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Original Article

Preoperative alkaline phosphatase-to-platelet ratio predicts survival in primary HBV-positive hepatocellular carcinoma after curative resection

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Abstract: Background: Several predictive biomarkers associated to platelets and serum liver enzyme have been confirmed as prognostic factor for patients with hepatocellular carcinoma (HCC). The purpose of this study was to analyze prognosis significance of preoperative alkaline phosphatase-to-platelet ratio (APPRI) in post-curative resection HBV related hepatocellular carcinoma. Methods: In this retrospective study, we enrolled 253 patients who underwent curative operation for primary HBV-positive hepatocellular carcinoma. The correlation between the preoperative APPRI and survival was analyzed using Kaplan-Meier curves and multivariate Cox regression analyses. Results: The patients with a low APPRI had a significantly higher mean overall survival than those with a high LMR (67 months VS 53 months, P=0.021) and this result remained significant in the multivariate analysis (HR, 0.152; 95% CI: 0.084-0.853; P=0.031). Furthermore, patients with a low LMR also had higher median recurrence-free survival than patients with a high LMR in in univariate analyses (58 months VS 46 months, P=0.022) and multivariate analyses (HR, 0.281; 95% CI: 0.035-1.123; P=0.036). Otherwise, the APPRI was significantly related to cirrhosis. Conclusions: The APPRI can be used as an independent prognostic biomarker for primary HBV-positive hepatocellular carcinoma after curative resection.

Keywords: Alkaline phosphatase-to-platelet ratio, survival, HBV, hepatocellular carcinoma

Introduction

Hepatocellular carcinoma (HCC) is considered as the most common cancer and the second leading cause of cancer-related death in China, and its morbidity and mortality keep increasing with growth of carriers of HBV [1, 2]. The development of comprehensive treatment and advances in surgery have improved the clinical efficacy of HCC, however, the prognosis of HCC remains far from satisfactory mainly due to high relapse and metastasis rates after surgery, especially for HBV positive hepatocellular carcinoma [3, 4]. Therefore, the important of predictive biomarkers classified the patients though evaluating the recurrence risk and prognosis in providing individualized therapeutic interventions for patients with different risk level have been recognized increasingly [5, 6]. However, biomarkers definitely showed prognostic significance in previous studies only can be obtained through postoperative histological reports and findings during surgery, such as histological stage, serum alpha-fetoprotein (AFP), or Barcelona-clinic liver cancer (BCLC) stage [7, 8]. So developing new pretreatment predictive biomarkers that are inexpensive and technically feasible and easy to evaluate the postoperative recurrence risk and poor prognosis is required.

Recently, it has been widely recognized that several components from peripheral blood have potential prognostic significance in patients with various types of malignancies [9, 10]. For example, platelets not only play curial roles in thrombosis and hemostasis, but also function as part of the tumor microenvironment and associate with metastasis formation via increasing the rate of tumor embolus formation

Table 1. Correlation between the APPRI and clinicpathologic characteristics of HBV(+) HCC

Characteristic	APPRI		*p*
	≥ 0.48 (n=172)	< 0.48 (n=81)	
Age (years)			0.509
≥ 60	71	37	
< 60	101	44	
Gender			0.291
Male	105	55	
Female	67	26	
Liver cirrhosis			0.025
Yes	147	77	
No	25	4	
Child-pugh stage			0.099
A	126	67	
B	46	14	
AFP (ng/ml)			0.428
≤ 20	64	26	
> 20	108	55	
BCLC stage			0.826
A	123	59	
B	49	22	
Tumor size (cm)			0.520
≥ 5.0	71	30	
< 5.0	101	51	
Tumor site			0.826
Left lobe	50	29	
Right lobe	102	44	
Left and right lobes	20	8	
TNM stage			0.147
I+II	76	28	
III	96	53	
Pathological differentiation			0.800
Well/Moderate	90	41	
Poor	82	40	
Operation type			0.554
Laparoscopic	51	27	
Open	121	54	

AFP, alpha-fetoprotein; APPRI, ALP-to-platelets ratio index; HCC, hepatocellular carcinoma.

in microvasculature [11, 12]. Otherwise, increased platelet count were unfavorable prognostic factors for various malignancies including HCC [13, 14]. Furthermore, it has been widely recognized that use of serum liver enzyme including alkaline phosphatase as a non-invasive tool to detect liver cirrhosis and significant fibrosis in setting of chronic HBV infection [15]. More importantly, it has been confirmed that several serum liver enzyme to peripheral blood platelet count ratio have potential prognostic significance in patients with HCC patients, such as aspartate aminotransferase-to-platelet ratio (APRI), alkaline phosphatase-to-platelet ratio (APPRI) and γ-GT-to-platelet ratio [16-19]. However, there was still no report associated preoperative APPRI with prognosis of HBV positive hepatocellular carcinoma patients who underwent curative resection. In this study, we try to assess prognosis significance of preoperative APPRI in HBV positive hepatocellular carcinoma patient underwent curative surgery.

