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Novel predictive nomograms based on aspartate aminotransferase-to-platelet ratio index for hepatocellular carcinoma with post-operative adjuvant transarterial chemoembolization

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Abstract. The clinical significance of systemic inflammation assessed with laboratory analysis of blood samples has been validated in a variety of cancers. The present study was conducted to investigate prognostic significance of preoperative aspartate aminotransferase-to-platelet ratio index (APRI) for the outcome of hepatocellular carcinoma (HCC) patients receiving post-operative adjuvant transarterial chemoembolization (PATACE). A total of 201 patients who underwent PATACE were retrospectively analyzed. A nomogram for HCC was developed using predictors based on multivariate Cox models, and bootstrapping was performed for validation. According to the ROC curve, which was used to divide patients into two cohorts: High APRI group (APRI>1.02) and Low APRI group (APRI≤1.02). In subgroup survival analysis, patients with a relatively low APRI had significantly longer disease-free survival (DFS) and overall survival (OS) than patients with a relatively high APRI, regardless of Barcelona Clinic Liver Cancer (BCLC) stages (BCLC 0/A or BCLC B/C, both P<0.05); while in China liver cancer staging I/II and TNM I/II stage patients, relatively low APRI was associated with improved DFS and OS (both P<0.05). Multivariate Cox models demonstrated that APRI and BCLC stages were independent prognostic factors of DFS and OS (both P<0.05). Nomograms for DFS and OS were constructed, respectively. Calibration curve analysis showed that the standard curve fitted well with the predicted curve. Time-receiver operating characteristic curve analysis revealed that the nomogram had high efficiency. Decision curve analysis demonstrated the high clinical value of the nomogram. APRI is an independent prognostic factor of DFS and OS in HCC patients receiving PATACE, and the combination of APRI with the HCC staging system can refine risk stratification to provide a more accurate prognostic assessment for the outcome of patients receiving PATACE.

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Introduction

Primary liver cancer is the fourth most common malignancy and the second cause of cancer-related death in China, posing a severe threat to the life and health of Chinese patients. Besides, the morbidity and mortality of primary liver cancer are increasing on a global scale (1,2). In pathology, liver cancers mainly include hepatocellular carcinoma (HCC, 75-85%), intrahepatic cholangiocarcinoma (10-15%), and combined hepatocellular-cholangiocarcinoma (3). The present study focused on HCC for analysis. For the past few years, treatment for HCC has been significantly advanced, and surgery remains the first choice (4). However, the incidence of complications after hepatectomy remains high, especially in patients complicated by primary liver fibrosis and cirrhosis (5). According to the Barcelona Clinic Liver Cancer (BCLC) Staging System, transarterial chemoembolization (TACE) is recommended as the standard therapy for patients with advanced or unresectable tumor (hepatic compensation, Child B) (6,7). Some clinical trials have proved the effectiveness of the TACE as an adjuvant therapy for HCC (6,8,9). For example, a randomized controlled trial revealed that post-operative adjuvant TACE (PATACE) was highly effective in HCC patients but at a high risk of recurrence, such as those with multiple tumor nodules, macroscopic vascular invasion, or large tumor diameter (>5 cm) (8). Multiple studies

recommended PATACE for HCC patients with multiple tumor nodules, a tumor of a large size, or vascular invasion (10-12). The efficacy of PATACE can be attributed to its effect to improve the prognosis of HCC patients, as traditional imaging fails to discover the microscopic tumor foci and concealed multiple foci in the liver before surgery (10). Therefore, PATACE has been extensively applied in post-operative HCC patients who have multiple risk factors of recurrence, such as large tumor diameter, multiple tumor nodules, microvascular invasion (MVI) and satellite lesions (6,10).

Nevertheless, the long-term survival of this population remains unclear (4,13). Even though TACE and liver resection are considered the most effective therapies, this population may likely not receive benefits from surgery and therefore have poor survival outcomes (14). Assessment for the hepatic functional reserve is critical for HCC treatment, as liver cirrhosis potentially is a major cause of post-operative death (15) and it is also a leading cause of 70-90% HCC cases. Liver reserve is markedly more important in early HCC than that in advanced disease (16,17). Different from other malignancies, the survival outcome of HCC patients is largely dependent on the baseline liver function and the dissemination of the primary tumor. In this context, there is an urgent need to look for non-invasive, accurate biomarkers that are indicative of liver function and inflammation. In the meantime, a prognostic model based on the biomarker, liver function and tumor stage is also in demand. Hematological parameters following systemic inflammation have been assembled as an inflammation-based prognostic scoring system to predict cancer survival. For example, peripheral blood subpopulations, including lymphocytes, monocytes and platelets (PLT), are prognostic for the outcome of varying cancers. A previous study found that anti-PLT therapy could prevent HCC and improve the survival of mice with chronic hepatitis B (CHB) (18). Moreover, numerous studies have reported the relationship between PLT and HCC diagnosis, post-operative complications, and survival (19-24). A previous study found that preoperative PLT decline predicted an increased incidence of complications, liver insufficiency and death in HCC patients after tumor resection (22). The preoperative aspartate aminotransferase (AST)-to-PLT ratio index (APRI) has been identified as an independent prognostic index for liver failure in HCC patients after hepatectomy (20). However, it has been controversial how the preoperative PLT increase affects the survival outcome of HCC patients. Amano *et al* (21) reported that a PLT count lower than $10^5/mm^3$ was unfavorable for the overall survival (OS) and disease-free survival (DFS) of HCC patients. They also found that patients beyond the Milan criteria could benefit from hepatectomy, and patients with a sufficiently high PLT count enjoyed an improved survival outcome. By contrast, Hwang *et al* (23) pointed out that HCC patients with PLT increase reversely had significantly shorter survival times. Combining the studies, it is of paramount importance to identify the prognostic significance of PLT-related indicators, including PLT count, PLT-to-lymphocyte ratio (PLR), and APRI. AST, a spectrum ranging from hepatitis to fatty liver, is commonly used to assess liver injury. Previous studies have proved that inflammation-based prognostic factors, including PLR, Glasgow outcome scale score, neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and AST/alanine aminotransferase ratio (AST/ALT), are prognostic for the outcome of HCC. APRI is reported as a convenient indicator that can predict the post-operative outcome of HBV-related HCC patients (16,25-27). It is applicable in clinical practice as a tool for fast and reliable assessment of the severity of liver function and cirrhosis, and it even can be used as an alternative to liver biopsy. However, it remains unclear whether APRI remains applicable for identifying the patients responsive to PATACE.

Clinical staging is critical for patient prognosis and treatment selection. Motivated by this fact, multiple staging systems have been developed all over the world for the past few years, including TNM staging (28), Okuda staging (29), BCLC (30), Japan-integrated staging (JIS) (31), Cancer of the Liver Italian Program (CLIP) (32), China liver cancer staging (CNLC) and Hong Kong liver cancer (HKLC). Okuda staging is the first to consider liver function as a tumor-influencing factor, but it does not include certain important prognostic factors such as vascular invasion, tumor number and metastasis. JIS is an assembly of the TNM staging and Child-Pugh scoring systems released by the Liver Cancer Study Group of Japan (LCSGJ), while the patient's personal situation is not considered. CLIP fails to identify patients with early-stage disease and assess cancer-related symptoms that are essential for patient prognosis. HKLC was developed in 2014 based on a large group of patients with HBV-related HCC patients. It is more sensitive than the BCLC staging system to patients requiring aggressive treatment. Despite several studies (33,34) reporting the superior capability of HKLC to BCLC in predicting survival outcomes, validation in different cohorts is still required. Presently, the BCLC and AJCC-TNM remain the most effective and reliable staging systems (28). Since the present study mainly focused on HCC patients in China, the CNLC staging system was also applied here.

Nomogram is devised as a prognostic tool combining known prognostic markers to quantify the prognostic risk as precisely as possible. The present study attempted to discuss the prognostic significance of the APRI for OS and DFS of HCC patients receiving radical hepatectomy and PATACE. In addition, a potent nomogram of high clinical prognostic value was established based on the APRI and HCC staging systems. The present study was in accordance with the TRIPOD reporting checklist.

Materials and methods

Patients. The current study retrospectively analyzed the data from 201 HCC patients, who received radical hepatectomy in the Second Hospital of Nanjing from January 2012 to December 2018 (Fig. 1). Data on follow-up were collected from outpatient medical records, telephone interviews, or WeChat conversations. Inclusion criteria were as follows: i) pathological diagnosis of HCC; ii) presence of any of the following risk factors, such as multiple tumor nodules, macroscopic vascular invasion, tumor diameter >5 cm, and microsatellite lesions; iii) no preoperative interventional, targeted, or immune therapy; iv) without or complicated by other malignancies; v) complete tumor resection; vi) first PATACE (lobaplatin and iodized oil) within 4-6 weeks after hepatectomy; and vii) long-term treatment with oral antivirals.

