Research Square

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Can Non-Invasive Assessment of Liver Fibrosis Serve as a Prognostic Predictor for HBV-Related Cirrhotic Patients with Hepatocellular Carcinoma?

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Research Article

Keywords: aspartate aminotransferase, platelet, hepatocellular carcinoma, liver cirrhosis, prognosis

Posted Date: November 5th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10842232/v1

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Additional Declarations: No competing interests reported.

Abstract

Purpose This study aimed to investigate the association between the aspartate aminotransferase-to-platelet ratio index (APRI) and postoperative prognosis in patients with hepatocellular carcinoma (HCC) complicated by liver cirrhosis.

Methods Clinical data of cirrhotic HCC patients undergoing hepatectomy were retrospectively analyzed. A receiver-operating-characteristic (ROC) curve was constructed to identify the optimal APRI cut-off value for prognostic prediction. Univariate prognostic analysis was performed using Kaplan-Meier survival analysis coupled with the Log-rank test, and multivariate analysis was conducted via Cox proportional-hazards regression models. Survival endpoints were compared between high-APRI and low-APRI groups.

Results ROC-curve analysis determined the optimal APRI cut-off value of 0.61. Patients were stratified into the high-APRI group (APRI ≥ 0.61) and the low-APRI group (APRI < 0.61). At the end of follow-up, liver-failure-related mortality was significantly higher in the high-APRI group (χ^2 = 5.232, P = 0.022) than in the low-APRI group. Survival analyses revealed that maximum tumor diameter > 0.5 cm, multiple tumor lesions, liver capsule invasion, vascular tumor thrombus, alpha-fetoprotein (AFP) > 20 ng/mL, and APRI ≥ 0.61 were independent risk factors for shortened disease-free survival (DFS) after hepatectomy among cirrhotic HCC patients (all P < 0.05). The 1-, 2-, and 5-year DFS rates were 79.4%, 61.4%, and 43.7% in the low-APRI group versus 71.4%, 51.6%, and 27.0% in the high-APRI group. The corresponding 1-, 2-, and 5-year tumor recurrence rates were 20.5%, 38.1%, 54.1% and 28.0%, 47.1%, 69.8%, respectively (P < 0.001). Patients with portal hypertension (PH) and Child-Pugh B liver function exhibited significantly higher APRI values than patients without PH and those with Child-Pugh A liver function (P < 0.05).

Conclusion Cirrhotic HCC patients with preoperative APRI ≥ 0.61 have an unfavorable postoperative prognosis following hepatectomy.

Introduction

Liver cancer is among the most common malignancies worldwide and ranks as the second leading cause of cancer-related death globally. Primary hepatocellular carcinoma (HCC) represents its predominant pathological subtype, and surgical resection remains one of the major curative therapeutic options for early-stage disease [1]. Persistent hepatitis B virus (HBV) infection causes chronic, recurrent hepatic inflammation that sequentially drives liver fibrosis, cirrhosis, and ultimately HCC development. Cumulative evidence shows that more than 50% of HCC patients have underlying liver cirrhosis, which is closely associated with poor clinical prognosis [2–3]. Proposed by Wai et al. [4], the aspartate aminotransferase-to-platelet ratio index (APRI) is a composite biomarker integrating serum aspartate aminotransferase (AST) and platelet counts. It has been validated for evaluating liver-fibrosis severity in chronic liver diseases [5–6]. At present, preoperative assessment for HCC mainly focuses on overall hepatic function and liver functional reserve, whereas systematic evaluation of liver-fibrosis severity is

frequently overlooked. Whether different degrees of hepatic fibrosis influence postoperative prognosis in cirrhotic HCC patients remains incompletely clarified. In this study, APRI was applied as a non-invasive tool to quantify liver-fibrosis burden, and we comprehensively analyzed the association between preoperative APRI values and postoperative clinical outcomes in HBV-related cirrhotic HCC patients receiving hepatectomy.

