Prognostic significance of the preoperative alkaline phosphatase-to-albumin ratio in patients with hepatocellular carcinoma after hepatic resection

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Abstract. This study aimed to investigate the prognostic value of the preoperative alkaline phosphatase-to-albumin ratio (APAR) in patients with hepatocellular carcinoma (HCC) who underwent radical hepatectomy. The clinicopathological data from 330 patients was retrospectively analyzed. Receiver operating characteristic curves of APAR for diagnostic tumor recurrence were plotted with a cut-off value of 1.74. A high preoperative APAR value was significantly associated with hepatitis B surface antigen level, tumor diameter, and tumor-node-metastasis stage. The disease-free survival (DFS) and overall survival (OS) of patients with a high preoperative APAR were shorter than those with a low APAR. The independent risk factors for DFS were an APAR ≥1.74, and macrovascular invasion or tumor thrombus. The independent risk factors for OS were an APAR ≥1.74, existing clinical symptoms, α-fetoprotein level ≥20 ng/ml, macrovascular invasion or tumor thrombus, and family history of cancer. In conclusion, a preoperative APAR (≥1.74) is an independent risk factor influencing the poor prognosis of patients with HCC after curative hepatectomy, and patients with such a result should be closely monitored.

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Abbreviations: APAR, alkaline phosphatase-to-albumin ratio; HCC, hepatocellular carcinoma; DFS, disease-free survival; OS, overall survival; ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALB, albumin; APPRI, alkaline phosphatase-to-platelet ratio index; AGR, albumin-to-globulin ratio; AFP, α-fetoprotein; ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval; HBsAg, hepatitis B surface antigen; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; HBV, hepatitis B virus; US, ultrasound; CT, computed tomography; MRI, magnetic resonance imaging

Key words: hepatocellular carcinoma, hepatectomy, alkaline-phosphatase-to-albumin ratio, survival rate, prognosis

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common type of cancer and the third leading cause of cancer-related death worldwide (1,2). Although significant progress in the diagnosis and treatment of HCC has been achieved in recent decades, the survival of patients with HCC after resection remains poor. Tumor relapse and metastasis are the major complications of hepatectomy, occurring in >70% of patients within 5 years of follow-up (3). Therefore, non-invasive preoperative tumor biomarkers that can better predict HCC relapse and metastasis are urgently required. Consequently, early detection of patients with a high risk of recurrence or mortality and timely intervention may improve the postoperative survival of patients with HCC.

Alkaline phosphatase (ALP) is a hydrolase enzyme widely distributed in the human tissues of the liver, bile duct, intestine, bone, and kidney, but most ALP in serum is primarily from the liver (4). A previous study has demonstrated that ALP is an independent prognostic risk factor for patients with HCC (5). ALP is an enzyme typically used to evaluate liver damage (6). Albumin (ALB) is a key component of serum proteins and is closely related to long-term malnutrition and systemic immune responses (7). Moreover, tumor-mediated malnutrition and systemic inflammatory responses can affect the long-term postoperative survival of patients with HCC (8). To date, the significance of the preoperative ALP-to-ALB ratio (APAR) in predicting tumor relapse and survival of postoperative patients with HCC has yet to be established, although the preoperative

ALP-to-platelet ratio index (APPRI) (9), aspartate aminotransferase (AST)-to-lymphocyte ratio (10), and ALB-to-globulin ratio (AGR) (11) have been demonstrated to be independent risk factors for poor survival. The APPRI, AST-to-lymphocyte ratio, and AGR indicators are single feedback indicators for either liver function impairment or nutritional status, but none of these are useful markers for both. As an indicator of liver function, serum ALP levels are frequently used as a biomarker to determine the progression of liver diseases (6) and are significantly associated with poor survival in patients with HCC (12). Compared with APPRI, the AST-to-lymphocyte ratio, AGR, and APAR can reflect the systemic inflammatory response, immunity level, and nutritional status of patients under the influence of tumors. Therefore, this novel indicator is significantly important for the prognosis of patients with HCC after surgery.

This study aimed to investigate the correlation between preoperative APAR and the clinicopathological features of HCC and to evaluate the prognostic value of APAR after curative resection in patients with HCC.

Table I. Clinicopathological data of the 330 patients with hepatocellular carcinoma.

Parameters	Mean ± SD
Age, years	50.95±0.83
α-fetoprotein, ng/ml	3,221.76±942.84
Tumor size, cm	4.52±0.15
Hemoglobin, g/l	141.82±0.90
White blood cell, $x10^9$/l	6.29±0.70
Platelets, $x10^9$/l	160.09±3.26
Alkaline phosphatase, U/l	85.14±1.89
Aspartate aminotransferase, U/l	44.43±6.01
Alanine aminotransferase, U/l	45.59±6.04
Albumin, g/l	42.50±1.17
Total bilirubin, μmol/l	12.49±0.80
Direct bilirubin, μmol/l	4.97±0.62
Alkaline phosphatase-to-albumin ratio	2.11±0.06

Materials and methods

Study population. The clinical and pathological data of 370 patients with HCC treated with radical hepatectomy between November 2010 and January 2014 were retrospectively analyzed. The criteria for admission were as follows: i) radical hepatectomy, ii) pathologically proven HCC after surgery, and iii) absence of anti-tumor treatment before surgery. Patients were excluded if they i) died during the perioperative period, ii) were diagnosed with intrahepatic cholangiocarcinoma or non-primary liver cancer, iii) were positive for human immunodeficiency virus, iv) did not have complete clinical and pathological data, or v) had severe infections or immune system diseases or used hematology-related drugs within 1 month before enrollment in this study. Among the 370 patients, 3 died during the perioperative period, 8 had intrahepatic cholangiocarcinoma, 13 did not have primary liver cancer, and 16 did not have complete clinical data. Thus, 330 patients (271 men and 59 women) were enrolled in this study. Their ages ranged from 19 to 79 years, and the median age was 52 years. Written informed consent was obtained from all enrolled patients. The clinicopathological characteristics of these patients, including age, sex, clinical symptoms, hepatitis B surface antigen (HBsAg) level, serum α-fetoprotein (AFP) level, tumor diameter, tumor number, liver cirrhosis, macrovascular invasion or tumor thrombus, family history of cancer, and tumor-node-metastasis (TNM) stage, are displayed in Table I.