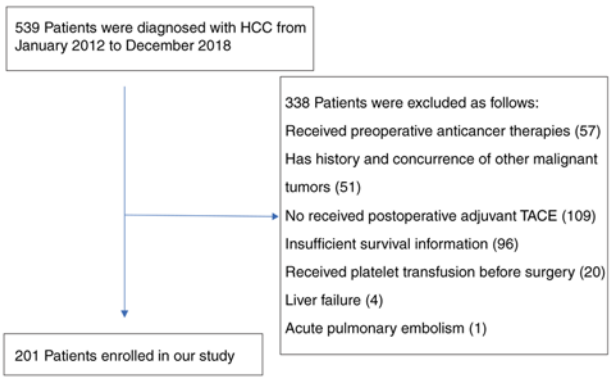

Figure 1. Flow diagram of the study design. HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization.

All participants were reviewed 4 weeks after hepatectomy, and PATACE was recommended in cases without recurrent lesions in the liver. Recurrence was considered in the presence of a new tumor focus within 4 weeks after radical hepatectomy, and the cases were excluded from the present study. Patients who underwent preoperative anti-cancer treatment, had not received a PATACE, had a history of other malignancy or had incomplete follow-up data were excluded from the present study. The present study was approved (approval no. B2021-322) by the Second Hospital of Nanjing ethics committee (Nanjing, China) and was conducted in line with the standards of the Declaration of Helsinki (as revised in 2013). As part of the consent process, written informed consent was provided by all participants.

Data collection and definitions. Clinical data were collected within one week preceding surgery, including age, sex, pathology report, serum albumin, total bilirubin, ALT, AST, alpha-fetoprotein (AFP), PLT, tumor parameters and globulin. Staging systems adopted the AJCC-TNM (8th edition), BCLC and CNLC staging systems. APRI was calculated as follows: APRI={[AST (IU/l)/upper limit of normal]/PLT(x10^9/l)} x100 (35). Any discrepancy was resolved by discussion.

Follow-up. Follow-up data as of December 2021 were acquired. OS was defined by a period from the beginning of PATACE to patient death. Patients surviving the last follow-up were censored. DFS was defined by a period from the beginning of PATACE to recurrence or the last follow-up. Follow-up examinations included HCC markers (AFP, AFP-L3, DCP and GP73), abdominal ultrasound, upper abdominal contrast-enhanced CT or Gd-EOB-DTPA MRI, and liver function test. All participants were followed up every 3-4 months within 2 years after surgery and every 6 months after 2 years. Recurrence was diagnosed in the context of post-operative serum AFP >20 ng/ml and the presence of a new focus on abdominal ultrasound, upper abdominal contrast-enhanced CT, or Gd-EOB-DTPA MRI. Patient death, time to recurrence, imaging results and HCC markers during the follow-up period were recorded in detail. Follow-up and outcome assessments were fulfilled by two researchers to minimize bias.

Treatment process. Radical surgery a right subcostal 'inverted-L' incision was created, and it was extended to the left subcostal region if necessary. Careful examination for peritoneal cavity was needed to confirm the tumor extent, extrahepatic metastasis or possible intraperitoneal dissemination. Anatomical hepatectomy was preferred for the tumor occupying half of the liver, or in the liver lobe or segment. For the tumor with a large size, a deep position, or next to blood vessel, preoperative 3D CT image was obtained to confirm the tumor border and the extent of resection. Liver parenchyma devascularization was performed with a cavitron ultrasonic surgical aspirator (CUSA) and bipolar electrocoagulation, during which corresponding blood vessels were ligated or sutured by silk or 3-0 Proline. The Pringle maneuver was used to control hepatic portal blood flow if necessary, with the time strictly controlled to be less than 15 min.

PATACE. After 4-6 weeks of hepatectomy, TACE was conducted for the remaining liver when the liver function recovered. The Seldinger technique was applied to gain vascular access in the femoral artery (or the radial artery), and the catheter was extended to the celiac trunk or common hepatic artery to complete DSA. Subtraction images were acquired in the arterial, parenchymal and venous phases. The catheter head was selectively inserted into the right or left hepatic artery, and the emulsion mixed with 2-10 ml Lipiodol Ultra Fluide (Guerbet) and 10-20 mg Lobaplatin for Injection (Hainan Changan International Pharmaceutical Co., Ltd.) was injected through a microcatheter (Progreat; Terumo Corp.). A combination of liver function and area of the body was used to determine the doses of chemotherapeutics and iodized oil to be given.

Statistical analysis. Statistical analysis was fulfilled with the SPSS 26.0 (IBM Corp.) and GraphPad Prism 8 (Dotmatics). The optimal cut-off value for APRI was determined by drawing a receiver operating characteristic (ROC) curve. Chi-square test, Fisher's exact test, and Mann-Whitney U test was applied to analyze the relationship between clinical pathological features and APRI. One-way analysis of variance was used for pairwise comparisons. Kaplan-Meier method together with the log-rank test was adopted to explore the effect of APRI on DFS and OS. Backward stepwise Cox regression modeling was applied to perform multivariate analysis for the variables with $P<0.1$ in univariate analysis. $P<0.05$ demonstrated a difference with statistical significance. Concordance index values (C-index) and calibration plots were employed to assess the performance of nomogram using the R package 'rms' (v4.2.1, http://www.r-project.org/). Time-dependent ROC curves and estimates of the area under the curve (AUC) were used to compare the predictive value of the nomogram with OS and DFS. Using the decision curve analysis (DCA), net benefits and threshold probabilities were quantified for the nomogram, and the clinical benefit was quantified.

Results

Clinicopathological characteristics of patients and optimal cut-off value of APRI. There were more male than female patients (83.6 vs. 16.4%). Among all patients, ages ranged from 11-81 years (median, 53.6±10.9 years). A total of 96% of the cases were caused by hepatitis B. Patients with

