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The preoperative platelet to albumin ratio predicts the prognosis of hepatocellular carcinoma patients without portal hypertension after liver resection

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Abstract

There is little information concerning the predictive ability of the preoperative platelet to albumin ratio (PAR) in hepatocellular carcinoma (HCC) patients after liver resection. In the current study, we aimed to assess the prognostic power of the PAR in HCC patients without portal hypertension (PH) following liver resection.

Approximately 628 patients were included in this study. A receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive value of the PAR for both recurrence-free survival (RFS) and overall survival (OS). Univariate and multivariate analyses were used to identify the independent risk factors for both RFS and OS.

During the follow-up period, 361 patients experienced recurrence, and 217 patients died. ROC curve analysis suggested that the best cut-off value of the PAR for RFS was greater than 4.8. The multivariate analysis revealed that microvascular invasion (MVI), tumor size >5 cm, high aspartate aminotransferase-to-platelet count ratio index (APRI) and high PAR were four independent risk factors for both RFS and OS. Patients with a low PAR had significantly better RFS and OS than those with a high PAR.

The PAR may be a useful marker to predict the prognosis of HCC patients after liver resection. HCC patients with a high preoperative PAR had a higher recurrent risk and lower long-term survival rate than those with a low preoperative PAR.

Abbreviations: AUC = area under the receiver operating characteristic curve, HBV-DNA = hepatitis B virus-DNA, HCC = hepatocellular carcinoma, MVI = microvascular invasion, NLR = neutrophil to lymphocyte ratio, OS = overall survival, PAR = platelet to albumin ratio, PH = portal hypertension, PLR = platelet to lymphocyte ratio, RFS = recurrence-free survival.

Keywords: hepatocellular carcinoma, liver resection, platelet to albumin ratio

1. Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignancy and third most frequent tumor-related death in the world.[1] Every year, approximately 800,000 new HCC patients are diagnosed.[1] Unfortunately, death is almost the same due to the aggressive biological behavior of HCC.[1] Liver resection is widely accepted as a curative treatment for HCC. Although advances in surgical technology and perioperative management have been achieved, the long-term survival of HCC patients after liver resection is still not satisfactory due to the high postoperative recurrence rate.[2] Published investigations have suggested that the recurrence rates of patients with HCC may be as high as 50% within the first 3 years and greater than 70% during the first 5 years after surgery.[3,4]

Many factors could influence the outcomes of patients with HCC after liver resection. Recently, systemic inflammation has been confirmed to be involved in carcinogenesis, tumor progression and metastasis of HCC.[5] A number of inflammation-based prognostic models, including the platelet to lymphocyte ratio (PLR) and neutrophil to lymphocyte ratio (NLR), were proposed to predict HCC patients' prognosis.[6,7] However, there is little information regarding the platelet to albumin ratio (PAR) in HCC patients after liver resection. Published investigations also suggested that preoperative platelet counts and serum albumin levels were associated with patient prognosis after liver resection.[8,9] Low preoperative albumin levels contributed to a high incidence of postoperative complications and recurrence, as well as poor long-term survival for patients with HCC.[9,10] Basic studies have confirmed that platelets could interact with tumor cells, which could promote tumor growth and metastasis.[11,12] Clinical investigations also revealed that platelets are closely correlated with the progression of many malignancies, including HCC.[13–16] PAR is an inflammation-based model that

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incorporates both platelets and albumin. In this study, we tried to identify whether the PAR is a marker for predicting the prognosis of patients with HCC after liver resection.

2. Patients and methods

Patients with diagnosed HCC within Barcelona clinic liver cancer stage 0/A who received liver resection at our center from 2008 to 2019 were enrolled in this study. The exclusion criteria were as follows: re-resection, ruptured HCC, receipt of preoperative antitumor treatment, a positive surgical margin, and the presence of other types of tumors. All HCCs were confirmed by postoperative pathology. Written informed consent was obtained from all patients. This study was approved by the ethics committee of West China Hospital of Sichuan University.