Receiver operating characteristic (ROC) curve. ROC curve analysis was performed to determine the best cut-off value of APAR to predict the prognosis of patients with HCC after the surgery (ALP unit, U/l albumin unit, g/l). The optimal cut-off value was determined as the value closest to the point with maximum specificity and sensitivity according to the correct index. The correct index, also known as the Youden's index, is the sum of the sensitivity and specificity minus 1. The best critical point of the cut-off value was determined using the following equation: Youden's index=sensitivity + specificity-1=sensitivity-(1-specificity). The best cut-off value was determined based on the maximum value of the Youden's index.

Follow-up. All patients were regularly followed up every 3 months during the first 3 postoperative years and every 6 months thereafter. Patients were followed up through outpatient reviews, phone calls, or house visits. The follow-up primarily consisted of liver function tests (ALT, ALP, γ-glutamyltransferase, total bilirubin, direct bilirubin, total protein, ALB, globulin, AGR, triglyceride, cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and glucose levels), tumor marker tests [AFP, carcinoembryonic antigen (CEA), and CA19-9], chest radiography, and abdominal ultrasound (US). Computed tomography (CT) or magnetic resonance imaging (MRI) was performed when clinical recurrence was suspected. Clinical relapse was confirmed if i) the AFP level increased again (AFP level ≥400 μg/l), ii) new lesions were detected by US, CT, or MRI, and iii) the patient was proven to have HCC after reoperation. Disease-free survival (DFS) was defined as the interval between the date of surgery and recurrence, metastasis, or death, whereas overall survival (OS) was defined as the interval between the date of surgery and death. Any missing data were treated as censored data for survival analysis.

Statistical analysis. Statistical analysis was performed using SPSS version 21.0 (IBM Corp.). A χ^2 test was used to compare the categorical variables. ROC curve analysis was performed to determine the best APAR cut-off value. Univariate analysis was performed to determine the significance of parameters found to be significant in the log-rank test for survival. The Cox proportional hazards model was used to perform multivariate survival analyses. Survival curves for patients with HCC were plotted using the Kaplan-Meier method. $P<0.05$ was considered to indicate a statistically significant difference.

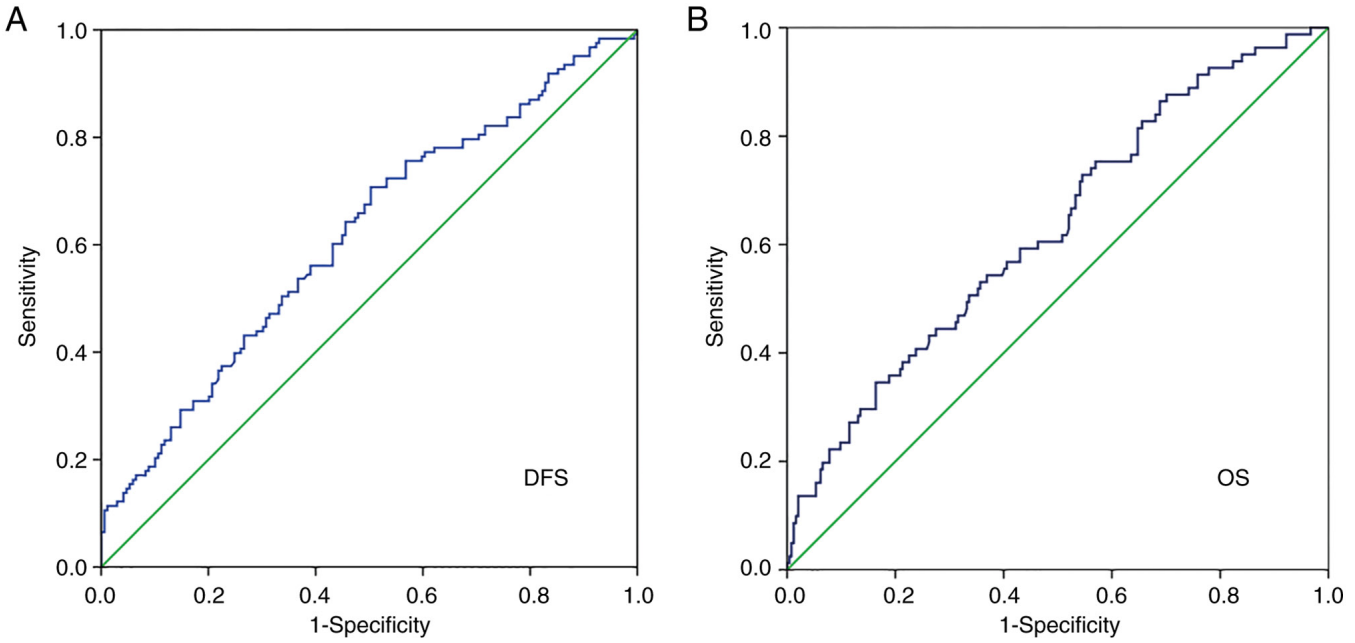

Figure 1. Receiver operating characteristics curve assessing the cut-off value of the APAR. (A) APAR cut-off value for DFS and (B) OS in patients with hepatocellular carcinoma after radical surgery. DFS, disease-free survival; OS, overall survival; APAR, alkaline phosphatase-to-albumin ratio.

Results

Biochemical and clinicopathological characteristics of the enrolled patients. Hemoglobin, AFP, ALT, ALP, ALB, globulin, total bilirubin, direct bilirubin, preoperative APAR values, and white blood cell and platelet counts are presented in Table I. The preoperative APAR value in this study was calculated using the following formula: (ALP value/ALB value) x g/U.