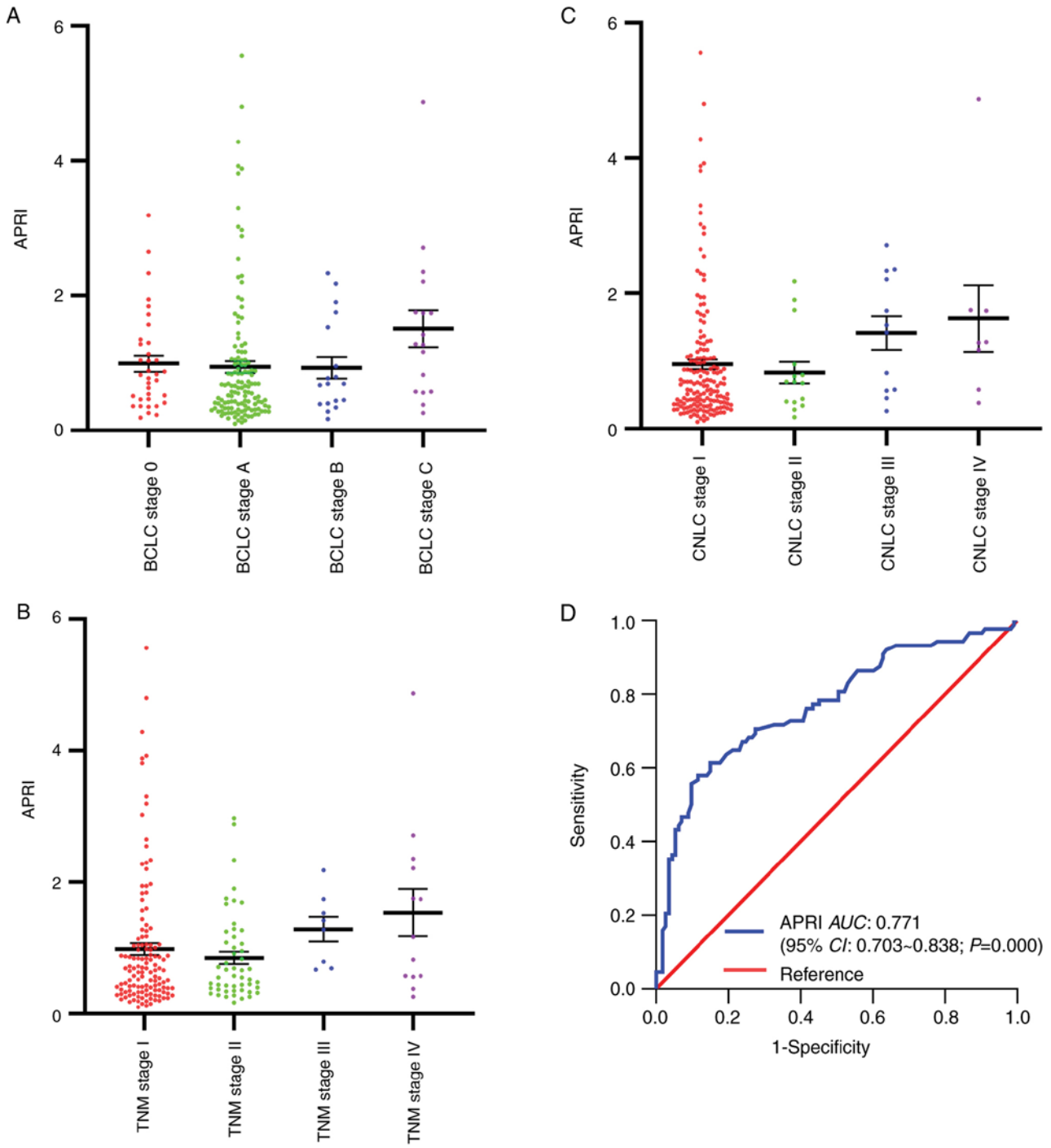

Figure 2. Levels of APRI were compared between subgroups characterized by: (A) BCLC stage (P=0.136); (B) TNM stage (P=0.100); (C) CNLC stage (P=0.080). (D) ROC curves of APRI for predicting the survival of HCC patients after PATACE. APRI, preoperative aspartate aminotransferase-to-platelet ratio index; BCLC, Barcelona Clinic Liver Cancer; TNM, Tumor Node Metastasis classification; CNLC, China liver cancer staging; PATACE, post-operative adjuvant transarterial chemoembolization.

HCV-RNA or HBV-DNA levels exceeding 500 IU/ml were 1.5 or 23.9% of the total, respectively, while 59.7% of the patients developed liver cirrhosis. The number of APRI exhibits non-significant difference among samples of different BCLC stage, TNM and CNLC stage (Fig. 2A-C). The time-dependent ROC curve was generated to identify the optimal cut-off value of APRI for OS prediction (Fig. 2D). The cut-off value of APRI was determined as 1.02, associated with an AUC of 0.771, sensitivity of 58.0%, specificity of 88.5, and 95% confidence interval (95% CI) of 0.703-0.838 (Table I).

Correlation between APRI and clinicopathological features. According to the cut-off value, patients were divided into the High-APRI group (APRI >1.02) and Low-APRI group (APRI ≤1.02). Correlational analysis demonstrated that APRI was significantly associated with AST, total bilirubin, prothrombin time (PT), ALT, albumin, HBV-DNA, PLT, WBC, CNLC

Table I. Analysis of ROC curves of APRI.

Variable	AUC	Optimal cutoff value	Youden index	Sensitivity (%)	Specificity (%)	P-value	95% CI
APRI	0.771	1.02	0.465	58.0	88.5	0.000	0.703-0.838

AUC, area under the curve; ROC, receiver operating characteristic; CI, confidence interval; APRI, aspartate aminotransferase-to-platelet ratio index.

stage, BCLC stage and AJCC-TNM stage (all P<0.05). The relationship between APRI and clinicopathological features of HCC patients was detailed in Table II.

Survival analysis of APRI. The relationship between the APRI and survival outcomes (OS and DFS) of HCC patients was then analyzed in the High-APRI and Low-APRI groups using the Kaplan-Meier method followed by log-rank test. The results revealed that the DFS (P<0.0001) and OS (P<0.0001) of patients in the low-APRI group were significantly improved than those of patients in the High-APRI group (Fig. 3A and B). Subsequently, stratification analysis was performed based on CNLC, BCLC and AJCC-TNM staging systems. In the present study, early-stage tumor was classified as CNLC I/II, BCLC 0/A, and TNM I/II, while late-stage tumor was classified as CNLC III/IV, BCLC B/C, and TNM III/IV. It was revealed that either in BCLC 0/A or BCLC B/C stage, patients with a relatively low APRI had significantly longer DFS and OS than patients with a relatively high APRI (both P<0.05) (Fig. 3C-F). While in CNLC I/II (Fig. 3G and H) and TNM I/II (Fig. 3K and L) stage patients, relatively low APRI was associated with improved DFS and OS (both P<0.05). There were no distinct differences in DFS and OS between the High-APRI and Low-APRI groups in CNLC III/IV (DFS, P=0.502; OS, P=0.775; Fig. 3I and J) and TNM III/IV (DFS, P=0.184; OS, P=0.212; Fig. 3M and N) patients.

Risk factors influencing the survival of HCC patients. The uni- and multi-variate Cox regression analyses on the prognostic significance of APRI for DFS in patients with HCC patients are shown in Table III. Univariate analysis demonstrated that AFP (P=0.017), PLT (P=0.022), ALT (P=0.004), AST (P<0.0001), total bilirubin (P=0.001), PT (P=0.010), tumor size (P=0.025), tumor number (P=0.002), tumor capsule (P<0.0001), vascular invasion (P<0.0001), neural invasion (P=0.005), Edmondson-Steiner grade (P=0.002), TNM stage (P<0.0001), CNLC stage (P<0.0001), BCLC stage (P<0.0001) and APRI (P<0.0001) were prognostic for the DFS of patients. The variables with P<0.1 were further included in the backward stepwise Cox regression model. The result showed that tumor capsule (P=0.040), Edmondson-Steiner grade (P=0.038), BCLC stage (P<0.0001) and APRI (P<0.0001) were independent prognostic factors of DFS in HCC patients.

The uni- and multi-variate Cox regression analyses on the prognostic significance of APRI for OS in HCC patients are demonstrated in Table IV. The result of univariate analysis revealed significant prognostic value of AFP (P=0.015), PLT (P<0.0001), ALT (P=0.003), AST (P<0.0001), total bilirubin (P<0.0001), PT (P=0.003), tumor size (P=0.003), tumor number, tumor capsule, vascular invasion, neural invasion, Edmondson-Steiner grade, TNM, CNLC and BCLC stage and APRI (all P<0.0001). In the backward stepwise Cox regression model, tumor size (P=0.003), Edmondson-Steiner grade (P=0.007), BCLC stage (P<0.0001) and APRI (P<0.0001) were independent prognostic factors of OS in HCC patients.

Nomogram construction and validation. To improve stratification of patients with different prognoses, a nomogram was constructed based on the multivariate Cox regression analysis of the DFS and OS (Fig. 4). Scores were assigned to each risk factor, and each included patient's grade was determined by the sum of these scores. In this nomogram, a higher score predicts an improved survival outcome. Internal validation was performed with 500 re-samplings. The calibration curves plotted with the 1-, 3- and 5-year DFS (Fig. 5A-C, respectively) were well matched with the idealized 45 line (the x-axis represents the nomogram-predicted probability of DFS, whereas the y-axis shows the actual DFS). The calibration curves plotted with 1-, 3- and 5-year OS were well matched with the idealized 45 line [Fig. 5D-F, (the x-axis represents the nomogram-predicted probability of OS, whereas the y-axis shows the actual OS). The C-index of the nomogram for predicting DFS and OS probability were 0.700 (95% CI: 0.650-0.750) and 0.775 (95% CI: 0.726-0.824) (Tables V and VI). The C-index for 1-, 3- and 5-year DFS was 0.735 (95% CI: 0.636-0.834), 0.735 (95% CI: 0.659-0.810), and 0.686 (95% CI: 0.599-0.774), respectively; while that for 1, 3, and 5-year OS was 0.864 (95% CI: 0.792-0.936), 0.812 (95% CI: 0.731-0.893), and 0.783 (95% CI: 0.704-0.862), respectively (Table VII). The time-dependent AUC (t-AUC) for predicting the 1-, 3- and 5-year and all DFS was 0.734 (95% CI: 0.657-0.810) (Fig. 6A), 0.722 (95% CI: 0.651-0.793) (Fig. 6B) and 0.756 (95% CI: 0.690-0.821) (Fig. 6C), and 0.776 (95% CI: 0.712-0.839; Fig. 6D), respectively (Table VIII). The t-AUC for predicting the 1-, 3-, 5-year and all OS was 0.815 (95% CI: 0.729-0.900) (Fig. 7A), 0.807 (95% CI: 0.739-0.874) (Fig. 7B), 0.842 (95% CI: 0.784-0.899) (Fig. 7C), and 0.843 (95%CI: 0.787-0.900) (Fig. 7D), respectively (Table VIII). The result demonstrated high consistency between the predicted and actual outcome, suggesting favorable performance of the nomogram.

To gain insight into the performance of the nomogram, the nomogram with other significant prognostic factors was compared (Tables V and VI). For DFS, the C-index of nomogram (0.700) was markedly higher than that of tumor capsule (0.592), Edmondson-Steiner grade (0.593), APRI (0.607) and BCLC stage (0.598); while for OS, the C-index of nomogram (0.775) was also improved as compared with that of tumor size (0.604), Edmondson-Steiner grade (0.607), APRI (0.673)

Table II. Relations of APRI with the clinicopathological characteristics of HCC patients.

