSIONS: The preoperative AAPR level was related to the prognosis of HCC patients after radical resection and can be used as a routine preoperative test, which is important for early detection of high-risk patients and taking personalized adjuvant treatment.

Keywords: Albumin-alkaline phosphatase ratio, survival rates, surgery, hepatocellular carcinoma, prognosis

1. Introduction

Primary liver cancer (PLC) is a relatively common malignancy worldwide. It is also a major contributor to cancer deaths. Approximately 75 to 85% of PLC cases are hepatocellular carcinoma (HCC) [1]. There are various treatments for HCC, among which surgical resection of the tumor and liver transplantation have the best therapeutic effects [2]. However, due to a shortage of liver donors, the popularization and application of

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liver transplantation are limited [3]. Therefore, patients with HCC are most likely to benefit from surgical resection. The technical expertise involved in performing surgical resection of HCC has greatly improved over the years as medical technologies have developed and progressed. Even so, an unacceptably large proportion of HCC patients who undergo surgical resection have the possibility of recurrence and metastasis, and this is detrimental to their prognosis. Therefore, it would be advantageous to explore a simple and useful postoperative prognosis evaluation index for patients, which will potentially help clinicians identify those at high risk early and implement appropriate interventions.

Over the past few years, with the exception of alpha-fetoprotein (AFP) levels, studies have continued to show that the ratios of a number of combined indexes were related to the prognosis of HCC patients that after surgical resection. These included neutrophil-lymphocyte ratio (NLR), albumin-glutamyl transferase ratio (AGR) and albumin-bilirubin (ALBI) [4–6]. The prognosis of HCC is determined by several factors including liver function. Albumin (ALB) as well as alkaline phosphatase (ALP) are important indexes for the assessment of liver function and they can reflect the status of this organ. ALB is produced by the liver and is closely related to inflammation [7]. It can also inhibit the proliferation of HCC by changing the phosphorylation of Rb protein [8]. As a substance related to both the liver and bones, elevated levels of ALP are known to be closely related to patients' survival rates for HCC, and often indicate a poor prognosis [9,10]. Chan and his team first proposed that the AAPR may have prognostic significance in HCC [11], and this index has gradually proven to reflect upon the prognosis of patients with HCC. According to previous studies, there is an association between the preoperative AAPR and the prognosis of HCC patients after liver transplantation as well as in hepatitis B virus (HBV)-related HCC patients after hepatectomy [12,13]. This index also has a strong correlation with the clinical prognosis among patients with early-diagnosed breast cancer, IB-IIA cervical cancer and those with pancreatic ductal adenocarcinoma that cannot undergo resection [14–16]. At present, the relationship between preoperative AAPR and the prognosis of HCC patients after radical resection is not comprehensive. We undertook this study primarily to determining the prognostic significance of preoperative AAPR among HCC patients that after radical resection.

2. Materials and methods

2.1. Research population

We used the active health management platform to construct a retrospective cohort study. (Registration site: http://www.chictr.org.cn/index.aspx; registration number: ChiCTR2200062446). Briefly, the active health management platform used an advanced medical data management system to manage the patients, and connected and indexed all the diagnosis and treatment records held at the hospital. It contains outpatient, inpatient and physical examination data, covering the diagnosis and treatment regimens, test reports, examination reports, electronic medical records and other medical data of the outpatients, inpatients and those undergoing physical examinations. All the medical information assessed was obtained from the electronic database, including demographic characteristics, medical diagnostic codes, surgical codes, drug prescriptions and death-related data. The information regarded a patient was automatically integrated into this platform whenever someone attended the clinic.

We reviewed inpatients diagnosed with HCC at the Guangxi Academy of Medical Sciences and the People's Hospital of Guangxi Zhuang Autonomous Region from May 2013 to March 2022. The criteria for inclusion were: (1) HCC was diagnosed for the first time by pathology (2) the patient had undergone radical hepatectomy (negative margin) (3) comprehensive clinicopathological and follow-up information were available for the patients. The criteria for exclusion were: (1) patients who had received antitumor therapy such as interventional, targeted and immune therapy or they had undergone liver transplantation, before surgery (2) patients with other malignant tumors and hematological diseases (3) those with missing either clinical baseline data or follow-up information. After screening, 656 HCC patients took part in this present study (Fig. 1). The study was approved by the Ethics Committee of Guangxi Academy of Medical Sciences and Guangxi Zhuang Autonomous Region People's Hospital, and it met the guidelines set by the Helsinki Declaration. As the data was anonymized, individual informed consent was not needed for this study.