Optimal cut-off value of APAR for survival analysis. ROC curve analysis showed that the optimal cut-off value of APAR for DFS and OS was 1.74. It was considered the uniform point for survival analysis (Fig. 1A and B). The area under the curve (AUC) of APAR was 0.616 [95% confidence interval (CI): 0.550-0.681]. The optimal cut-off value of 1.74 presented a sensitivity of 0.707 and a specificity of 0.503.

Correlation between preoperative APAR and the clinicopathological characteristics of patients with HCC. The correlation between preoperative APAR and the clinicopathological factors of patients with HCC is shown in Table II. Based on the cut-off value of APAR, all patients were divided into a high APAR group (≥1.74, n=195) and a low APAR group (<1.74, n=135). The results demonstrated that a high preoperative APAR value was closely associated with positive HBsAg levels (P=0.041), tumor diameter (≥5 cm, P<0.001), and TNM stage (III/IV, P<0.044). No significant association was noted between APAR and age, sex, clinical symptoms, AFP level, tumor number, macrovascular invasion or tumor thrombus, or a family history of cancer (P>0.05).

Univariate analysis of prognostic factors in patients with HCC. Univariate analysis showed that a preoperative APAR value ≥1.74 (P=0.005) and macrovascular invasion or tumor thrombus (P=0.001) were associated with the median DFS of the patients. The significant predictors of OS were APAR ≥1.74 (P=0.008), clinical symptoms (P=0.002), AFP level ≥20 ng/ml (P=0.001), macrovascular invasion or tumors thrombus (P<0.001), and a family history of cancer (P=0.015) (Table III).

Multivariate analysis of prognostic factors in patients with HCC. The Cox proportional hazards regression model was used to examine the independent risk factors for the survival of postoperative patients with HCC. A stepwise multivariate Cox proportional hazards model revealed that a preoperative APAR value ≥1.74 [hazard ratio (HR): 1.781; 95% CI: 1.192-2.661; P=0.013] and macrovascular invasion or tumor thrombus (HR: 2.080; 95% CI: 1.284-3.368; P=0.003) were independent prognostic factors for DFS in patients with HCC. A preoperative APAR value ≥1.74 (HR: 1.828; 95% CI: 1.063-3.141; P=0.029), clinical symptoms (HR: 1.747; 95% CI: 1.045-2.918; P=0.046), AFP ≥20 ng/ml (HR: 1.739; 95% CI: 1.057-2.862; P=0.029), macrovascular invasion or tumor thrombus (HR: 2.216; 95% CI: 1.269-3.869; P=0.005), and a family history of cancer (HR: 1.833; 95% CI: 1.099-3.059; P=0.020) were independent prognostic predictors of OS in postoperative patients with HCC (Table IV).

Correlation between preoperative APAR and postoperative survival in patients with HCC. The above data confirmed that a preoperative APAR value ≥1.74 was significantly associated with a shorter DFS (P=0.005 and P=0.013, respectively) and OS (P=0.029 and P=0.001, respectively) in patients with HCC (Fig. 2A and B). Kaplan-Meier analysis showed that the 1, 3, and 5-year DFS rates of the APAR <1.74 group were significantly higher than those of the APAR ≥1.74 group (91.4, 73.2 and 68.3% vs. 81.1, 57.9 and 49.8% respectively, P=0.004). The 1, 3, and 5-year OS rates of the APAR <1.74 group were

Table II. Correlation between clinicopathological parameters and preoperative APAR.

			APAR		
Clinical factor	Variable	No. of patients (n=330)	<1.74 (n=135)	≥1.74 (n=195)	P-value
Age, years	<50	101	47	54	0.167
	≥50	229	88	141	
Sex	Female	59	23	36	0.740
	Male	271	112	159	
Clinical symptoms	No	267	113	154	0.282
	Yes	63	22	41	
Hepatitis B surface antigen	Negative	96	31	65	0.041[a]
	Positive	234	104	130	
α-fetoprotein, ng/ml	<20	194	81	113	0.710
	≥20	136	54	82	
Tumor diameter, cm	<5	217	107	110	<0.001[b]
	≥5	113	28	85	
Tumor number	Single	299	125	174	0.303
	Multiple	31	10	21	
Macrovascular invasion or tumor thrombus	No	280	116	164	0.65
	Yes	50	19	31	
Liver cirrhosis	No	127	56	71	0.352
	Yes	203	79	124	
Indocyanine green retention rate at 15 min	<10%	172	76	96	0.219
	≥10%	158	59	99	
Family history of cancer	No	254	104	150	0.981
	Yes	76	31	45	
TNM stage	I/II	320	134	186	0.044[a]
	III/IV	10	1	9	

[a]P<0.05, [b]P<0.001. APAR, alkaline phosphatase-to-albumin ratio.

also markedly higher than those of the APAR ≥1.74 group (95.3, 88.8 and 84.1% vs. 93.5, 79.9 and 66.3%, respectively, P=0.008).

Discussion

Predicting the postoperative survival of patients with HCC plays a key role in HCC treatment. To improve the accuracy and reliability of predictions, significant efforts have been made to identify effective prognostic indicators of HCC. Currently, clinicians and researchers commonly rely on conventional clinicopathological parameters, such as serum AFP, CEA, CA19-9 level, tumor size, tumor number, vascular invasion, and TNM stage. However, the sensitivity and specificity of AFP, CEA, and CA19-9 for predicting the prognosis of patients with HCC are limited. For example, serum AFP levels are not elevated in ~30% of patients (13), and various confounding factors can influence the reliability and accuracy of CEA in predicting the prognosis of patients with cholangiocarcinoma (14). Elevated serum CA19-9 levels are frequently found in normal bile secreted by a healthy biliary tract (15). Therefore, identifying less invasive and effective tumor biomarkers is important for the prognostic evaluation of HCC.