Materials and Methods

Study Population

Clinical data of consecutive patients diagnosed with HBV-related cirrhotic HCC who underwent curative hepatectomy at the Affiliated Hospital of Qingdao University between 2014 and 2019 were retrospectively collected. This study was performed in accordance with the Declaration of Helsinki. This study was approved by the Institutional Ethics Committee of the Affiliated Hospital of Qingdao University. Written informed consent was obtained from all patients prior to surgery.

Inclusion criteria:

Pathologically confirmed HCC accompanied by liver cirrhosis;

HBV infection confirmed as the underlying etiology.

Exclusion criteria:

History of prior splenectomy;

Loss to follow-up after surgery;

Perioperative death attributable to surgical complications, including liver failure, pulmonary infection, and intra-abdominal hemorrhage.

A total of 655 patients were enrolled for final analysis (561 males, 94 females; median age 55 years, range 17–82 years).

Observation Indicators and Follow-Up Protocol

Perioperative clinical and pathological data were systematically extracted. Preoperative variables included sex, age, history of oral anti-HBV therapy, Child-Pugh classification, portal hypertension status, serum alpha-fetoprotein (AFP), and peripheral platelet counts. Intraoperative parameters contained portal-vein occlusion time, intraoperative blood loss, and volume of allogeneic blood transfusion.

Postoperative pathological variables included tumor number, maximum tumor diameter, liver-capsule invasion, microvascular tumor thrombus, and minimal surgical-margin width.

APRI was calculated using the previously validated formula: APRI = (AST / upper limit of normal AST) / platelet count (10^9/L) × 100 [4].All enrolled patients received standardized postoperative surveillance. In the first three months after hepatectomy, serum AFP testing, liver-function assays, abdominal ultrasonography or contrast-enhanced computed tomography (CT), and chest CT were performed monthly. Thereafter, follow-up examinations were performed every three months to monitor tumor recurrence. The follow-up endpoint was defined as tumor recurrence or the final follow-up date (September 30, 2021).

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics 23.0. Normally-distributed continuous variables were expressed as mean ± standard deviation and compared using the independent-samples t-test. Categorical variables were presented as counts and percentages and analyzed with the chi-square test. ROC-curve analysis was used to evaluate the prognostic performance of APRI and calculate the area under the curve (AUC). The optimal APRI cut-off value was determined according to the maximum Youden index.

All perioperative clinical-pathological variables were entered into Kaplan-Meier survival analysis with the Log-rank test for univariate prognostic screening. Variables achieving statistical significance ($P < 0.05$) in univariate analysis were further incorporated into the Cox proportional-hazards regression model for multivariate independent-prognostic analysis. A two-tailed $P < 0.05$ was regarded as statistically significant.

Results

Among the 655 enrolled cirrhotic HCC patients, postoperative tumor recurrence occurred in 452 patients; 324 patients died of liver failure and 27 died from HCC progression. Median DFS and overall survival (OS) were 31.4 months and 75.4 months, respectively. The 1-, 2-, and 5-year OS rates were 93.6%, 80.0%, and 55.7%; the corresponding 1-, 2-, and 5-year DFS rates were 74.7%, 56.6%, and 34.6%.

ROC-curve analysis yielded an AUC of 0.602 (95% CI: 0.554–0.650, $P < 0.001$) for preoperative APRI in prognostic prediction. The maximum Youden index was 0.192 (sensitivity 56.8%, specificity 62.4%), corresponding to an optimal cut-off value of 0.61 (Fig. 1). Patients were stratified into the low-APRI group (APRI < 0.61, n = 128) and the high-APRI group (APRI ≥ 0.61, n = 204).

Liver-failure-related mortality was significantly higher in the high-APRI group (20/204) than in the low-APRI group (4/128, $P = 0.022$) (Table 1). Univariate and multivariate regression analyses confirmed that maximum tumor diameter > 0.5 cm, multiple tumors, liver-capsule invasion, vascular tumor

thrombus, AFP > 20 ng/mL, and APRI ≥ 0.61 were independent risk factors for poor DFS after hepatectomy (all P < 0.05).