Materials and methods

Patients

In this retrospective study, we enrolled 253 patients who underwent curative resection for histologically confirmed primary hepatocellular carcinoma at the Department of Hepato-Billiary Surgery in Sun Yat-sen Memorial Hospital between March 1, 2011, and March 1, 2016. The inclusion criteria were histologically confirmed hepatocellular carcinoma and HBsAg positive, age older than 18 years, and life expectancy of more than 6 months. Patients who had preoperative acute and severe comorbidities, such as systemic infection, autoimmune diseases, and inflammation, and had received adjuvant treatments, such as preoperative chemotherapy, were excluded. The clinical and histopathological characteristics of all patients, including gender, age, tumor size, liver cirrhosis, Child-pugh stage, HBsAg, AFP level, BCLC stage, TNM stage, tumor site and size, pathological differentiation and operation type, were collected through review of clinical records by one surgeon and were verified by another surgeon. Histopathological and clinical staging were evaluated through postoperative histopathological examination and clinical assessment, respectively, according to the UICC TNM classification and BCLC classification. Blood routine test and biochemistry including liver enzymes were conducted on the day before surgery to obtain the platelet counts and the serum alkaline phosphatase (ALP) concentration. The APPRI was calculated using the following formula: (AST (IU/L)/its ULN)/platelet count (10^9/L) × 100.

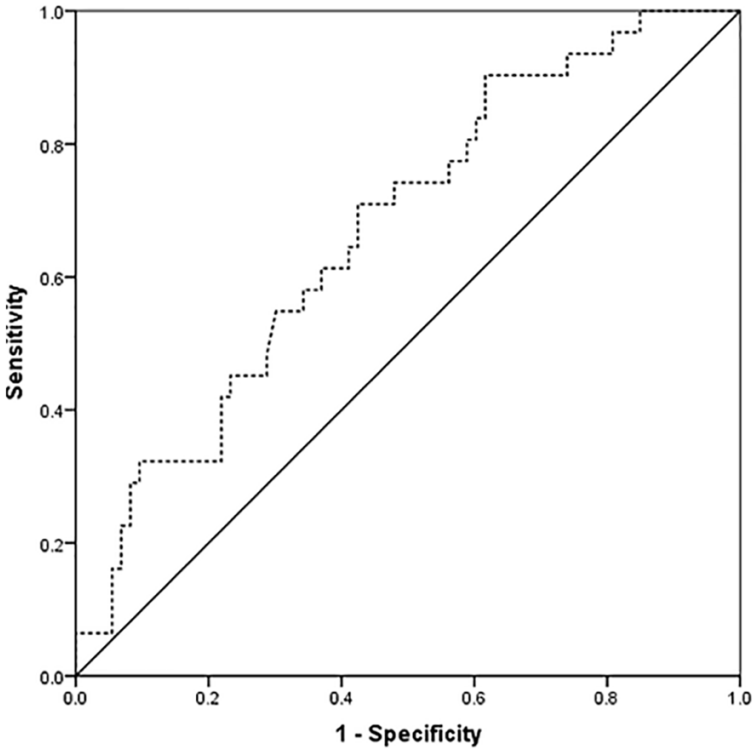

Figure 1. Receiver-operator characteristic curve for APPRI. The areas under the curve were 0.652 with a 95% confidence interval (95% CI) for the area between 0.561 and 0.782.

Follow-up

All patients were followed up at regular intervals through outpatient visits. Patients underwent physical and laboratory examinations and imaging studies, including routine blood test, biochemistry analysis, and tumor marker analysis, every 3 months for the first 2 years, every 6 months for the next 3 years, and once annually thereafter. Enhanced abdominal computed tomography or magnetic resonance imaging scans were generally obtained every 12 months. Clinical follow-up lasted from the date of surgery to either the time of death or March 1, 2017. This study was approved by the Institutional Review Board of Sun Yat-sen Memorial Hospital. Written informed consent was obtained from individual patients.