In this study, the clinicopathological parameters and prognosis of 330 patients with HCC who underwent radical hepatectomy were retrospectively analyzed. To avoid empirical selection bias, a reliable and objective cut-off value of 1.74 for APAR was determined via ROC curve analysis. Univariate analysis revealed that APAR ≥1.74 and macrovascular invasion or tumor thrombus was significantly correlated with DFS and OS after operation in patients with HCC. Meanwhile, Cox multivariate regression analysis showed that APAR ≥1.74, and macrovascular invasion or tumor thrombus were independent prognostic risk factors for DFS and OS in the overall cohort. In addition, univariate and Cox multivariate analyses showed that existing clinical symptoms, AFP level ≥20 ng/ml, and a family history of cancer were significantly associated with OS in these patients. The prognostic value of clinical symptoms, AFP level, macrovascular invasion or tumor thrombus, and a family history of cancer in patients with HCC has been reported in previous studies (16-18). Interestingly, an APAR ≥1.74 was found to be a novel prognostic indicator in patients with HCC after hepatectomy. The Cox regression model demonstrated that this indicator has an important prognostic value as an independent prognostic factor.

ALP is a hydrolase enzyme that plays a crucial role in the dephosphorylation of various biomolecules, including

Table III. Univariate analysis of the clinicopathological characteristics influencing prognosis.

Clinical factor	Variable	No. of patients (n=330)	Disease-free survival, months			Overall survival, months		
			Mean	95% CI	P-value	Mean	95% CI	P-value
Age, years	<50	101	49.48	44.08-54.88	0.566	59.98	56.24-63.71	0.431
	≥50	229	46.99	43.31-50.67		57.22	54.54-59.91	
Sex	Female	59	48.56	41.28-55.83	0.814	58.64	53.48-63.80	0.879
	Male	271	48.07	44.67-51.47		58.62	56.17-61.08	
Clinical symptoms	No	267	49.23	45.89-52.58	0.116	60.18	57.82-62.54	0.002[b]
	Yes	63	43.29	35.58-50.99		52.48	46.86-58.10	
Hepatitis B surface antigen	Negative	96	46.99	41.27-52.71	0.78	57.14	52.82-61.46	0.843
	Positive	234	48.42	44.79-52.05		58.90	56.34-61.45	
α-fetoprotein, ng/ml	<20	194	49.75	45.96-53.55	0.282	61.78	59.28-64.28	0.001[c]
	≥20	136	45.72	40.54-50.90		54.34	50.47-58.21	
Tumor diameter, cm	<5	217	49.90	46.17-53.62	0.135	59.69	57.10-62.27	0.238
	≥5	113	44.45	39.15-49.74		55.77	51.71-59.84	
Tumor number	Single	299	48.27	45.05-51.49	0.776	58.89	56.56-61.23	0.265
	Multiple	31	46.13	35.97-56.30		54.40	47.77-61.03	
Macrovascular invasion or tumor thrombus	No	280	50.10	46.88-53.32	0.001[c]	60.44	58.24-62.63	<0.001[c]
	Yes	50	33.97	26.13-41.82		46.60	39.42-53.77	
Liver cirrhosis	No	127	49.17	44.33-54.01	0.333	57.84	54.03-61.66	0.482
	Yes	203	47.18	43.25-51.11		58.60	55.95-61.26	
Family history of cancer	No	254	49.58	46.13-53.04	0.080	59.87	57.46-62.29	0.015[a]
	Yes	76	42.48	36.10-48.86		52.78	47.76-57.80	
TNM stage	I/II	320	48.04	44.92-51.16	0.582	58.87	56.63-61.11	0.102
	III/IV	10	52.71	35.21-70.22		48.29	34.67-61.91	
Alkaline phosphatase-to-albumin ratio	<1.74	135	53.53	49.13-57.93	0.004[b]	62.07	59.04-65.11	0.008[b]
	≥1.74	195	44.38	40.24-48.52		56.23	53.17-59.29	

[a]P≤0.05, [b]P≤0.01 and [c]P≤0.001. CI, confidence interval.

Table IV. Multivariate analysis of clinicopathological characteristics influencing prognosis in 330 patients with hepatocellular carcinoma.

Clinicopathological parameters	Disease-free survival		Overall survival	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Clinical symptoms, yes vs. no	1.286 (0.813-2.035)	0.283	1.747 (1.045-2.918)	0.046[a]
α-fetoprotein, ng/ml, ≥20 vs. <20	1.029 (0.697-1.520)	0.887	1.739 (1.057-2.862)	0.029[a]
Macrovascular invasion or tumor thrombus, yes vs. no	2.080 (1.284-3.368)	0.003[b]	2.216 (1.269-3.869)	0.005[b]
Family history of cancer, yes vs. no	1.438 (0.948-2.180)	0.087	1.833 (1.099-3.059)	0.020[a]
APAR, <1.74 vs. ≥1.74	1.781 (1.192-2.661)	0.005[b]	1.828 (1.063-3.141)	0.029[a]

[a]P<0.05 and [b]P<0.01. APAR, alkaline phosphatase-to-albumin ratio; CI, confidence interval; HR, hazard ratio.

nucleic acids, proteins, and alkaloids. It is widely distributed in human tissues of the liver, intestine, kidney, and bone. However, serum ALP is primarily present in the liver (19). Several reports have demonstrated increased secretion of ALP in the blood during some pathological conditions, such as pregnancy, urinary system diseases, and hepatic malignant tumors (20-22). In the correlation analysis, ALP levels were closely correlated with HBsAg levels. Preliminary statistical data showed that ~95% of patients with HCC in China also had hepatitis B virus (HBV) infection and liver cirrhosis (23). The three-step process of HBV infection, liver cirrhosis, and progression to HCC is well established (24). Chronic