2.1. Follow-up

All preoperative blood tests were performed within one week prior to liver resection. After surgery, patients were regularly screened for recurrence every 3 months by monitoring blood cell tests, liver function tests, serum alpha-fetoprotein (AFP), HBV-DNA tests, and visceral ultrasonography, as well as computed tomography or magnetic resonance imaging and chest radiography. Bone scintigraphy was performed whenever HCC recurrence was suspected. Before and after surgery, antiviral drugs (entecavir, lamivudine or tenofovir) were conventionally administered to patients with a positive hepatitis B virus-DNA (HBV-DNA) load. Postoperative recurrence was defined as newly local or distant tumors detected by visceral ultrasonography, as well as computed tomography or magnetic resonance with or without an increase in tumor markers or as confirmed by biopsy or resection.[17]

2.2. Definitions

The PAR was calculated as the platelet count (10^9/L) divided by the serum albumin level (g/L).[18] The NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count.[19] A NLR ≥ 3 was considered as a high NLR.[20] The PLR was defined as the platelet count divided by the lymphocyte count.[19] A PLR ≥ 150 was defined as a high PLR.[20] A preoperative AFP level greater than 400 ng/mL was considered a high AFP level.[17] Aspartate aminotransferase-to-platelet count ratio index (APRI) was calculated as [(AST value/ULN)/platelet count (109/L)] x 100.[21] APRI less than 0.5 was considered low APRI, whereas APRI ≥ 0.5 was defined as high APRI.[21] Clinical portal hypertension (PH) was defined as presence of esophageal and gastric varices, and a platelet count $<100 \times 10^9$/L associated with splenomegaly.[22]

2.3. Statistical analysis

All statistical analyses were performed using SPSS 21.0 (SPSS Company, Chicago, IL) for Windows. All continuous variables were analyzed using one-way analysis of variance. Univariate analyses for categorical variables were performed using the $\chi 2$ test or Fisher exact test. Recurrence-free survival (RFS) and overall survival (OS) rates were calculated by the Kaplan–Meier method and compared by the log-rank test. Multivariable analysis using Cox regression analysis was used to identify independent risk factors for OS and RFS with a backward elimination stepwise approach. All variables with a P value $<.2$ by univariate analysis were involved in the multivariate analysis. A receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive value of the PAR for both RFS. The area under the receiver operating characteristic curve (AUC) was used to estimate the cutoff value of the PAR. A P value of $<.05$ was considered statistically significant.

3. Results

A total of 628 patients were enrolled in this study. The demographic and clinical characteristics are summarized in Table 1. The mean age was 50.9 ± 12.7 years, and the predominance was male (n = 526, 83.8%). Multiple tumors were presented in 20 (3.2%) patients at the time of diagnosis. High preoperative AFP was observed in 232 (36.9%) patients. Microvascular invasion (MVI) was detected in 130 (20.7%) patients. Positive HBV-DNA was identified in 288 (45.9%) patients. The median tumor size was 5.0 cm. The median PAR was 3.7 for all patients.

Within a mean of 51.1 ± 31.8 months of follow-up, 361 (57.5%) patients suffered from recurrence, whereas 217 (34.6%) patients died. The 1-, 3-, and 5-year RFS rates were 74.3%, 54.3%, and 42.8%, respectively, for the entire cohort (Fig. 1). The 1-, 3-, and 5-year OS was 94.4%, 76.6%, and 63.0%, respectively, for the whole cohort (Fig. 1).

3.1. Comparison of the prognosis of HCC patients with high and low PARs

We used ROC analyses to identify the optimal cut-off values of the PAR in predicting postoperative recurrence and survival. As presented in Figure 2, the best cut-off value of the PAR for postoperative RFS was greater than 4.8, with a sensitivity of 33.0% and a specificity of 85.0%. The AUC was 0.577.

Table 1

Demographic and clinical characteristics of the study participants.

Variable	No/median (25%/75%interquartile range)
Age (years)	49.2 (41.3/59.8)
Tumor size (cm)	5.0 (3.5/7.0)
Multiple tumors (no, %)	20 (3.2%)
Female/male	102 (16.2%)/526 (83.8%)
AFP>400 ng/ml (no, %)	232 (36.9%)
Positive HBV-DNA load (no, %)	286 (45.5%)
Differentiation (poor/moderate/well)	209 (33.3%)/404 (64.3%)/15 (2.4%)
Cirrhosis (no, %)	473 (75.3%)
MVI (no, %)	130 (20.7%)
Platelet (10^9/L)	153.0 (124/204)
Albumin (g/L)	42.1 (39.4/44.8)
PLR	100.3 (74.7/140.6)
NLR	2.1 (1.6/3.0)
PAR	3.7 (2.9/4.9)
APRI	0.46 (0.32/0.64)
Etiology	
HBV	528
HCV	13
Alcoholic	9
Non-B, non-C	78

APRI = aspartate aminotransferase-to-platelet count ratio index, AFP = alpha-fetoprotein, HBV-DNA = hepatitis B virus-DNA, HCC = hepatocellular carcinoma, MVI = microvascular invasion, NLR = neutrophil to lymphocyte ratio, PAR = platelet to albumin ratio.