Variables	Number of patients, n (%)	APRI		χ^2	P-value
		≤1.02 n (%)	>1.02 n (%)		
Age, years					0.748
≤40	23 (11.4)	15 (0.9)	8 (12.5)	0.104	
>40	178 (88.6)	122 (89.1)	56 (87.5)		
Sex				1.050	0.305
Male	168 (83.6)	112 (81.8)	56 (87.5)		
Female	33 (16.4)	25 (18.2)	8 (12.5)		
Viral hepatitis				-	0.113
HBV	193 (96.0)	134 (97.8)	59 (92.2)		
HCV	8 (4.0)	3 (2.2)	5 (7.8)		
Liver cirrhosis				0.742	0.389
Yes	120 (59.7)	79 (57.7)	41 (64.1)		
No	81 (40.3)	58 (42.3)	23 (35.9)		
HBV-DNA, IU/ml				3.986	0.046
≤500	144 (71.6)	106 (77.4)	38 (59.4)		
>500	48 (23.9)	28 (20.4)	20 (31.3)		
HCV-RNA, IU/ml				-	0.226
≤500	6 (3.0)	1 (0.7)	5 (7.8)		
>500	3 (1.5)	2 (1.5)	1 (1.5)		
AFP, ng/ml				2.714	0.099
≥20	115 (57.2)	73 (53.3)	42 (65.6)		
<20	86 (42.8)	64 (46.7)	22 (34.4)		
AFP-L3, %				0.365	0.546
≥10	88 (43.8)	58 (42.3)	30 (46.9)		
<10	113 (56.2)	79 (57.7)	34 (53.1)		
Tumor size, cm				1.388	0.239
≤5	140 (69.7)	99 (72.3)	41 (64.1)		
>5	61 (30.3)	38 (27.7)	23 (35.9)		
AST level, U/l				60.208	<0.0001
<40	149 (74.1)	124 (90.5)	25 (39.1)		
≥40	52 (25.9)	13 (9.5)	39 (60.9)		
TB, μmol/l				7.299	0.007
<34.2	187 (93.0)	132 (96.4)	55 (85.9)		
≥34.2	14 (7.0)	5 (3.6)	9 (14.1)		
Prothrombin time, sec				34.280	<0.0001
<14	157 (78.1)	123 (89.8)	34 (53.1)		
≥14	44 (21.9)	14 (10.2)	30 (46.9)		
ALT level, U/l				21.083	<0.0001
<40	133 (66.2)	105 (76.6)	28 (43.8)		
≥40	68 (33.8)	32 (23.4)	36 (56.2)		
Albumin, g/dl				23.660	<0.0001
<35	41 (20.4)	15 (10.9)	26 (40.6)		
≥35	160 (79.6)	122 (89.1)	38 (59.4)		
PLT, x10^9/l				60.552	0.0001
<100	81 (40.3)	30 (21.9)	51 (79.7)		
≥100	120 (59.7)	107 (78.1)	13 (20.3)		
WBC, x10^9/l				17.702	<0.0001
<5	104 (51.7)	57 (41.6)	47 (73.4)		
≥5	97 (48.3)	80 (58.4)	17 (26.6)		

Table II. Continued.

Variables	Number of patients, n (%)	APRI		χ^2	P-value
		≤1.02 n (%)	>1.02 n (%)		
Tumour capsule				5.642	0.018
Complete	161 (80.1)	116 (84.7)	45 (70.3)		
Incomplete	40 (19.9)	21 (15.3)	19 (29.7)		
Vascular invasion[a]				3.101	0.078
Present	53 (26.4)	31 (22.6)	22 (34.4)		
Absent	148 (73.6)	106 (77.4)	42 (65.6)		
Nerve invasion				2.641	0.104
Present	16 (8.0)	8 (5.8)	8 (12.5)		
Absent	185 (92.0)	129 (94.2)	56 (87.5)		
Edmondson-Steiner grade				1.475	0.224
I-II	113 (56.2)	81 (59.1)	32 (50.0)		
III-IV	88 (43.7)	56 (40.9)	32 (50.0)		
Tumor number				2.641	0.104
≤3	185 (92.0)	129 (94.2)	56 (87.5)		
>3	16 (8.0)	8 (5.8)	8 (12.5)		
BCLC stage				5.466	0.019
0-A	166 (82.6)	119 (86.9)	47 (73.4)		
B-C	35 (17.4)	18 (13.1)	17 (26.6)		
CNLC stage				11.252	0.001
I-II	181 (90.0)	130 (94.9)	51 (79.7)		
III-IV	20 (10.0)	7 (5.1)	13 (20.3)		
TNM stage				6.917	0.009
I-II	180 (89.6)	128 (93.4)	52 (81.3)		
III-IV	21 (10.4)	9 (6.6)	12 (18.7)		

[a]Microscopic and macroscopic tumour thrombus. BCLC, Barcelona Clinic Liver Cancer; CNLC, China liver cancer staging; TNM, Tumor-Node-Metastasis system of the American Joint Committee on cancer; AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBV-DNA, hepatitis B virus deoxyribonucleic acid; HCV-RNA, hepatitis C virus ribonucleic acid; HCC, hepatocellular carcinoma; PLT, platelets; TB, total bilirubin; APRI, aspartate aminotransferase-to-platelet ratio index; WBC, white blood cell.

and BCLC stage (0.624). For DFS, the t-AUC of nomogram (0.776) was markedly higher than that of tumor capsule (0.613), Edmondson-Steiner grade (0.604), APRI (0.681), and BCLC stage (0.603); while for OS, the t-AUC of nomogram (0.843) was also improved as compared with that of tumor size (0.584), Edmondson-Steiner grade (0.656), APRI (0.732) and BCLC stage (0.638) (Table IX).

DCA is commonly used to evaluate the clinical net benefit of a nomogram. In the present study, DCA showed that the nomogram increased net benefits and exhibited a wider range of threshold probabilities in predicting 1-, 3-, and 5-year OS and DFS (Fig. 8A-D). Collectively, the combination of APRI and HCC staging systems can improve stratification of patients with different prognoses.

Discussion

The present study identified preoperative APRI and BCLC staging as independent prognostic factors for OS and DFS of HCC patients receiving PATACE. In addition, APRI was also significantly associated with the DFS and OS of patients stratified by BCLC, CNLC and TNM stages. It was also found that absence of tumor capsule and tumor size >5 cm were independently prognostic for the DFS and OS of patients, consistent with the previous literature (36). Moreover, the present study constructed a nomogram by combining the APRI and HCC staging systems (CNLC, BCLC and TNM) to help quantify the prognostic risk and then provide more prognostic information. It is known that HCC patients are usually accompanied by liver cirrhosis and fibrosis, which are great concerns for patients (17). Besides, hepatectomy can lead to post-operative alterations of neuroendocrine, metabolism and immune systems, resulting in immune dysfunction and increasing the risk of complications after PATACE. Theoretically, factors such as malnutrition, poor immune status and liver cirrhosis, may affect the prognosis of HCC patients after PATACE. Previous studies proved the prognostic value of APRI in liver malignancy (37-39), but its significance in prognosis of HCC patients undergoing PATACE is less studied (36). Therefore, more independent data are in demand to validate the prognostic value of APRI in HCC.