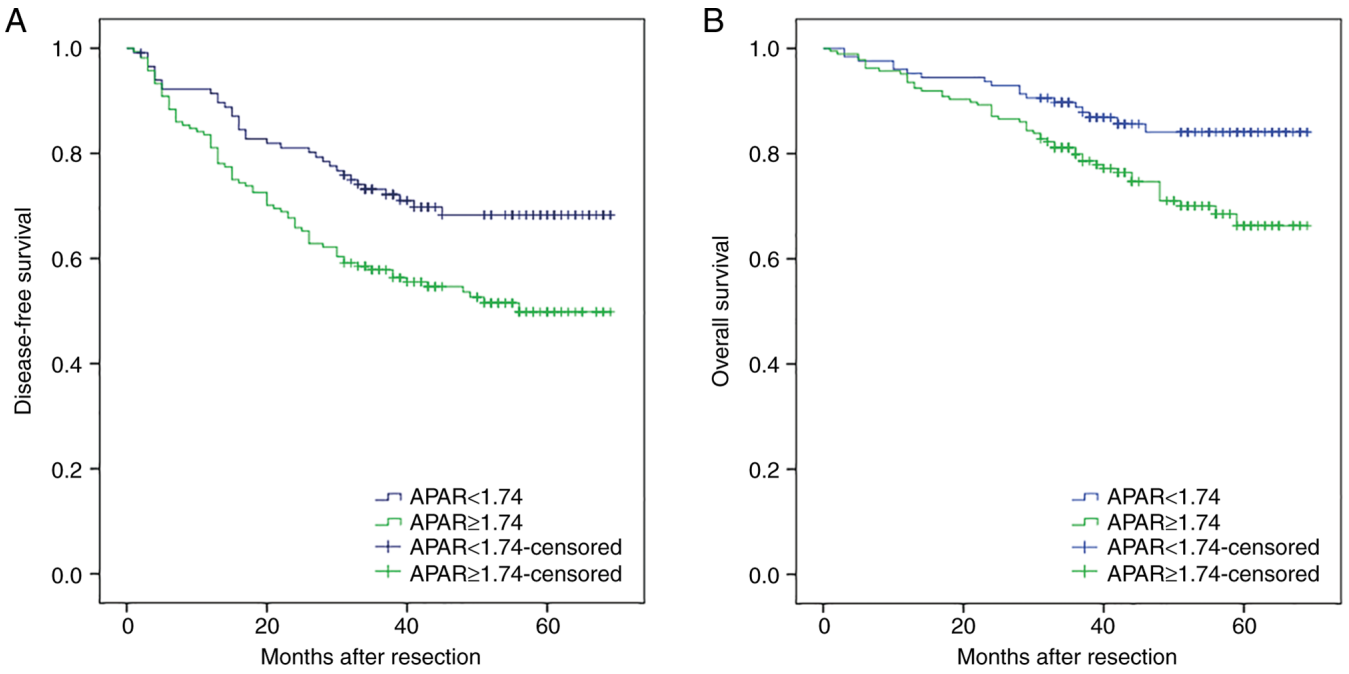

Figure 2. Kaplan-Meier survival analysis of preoperative APAR in 330 patients with hepatocellular carcinoma. (A) Disease-free survival according to APAR; and (B) overall survival according to APAR. APAR, alkaline phosphatase-to-albumin ratio.

HBV infection is the most severe factor causing progression to HCC, and the degree of liver fibrosis is correlated with tumor recurrence and OS in postoperative patients with small and solitary HBV-related HCC (25,26). This indicates that elevated serum ALP levels are closely correlated with HBV status and liver cirrhosis, which is consistent with the results of the present study in which high serum APAR was significantly associated with HBsAg positively in patients with HCC. Meanwhile, the correlation analysis showed that ALP was closely correlated with tumor size and TNM stage. ALP is related to the differentiation of embryonic cells and other stem cells derived from adipose tissue and bone (27). Proliferating tumor cells primarily induce aerobic glycolysis and elevated amino acid metabolism to maintain nucleotide biosynthesis and the transfer of amino groups, which are catalyzed by ALP (28). In addition, a study found that almost all cultured cancer cells, including HCC cells, had high ALP activity in the nucleolus, and the localization of ALP in cancer cells changed during the cell cycle (29). ALP may be involved in the proliferation and progression of malignant cells, indicating its role in tumor size and TNM stage (30). Moreover, advanced liver diseases, such as HCC, are typically accompanied by mitochondrial damage, which can substantially promote the release of ALP (31). However, liver fibrosis and cirrhosis reduce the plasma clearance of ALP, which also increases serum ALP levels (32). Therefore, high serum ALP levels are associated with HCC progression and patient survival.

In addition to ALP, the levels of serum liver enzymes, such as ALB, are also commonly elevated in patients with HCC and play crucial roles in the evaluation of the status of liver damage (33). ALB, the major component of serum proteins, is a nutritional indicator of the functions of stabilizing cell proliferation and DNA replication, buffering various biochemical variations, and exhibiting an antioxidant role against carcinogens, including nitrosamines and aflatoxins (34,35). Moreover, ALB is a reliable prognostic indicator in various malignant tumors, including HCC, colorectal, renal, and prostate cancers (36-38). The possible mechanisms for the association between low levels of serum ALB and poor survival of patients with HCC are systemic inflammatory response and malnutrition. Systemic inflammation and oxidative stress are pivotal in tumor progression (39-41). ALB is a reliable indicator of the host inflammatory response, which is important for tumorigenesis (42). Malnutrition, which is reflected by hypoproteinemia, can subvert the host's cellular and humoral immune response, resulting in an increased risk of infection and poor sensitivity to anti-cancer therapy (43,44). Furthermore, hypoalbuminemia in patients with HCC is caused by hepatic injury due to potential chronic liver disease, and a sustained systemic inflammatory reaction, either from the neoplasm itself or as a host response (45). Finally, malnutrition and systemic inflammatory response cause an imbalance in the tumor microenvironment, which can promote tumor growth, invasion, and metastasis (46). Therefore, decreased serum ALB levels may be closely associated with systemic inflammatory response and malnutrition, which may increase the risk of relapse and thus induce adverse survival in patients with HCC.