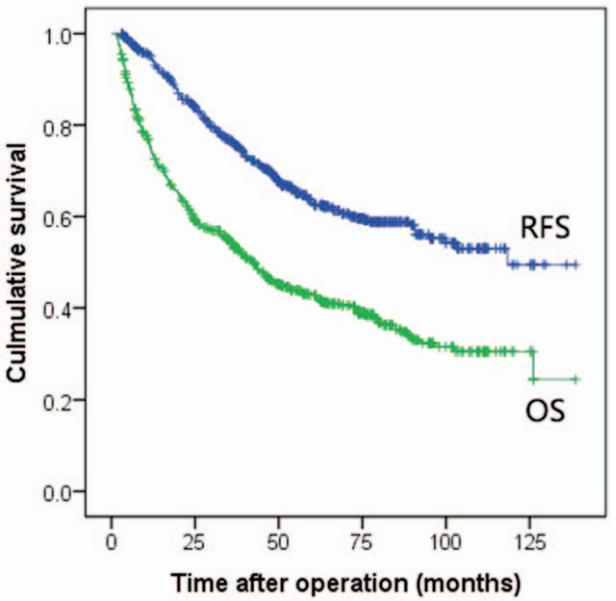

Figure 1. Receiver operating curve of preoperative platelet to albumin ratio for recurrence-free survival.

We compared the clinicopathological data of patients with high and low PARs. As shown in Table 2. More female patients, tumor size >5 cm, poor differentiation, high NLR and PLR were observed in patients with high PAR. Whereas, more cirrhosis and low APRI were observed in patients with low PAR.

The 1-, 3-, and 5-year RFS of HCC patients with high and low preoperative PARs were 65.9%, 42.2%, and 26.1%; and 77.1%, 58.5%, and 47.3%, respectively (Fig. 3A). The RFS of patients with a low (N=459) preoperative PAR was significantly better than those with a high (N=159) preoperative PAR ($P<.001$). The 1-, 3-, and 5-year OS rates were 91.5%, 65.9%, and 49.3%, respectively, in patients with a high (N=159) preoperative PAR and 95.3%, 79.7%, and 67.7%, respectively, in patients with a low (N=459) preoperative PAR (Fig. 3B). Statistical differences were observed ($P<.001$).

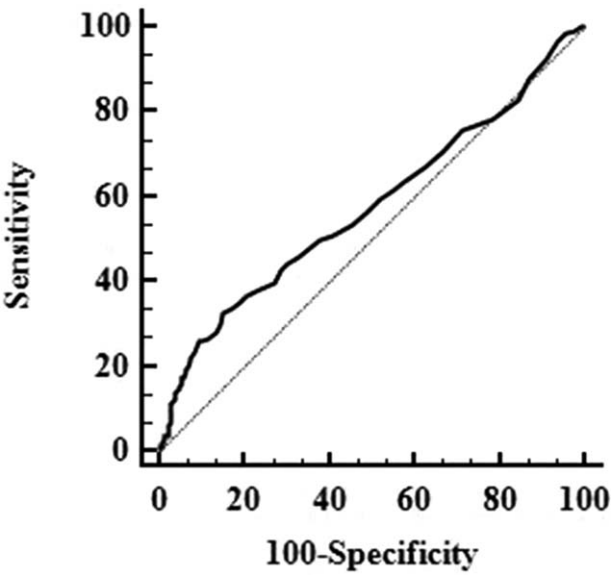

Figure 2. Recurrence-free and overall survival curves of the entire cohort.

Table 2

comparison of clinicopathological characteristics of patients with high and low PARs.