Table 1
Differences in the cause of death between high-value and low-value groups

Groups	Death (numbers)		X2 value	P value
	Liver failure	HCC		
APRI low-value	4	124	5.232	0.022
APRI high-value	20	184		

Table 2
Univariate and multivariate analysis of DFS for HCC patients with liver cirrhosis

Factors	Log-Rank test		Cox	
	months (median)	P value	HR (95% CI)	P value
Gender(male/female)	31.1/41.2	0.081	-	-
Age (≤ 60/>60 years)	34.3/27.6	0.161	-	-
Diabetes(no/yes)	33.0/23.6	0.415	-	-
PH(no/yes)	34.3/29.3	0.066	-	-
Anti-HBV treatment(no/yes)	24.0/55.0	0.000	1.092(0.810–1.473)	0.563
Child-Pugh(A/B)	33.0/16.5	0.106	-	-
AFP (≤ 20/>20ng/ml)	43.1/23.3	0.000	0.743(0.569–0.969)	0.029
Tumor number(1/≥2)	40.1/14.6	0.000	0.587(0.430–0.802)	0.001
Vascular tumor thrombus(no/yes)	35.0/9.2	0.000	0.496(0.300-0.821)	0.006
Microvascular tumor thrombus (no/yes)	46.5/20.9	0.000	0.870(0.643–1.177)	0.366
Maximum tumor size>5cm(no/yes)	44.9/13.9	0.000	0.663(0.496–0.886)	0.005
Liver capsule invasion(no/yes)	47.0/24.0	0.001	0.730(0.539–0.987)	0.041
APRI value ≥ 0.61(no/yes)	49.5/25.0	0.000	0.675(0.516–0.883)	0.004
Portal blood block>20min(no/yes)	37.0/20.9	0.004	0.803(0.601–1.073)	0.137
Blood loss>200ml(no/yes)	49.7/25.0	0.000	1.015(0.750–1.375)	0.922
Anatomical resection(no/yes)	29.5/39.3	0.159	-	-
Minimum surgical margin≥10mm(no/yes)	29.2/49.7	0.037	1.132(0.770–1.664)	0.529

Table 3 Comparison of clinical and pathological features between high-value and low-value groups

Factors	APRI value($x \pm s$)	*t* value	P value
Gender(male/female)	0.90 ± 0.95/ 0.87 ± 1.04	0.277	0.782
Age (≤ 60/>60 years)	0.89 ± 0.96/ 0.92 ± 0.98	0.362	0.717
Child-Pugh(A/B)	0.86 ± 0.91/ 1.92 ± 1.74	2.762	0.012
PH(no/yes)	0.72 ± 0.73/ 1.71 ± 1.39	7.334	0.000
Vascular tumor thrombus(no/yes)	1.04 ± 0.80/ 0.89 ± 0.97	0.884	0.377
Microvascular tumor thrombus (no/yes)	0.87 ± 1.08/ 0.91 ± 1.01	0.291	0.771
Maximum tumor size>5cm(no/yes)	0.90 ± 1.03/ 0.89 ± 0.80	0.103	0.918
Liver capsule invasion(no/yes)	0.84 ± 1. 10/ 0.93 ± 0.88	1.103	0.270
AFP (≤ 20/>20ng/ml)	0.85 ± 1.06/ 0.95 ± 0.86	1.278	0.202
HBV surface antigen (no/yes)	0.56 ± 0.42/ 0.90 ± 0.97	0.784	0.433
HBV e antigen (no/yes)	0.86 ± 0.80/ 1.02 ± 1.30	1.885	0.060

Median DFS was 49.5 months for the low-APRI group and 25.0 months for the high-APRI group ($P < 0.001$) (Table 2). The low-APRI group had significantly higher 1-, 2-, and 5-year DFS rates (79.4%, 61.4%, 43.7%) compared with the high-APRI group (71.4%, 51.6%, 27.0%; $P < 0.001$) (Fig. 2a). Meanwhile, 1-, 2-, and 5-year recurrence rates were markedly lower in the low-APRI group (20.5%, 38.1%, 54.1%) than in the high-APRI group (28.0%, 47.1%, 69.8%; $P < 0.001$) (Fig. 2b).