2.2. Data acquisition and patients' follow-up

The hospital big data retrieval platform was used to obtain the clinical data for the study subjects, including patients' general personal data, past medical

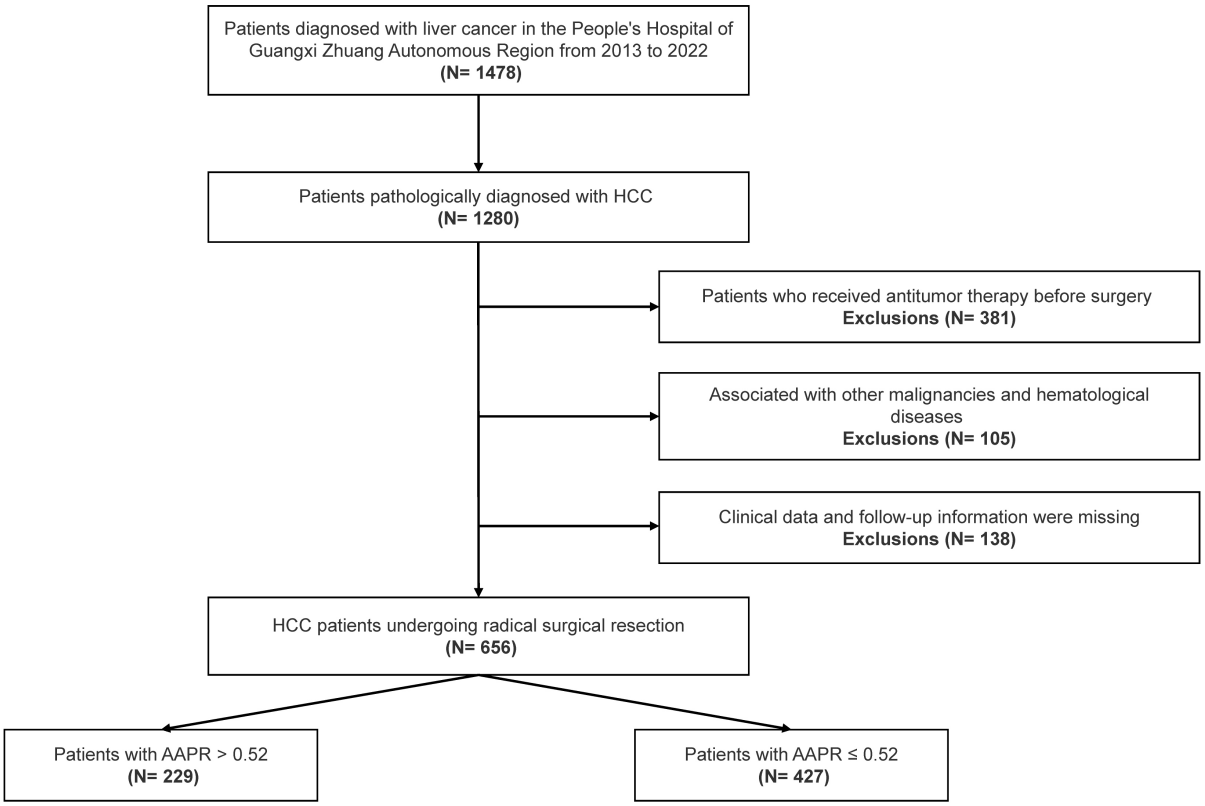

Fig. 1. A flow chart of inclusion and exclusion criteria of the patients in this study. (HCC: hepatocellular carcinoma; AAPR: albuminalkaline phosphatase ratio).

histories, preoperative blood test results, imaging data and postoperative pathological data. The tumor characteristics included diameter, number, portal vein invasion, microvascular invasion, tumor differentiation grade and recurrence or metastasis after tumor resection, which could all be obtained from the imaging and pathological data. The hospital's health management cloud platform was used for all the patients with postoperative routine follow-up at 1, 6, 12, 18 24, 30 and 36 months follow-up points within 3 years of discharge. For patients who have been discharged from hospital for more than 3 years, follow-up visits were carried out at least once a year. For some patients who were not able to return regularly at the appointed times, they were followed-up by telephone. The overall survival (OS) was calculated as the interval from the date of surgery until death or the last time the patient was followed up, and the recurrence-free survival (RFS) was calculated as the time interval between the date of surgery and recurrence.

2.3. Statistical analysis

We used the X-tile software [17] (https://x-tile.software.informer.com/) to access the optimal cut-off value of AAPR, and used this cut-off value to divide the patients into two groups. Numbers and percentages were used to express the categorical variables. All the continuous variables were presented as medians and interquartile ranges. For baseline data between AAPR > 0.52 and AAPR $\leqslant 0.52$ participants, continuous and categorical data were compared by using the Mann-Whitney U and chi-square tests, respectively. Kaplan-Meier analysis was used to perform survival analysis and further differences were compared by using log-rank tests. We used the Cox proportional regression models to assess the relationship between preoperative AAPR and the prognosis of HCC patients after radical resection, and the hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. We used Schoenfeld residuals to evaluate the proportional hazards assumption. Covariate selection was based on a backward selection procedure and other potential con-