Characteristics	High PAR (N=159)	Low PAR (N=469)	P
Age > 60 years (yes/no)	40/119	113/356	.787
Female/male	37/122	65/404	.005
Size > 5 cm (yes/no)	101/58	171/298	<.001
Multiple tumors (yes/no)	8/151	12/457	.125
AFP > 400 ng/ml (yes/no)	64/95	168/301	.317
Positive HBV-DNA load (yes/no)	67/92	221/248	.276
Differentiation (poor vs moderate/well)	65/94	144/325	.019
Cirrhosis (yes/no)	102/57	371/98	<.001
MVI (yes/no)	36/123	94/375	.485
PLR > 150 (yes/no)	86/73	43/426	<.001
NLR > 3 (yes/no)	58/101	92/377	<.001
APRI ≥ 0.5 (yes/no)	29/130	240/229	<.001

APRI = aspartate aminotransferase-to-platelet count ratio index, AFP = alpha-fetoprotein, HBV-DNA = hepatitis B virus-DNA, MVI = microvascular invasion, PAR = platelet to albumin ratio, PLR = platelet to lymphocyte ratio, NLR = neutrophil to lymphocyte ratio.

3.2. Univariate and multivariate analyses for RFS

Table 3 lists the results of univariate and multivariate Cox regression analyses of the predictors of RFS. Univariate analysis revealed that MVI, tumor size >5 cm, poor differentiation, positive HBV-DNA load, AFP > 400 ng/ml, high PLR, high NLR, high APRI and high PAR were potential risk factors for postoperative recurrence. Multivariate analysis confirmed that presence of MVI (HR=1.698; 95%CI=1.333–2.163; $P<.001$), tumor size >5 cm (HR=1.798; 95%CI=1.437–2.249; $P<.001$), high APRI (HR=1.382; 95%CI=1.106–1.727; $P=.004$) and high PAR (HR=1.700; 95%CI=1.332–2.171; $P=.001$) were four independent risk factors for RFS.

3.3. Univariate and multivariate analyses for OS

Prognostic factors affecting the OS of patients with HCC by univariate and multivariate Cox regression models are displayed in Table 4. Univariate analyses to identify factors significantly associated with postoperative survival found that the poor prognostic factors were poor tumor differentiation, AFP > 400 ng/ml, MVI, NLR, PLR, PAR, APRI and tumor size >5 cm. Among these factors, only presence of MVI (HR=1.759; 95% CI=1.298–2.384; $P<.001$), tumor size >5 cm (HR=1.578; 95%CI=1.172–2.124; $P=.003$), high APRI (HR=1.656; 95% CI=1.240–2.212; $P=.001$) and the high PAR (HR=1.778; 95% CI=1.291–2.449; $P<.001$) were identified as independent prognostic factors by Cox regression analysis.

4. Discussion

Recently, many investigations have suggested that the systemic inflammatory response is associated with the prognosis of patients with HCC following liver resection, liver transplantation, and radiofrequency ablation. Some inflammation markers were proven to be predicters of postoperative recurrence and survival, such as the NLR and PLR. However, whether the PAR could contribute to the postoperative outcomes of patients with