Taken together, high serum ALP levels are significantly associated with poorer clinical outcomes in patients with HCC. Conversely, a significant decrease in serum ALB levels is closely correlated with the adverse survival of patients with HCC. Therefore, high APAR is a reasonable indicator of poor survival in postoperative patients with HCC. Previous studies have demonstrated that a high preoperative APPRI (10), AST to lymphocyte ratio (11), and AGR (12) are associated with a high recurrence rate and poor survival in patients with HCC. In contrast to previous studies, the present study showed that a

high preoperative APAR was associated with poor outcomes in patients with HCC after resection. As mentioned above, it is hypothesized that the host systemic immune response, inflammatory state, viral infection, liver fibrosis, liver cirrhosis, and liver function play key roles in promoting recurrence and poor clinical outcomes in patients with HCC (47-49). Accordingly, it is emphasized that a focus should be placed on not only hepatic tumors alone, but also on the host liver function, preoperative systemic response, and nutritional status of patients with HCC after resection. Interestingly, the analysis showed that an APAR <1.74 had a better prognostic value than APAR ≥1.74. Compared to patients with APAR ≥1.74, those with APAR<1.74 had better DFS and OS rates, with 3- and 5-year DFS rates of 72.2 and 68.3%, respectively, and 3- and 5-year OS rates of 88.8 and 84.1%, respectively. However, the outcomes of patients with APAR ≥1.74 were worse, with 3- and 5-year DFS rates of only 57.9 and 49.8%, respectively, and 3- and 5-year OS rates of only 79.9 and 66.3%, respectively. From the above data, an APAR ≥1.74 indicates a high risk of recurrence and mortality, whereas an APAR <1.74 indicates a low risk of recurrence and mortality.

Accurately predicting the prognosis of patients with HCC who undergo curative resection is important. Concurrently, APAR is important in developing follow-up and further treatment plans for patients after hepatectomy. Going forward, in our daily practice, every patient will have their own table of APAR scores, and physicians will determine their APAR values. For patients with an APAR ≥1.74, follow-up will be performed at close intervals for the early detection of tumor recurrence and progression. For example, once-a-month follow-up is recommended for such patients, and more adjuvant therapies are recommended, such as transarterial chemoembolization, systemic chemotherapy, and cellular immunotherapy. Notably, antiviral therapy may reduce the host inflammatory response, enhance liver functional reserves, and increase the survival time of patients with HCC who have chronic hepatitis infection (50,51).

The present study has several strengths. First, the prognostic significance of APAR in postoperative patients with HCC and its correlation with other clinicopathological parameters were retrospectively analyzed, which has not been performed in previous studies. Second, the APAR values can be readily and objectively determined from the peripheral blood of the host. Finally, APAR <1.74 as an indicator for prognosis demonstrated a better prognostic value than the simple summation of ALP and ALB. However, this study has some limitations. First, this was a single-center study comprising only Chinese patients. Second, this was a retrospective study with an inherent bias. In the DFS analysis, there were 49 patients with censored data. Thus, the statistical analysis for DFS included was of only 281 patients. Moreover, in the OS analysis, 17 patients were lost to follow-up. For patients who were lost to follow-up, additional attempts to contact them or their families will be made through their phone numbers, email addresses, and family contact information left in the medical record system. Additionally, local hospitals or local health authorities will be contacted for home follow-up, hoping to obtain this part of the missing data. The statistical data used for the final analysis were obtained from 313 patients. Third, a stratified analysis was not performed to evaluate the prognostic value of APAR during the different tumor stages given the relatively small cohorts after subcategorization. In addition, the optimal cut-off value of APAR also requires external validation. In this study, due to the limited number of patients enrolled from a single center, all the cases were utilized to determine the cut-off value to ensure that we could obtain the most accurate cut-off value with the highest sensitivity and specificity. As a result, the validation queue for the cut-off value was lost. Therefore, future prospective clinical trials and larger multicenter studies are warranted to validate the prognostic significance of APAR in further studies.

In conclusion, the best preoperative APAR cut-off value for predicting the survival of patients with HCC is 1.74. APAR is a novel prognostic indicator in patients with HCC after radical surgery. Moreover, a preoperative APAR of ≥1.74 is closely correlated with HBsAg positivity, a larger tumor size, and a more advanced TNM stage, whereas a preoperative APAR of <1.74 is significantly related to improved clinicopathological characteristics. Hence, patients with HCC with a higher APAR should be closely followed up and timely postoperative therapeutic intervention is required to improve their survival and quality of life. Finally, the mechanisms for the potential correlation between high preoperative APAR and poor prognosis in postoperative patients with HCC need to be further investigated.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding authors upon reasonable request.

Authors' contributions

YKW performed the research and drafted the manuscript. YJR and JQC designed the study and revised the manuscript. XYB, HZ, ZYL, JJZ, JGZ, ZH, YFZ, XC, and CDZ analyzed the data and revised the article for important intellectual content. YKW collected the data and participated in data interpretation. All authors have read and approved the final manuscript. YJR and JQC confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Ethical approval was granted by the Ethical Committee of the Cancer Hospital, Chinese Academy of Medical Sciences and

Peking Union Medical College (Cancer Hospital, approval no. CAMS 15-121/1048). Written consent was obtained from all examined patients or their guardians prior to surgery.

Patient consent for publication

Informed consent for publication was obtained from all individual participants included in this study.

Competing interests

The authors declare that they have no competing interests.