Statistical analysis

Statistical analyses were performed by SPSS 21.0 (IBM, USA). $P < 0.05$ (two sided) was considered as statistically significant. The optimal cutoff values for the APPRI were confirmed by receiver operating characteristic (ROC) curve analysis. Overall survival (OS) was accurately defined as the duration from date of surgery to death whereas recurrence-free survival (RFS) was calculated by the time of surgery to tumor recurrence. The χ^2 test or Fisher's exact test was used to analyze the association between qualitative variables while quantitative values were analyzed by in dependent student's t test. The survival was analyzed using Kaplan-Meier curves and the log-rank test. The Cox regression model was used to assess the hazard ratio and multivariate analysis.

Results

The baseline clinicopathological characteristics of the 253 patients who underwent curative resection for histologically confirmed primary localized hepatocellular carcinoma are listed in **Table 1**. Of the 274 patients, 160 were men and 93 were women, and their average age was with 58.1±3.2 years. The most frequently involved tumor site was the right lobe, accounting for tumors in 146 of the 253 patients. According to TNM staging, 104 patients had T1 or T2 tumor, and 149 patients had T3 or T4 tumor. Regarding pathology, 131 patients had well and moderately differentiated adenocarcinoma, whereas 122 patients had poorly differentiated tumors. Moreover, no significant association was observed between the APPRI and the clinicopathological characteristics, except liver cirrhosis.

Prognostic significant of APPRI for HBV(+) hepatocellular carcinoma

According to the ROC curve analysis, the optimal cutoff levels for the APPRI were 0.48 using a sensitivity of 68.3% and a specificity of 83.7% as optimal conditions, respectively. The area under the curve was 0.652 with a 95% confidence interval (95% CI) for the area between 0.561 and 0.782 (**Figure 1**). The median follow-up duration was 33 months (Range 6 to 85 months). There were significant associations

Table 2. Univariate and multivariate analyses of the association of the prognostic factors with OS for HCC

	Univariate			Multivariate		
	n	MS (months)	*p*	HR	95% CI	P
Age (years)			0.126			
≥ 60	108	58				
< 60	145	57				
Gender			0.514			
Male	160	55				
Female	93	62				
Liver cirrhosis			0.228			
Yes	224	53				
No	29	58				
Child-pugh stage			0.504			
A	193	57				
B	60	53				
AFP (ng/ml)			0.791			
≤ 20	90	62				
> 20	163	64				
BCLC stage			0.024	7.512	3.804-9.561	0.032
A	182	67				
B	71	53				
Tumor size (cm)			0.182			
≥ 5.0	101	57				
< 5.0	152	62				
Tumor site			0.632			
Left	79	64				
Right	146	62				
Left and right	28	58				
Tumor stage			0.001	4.432	3.161-9.183	0.000
I+II	104	78				
III	149	48				
Pathological differentiation			0.035	0.621	0.312-1.952	0.022
Well/Moderate	131	67				
Poor	122	45				
Operation type			0.215			
Laparoscopic	78	58				
Open	175	57				
APPRI			0.021	0.152	0.084-0.853	0.031
< 0.48	81	67				
≥ 0.48	172	53				

MS, mean survival; CI, confidence interval; HR, hazard ratio; APPRI, ALP-to-platelets ratio index.

between BCLC stage, TNM stage and the APPRI with OS and RFS (**Tables 2** and **3**).

At the endpoint of this study, 83 (32.8%) out of all 253 patients studied had died, including 18 (22.2%) in 81 patients with a APPRI < 0.48 and 65 (37.8%) out of 172 patients with a APPRI ≥ 0.48, respectively. 78 (45.3%) in group of 172 patients with a APPRI ≥ 0.48 had tumor relapse while 27 (33.3%) in patients group with APPRI < 0.48 suffered from recurrence. Kaplan-Meier univariate survival analysis showed TNM stage, BCLC stage, histological differentiation type and preoperative APPRI were related to postoperative survival of HCC patients. Among these prognostic factors, APPRI ≥ 0.48 was associated with a shorter OS of HCC patients. The mean OS of patients with preoperative APPRI < 0.48 was 67 months, which statistically significantly higher than 53 months of those with a APPRI ≥ 0.48 (P=0.021) (**Table 2**; **Figure 2**). Furthermore, we obtained similar result in the multivariate analysis for OS (HR, 0.152; 95% CI: 0.084-0.853; P=0.031) (**Table 2**). Otherwise, in univariate analysis of RFS, patients with low APPRI also had higher mean RFS than patients with high APPRI (58 months VS 46 months, P=0.022), and the APPRI was also confirmed as a significant independent predictor for RFS in multivariate analysis (HR, 0.281; 95% CI: 0.035-1.123; P=0.036) (**Table 3**).