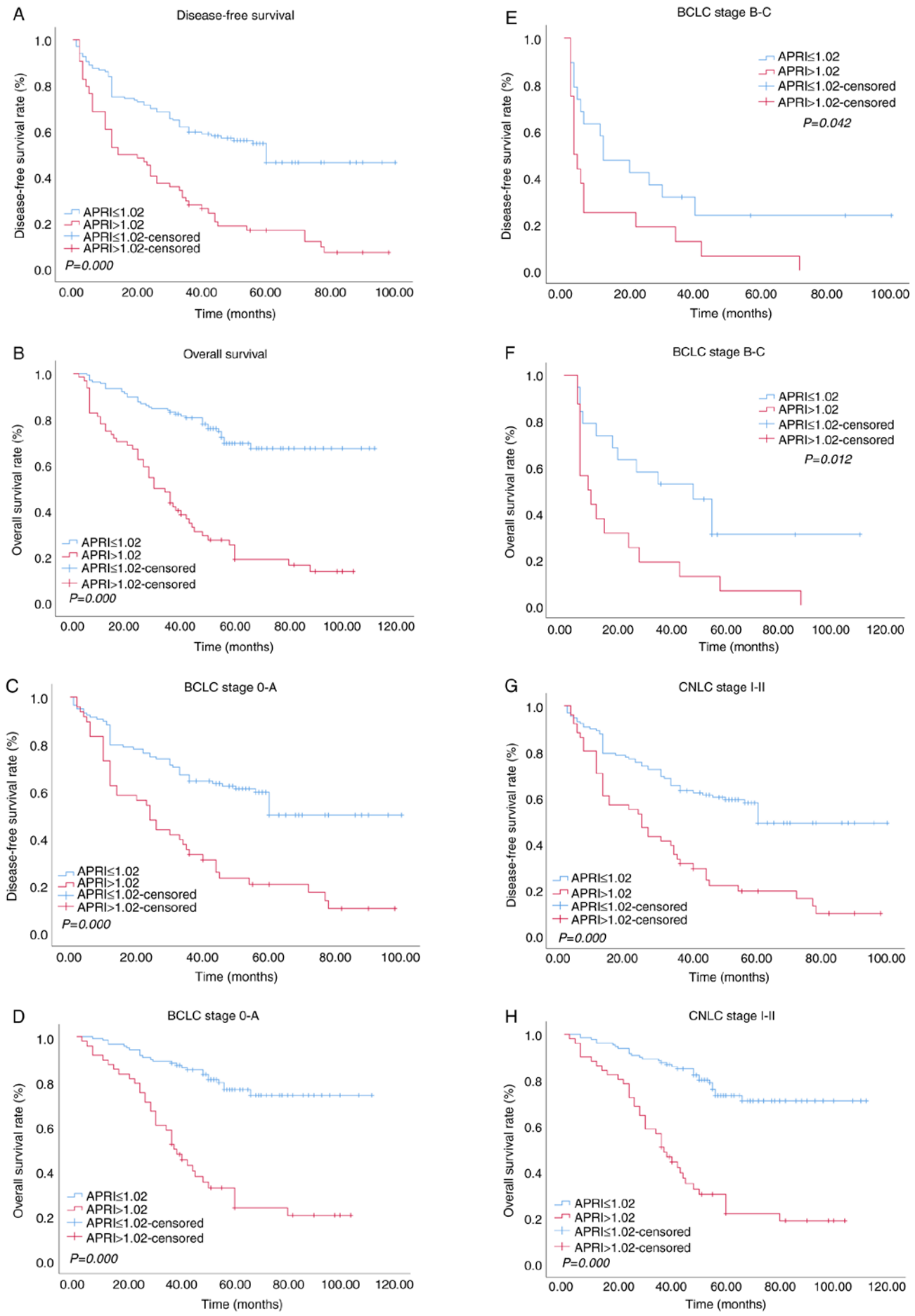

Figure 3. Continued.

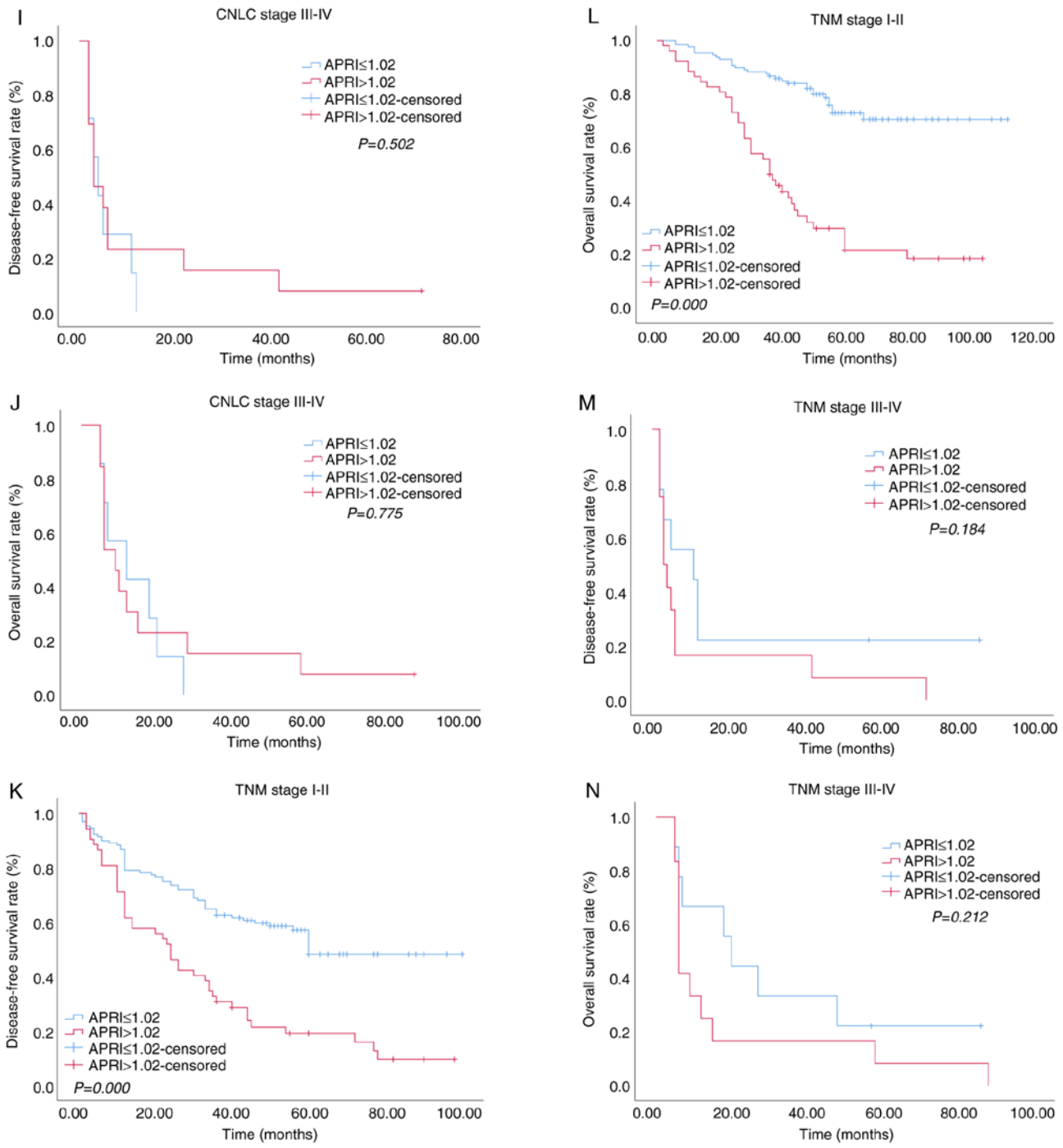

Figure 3. Kaplan-Meier survival curves of HCC patients in high APRI group and low APRI group after BCLC, CNLC and TNM stage stratification. Patients were divided into two groups, APRI ≤1.02 and >1.02, by optimal cutoff value of APRI. (A) DFS of patients with APRI ≤1.02 was higher than those with APRI >1.02 (P<0.0001, log-rank test). (B) OS of patients with APRI ≤1.02 was also higher than those with APRI >1.02 (P<0.0001, log-rank test). (C) DFS curves of patients classified as BCLC 0-A stage (P<0.0001). (D) OS curves of patients classified as BCLC 0-A stage (P<0.0001). (E). DFS curves of patients classified as BCLC B-C stage (P=0.042). (F) OS curves of patients classified as BCLC B-C stage (P=0.012). (G) DFS curves of patients classified as CNLC I-II stage (P<0.0001). (H) OS curves of patients classified as CNLC I-II stage (P<0.0001). (I) DFS curves of patients classified as CNLC III-IV stage (P=0.502). (J) OS curves of patients classified as CNLC III-IV stage (P=0.775). (K) DFS curves of patients classified as TNM I-II stage (P<0.0001). (L) OS curves of patients classified as TNM I-II stage (P<0.0001). (M) DFS curves of patients classified as TNM III-IV stage (P=0.184). (N) OS curves of patients classified as TNM III-IV stage (P=0.212). HCC, hepatocellular carcinoma; APRI, preoperative aspartate aminotransferase-to-platelet ratio index; BCLC, Barcelona Clinic Liver Cancer; CNLC, China liver cancer staging; TNM, Tumor Node Metastasis classification; DFS, disease-free survival; OS, overall survival.

Growing evidence has suggested that host inflammatory responses are predictive of the clinical outcome of HCC patients given their significant implications for tumorigenesis and metastasis. In addition, HCC patients receiving PATACE are at a high risk of recurrence and post-operative alterations in the immune system. A recent study revealed that APRI is an effective and non-invasive indicator that can be used to assess the risk of liver fibrosis in patients with CHB and chronic hepatitis C (CHC). APRI was first reported by Wai *et al* (35) as a biochemical alternative to predict the advanced fibrosis and

Table III. Univariate and multivariate Cox proportional hazards regression analysis of factors for DFS of HCC patients.