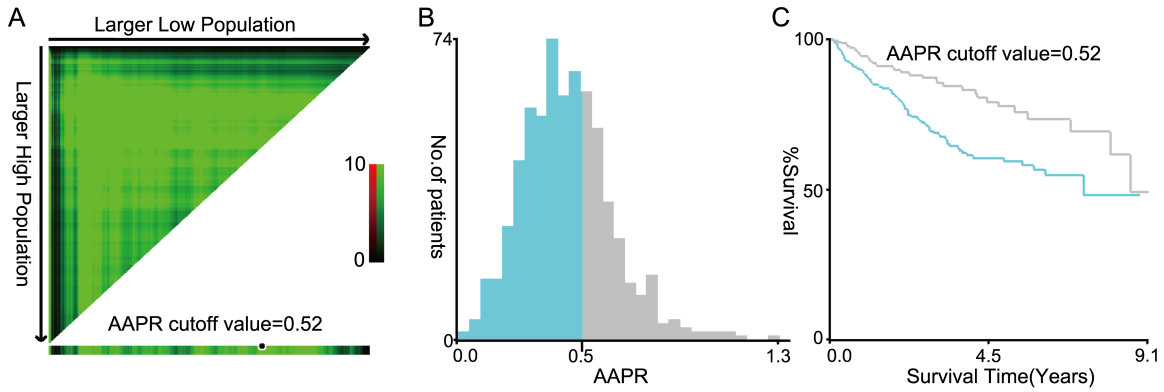

Fig. 2. The cut-off value of AAPR obtained by using the X-tile software was 0.52 where it was shown to have the strongest prognostic ability (A–C). (AAPR: albuminalkaline phosphatase ratio).

founders were identified from the literature. SPSS 22.0 software (IBM Corp., Armonk, NY, USA) was used for statistical analysis. A P value < 0.05 was considered to be statistically significant.

3. Results

3.1. Correlation of AAPR with clinical data

X-tile software analysis showed that the optimal AAPR cut-off value for evaluating OS and RFS was 0.52 (Figs 2A–C). On the basis of this cut-off value, the population we studied could be divided into two groups with high (> 0.52) and low (< 0.52) AAPR, and these included 229 (34.9%) and 427 patients (65.1%), respectively.

Table 1 shows the general personal data and clinicopathological characteristics of the participants in each group. In comparison with the high AAPR group, the patients in the low AAPR group were older ($P = 0.001$). Aspartate aminotransferase (AST), gamma glutamyl transpeptidase (GGT) and alanine aminotransferase (ALT) levels were higher, respectively ($P < 0.001$ in each case). The levels of ALP were also higher ($P < 0.001$) but those of ALB were lower ($P < 0.001$) in the low when compared to the high AAPR group. The rate of positivity to HBV-DNA was higher ($P = 0.029$). The levels of AFP were higher ($P = 0.022$) and the tumor diameters were larger ($P < 0.001$), respectively. In addition, the incidence of multiple intrahepatic tumors, portal vein tumor thrombus (PVTT) and microvascular infiltration (MVI) were also higher ($P = 0.001$, in all cases respectively) in the low AAPR group. Liver cirrhosis ($P = 0.001$) and the occurrence of grade B Child-Pugh were more common ($P < 0.001$) in the low in comparison to the high AAPR group. It was also found that significantly more patients had an advanced Barcelona Clinic Liver Cancer (BCLC) stage ($P = 0.007$) in the low AAPR group. However, no significance was found in the correlation between preoperative AAPR levels and gender, total bilirubin levels, tumor differentiation, paracancerous tissue invasion and liver capsule invasion ($P > 0.05$ in all cases).

3.2. Prognostic factors related to OS and RFS

The impact of AAPR and other clinicopathological features on the prognosis of patients after surgery was investigated using COX regression analysis. Univariate analysis showed significant associations between preoperative AAPR, age, gender, tumor diameter, tumor number, PVTT, MVI, Child-Pugh grade and BCLC stage with OS ($P < 0.05$). Multivariate regression analysis found that preoperative AAPR (HR = 0.66, 95%CI 0.45–0.97, $p = 0.036$), age (HR = 0.98, 95%CI 0.97–1.00, $p = 0.033$), gender (HR = 1.66, 95%CI 1.02–2.71, $p = 0.043$), tumor diameter (HR = 1.09, 95%CI 1.04–1.14, $p < 0.001$), tumor number (HR = 1.62, 95%CI 1.04–2.54, $p = 0.033$) and MVI (HR = 1.98, 95%CI 1.38–2.84, $p < 0.001$) were independent prognostic factors for OS. A high level of preoperative AAPR (> 0.52) was significantly correlated with a longer OS (Table 2).