A multivariate analysis enrolled sex and gender of patients, tumor size, histological differentia-

Table 3. Univariate and multivariate analyses of the association of the prognostic factors with RFS

	Univariate			Multivariate		
	n	MS (months)	*p*	HR	95% CI	p
Age (years)			0.262			
≥ 60	108	52				
< 60	145	53				
Gender			0.314			
Male	160	52				
Female	93	56				
Liver cirrhosis			0.522			
Yes	224	52				
No	29	54				
Child-pugh stage			0.613			
A	193	54				
B	60	51				
AFP (ng/ml)			0.565			
≤ 20	90	58				
> 20	163	53				
BCLC stage			0.021	3.621	0.974-5.142	0.031
A	182	60				
B	71	52				
Tumor size (cm)			0.412			
≥ 5.0	101	57				
< 5.0	152	52				
Tumor site			0.921			
Left	79	58				
Right	146	57				
Left and right	28	55				
Tumor stage			0.013	5.113	2.167-8.531	0.021
I+II	104	66				
III	149	48				
Pathological differentiation			0.038			
Well/Moderate	131	58				
Poor	122	40				
Operation type			0.381			
Laparoscopic	78	54				
Open	175	52				
APPRI			0.022	0.281	0.035-1.123	0.036
< 0.48	81	58				
≥ 0.48	172	46				

MS, mean survival; CI, confidence interval; HR, hazard ratio; LMR, APPRI, ALP-to-platelets ratio index.

tion, Child-pugh stage, BCLC stage, TNM stage and preoperative APPRI into the COX regression model to determine independent prognostic factors foroperable HBV related hepatocellular carcinoma. The result showed that APPRI (HR, 0.152; 95% CI: 0.084-0.853; P=0.031) and TNM (Hazard ratio, 4.432; 95% CI, 3.161-9.183; P=0.000) and pathological differentiation (Hazard ratio, 0.621; 95% CI, 0.312-1.952; P=0.022) and BCLC stage (Hazard ratio, 7.512; 95% CI, 3.804-9.561; P=0.032) were the independent prognostic factors for OS (**Table 2**). Furthermore, the APPRI (HR, 0.281; 95% CI: 0.035-1.123; P=0.036), TNM (Hazard ratio, 5.113; 95% CI, 2.167-8.531; P=0.021) and BCLC stage (Hazard ratio, 3.621; 95% CI, 0.974-5.142; P=0.031) were the independent prognostic factors for RFS (**Table 3**).

Discussion

In this study, we retrospectively examined preoperative APPRI of a large cohort of patients who underwent curative resection for operable HBV positive hepatocellular carcinoma and its association with the prognosis of cancer. We found that a lower preoperative APPRI was significantly correlated with a longer OS, and that APPRI was an independent prognostic predictor of OS and RFS in patients with operable HBV positive hepatocellular carcinoma. Therefore, we confirmed that the preoperative APPRI can be examined for optimal preoperative risk stratification of individual patients, and the preoperative APPRI