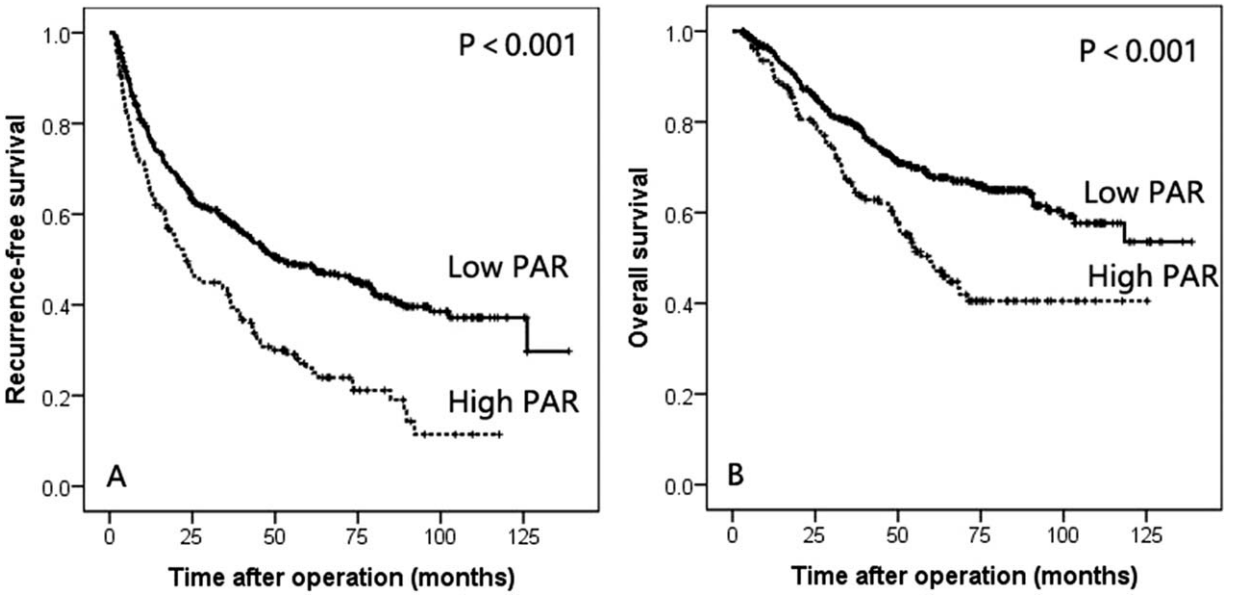

Figure 3. Comparison of the recurrence-free survival (A) and overall survival (B) of patients with a high preoperative PAR and low preoperative PAR. PAR = platelet to albumin ratio.

HCC is not well established. The current study confirmed that a high preoperative PAR adversely impacted HCC patients' postoperative RFS and OS after liver resection.

A number of investigations have confirmed that thrombocytosis at the time of diagnosis contributes to poor long-term survival in many types of solid tumors.[23–25] The systemic inflammation response and protection from host immune surveillance may be the potential mechanisms of this correlation.[24,25] Stone et al[26] reported that serum thrombopoietin and interleukin-6 were significantly elevated in ovarian cancer patients who had thrombocytosis compared with those who did not. The platelet counts were significantly reduced in both patients with epithelial ovarian cancer and in tumor-bearing mice when using anti-interleukin-6 antibody treatment.[26] Moreover, platelets could guard tumor cells from the attack of the host's immune system and promote their arrest at the endothelium.[27,28] Palumbo et al[29] confirmed that platelets could protect tumor cells from natural killer cell-mediated elimination. Moreover, platelets could also help the tumor cells take over the MHC-1, thereby mimicking host cells and escaping immune surveillance.[28,30] Clinical studies also suggested that high preoperative platelets were associated with poor prognosis of patients with HCC. Xue et al[31] confirmed that high platelet counts increase the incidence of metastasis in patients with huge HCC who received transarterial chemoembolization. Pang et al[8] revealed that preoperative platelet counts greater than 148×10^9/L were related to a high incidence of postoperative recurrence. Zhang et al[12] confirmed that inhibiting platelet function could block tumor metastasis.

In this study, we excluded patients with PH. In patients with PH, the preoperative platelet counts may be very low. In this case, the PAR may also be very low. However, many published studies have suggested that PH is associated with high perioperative

Table 3

Univariate and multivariate analyses of prognostic factors for RFS.

	Univariate analysis			Multivariate analysis		
Variable	**HR**	**95%CI**	***P***	**HR**	**95%CI**	***P***
Age > 60 years	0.948	0.748–1.202	.660			
Tumor size > 5 cm	2.256	1.831–2.780	<.001	1.798	1.437–2.249	<.001
Multiple tumors	1.361	0.781–2.371	.276			
Female/male	0.890	0.677–1.170	.403			
AFP > 400 ng/ml	1.333	1.080–1.646	.008			
Positive HBV-DNA load	1.216	0.989–1.469	.064			
Differentiation (poor vs well/moderate)	1.229	0.989–1.526	.062			
Cirrhosis	1.084	0.848–1.385	.520			
MVI	2.071	1.639–2.617	<.001	1.698	1.333–2.163	<.001
PLR > 150	1.511	1.186–1.924	.001			
NLR >3	1.479	1.174–1.863	.001			
PAR > 4.8	1.799	1.443–2.243	<.001	1.700	1.332–2.171	.001
APRI ≥ 0.5	1.288	1.047–1.585	.017	1.382	1.106–1.727	.004

APRI = aspartate aminotransferase-to-platelet count ratio index, HBV-DNA = hepatitis B virus-DNA, MVI = microvascular invasion, PAR = platelet to albumin ratio, PLR = platelet to lymphocyte ratio, NLR = neutrophil to lymphocyte ratio.