With respect to RFS, univariate analysis showed that preoperative AAPR, age, HBV-DNA, tumor diameter, tumor number, tumor differentiation grade, PVTT, MVI, hepatic capsule invasion and Child-Pugh grade and BCLC stage were significantly related to RFS ($P < 0.05$ in all cases). After including the above factors in the multivariate COX regression analysis, the following results were obtained: preoperative AAPR (HR = 0.70,

Table 1
Association of AAPR with patients' clinical data

Variables	Type	Total ($n = 656$)	AAPR $\leqslant 0.52$ ($n = 427$)	AAPR > 0.52 ($n = 229$)	P-value
Age (year)		53.0 (44.0–62.0)	54.0 (46.5–63.0)	50.0 (41.0–61.0)	0.001
Gender					0.981
	Female	120 (18.3%)	78 (18.3%)	42 (18.3%)	
	Male	536 (81.7%)	349 (81.7%)	187 (81.7%)	
BCLC					0.007
	0-A	293 (44.7%)	170 (39.8%)	123 (53.7%)	
	B	31 (4.7%)	23 (5.4%)	8 (3.5%)	
	C	323 (49.2%)	227 (53.2%)	96 (41.9%)	
	D	9 (1.4%)	7 (1.6%)	2 (0.9%)	
Child-Pugh					< 0.001
	A	599 (91.3%)	376 (88.1%)	223 (97.4%)	
	B	57 (8.7%)	51 (11.9%)	6 (2.6%)	
Tumor diameter (cm)		5.0 (3.0–7.7)	5.5 (3.2–8.6)	4.2 (2.7–6.0)	< 0.001
Tumor number					0.001
	1	555 (84.6%)	347 (81.3%)	208 (90.8%)	
	Multiple	101 (15.4%)	80 (18.7%)	21 (9.2%)	
Differentiation					0.358
	Low	57 (8.7%)	42 (9.8%)	15 (6.6%)	
	Middle	533 (81.2%)	342 (80.1%)	191 (83.4%)	
	High	66 (10.1%)	43 (10.1%)	23 (10.0%)	
PVTT					0.001
	No	583 (88.9%)	367 (85.9%)	216 (94.3%)	
	Yes	73 (11.1%)	60 (14.1%)	13 (5.7%)	
MVI					< 0.001
	No	383 (58.4%)	227 (53.2%)	156 (68.1%)	
	Yes	273 (41.6%)	200 (46.8%)	73 (31.9%)	
Paracancerous tissue infiltration					0.07
	No	579 (88.3%)	384 (89.9%)	195 (85.2%)	
	Yes	77 (11.7%)	43 (10.1%)	34 (14.8%)	
Invasion of liver capsule					0.641
	No	503 (76.7%)	325 (76.1%)	178 (77.7%)	
	Yes	153 (23.3%)	102 (23.9%)	51 (22.3%)	
Cirrhosis					0.001
	No	407 (62.0%)	246 (57.6%)	161 (70.3%)	
	Yes	249 (38.0%)	181 (42.4%)	68 (29.7%)	
HBV-DNA					0.029
	No	404 (61.6%)	250 (58.5%)	154 (67.2%)	
	Yes	252 (38.4%)	177 (41.5%)	75 (32.8%)	
AFP (ng/dL)		80.8 (7.7–800.0)	101.3 (11.7–800.0)	65.6 (5.2–800.0)	0.022
ALT (IU/L)		33.0 (23.0–51.0)	35.0 (24.0–56.5)	29.0 (21.0–45.0)	< 0.001
AST (IU/L)		38.0 (28.0–57.0)	43.7 (32.0–63.5)	30.0 (24.0–42.0)	< 0.001
TBIL (μmol/L)		13.5 (10.2–18.3)	13.4 (10.1–18.9)	13.6 (10.4–17.2)	0.596
ALP (U/L)		84.0 (68.8–110.0)	99.0 (84.5–126.0)	65.0 (55.6–71.0)	< 0.001
ALB (g/L)		38.2 (35.1–40.9)	37.0 (34.0–40.0)	39.9 (37.6–42.6)	< 0.001
GGT (IU/L)		58.1 (35.0–112.2)	76.0 (46.5–141.0)	39.0 (26.0–58.0)	< 0.001
HGB (g/L)		135.0 (123.0–148.0)	135.0 (121.5–149.0)	137.0 (125.0–147.0)	0.106
PT (s)		13.8 (13.2–14.4)	13.8 (13.2–14.5)	13.8 (13.2–14.3)	0.449
Values are expressed as medians (Q1–Q3) or number (%)					

AAPR: albumin-alkaline phosphatase ratio; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TBIL: total bilirubin; ALP: alkaline phosphatase; ALB: albumin; GGT: gamma glutamyl transpeptidase; HGB: hemoglobin; PT: prothrombin time; HBV: hepatitis B virus; AFP: alpha-fetoprotein; PVTT: portal vein tumor thrombus; MVI: microvascular infiltration; BCLC: Barcelona Clinic Liver Cancer.

95% CI 0.53–0.92, $p = 0.011$), age (HR = 0.99, 95% CI 0.98–1.00, $p = 0.011$), tumor diameter (HR = 1.07, 95% CI 1.04–1.11, $p < 0.001$), tumor number (HR = 1.55, 95% CI, 1.14–2.11, $p = 0.005$) and MVI (HR = 1.80, 95%CI 1.40–2.31, $p < 0.001$) were independent prognostic factors for RFS. A high level of AAPR (> 0.52) was significantly associated with longer RFS (Table 3). From the above results, it can also be seen that preoperative AAPR, age, tumor diameter, tumor number and MVI were common significant independent prognostic factors for OS and RFS.