Subgroup analysis of clinical-pathological features demonstrated that patients with portal hypertension or Child-Pugh B liver function had significantly higher APRI values ($P < 0.05$) (Fig. 3).

Discussion

HCC is a highly aggressive malignancy, and chronic HBV infection is the dominant etiological risk factor for HCC worldwide [7]. Persistent HBV-driven hepatic inflammation induces progressive liver fibrosis, which further evolves into liver cirrhosis and HCC. Most HCC patients have underlying HBV-related cirrhosis. Multiple clinical studies have confirmed that cirrhosis aggravates tumor recurrence and impairs long-term survival; advanced cirrhosis correlates with progressively worse clinical outcomes [2–3, 8]. Therefore, accurate evaluation of liver-fibrosis severity is critical for therapeutic decision-making and prognostic assessment in cirrhotic HCC patients.

Liver biopsy remains the gold standard for liver-fibrosis staging; however, its clinical application is limited by its invasive nature and potential procedure-related complications. Non-invasive fibrosis-assessment tools mainly rely on serological biomarkers, including transaminases, markers of hepatic synthetic function (albumin, bilirubin, prothrombin time), and cirrhosis-associated hematological markers (platelet

counts), to construct predictive scoring models for fibrosis grading [9–11]. As a simple and convenient non-invasive scoring tool, APRI has proven useful for identifying significant liver fibrosis (F ≥ 2) and advanced cirrhosis (F5-F6) in chronic viral hepatitis [4–5, 12]. Nevertheless, the prognostic value of APRI for postoperative outcomes among cirrhotic HCC patients has not been fully elucidated. Accordingly, this study explored the clinical association between preoperative APRI and postoperative prognosis within this patient cohort.

Cox multivariate regression analysis showed that tumor-related features (large tumor size, multiple tumor lesions, vascular invasion, and liver-capsule invasion) constituted major independent risk factors for inferior DFS and tumor recurrence. These findings are partially consistent with previous reports [13–15]. Importantly, preoperative APRI emerged as an independent non-tumor-related prognostic factor for postoperative recurrence and survival. Given that post-recurrence salvage therapies may affect long-term overall survival, we did not analyze the association between APRI and OS in the present study.

Two key pathological mechanisms explain elevated APRI values in advanced cirrhosis. First, progressive liver fibrosis and splenomegaly cause excessive platelet sequestration and splenic destruction, leading to thrombocytopenia [16]. Impaired hepatocyte synthetic function in cirrhotic livers further reduces thrombopoietin production and lowers peripheral platelet counts [17]. Second, cirrhotic hepatic tissue exhibits reduced metabolic clearance for AST. Severe mitochondrial injury of hepatocytes in advanced liver fibrosis triggers substantial AST release into systemic circulation and raises serum AST concentrations [18].

Our subgroup analysis revealed that elevated APRI correlated significantly with advanced Child-Pugh grade and portal hypertension rather than oncological tumor characteristics. This observation supports that APRI reflects the severity of underlying hepatic cirrhosis instead of tumor biological aggressiveness [19]. The high-APRI group presented higher liver-failure-related mortality and poorer overall prognosis, implying that targeted preoperative hepatoprotective management and postoperative anti-fibrotic interventions may retard fibrosis progression and improve clinical outcomes.

Notably, conventional monitoring for anti-HBV therapy mainly focuses on transaminase levels and HBV-DNA viral loads. Whether APRI can serve as an auxiliary non-invasive marker for dynamically evaluating liver-fibrosis progression and assessing antiviral treatment efficacy warrants further prospective investigation.

In summary, preoperative APRI is a reliable non-invasive biomarker for predicting postoperative prognosis in cirrhotic HCC patients. Active hepatoprotective strategies and targeted interventions to slow liver-fibrosis progression can effectively improve long-term survival for HBV-related cirrhotic HCC patients after hepatectomy.

Declarations

Funding

Not applicable.

Clinical trial number

Not applicable.

Author Contribution

Mu Siyu compiled relevant data and drafted the manuscript, while Xu Lin was responsible for the preliminary review and polishing of the manuscript.