Table 4

Univariate and multivariate analyses of prognostic factors for OS.

Variable	Univariate analysis			Multivariate analysis		
	HR	95%CI	*P*	HR	95%CI	*P*
Age > 60 years	1.183	0.883–1.584	.260			
Tumor size > 5 cm	2.161	1.651–2.829	<.001	1.578	1.172–2.124	.003
Multiple tumors	1.215	0.599–2.463	.589			
Female/male	1.071	0.743–1.544	.714			
AFP > 400 ng/ml	1.215	0.924–1.596	.163			
Positive HBV-DNA load	1.058	0.809–1.382	.681			
Differentiation (poor vs well/moderate)	1.575	1.200–2.067	.001			
Cirrhosis	1.135	0.824–1.564	.439			
MVI	2.187	1.631–2.932	<.001	1.759	1.298–2.384	<.001
PLR > 150	1.902	1.417–2.553	<.001			
NLR > 3	1.901	1.429–1.529	<.001			
PAR > 4.8	1.825	1.378–2.416	<.001	1.778	1.291–2.449	<.001
APRI ≥ 0.5	1.447	1.108–1.889	.007	1.656	1.240–2.212	.001

APRI = aspartate aminotransferase-to-platelet count ratio index, HBV-DNA = hepatitis B virus-DNA, MVI = microvascular invasion, PAR = platelet to albumin ratio, PLR = platelet to lymphocyte ratio, NLR = neutrophil to lymphocyte ratio.

complications and poor long-term outcomes.[32,33] Choi et al[32] reported that the 5-year OS of HCC patients with PH who underwent liver resection was 37.9%, which was significantly lower than in those without PH (5-year OS 78.7%). Many studies have also suggested that PH could significantly increase the incidence of postoperative liver failure in HCC patients.[33,34] Recently, a meta-analysis also confirmed that clinical PH could negatively influence both short-term and long-term outcomes of patients with HCC after liver resection.[35] Accordingly, in the present study, we excluded patients with portal hypertension.

Low serum albumin levels could also result in a high PAR. The serum albumin level could reduce the patient's liver function and nutrition status. Hypoalbuminemia was often observed in patients with poor liver function and/or malnutrition. Both preoperative and postoperative poor liver function and malnutrition were confirmed to increase the patient's surgical risk and decrease the patient's long-term survival.[36–39] Moreover, albumin has been proven to have antitumor effects. Bagirsakci et al[40] confirmed that albumin may directly inhibit the growth of HCC, either via modulation of AFP or via its actions on growth-controlling kinases. A systematic review was conducted by Gupta et al[41] to assess the influence of pretreatment albumin on cancers including breast cancer, non-small cell lung cancer, gastrointestinal cancer, colorectal cancer, HCC, pancreatic cancer and so on. Finally, Gupta et al[41] confirmed that pretreatment serum albumin levels showed useful prognostic significance in cancer.

There are also some limitations in this study. First, this is a single-center retrospective study. Second, our study confirmed that both RFS and OS of HCC patients with a low PAR were better than those in patients with a high PAR. However, the AUC of the PAR in predicting RFS in the current study is low. Accordingly, the optimal cut-off value of the PAR in predicting the prognosis of HCC patients need further large sample studies. Moreover, platelet counts may be adversely influenced by PH. Although we have excluded all patients with clinical PH. Some patients with severe cirrhosis may also have a relatively low platelet count although they didn't have clinical PH. Accordingly, the relationship between PAR and RFS/OS maybe not linear. This may also explain why more patients with cirrhosis and high APRI in the low PAR group.

In conclusion, our study confirmed that the preoperative PAR may serve as a surrogate marker to predict postoperative recurrence and mortality in HCC patients without PH following liver resection. HCC patients with a high preoperative PAR had a higher recurrent risk and lower long-term survival rate than those with a low preoperative PAR.

Author contributions

Conceptualization: Chuan Li, Li-Ping Chen.
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Formal analysis: Chuan Li, Wei Peng, Xiao-Yun Zhang, Li-Ping Chen.
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Software: Li-Ping Chen.
Supervision: Li-Ping Chen.
Writing – original draft: Chuan Li.
Writing – review & editing: Li-Ping Chen.

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