Table 2
Univariate and multivariate analysis of the factors associated with OS

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (year)	0.98 (0.97, 1.00)	0.021	0.98 (0.97–1.00)	0.033
Gender				
Female	1			
Male	1.66 (1.02, 2.68)	0.041	1.66 (1.02–2.71)	0.043
ALT (IU/L)	1.00 (1.00, 1.00)	0.704		
AST (IU/L)	1.00 (1.00, 1.00)	0.957		
TBIL (μmol/L)	1.00 (0.99, 1.01)	0.935		
PT (s)	1.06 (0.91, 1.23)	0.461		
HBV-DNA				
No	1			
Yes	1.19 (0.85, 1.65)	0.305	0.89 (0.63–1.26)	0.512
Tumor diameter (cm)	1.13 (1.09, 1.18)	< 0.001	1.09 (1.04–1.14)	< 0.001
Tumor number				
1	1			
Multiple	1.62 (1.05, 2.51)	0.03	1.62 (1.04–2.54)	0.033
Differentiation				
Low	1			
Middle	0.86 (0.51, 1.45)	0.572		
High	0.48 (0.22, 1.05)	0.068		
PVTT				
No	1			
Yes	2.39 (1.52, 3.75)	< 0.001	1.12 (0.66–1.89)	0.677
MVI				
No	1			
Yes	2.62 (1.88, 3.66)	< 0.001	1.98 (1.38–2.84)	< 0.001
Paracancerous tissue infiltration				
No	1			
Yes	0.92 (0.57, 1.48)	0.731		
Invasion of liver capsule				
No	1			
Yes	1.34 (0.93, 1.92)	0.119		
Cirrhosis				
No	1			
Yes	0.93 (0.65, 1.34)	0.705	0.90 (0.62–1.32)	0.601
Child-Pugh				
A	1			
B	1.78 (1.02, 3.11)	0.043	1.15 (0.64–2.05)	0.639
BCLC				
0-A	1			
B	1.09 (0.44, 2.70)	0.856		
C	1.43 (1.02, 2.03)	0.041		
D	0.82 (0.11, 5.90)	0.841		
AAPR group				
$\leqslant 0.52$	1		1	
> 0.52	0.55 (0.38, 0.80)	0.002	0.66 (0.45–0.97)	0.036

OS: overall survival; HR: Hazard ratio; AAPR: albumin-alkaline phosphatase ratio; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TBIL: total bilirubin; HGB: hemoglobin; PT: prothrombin time; HBV: hepatitis B virus; PVTT: portal vein tumor thrombus; MVI: microvascular infiltration; BCLC: Barcelona Clinic Liver Cancer.

3.3. Survival analysis

The 1st, 3rd and 5th year OS rates of the high AAPR (> 0.52) group were 93.12%, 85.58% and 76.24%, and these were significantly higher than the patients in the low AAPR ($\leqslant 0.52$) group (88.53%, 69.45% and 59.89%, respectively) ($P < 0.05$; Fig. 3A). When compared to the OS median of the low AAPR group (7.20 years), the high AAPR group (8.54 years) were significantly longer ($P < 0.05$). In RFS we obtained the same results. The RFS rates of the high AAPR group at 1st, 3rd and 5th year were 77.14%, 63.74% and 55.68%, which were significantly higher than the patients in the low AAPR group (62.99%, 43.40% and 34.43% respectively) ($P < 0.05$; Fig. 3B). Patients in

Table 3
Univariate and multivariate analysis of the factors associated with RFS

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (year)	0.98 (0.98, 0.99)	0.002	0.99 (0.98–1.00)	0.011
Gender				
Female	1			
Male	1.25 (0.91, 1.70)	0.169	1.18 (0.86–1.62)	0.307
ALT (IU/L)	1.00 (1.00, 1.00)	0.986		
AST (IU/L)	1.00 (1.00, 1.00)	0.514		
TBIL(μmol/L)	1.00 (0.98, 1.01)	0.358		
PT (s)	1.05 (0.95, 1.17)	0.322		
HBV-DNA				
No	1			
Yes	1.47 (1.16, 1.85)	0.001	1.21 (0.95–1.54)	0.118
Tumor diameter (cm)	1.12 (1.08, 1.15)	< 0.001	1.07 (1.04–1.11)	< 0.001
Tumor number				
1	1			
Multiple	1.62 (1.20, 2.19)	0.002	1.55 (1.14–2.11)	0.005
Differentiation				
Low	1			
Middle	0.71 (0.49, 1.03)	0.068		
High	0.51 (0.31, 0.87)	0.012		
PVTT				
No	1			
Yes	2.15 (1.53, 3.02)	< 0.001	1.07 (0.73–1.59)	0.722
MVI				
No	1			
Yes	2.22 (1.76, 2.81)	< 0.001	1.80 (1.40–2.31)	< 0.001
Paracancerous tissue infiltration				
No	1			
Yes	1.06 (0.75, 1.48)	0.753		
Invasion of liver capsule				
No	1			
Yes	1.57 (1.22, 2.03)	< 0.001		
Cirrhosis				
No	1			
Yes	1.04 (0.82, 1.33)	0.73	0.94 (0.73–1.21)	0.629
Child-Pugh				
A	1			
B	1.65 (1.12, 2.43)	0.011	1.09 (0.72–1.63)	0.687
BCLC				
0–A	1			
B	1.84 (1.12, 3.03)	0.015		
C	1.13 (0.88, 1.44)	0.345		
D	0.60 (0.15, 2.43)	0.473		
AAPR group				
$\leqslant 0.52$	1			
> 0.52	0.58 (0.45, 0.75)	< 0.001	0.70 (0.53–0.92)	0.011