	Univariate			Multivariate		
Variable	HR	95% CI	P-value	HR	95% CI	P-value
Sex (male vs. female)	1.256	0.761-2.072	0.373			
Age (≤40 vs. >40, years)	0.685	0.410-1.145	0.148			
Types of viral hepatitis (HBV vs. HCV)	1.309	0.610-2.811	0.489			
Livers cirrhosis (Yes vs. No)	1.092	0.757-1.575	0.639			
AFP (<20 vs. ≥20, ng/ml)	1.574	1.086-2.281	0.017	1.203	0.799-1.812	0.376
AFP-L3 (<10 vs. ≥10, %)	1.336	0.935-1.911	0.112			
HBV-DNA (≤500 vs. >500, IU/ml)	0.895	0.576-1.392	0.623			
HCV-DNA (≤500 vs. >500, IU/ml)	0.707	0.135-3.697	0.681			
WBC (<5 vs. ≥5, x10^9/l)	1.097	0.768-1.567	0.610			
PLT (<100 vs. ≥100, x10^9/l)	0.660	0.461-0.943	0.022	0.984	0.607-1.594	0.947
Albumin (<35 vs. ≥35, g/dl)	0.824	0.540-1.258	0.370			
ALT level (<40 vs. ≥40, U/l)	1.705	1.188-2.447	0.004	1.056	0.688-1.620	0.804
AST level (<40 vs. ≥40, U/l)	2.477	1.710-3.589	0.000	0.931	0.523-1.659	0.810
TB (<34.2 vs. ≥34.2, μmol/l)	2.604	1.459-4.646	0.001	1.717	0.931-3.166	0.083
Prothrombin time (≤14 vs. >14, sec)	1.675	1.130-2.483	0.010	1.128	0.716-1.778	0.603
Tumour size (≤5 vs. >5, cm)	1.541	1.056-2.248	0.025	1.381	0.928-2.056	0.112
Tumour number (≤3 vs. >3)	2.468	1.382-4.408	0.002	0.960	0.432-2.134	0.920
Tumour capsule (Complete vs. Incomplete)	2.616	1.759-3.889	0.000	1.595	1.022-2.490	0.040
Vascular invasion (Present vs. Absent)	2.170	1.485-3.170	0.000	0.875	0.512-1.496	0.626
Nerve invasion (Present vs. Absent)	2.286	1.281-4.077	0.005	1.165	0.595-2.279	0.656
Edmondson-Steiner grade (I-II vs. III-IV)	1.783	1.247-2.549	0.002	1.478	1.021-2.140	0.038
BCLC stage (0-A vs. B-C)	3.214	2.122-4.869	0.000	2.310	1.467-3.638	<0.001
CNLC stage (I-II vs. III-IV)	5.466	3.322-8.993	0.000	1.631	0.731-3.641	0.232
TNM stage (I-II vs. III-IV)	3.422	2.082-5.624	0.000	0.742	0.312-1.762	0.499
APRI (≤1.02 vs. >1.02)	2.641	1.842-3.788	0.000	2.159	1.480-3.150	<0.001

CI, confidence interval; HR, hazard ratio; BCLC, Barcelona Clinic Liver Cancer; CNLC, China liver cancer staging; TNM, Tumor Node Metastasis classification; AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBV-DNA, hepatitis B virus deoxyribonucleic acid; HCV-RNA, hepatitis C virus ribonucleic acid; HCC, hepatocellular carcinoma; PLT, platelets; TB, total bilirubin; APRI, aspartate aminotransferase-to-platelet ratio index; WBC, white blood cell.

liver cirrhosis in patients with CHC. In the following years, the effect of APRI was further explored in identifying HIV infection and differentiating liver cirrhosis in hepatitis B cohorts. While in previous years, APRI has been proven as capable of predicting the risk of developing HCC in patients with liver cirrhosis and the death rate associated with tumor resection (16,20,40). It was also revealed that APRI can be used as a valuable prognostic indicator for HCC patients undergoing radiofrequency ablation and hepatectomy (26,41).

The present study applied ROC analysis to determine the optimal cut-off value of APRI as 1.02 for OS of HCC patients, and classified patients into the High- and Low-APRI groups. It was found that the DFS (P<0.0001) and OS (P<0.0001) of patients in the Low-APRI group were significantly improved than those of patients in the High-APRI group. In the multivariate Cox regression analysis, tumor capsule (P=0.040), Edmondson-Steiner grade (P=0.038), BCLC stage (P<0.0001) and APRI (P<0.0001) were identified as significantly prognostic for the DFS of patients; while tumor size (P=0.003), Edmondson-Steiner grade (P=0.007), BCLC stage (P<0.0001) and APRI (P<0.0001) were independent prognostic factors for OS of patients. It was previously reported that in patients with single HCC, APRI<0.47 was associated with a significantly higher OS rate and a remarkably lower recurrence rate, as compared with the control group (26). Hung *et al* (40) and Shen *et al* (26) reported a cut-off value of APRI of 0.47 and 0.62, respectively. The discrepancy may be attributed to the different methods used to calculate APRI cut-off value and the different etiologies of HCC. In addition, the differences in tumor status, sample size, and patient inclusion criteria can also make an effect. In a previous study by Hung *et al* (40) involving 76 HBV-mono-infected HCC patients from 12 trials, all the tumors were <5 cm in diameter with the median value of 2.5 cm, which is significantly smaller than the 4.8 cm (median) in the present study. In another study made by Shen *et al* (26) included 332 HCC patients with a mean tumor size of 8.76 cm. Among them, 25.6% had large vessels, and 20.8% were complicated by portal vein tumor thrombosis. All these patients with such characteristics were

Table IV. Univariate and multivariate Cox proportional hazards regression analysis of factors for OS of HCC patients.

	Univariate			Multivariate		
Variables	HR	95% CI	P-value	HR	95% CI	P-value
Sex (male vs. female)	0.980	0.562-1.708	0.943			
Age (≤40 vs. >40, years)	0.721	0.399-1.302	0.278			
Viral hepatitis (HBV vs. HCV)	0.913	0.335-2.491	0.859			
Livers cirrhosis (Yes vs. No)	0.922	0.604-1.408	0.707			
AFP (<20 vs. ≥20, ng/ml)	1.734	1.111-2.705	0.015	1.171	0.70-1.954	0.546
AFP-L3 (<10 vs. ≥10, %)	1.246	0.819-1.894	0.304			
HBV-DNA (≤500 vs. >500, IU/ml)	0.958	0.575-1.597	0.869			
HCV-DNA (≤500 vs. >500, IU/ml)	0.844	0.152-4.685	0.846			
WBC (<5 vs. ≥5, x10^9/l)	0.810	0.531-1.233	0.325			
PLT (<100 vs. ≥100, x10^9/l)	0.446	0.292-0.681	0.000	0.855	0.492-1.486	0.579
Albumin (<35 vs. ≥35, g/dl)	0.700	0.432-1.136	0.149			
ALT level (<40 vs. ≥40, U/l)	1.900	1.247-2.895	0.003	0.907	0.532-1.547	0.720
AST level (<40 vs. ≥40,U/l)	3.492	2.292-5.321	0.000	0.940	0.468-1.887	0.862
TB (<34.2 vs. ≥34.2, μmol/l)	3.163	1.675-5.974	0.000	1.857	0.943-3.658	0.073
Prothrombin time (≤14 vs. >14, sec)	1.975	1.260-3.094	0.003	1.276	0.779-2.091	0.333
Tumour size (≤5 vs. >5, cm)	1.907	1.244-2.926	0.003	1.982	1.271-3.089	0.003
Tumour number (≤3 vs. >3)	3.149	1.664-5.959	0.000	1.316	0.571-3.033	0.519
Tumour capsule (Complete vs. Incomplete)	2.914	1.870-4.541	0.000	1.163	0.620-2.180	0.638
Vascular invasion (Present vs. Absent)	3.040	1.983-4.660	0.000	0.947	0.490-1.830	0.872
Nerve invasion (Present vs. Absent)	3.581	1.976-6.489	0.000	1.454	0.711-2.972	0.305
Edmondson-Steiner grade (I-II vs. III-IV)	2.355	1.533-3.619	0.000	1.838	1.182-2.860	0.007
BCLC stage (0-A vs. B-C)	4.198	2.675-6.585	0.000	3.370	2.102-5.403	<0.001
CNLC stage (I-II vs. III-IV)	8.272	4.915-13.923	0.000	1.918	0.816-4.508	0.135
TNM stage (I-II vs. III-IV)	5.100	3.047-8.536	0.000	0.809	0.295-2.221	0.681
APRI (≤1.02 vs. >1.02)	4.381	2.859-6.714	0.000	3.590	2.300-5.604	<0.001

CI, confidence interval; HR, hazard ratio; BCLC, Barcelona Clinic Liver Cancer; CNLC, China liver cancer staging; TNM, Tumor Node Metastasis classification; AFP, α-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBV-DNA, hepatitis B virus deoxyribonucleic acid; HCV-RNA, hepatitis C virus ribonucleic acid; HCC, hepatocellular carcinoma; PLT, platelets; TB, total bilirubin; APRI, aspartate aminotransferase-to-platelet ratio index; WBC, white blood cell.

not considered in the present study. In spite of the different cut-off values of APRI, a lower value of APRI generally predicts an improved OS rate.