References

1. Forner A, Llovet JM and Bruix J: Hepatocellular carcinoma. Lancet 379: 1245-1255, 2012.
2. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J and Jemal A: Global cancer statistics, 2012. CA Cancer J Clin 65: 87-108, 2015.
3. Gluer AM, Cocco N, Laurence JM, Johnston ES, Hollands MJ, Pleass HC, Richardson AJ and Lam VW: Systematic review of actual 10-year survival following resection for hepatocellular carcinoma. HPB (Oxford) 14: 285-290, 2012.
4. Greene PJ and Sussman HH: Structual comparison of ectopic and normal placental alkaline phosphatase. Proc Natl Acad Sci USA 70: 2936-2940, 1973.
5. Yu MC, Chan KM, Lee CF, Lee YS, Eldeen FZ, Chou HS, Lee WC and Chen MF: Alkaline phosphatase: Does it have a role in predicting hepatocellular carcinoma recurrence? J Gastrointest Surg 15: 1440-1449, 2011.
6. Liao FL, Peng DH, Chen W, Hu HN, Tang P, Liu YY, Luo Y and Yao T: Evaluation of serum hepatic enzyme activities in different COVID-19 phenotypes. J Med Virol 93: 2365-2373, 2021.
7. McMillan DC, Watson WS, O'Gorman P, Preston T, Scott HR and McArdle CS: Albumin concentrations are primarily determined by the body cell mass and the systemic inflammatory response in cancer patients with weight loss. Nutr Cancer 39: 210-213, 2001.
8. Liu J, Dai Y, Zhou F, Long Z, Li Y, Liu B, Xie D, Tang J, Tan J, Yao K, *et al*: The prognostic role of preoperative serum albumin/globulin ratio in patients with bladder urothelial carcinoma undergoing radical cystectomy. Urol Oncol 34: 484.e1-484.e8, 2016.
9. Yu YQ, Li J, Liao Y, Chen Q, Liao WJ and Huang J: The preoperative alkaline phosphatase-to-platelet ratio index is an independent prognostic factor for hepatocellular carcinoma after hepatic resection. Medicine (Baltimore) 95: e5734, 2016.
10. Jin J, Zhu P, Liao Y, Li J, Liao W and He S: Elevated preoperative aspartate aminotransferase to lymphocyte ratio index as an independent prognostic factor for patients with hepatocellular carcinoma after hepatic resection. Oncotarget 6: 19217-19227, 2015.
11. Suh B, Park S, Shin DW, Yun JM, Keam B, Yang HK, Ahn E, Lee H, Park JH and Cho B: Low albumin-to-globulin ratio associated with cancer incidence and mortality in generally healthy adults. Ann Oncol 25: 2260-2266, 2014.
12. Zhou M, Luo J, Chen M, Yang H, Learned RM, DePaoli AM, Tian H and Ling L: Mouse species-specific control of hepatocarcinogenesis and metabolism by FGF19/FGF15. J Hepatol 66: 1182-1192, 2017.
13. Zhu AX, Abbas AR, de Galarreta MR, Guan Y, Lu S, Koeppen H, Zhang W, Hsu CH, He AR, Ryoo BY, *et al*: Molecular correlates of clinical response and resistance to atezolizumab in combination with bevacizumab in advanced hepatocellular carcinoma. Nat Med 28: 1599-1611, 2022.
14. Izquierdo-Sanchez L, Lamarca A, La Casta A, Buettner S, Utpatel K, Klümpen HJ, Adeva J, Vogel A, Lleo A, Fabris L, *et al*: Cholangiocarcinoma landscape in Europe: Diagnostic, prognostic and therapeutic insights from the ENSCCA Registry. J Hepatol 76: 1109-1121, 2022.
15. Singhi AD, Nikiforova MN, Chennat J, Papachristou GI, Khalid A, Rabinovitz M, Das R, Sarkaria S, Ayasso MS, Wald AI, *et al*: Integrating next-generation sequencing to endoscopic retrograde cholangiopancreatography (ERCP)-obtained biliary specimens improves the detection and management of patients with malignant bile duct strictures. Gut 69: 52-61, 2020.
16. Peng Z, Fan W, Zhu B, Wang G, Sun J, Xiao C, Huang F, Tang R, Cheng Y, Huang Z, *et al*: Lenvatinib combined with transarterial chemoembolization as first-line treatment for advanced hepatocellular carcinoma: A phase III, randomized clinical trial (LAUNCH). J Clin Oncol 41: 117-127, 2023.
17. Lyu N, Wang X, Li JB, Lai JF, Chen QF, Li SL, Deng HJ, He M, Mu LW and Zhao M: Arterial chemotherapy of oxaliplatin plus fluorouracil versus sorafenib in advanced hepatocellular carcinoma: A biomolecular exploratory, randomized, phase III trial (FOHAIC-1). J Clin Oncol 40: 468-480, 2022.
18. Rimassa L, Personeni N, Czauderna C, Foerster F and Galle P: Systemic treatment of HCC in special populations. J Hepatol 74: 931-943, 2021.
19. Cheng D, Xu W, Gong X, Yuan L and Zhang XB: Design strategy of fluorescent probes for live drug-induced acute liver injury imaging. Acc Chem Res 54: 403-415, 2021.
20. van Aerts RMM, van de Laarschot LFM, Banales JM and Drenth JPH: Clinical management of polycystic liver disease. J Hepatol 68: 827-837, 2018.
21. Wu Y, Huang S, Wang J, Sun L, Zeng F and Wu S: Activatable probes for diagnosing and positioning liver injury and metastatic tumors by multispectral optoacoustic tomography. Nat Commun 9: 3983, 2018.
22. Kemeny NE, Chou JF, Capanu M, Chatila WK, Shi H, Sanchez-Vega F, Kingham TP, Connell LC, Jarnagin WR and D'Angelica MI: A randomized phase II trial of adjuvant hepatic arterial infusion and systemic therapy with or without panitumumab after hepatic resection of KRAS Wild-type colorectal cancer. Ann Surg 274: 248-254, 2021.
23. Seto WK, Lo YR, Pawlotsky JM and Yuen MF: Chronic hepatitis B virus infection. Lancet 392: 2313-2324, 2018.
24. Kim HS, Yu X, Kramer J, Thrift AP, Richardson P, Hsu YC, Flores A, El-Serag HB and Kanwal F: Comparative performance of risk prediction models for hepatitis B-related hepatocellular carcinoma in the United States. J Hepatol 76: 294-301, 2022.
25. Kulik L and El-Serag HB: Epidemiology and management of hepatocellular carcinoma. Gastroenterology 156: 477-491.e1, 2019.
26. Shih C, Yang CC, Choijilsuren G, Chang CH and Liou AT: Hepatitis B Virus. Trends Microbiol 26: 386-387, 2018.
27. Zou Y, Qazvini NT, Zane K, Sadati M, Wei Q, Liao J, Fan J, Song D, Liu J, Ma C, *et al*: Mgelatin-derived graphene-silicate hybrid materials are biocompatible and synergistically promote BMP9-Induced osteogenic differentiation of mesenchymal stem cells. ACS Appl Mater Interfaces 9: 15922-15932, 2017.
28. al-Rashida M and Iqbal J: Iqbal, Inhibition of alkaline phosphatase: An emerging new drug target. Mini Rev Med Chem 15: 41-51, 2015.
29. Yamamoto K, Awogi T, Okuyama K and Takahashi N: Nuclear localization of alkaline phosphatase in cultured human cancer cells. Med Electron Microsc 36: 47-51, 2003.
30. Muñoz-González JI, Álvarez-Twose I, Jara-Acevedo M, Zanotti R, Perkins C, Jawhar M, Sperr WR, Shoumariyeh K, Schwaab J, Greiner G, *et al*: Proposed global prognostic score for systemic mastocytosis: A retrospective prognostic modelling study. Lancet Haematol 8: e194-e204, 2021.
31. Zhou H, Du W, Li Y, Shi C, Hu N, Ma S, Wang W and Ren J: Effects of melatonin on fatty liver disease: The role of NR4A1/DNA-PKcs/p53 pathway, mitochondrial fission, and mitophagy. J Pineal Res: 64, 2018.
32. Villa-Bellosta R, González-Parra E and Egido J: Alkalosis and dialytic clearance of phosphate increases phosphatase activity: A hidden consequence of hemodialysis. PLoS One 11: e0159858, 2016.
33. Takagi A, Hawke P, Tokuda S, Toda T, Higashizono K, Nagai E, Watanabe M, Nakatani E, Kanemoto H and Oba N: Serum carnitine as a biomarker of sarcopenia and nutritional status in preoperative gastrointestinal cancer patients. J Cachexia Sarcopenia Muscle 13: 287-295, 2022.
34. Garcia-Martinez R, Caraceni P, Bernardi M, Gines P, Arroyo V and Jalan R: Albumin: Pathophysiologic basis of its role in the treatment of cirrhosis and its complications. Hepatology 58: 1836-1846, 2013.
35. Vincent JL, Russell JA, Jacob M, Martin G, Guidet B, Wernerman J, Ferrer R, McCluskey SA and Gattinoni L: Albumin administration in the acutely ill: What is new and where next? Crit Care 18: 231, 2014.