RFS: recurrence-free survival; HR: Hazard ratio; AAPR: albumin-alkaline phosphatase ratio; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TBIL: total bilirubin; HGB: hemoglobin; PT: prothrombin time; HBV: hepatitis B virus; PVTT: portal vein tumor thrombus; MVI: microvascular infiltration; BCLC: Barcelona Clinic Liver Cancer.

the high AAPR group had a significantly longer median RFS (6.18 years) compared to those in the low AAPR group (2.20 years) ($P < 0.05$).

3.4. Subgroup analysis

In this study, the preoperative AAPR was negatively correlated with the probability of death and recurrence of HCC patients after radical resection. In order to further confirm the prognostic significance of preoperative AAPR, we conducted subgroup analysis on age, gender, HBV-DNA, tumor diameter, tumor number, PVTT, MVI, cirrhosis and the Child-Pugh grade (Table 4). Based on AAPR $\leqslant 0.52$ as reference group, we found that AAPR > 0.52 were protective factors for OS and

Table 4
Subgroup analysis of prognostic factors

Subgroup	OS		RFS	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (year)				
< 60	0.63 (0.41, 0.95)	0.026	0.65 (0.49, 0.87)	0.004
$\geqslant 60$	0.28 (0.11, 0.71)	0.008	0.37 (0.21, 0.65)	< 0.001
Gender				
Female	0.41 (0.14, 1.23)	0.112	0.99 (0.55, 1.81)	0.983
Male	0.57 (0.39, 0.85)	0.005	0.52 (0.39, 0.69)	< 0.001
HBV-DNA				
No	0.43 (0.26, 0.71)	< 0.001	0.52 (0.37, 0.73)	< 0.001
Yes	0.81 (0.46, 1.42)	0.466	0.74 (0.50, 1.10)	0.133
Tumor diameter (cm)				
$\leqslant 5$	0.65 (0.37, 1.14)	0.135	0.76 (0.53, 1.09)	0.131
$\geqslant 5$	0.59 (0.35, 0.99)	0.044	0.53 (0.36, 0.78)	0.001
Tumor number				
1	0.56 (0.38, 0.83)	0.004	0.61 (0.47, 0.81)	< 0.001
Multiple	0.62 (0.23, 1.69)	0.352	0.51 (0.25, 1.05)	0.066
PVTT				
No	0.57 (0.39, 0.85)	0.006	0.61 (0.47, 0.80)	< 0.001
Yes	0.58 (0.17, 1.97)	0.384	0.59 (0.25, 1.43)	0.243
MVI				
No	0.55 (0.32, 0.94)	0.027	0.63 (0.44, 0.89)	0.01
Yes	0.66 (0.40, 1.12)	0.121	0.63 (0.43, 0.93)	0.019
Cirrhosis				
No	0.51 (0.33, 0.78)	0.002	0.55 (0.40, 0.75)	< 0.001
Yes	0.68 (0.33, 1.38)	0.28	0.67 (0.42, 1.07)	0.096
Child-Pugh				
A	0.58 (0.40, 0.84)	0.004	0.56 (0.43, 0.73)	< 0.001
B	0.50 (0.07, 3.88)	0.508	3.04 (1.14, 8.15)	0.027

The AAPR $\leqslant 0.52$ group was reference group. OS: overall survival; RFS: recurrence-free survival; HR: Hazard ratio; AAPR: albumin-alkaline phosphatase ratio; HBV: hepatitis B virus; PVTT: portal vein tumor thrombus; MVI: microvascular infiltration.

RFS in these subgroups of the population that were all-age, male, HBV-DNA negative, tumour diameter > 5 cm, single tumour, no PVTT, no MVI, no combined cirrhosis, and Child-Pugh class A. In addition, AAPR > 0.52 also provided better RFS for patients with combined MVI.