However, the relationship between APRI increase and poor prognosis remains unclear. It is hypothesized that numerous HCC patients with APRI increase have a low preoperative PLT, which may be a result of spleen enlargement that leads to PLT destruction or progressive liver fibrosis that leads to decreased production of thrombopoietin. In addition, the low preoperative PLT may also correlate to major post-operative complications, liver failure and mortality. It has also been reported that PLT increase is associated with the poor prognosis of nasopharyngeal carcinoma, gastric, colorectal and endometrial cancer (23,42-44). Similarly, there is no specific explanation for the relationship between PLT increase and poor prognosis. The current potential explanations are as follows: First, PLT increase can promote tumor growth by advancing angiogenesis. As cancer patients usually present with coagulation abnormalities leading to disturbed PLT function, increase in PLT secrets more angiogenic factors to stimulate tumor angiogenesis. Second, PLT can interact with tumor cells via receptor-ligand pairs, thereby promoting tumor cell growth and invasion (45-47). Third, PLT are actively involved in host immune attack to tumor (48,49). Previous studies theorized that PLT decrease the cytolytic activity of NK cells to protect tumor cells from NK attack (48). Inflammation of the liver caused by viral infection and alcohol consumption leads to HCC onset (36), and AST from the mitochondria in hepatocytes is a reliable and sensitive biomarker of liver inflammation. Disorders in the liver result in mitochondrial damage and subsequent release of intrahepatic AST into the blood, suggesting heavily impaired liver function. It is known that hepatocellular injury is tightly associated with the occurrence of HCC (50). Moreover, a large group of HCC patients with APRI elevation may also have an increase in AST, indicating stress response or injury of the liver, such as reactivation of HBV replication or progressive liver fibrosis (51). These events are associated with a poor survival rate in HCC patients. This also supports the finding of the present study that patients with APRI >1.02

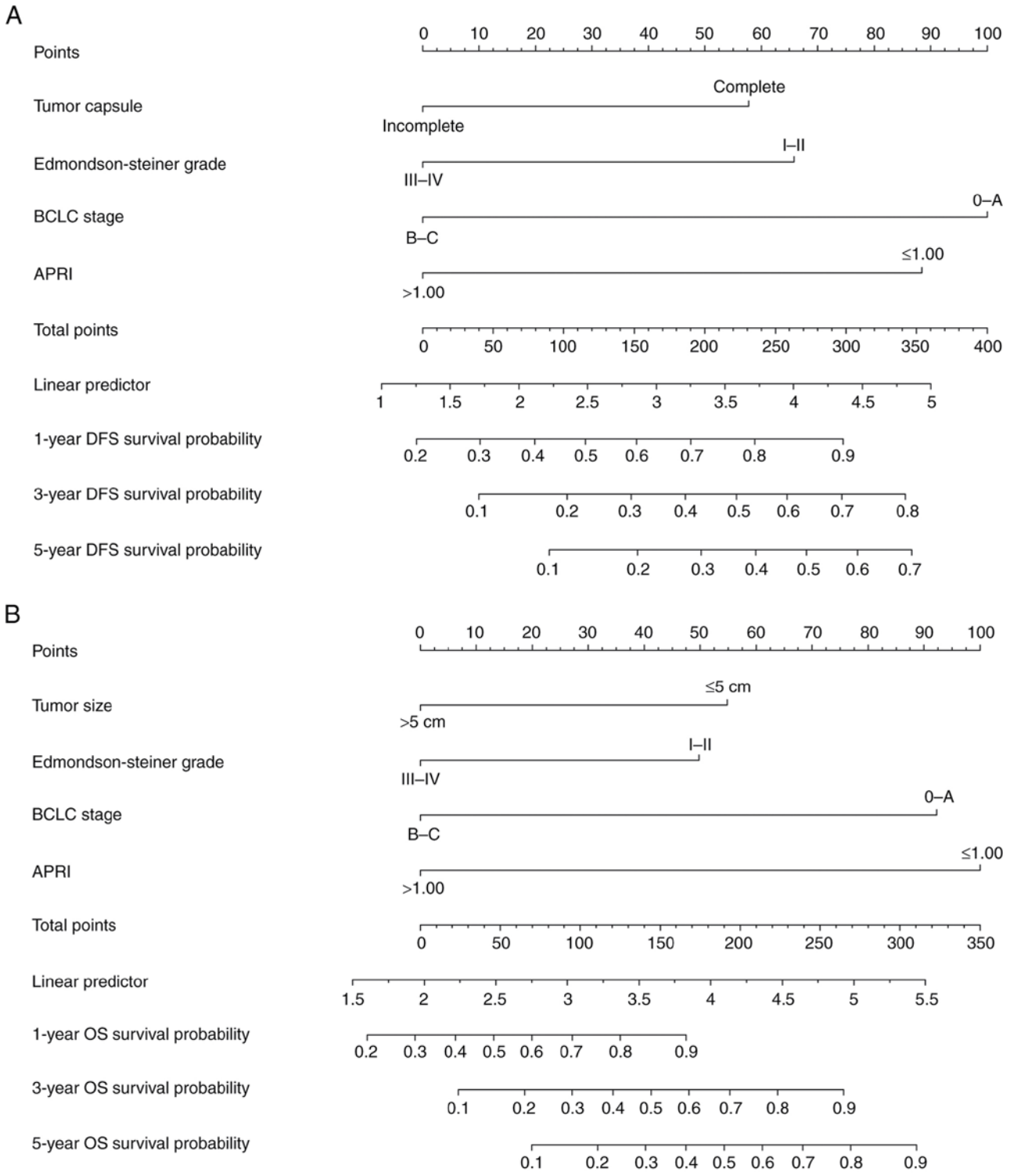

Figure 4. Nomogram shows the assessment of DFS and OS of patients with HCC who underwent PATACE. (A) Nomogram shows the assessment of 1-, 3- and 5-year DFS of patients with HCC who underwent PATACE. (B) Nomogram shows the assessment of 1-, 3- and 5-year OS of patients with HCC who underwent PATACE. DFS, disease-free Survival; OS, overall survival; HCC, hepatocellular carcinoma; PATACE, post-operative adjuvant transarterial chemoembolization.

had poorer survival outcomes and a higher risk of recurrence. Therefore, APRI elevation indicates severely impaired liver function and poor tumor prognosis.

CNLC, BCLC and AJCC-TNM (8th edition) staging systems were found to be capable of stratifying HCC patients based on their risk categories in the present study. BCLC and AJCC-TNM (8th edition) staging systems are the most widely used tools currently. Multivariate Cox regression analysis demonstrated that the BCLC stage was an independent risk factor of prognosis in HCC patients undergoing PATACE. The nomogram established by significant independent prognostic factors is intuitive and can maximize the predictive accuracy

Table V. C-index of nomogram and other predictors in OS.

	OS		
Predictors	C-index	95% CI	P-value
Nomogram	0.775	0.726-0.824	<0.001
APRI	0.673	0.623-0.723	<0.001
Tumour size	0.604	0.550-0.658	0.003
Edmondson-Steiner grade	0.607	0.553-0.661	<0.001
BCLC stage	0.624	0.576-0.672	<0.001

C-index, concordance index; OS, overall survival; CI, confidence interval; APRI, aspartate aminotransferase-to-platelet ratio index; BCLC, Barcelona Clinic Liver Cancer.

Table VI. C-index of nomogram and other predictors in DFS.

	DFS		
Predictors	C-index	95% CI	P-value
Nomogram	0.700	0.650-0.750	<0.001
APRI	0.607	0.564-0.650	<0.001
Tumour capsule	0.592	0.553-0.631	<0.001
Edmondson-Steiner grade	0.593	0.547-0.639	<0.001
BCLC stage	0.598	0.558-0.637	<0.001

C-index, concordance index; DFS, Disease-Free Survival; CI, confidence interval; APRI, aspartate aminotransferase-to-platelet ratio index; BCLC, Barcelona Clinic Liver Cancer.