36. China L, Freemantle N, Forrest E, Kallis Y, Ryder SD, Wright G, Portal AJ, Becares Salles N, Gilroy DW and O'Brien A; ATTIRE Trial Investigators: A randomized trial of albumin infusions in hospitalized patients with cirrhosis. N Engl J Med 384: 808-817, 2021.
37. Wong F, Pappas SC, Curry MP, Reddy KR, Rubin RA, Porayko MK, Gonzalez SA, Mumtaz K, Lim N, Simonetto DA, *et al*: Terlipressin plus albumin for the treatment of type 1 hepatorenal syndrome. N Engl J Med 384: 818-828, 2021.
38. Boada M, López OL, Olazarán J, Núñez L, Pfeffer M, Paricio M, Lorites J, Piñol-Ripoll G, Gámez JE, Anaya F, *et al*: A randomized, controlled clinical trial of plasma exchange with albumin replacement for Alzheimer's disease: Primary results of the AMBAR Study. Alzheimers Dement 16: 1412-1425, 2020.
39. Carr BI and Guerra V: Serum albumin levels in relation to tumor parameters in hepatocellular carcinoma patients. Int J Biol Markers 32: e391-e396, 2017.
40. Bağırsakçı E, Şahin E, Atabey N, Erdal E, Guerra V and Carr BI: Role of albumin in growth inhibition in hepatocellular carcinoma. Oncology 93: 136-142, 2017.
41. Ram AK, Pottakat B and Vairappan B: Increased systemic zonula occludens 1 associated with inflammation and independent biomarker in patients with hepatocellular carcinoma. BMC Cancer 18: 572, 2018.
42. Lv LL, Feng Y, Wen Y, Wu WJ, Ni HF, Li ZL, Zhou LT, Wang B, Zhang JD, Crowley SD and Liu BC: Exosomal CCL2 from tubular epithelial cells is critical for albumin-induced tubulointerstitial inflammation. J Am Soc Nephrol 29: 919-935, 2018.
43. Sapienza C and Issa JP: Nutrition, and cancer epigenetics. Annu Rev Nutr 36: 665-681, 2016.
44. Kaymak I, Williams KS, Cantor JR and Jones RG: Immunometabolic interplay in the tumor microenvironment. Cancer Cell 39: 28-37, 2021.
45. Esper DH and Harb WA: The cancer cachexia syndrome: A review of metabolic and clinical manifestations. Nutr Clin Pract 20: 369-376, 2005.
46. Mantovani A, Allavena P, Sica A and Balkwill F: Cancer-related inflammation. Nature 454: 436-444, 2008.
47. Atasheva S, Emerson CC, Yao J, Young C, Stewart PL and Shayakhmetov DM: Systemic cancer therapy with engineered adenovirus that evades innate immunity. Sci Transl Med 12: eabc6659, 2020.
48. Gola A, Dorrington MG, Speranza E, Sala C, Shih RM, Radtke AJ, Wong HS, Baptista AP, Hernandez JM, Castellani G, *et al*: Commensal-driven immune zonation of the liver promotes host defence. Nature 589: 131-136, 2021.
49. Ringelhan M, Pfister D, O'Connor T, Pikarsky E and Heikenwalder M: The immunology of hepatocellular carcinoma. Nat Immunol 19: 222-232, 2018.
50. Limketkai BN, Mehta SH, Sutcliffe CG, Higgins YM, Torbenson MS, Brinkley SC, Moore RD, Thomas DL and Sulkowski MS: Relationship of liver disease stage and antiviral therapy with liver-related events and death in adults coinfected with HIV/HCV. JAMA 308: 370-378, 2012.
51. Carrat F, Fontaine H, Dorival C, Simony M, Diallo A, Hezode C, De Ledinghen V, Larrey D, Haour G, Bronowicki JP, *et al*: Clinical outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment: A prospective cohort study. Lancet 393: 1453-1464, 2019.

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