4. Discussion

At present, HCC represents a difficult and challenging malignant tumor to treat. This study was undertaken to further confirm whether preoperative AAPR can be a strong prognostic factor for HCC patients that after radical resection, so as to promote its use in clinical practice. Through our observations of the association between the preoperative AAPR and other clinicopathological features on the prognosis of HCC patients after radical resection, it was found that this ratio exhibited significant independent prognostic value. There was a significant association between a preoperative AAPR > 0.52 and a longer OS and RFS among HCC patients after radical resection.

Liver function is one of the important test indexes for HCC patients, and ALB and ALP are the related test indexes of this organ. ALB is abundant in plasma [18]. Its main physiological effects are to maintain colloid osmotic pressure within the body and transport various important substances. ALB also has been shown to have an inhibitory effect on proliferation of liver cancer cells [8]. In addition, inflammation and antioxidant processes are regulated by ALB in different organs of the body, and its plasma level has become a favorable factor for cancer patients [7]. ALB can be used in the treatment of many diseases in the clinic, and it is also one of the important markers of cancer [19]. Its level is related to the prognosis of patients with malignant tumors of the intrahepatic bile duct [20], breasts [21], intestinal tract [22] and esophagus [23]. In addition, some studies have combined the levels of ALB with either bilirubin [24] or fibrinogen [25] and these have become important prognostic factors for HCC patients. ALP is a metalloenzyme, that is ubiquitous in various biological species in nature and it helps a variety of important biological processes to take place. Altered levels of ALP is responsible for many serious diseases [26].

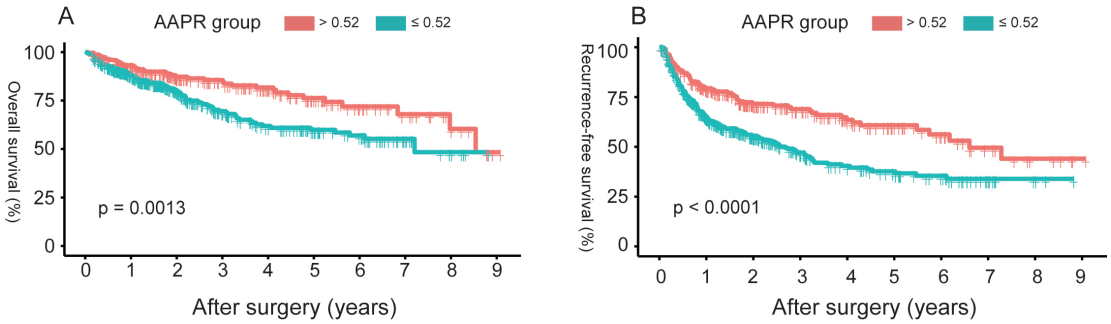

Fig. 3. The overall survival (A) and recurrence-free survival (B) based on the AAPR cut-off value of 0.52 in HCC patients undergoing radical resection. (HCC: hepatocellular carcinoma; AAPR: albuminalkaline phosphatase ratio).

Multiple studies have shown that there is a significant association between ALP levels and poor OS and RFS in HCC patients [9]. In addition, ALP is also related to the prognosis of patients with malignant tumors of the esophagus [27], rectum [28] and pancreas [29]. Therefore, it appears that the levels of ALB and ALP can reflect opposite effects in the occurrence and progression of tumors. Previously related studies showed decreased AAPR were found to correlate with shorter OS in cancer patients, suggesting poor clinical outcomes [30]. In addition to the various cancers previously mentioned, a low AAPR was considered to be an independent risk factor for OS as well as progression-free survival in metastatic nasopharyngeal carcinoma [31]. The AAPR is also related to poor OS and cancer-specific survival in uppertract urothelial carcinoma patients as well as those with non-metastatic renal cell carcinoma who have undergone surgical treatment [32,33]. This has also been demonstrated in lung malignancies [34,35]. Related studies pointed out that the c-index and X^2-value of AAPR, which can be derived from the circulating levels of albumin and alkaline phosphatase, had the highest prognostic evaluation ability among many liver biochemical indexes [11]. We combined these two closely related liver function indexes and assessed the prognosis of HCC patients after radical resection by employing correlation analysis.