Acknowledgement

We would like to express our sincere gratitude to Dr. Zuseng Wang for hisinvaluable contributions to the figure in this manuscript. His expertise andassistance greatly enhanced the visual representation of the contents of ourmanuscript.

Data Availability

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

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Figures

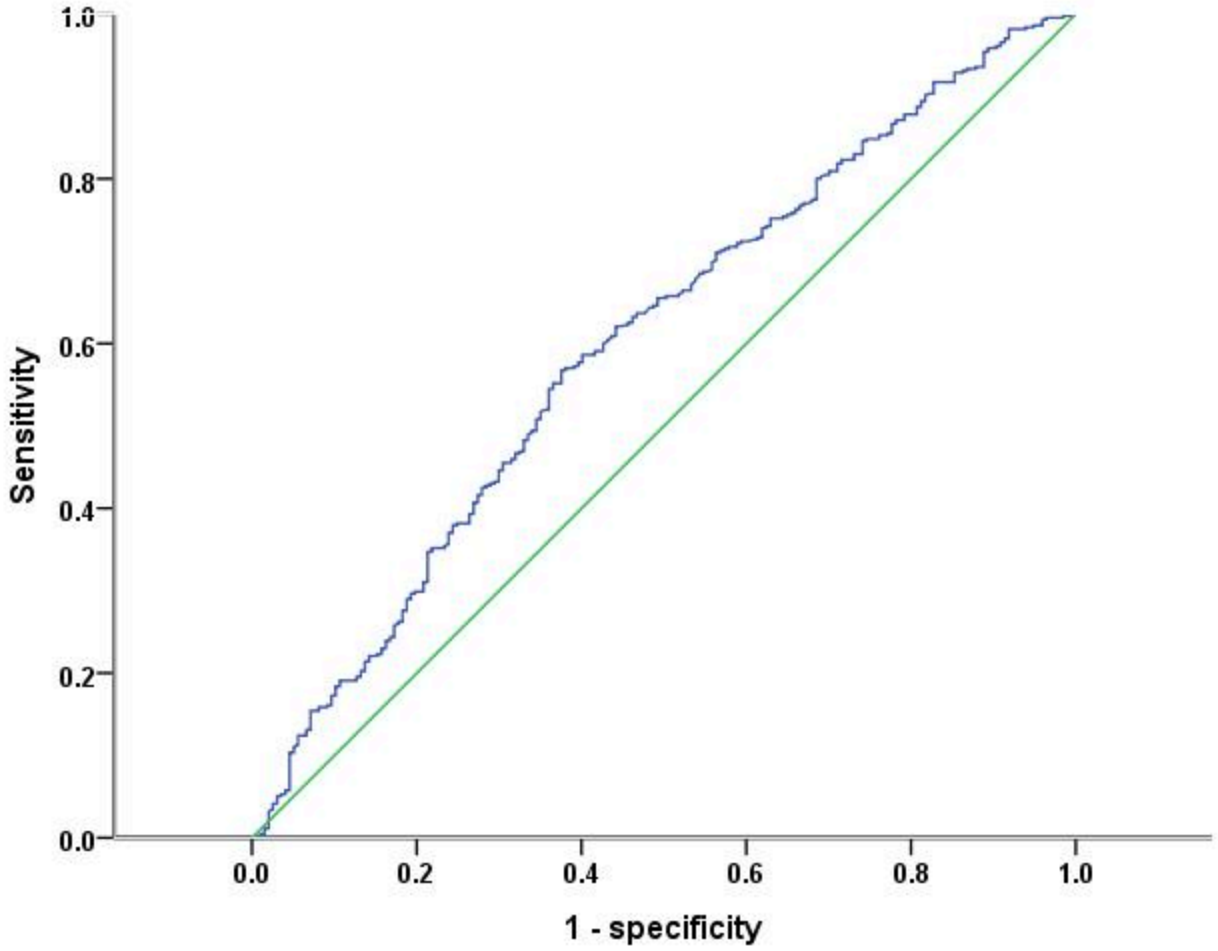
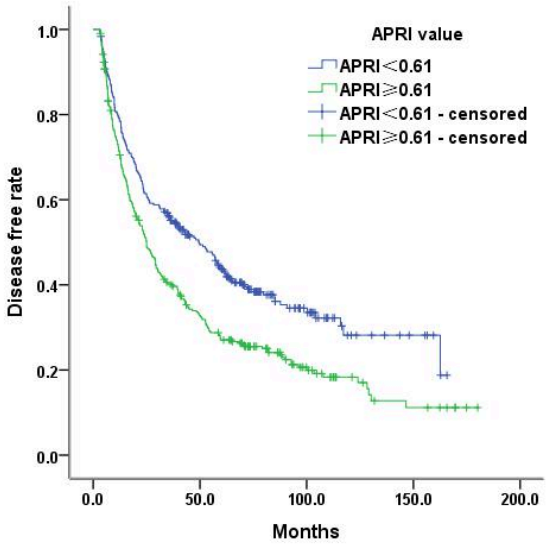
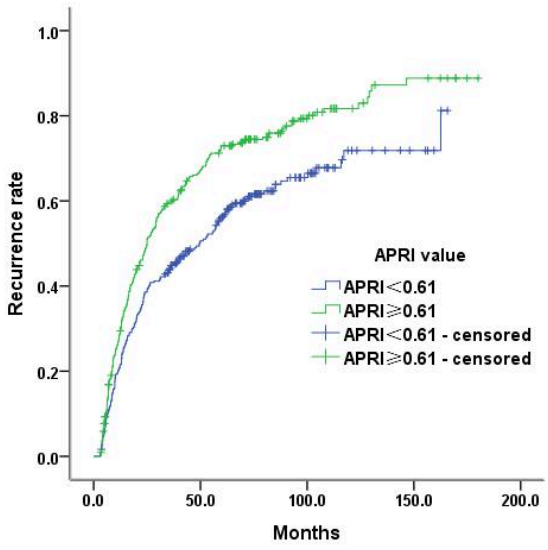