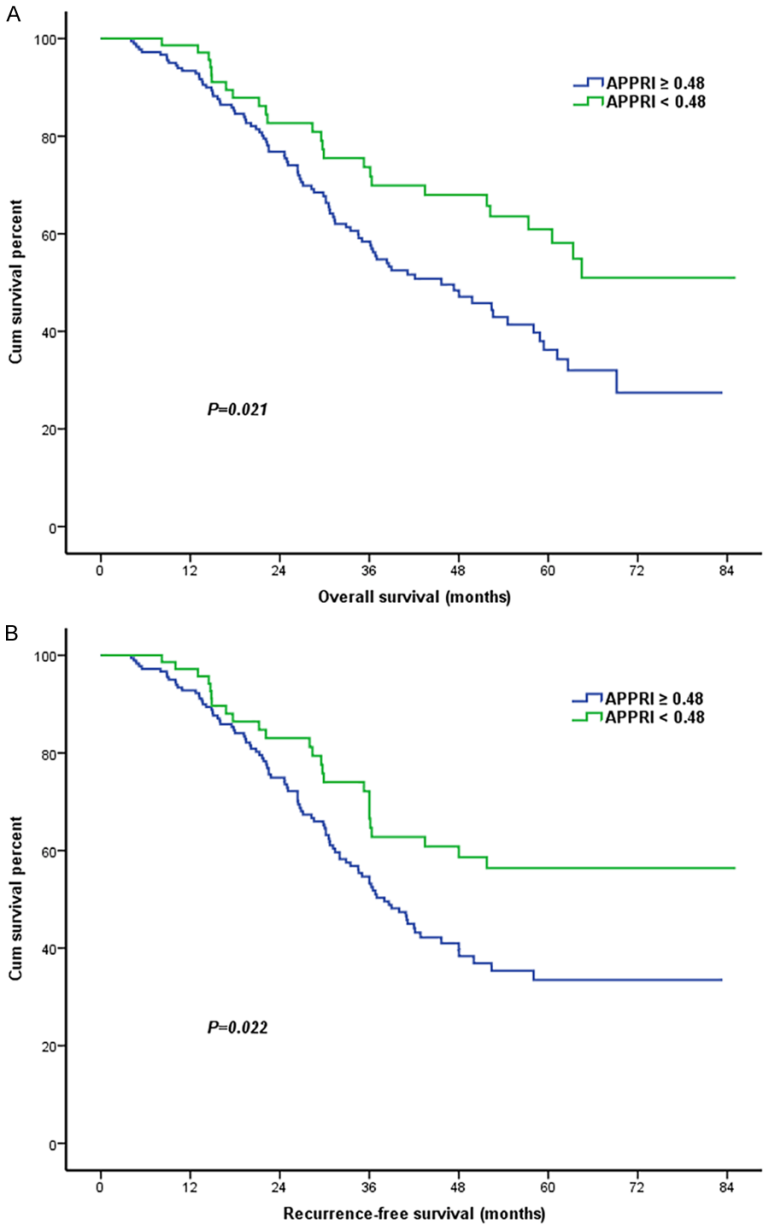

Figure 2. Kaplan-Meier estimates of survival. A. Showed the association between the APPRI and OS (mean survival in APPRI ≥ 0.48, 53 months; in APPRI < 0.48, 67 months, P=0.021). B. Showed the association between APPRI and RFS (mean survival in APPRI ≥ 0.48, 46 months; in APPRI < 0.48, 58 months, P=0.022).

can serve as a biomarker for predicting the prognosis of patients with hepatocellular carcinoma after curative resection, especially for HBV positive patients.

Both experimental and clinical data indicate platelets play an important role in cancer progression and metastasis, which also protect tumor cells from immunological killing and blood shear stress though coating their surface [20-24]. Moreover, several cytokines secreted from activated platelets can enhance the motility of both tumor and vascular endothelial cells as well as the growth of tumor cells at secondary sites, such as transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) [25-27]. Several studies showed that increased preoperative platelet count negatively correlated with survival in patients with malignancy [28].

ALP, as one kind of liver enzyme, is widely distributed in the tissues of the liver, bone, intestine, and kidney of human body [29]. And elevated ALP is common in patients with HCC, reflecting the status of liver injury and cirrhosis and significant fibrosis [30]. Otherwise, serum liverenzymes such as ALT, AST and ALP are routinely tested in HCC patients, which have long been recognized to play potential roles in the evaluation of HCC.

APPRI, abiomarker based platelets and ALP, has been confirmed as a significant prognosis for patients with HCC [19]. In present study, we further evaluated prognostic significance of the APPRI in patients with HBV(+) HCC. We found preoperativeAPPRI were not only an independent prognostic factor of primary HBV(+) hepatocellular carcinoma but also significantly related to liver cirrhosis. The results of the multivariate analysis showed that preoperative APPRI, TNM staging and BCLC staging were independent prognostic markers of DFS and OS in HCC patients.

These findings are consistent with reported results of previous studies [31, 32].

Several limitations may influence the interpretation of the results of this study. One limitation is the retrospective study design and a relatively short follow-up period. A large-scale, multicenter, prospective study should be conducted to confirm long-term results and obtain more definite evidence. Furthermore, we used the receiver-operator characteristic curve to assess the cutoff levels of the APPRI in survival evaluation, whereas other studies used median value as the cutoff value. Thus, the results of this study may not be comparable with those of other studies. A meta-analysis including various APPRI validation studies may be required to confirm more definite cutoff values for the APPRI.

In conclusion, APPRI, a simple, well-validated, and cost-effective biomarker, can be considered an independent prognostic factor for operable HBV(+) hepatocellular carcinoma.

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Disclosure of conflict of interest

None.

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