In this retrospective cohort study, we used X-tile software to obtain the optimum cut-off value of 0.52 for the AAPR in order to divide all patients into high ($>$ 0.52) and low AAPR ($\leqslant$ 0.52) groups. From the distribution of the clinicpathological characteristics of the patients, we can see that, the preoperative AAPR levels were lower among patients with high AFP levels, larger diameter or multiple tumors, accompanied by PVTT or MVI, grade B Child-Pugh and BCLC stage B-C. HCC patients complicated with either MVI or PVTT often had to a greater risk of recurrence after radical resection, which was significantly related to poor treatment outcomes and prognosis [36,37]. The other factors mentioned above were also generally associated with poorer outcomes after surgery. Based on univariate and multivariate analyses, a low level of preoperative AAPR reflected an increased risk of OS and RFS, and this was an independent prognostic factor for patients with HCC undergoing radical hepatectomy. In addition, the age, tumor diameter, number of intrahepatic tumors and MVI were independently associated with the risk of OS and RFS. As can be seen from the Kaplan-Meier curves, OS and RFS rates were higher in the high AAPR group when compared with patients in low AAPR, and the medians of OS and RFS were also significantly longer. This result is similar to the findings of Chan's team who also showed that AAPR is independently associated with OS and cancer-free survival among HCC patients [11]. It was found in a study conducted by Li et al. on HCC patients undergoing liver transplantation that high AAPR are associated with lower rates of ascites and higher rates of Child-Pugh A grade, and AAPR is an independent prognostic factor for OS [12]. In one study of HCC patients undergoing transcatheter arterial chemoembolization therapy, high AAPR is strongly associated with ChildPugh B grade, PVTT, late tumor staging and reduced incidence of lymph node metastasis, AAPR has also been recognized as an independent prognostic factor and provides important prognostic information for the patient's OS [38]. Similarly, in another study conducted by Zhang et al. low levels of preoperative AAPR result in reduced OS and RFS in patients with early-stage HCC who are initially treated with radiofrequency ablation, AAPR can help to predict clinical outcomes in these patients [39]. This series of studies on the prognostic role of AAPR in HCC populations has consistently demonstrated that relative to high AAPR, low AAPR is strongly associated with poorer clinicopathologic features and the presence of adverse

comorbidities, suggesting a poor prognosis for patients after treatment. AAPR is considered an independent prognostic factor. However, there are some differences between our research and the research of others, we focused on observing the prognostic role of preoperative AAPR in patients with HCC after radical resection. We included age, gender, HBV-DNA, tumor diameter, tumor number, PVTT, MVI, liver cirrhosis and Child-Pugh grade groups in the subgroup analysis to further determine the prognostic significance of preoperative AAPR, based on AAPR $\leqslant 0.52$ as reference group, the results show that AAPR > 0.52 were protective factors for OS and RFS in these subgroups of the population that were all-age, male, HBV-DNA negative, tumour diameter > 5 cm, single tumour, no PVTT, no MVI, no combined cirrhosis, and Child-Pugh class A. In addition, AAPR > 0.52 also provided better RFS for patients with combined MVI. Some indexes such as: BCLC stage, paracancerous tissue infiltration, Invasion of liver capsule, PVTT, which are rare in the previous literature, were included in the study. In addition, on the basis of the existing research findings of others, our study additionally found that age, gender, MVI, tumor number and diameter are significant in postoperative OS and RFS in HCC patients. Preoperative AAPR is simple to obtain, economical, reproducible, and the results are relatively intuitive and stable, it can be used as a routine preoperative test. It can provide useful and objective prognostic information for HCC patients undergoing radical resection, it helps clinicians to detect HCC patients with a potentially poor postoperative prognosis early, strengthen the dynamic monitoring of patient and take personalized adjuvant treatment.

Our study has the following advantages: Firstly, our study had a long follow-up period, a large sample size, and more convincing conclusions. Secondly the cut-off value in this study were obtained using the X-tile software, a very novel method for optimising the selection of cut-off value. Thirdly, we ensured the consistency of baseline data as much as possible by excluding patients who received antitumor therapy other than surgery, and this reduced the interference caused by other treatments. Finally, a subgroup analysis further confirmed the prognostic effect of the AAPR. However, some limitations existed in this study. Firstly, although our study strictly defined the enrolled patients according to the criteria set out, there was an unavoidable selection bias. Secondly, the data were only obtained from the database of a single medical institution and the study was only conducted on patients who had received surgical treatment. However, there was a considerable number of HCC patients in our Chinese population and they were already in the middle and late stages when diagnosed, these patients would have missed the opportunity for surgery [40], therefore, more similar studies on advanced HCC patients with other treatment modalities (such as hepatic arterial infusion chemotherapy, targeted therapy and immunotherapy) are needed. Thirdly, the AAPR cutoff value needs to be validated in future prospective studies. Fourthly, at present, the molecular regulatory mechanism of the AAPR and poor prognosis is not clear, so this needs to be further explored by establishing a pathological specimen tissue bank. This may also be partly resolved by experimental work on animal models. Finally, all our patients were from China, and most of the etiologies were related to HBV infection. Therefore, this study's findings may lack some scientific guidance for patients with HCC caused primarily by alcoholic liver disease. Similar studies also need to be performed in other countries and populations around the world.

5. Conclusions

In summary, based on our results, the preoperative AAPR was significantly correlated with the prognosis of OS and RFS among HCC patients that after radical resection. Preoperative AAPR can be routinely tested in the clinic and it can be considered as a biomarker for the clinical management of HCC patients undergoing radical resection. It is helpful for clinicians to detect high-risk patients early, thereby strengthening patient monitoring and intervention. However, the evaluation ability of AAPR needs to be verified by future multicenter studies that utilizes larger cohorts of patients.

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