Figure 1

ROC of APRI and HCC recurrence



2a

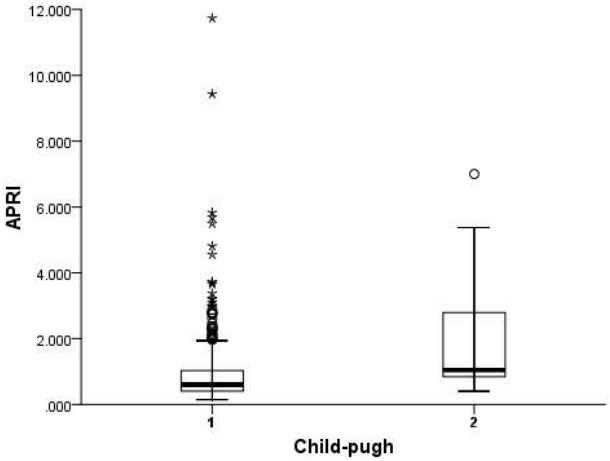


2b

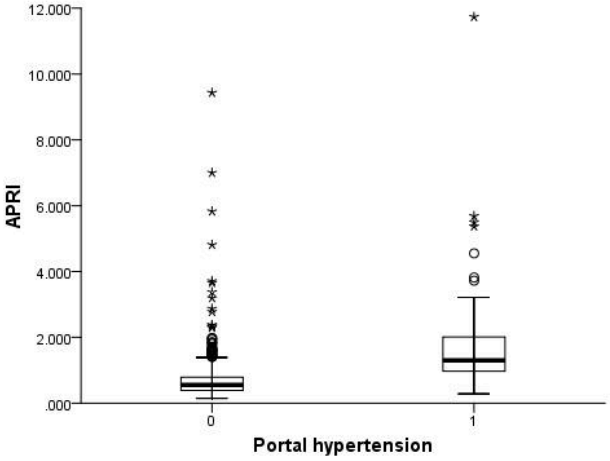
Figure 2

2 (a) Disease free survival curve of APRI groups

2 (b) HCC recurrence curve of APRI groups



3a



3b

Figure 3

3 (a) APRI value of Child-pugh A and B class

3 (b) APRI value of patients with and without PH