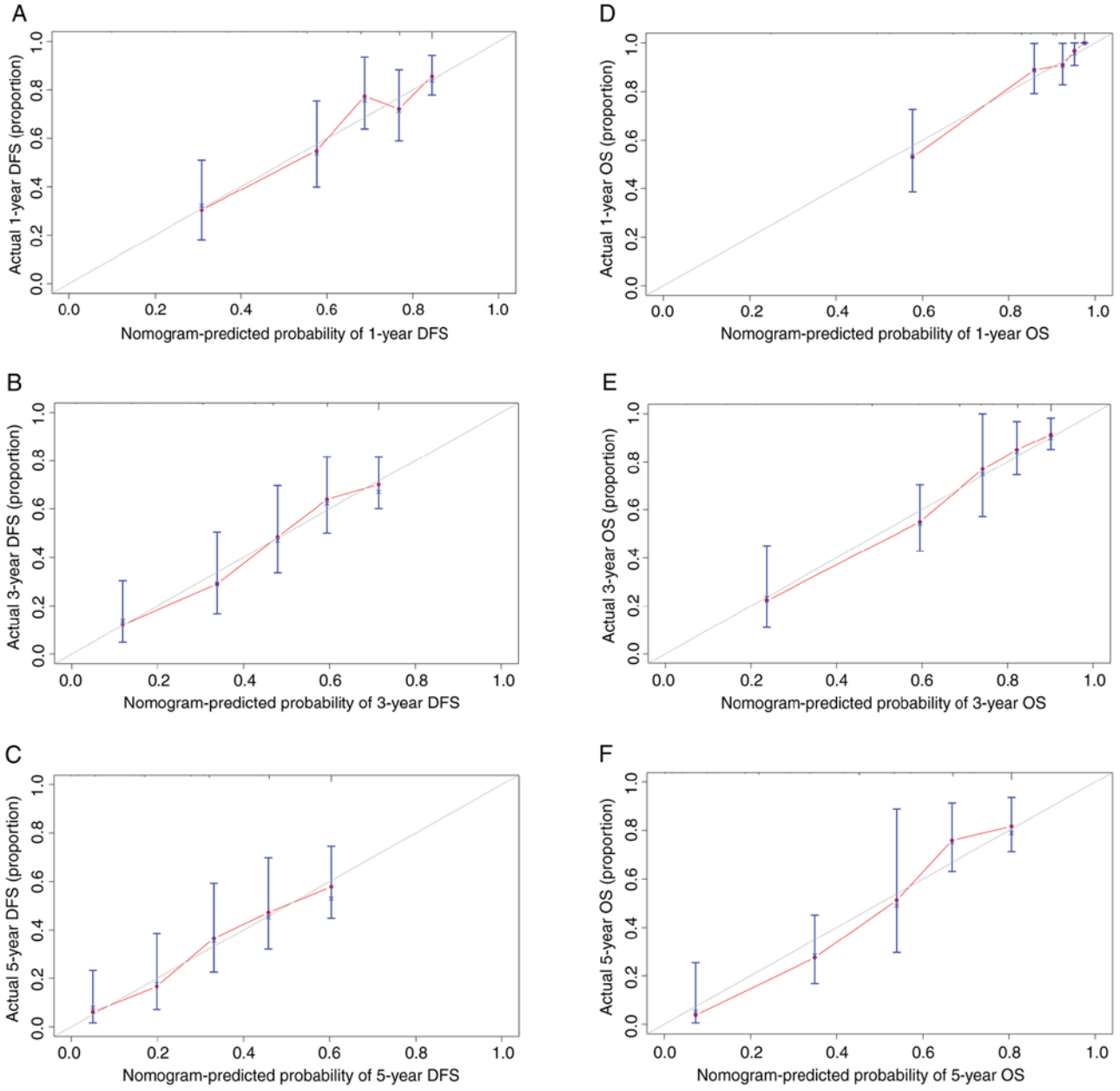

Figure 5. Calibration plot of the nomogram. (A-C) Calibration curves of the nomogram at (A) 1- (B) 3- and (C) 5-year DFS. (D-F) Calibration curves of the nomogram at (D) 1- (E) 3- and (F) 5-year OS. The calibration curves were well-matched with the idealized 45 line. DFS, disease-free Survival; OS, overall survival.

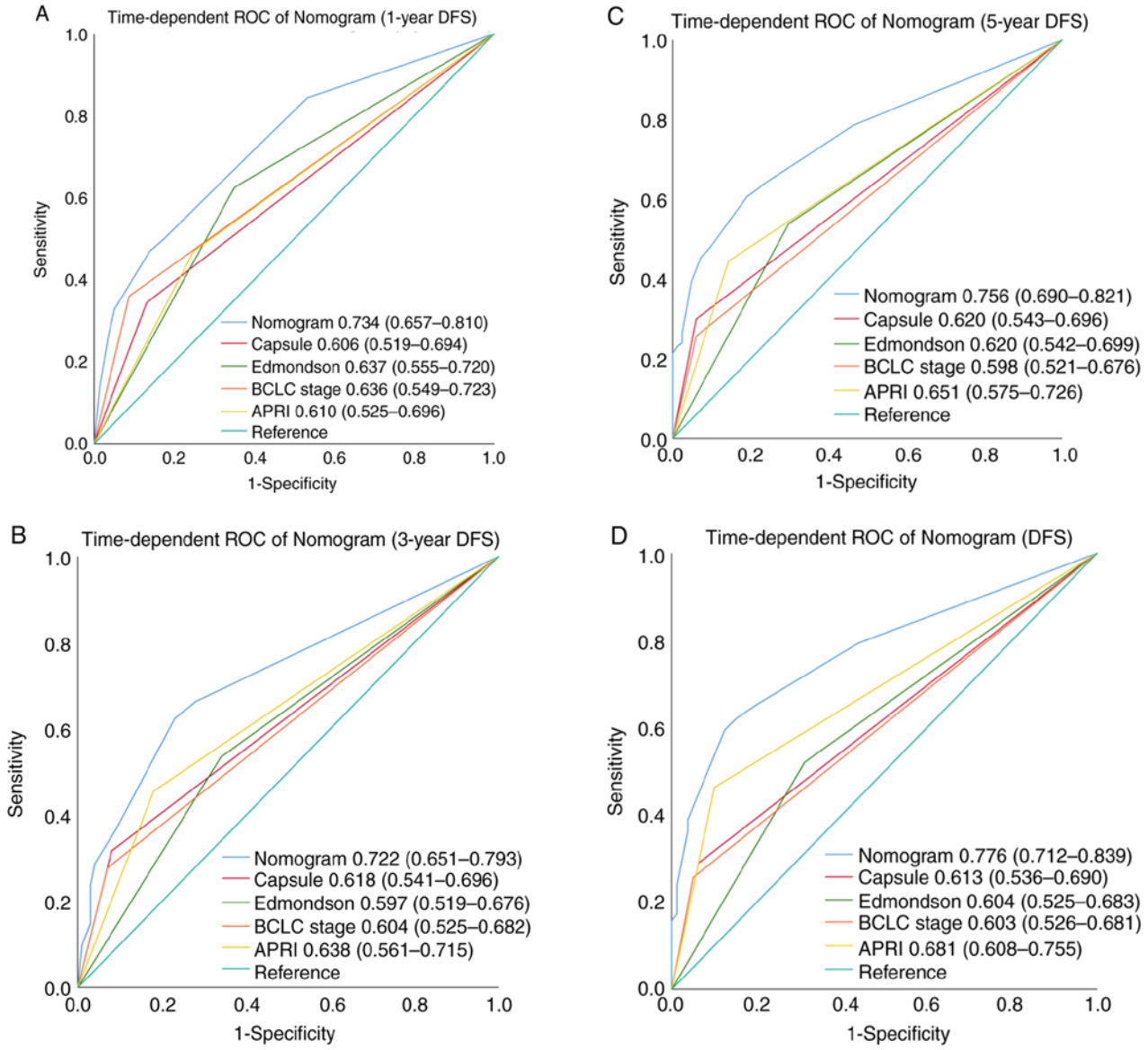

Figure 6. Time-ROC curves at (A) 1-, (B) 3- and (C) 5-years of DFS (D) based on the Nomogram, APRI, Tumour capsule, Edmondson-Steiner grade and BCLC stage. Time-ROC, Time-dependent receiver operating characteristic; DFS, disease-free survival; APRI, preoperative aspartate aminotransferase-to-platelet ratio index; BCLC, Barcelona Clinic Liver Cancer.

in assessment for prognosis in individuals. The present study constructed a nomogram based on the multivariate Cox regression analysis for DFS and OS of HCC patients. It was identified that tumor size, tumor capsule and BCLC stage were correlated with the prognosis of HCC patients receiving PATACE. The multivariate analysis of the present study also identified that APRI was superior to AST and PLT in predicting survival outcomes in this population. Referring to literature, there was only one study reporting the use of an APRI-based nomogram in predicting the prognosis of HCC patients receiving radical surgery followed by adjuvant TACE. However, the previous study did not further explore the relationship between the APRI and HCC stage and OS of patients (39,16,52). Besides, the case data in that study were limited and not sufficient for external validation, and certain bias existed in partial data. The present study generated a nomogram that combined tumor status, tumor stage and APRI. This nomogram can be used for individualized survival estimation in patients with HCC patients receiving radical surgery followed by adjuvant TACE and can also help surgeons make appropriate post-operative decisions for treatment and individualized monitoring.

Furthermore, there are some considerations when building a nomogram. The number of surviving and succumbed patients should be 10-fold greater than the number of variables used to construct the nomogram in order to reduce the prediction error in the predicted probability <10%. The number of deaths was 88, which is 22-fold larger than the number of variables in the present study. Due to the insufficient number of cases in the external validation group, an internal validation was conducted with 500 sets of bootstrap samples with a calibration curve and well verified the nomogram. Collectively, the present study proved the favorable performance of the nomogram

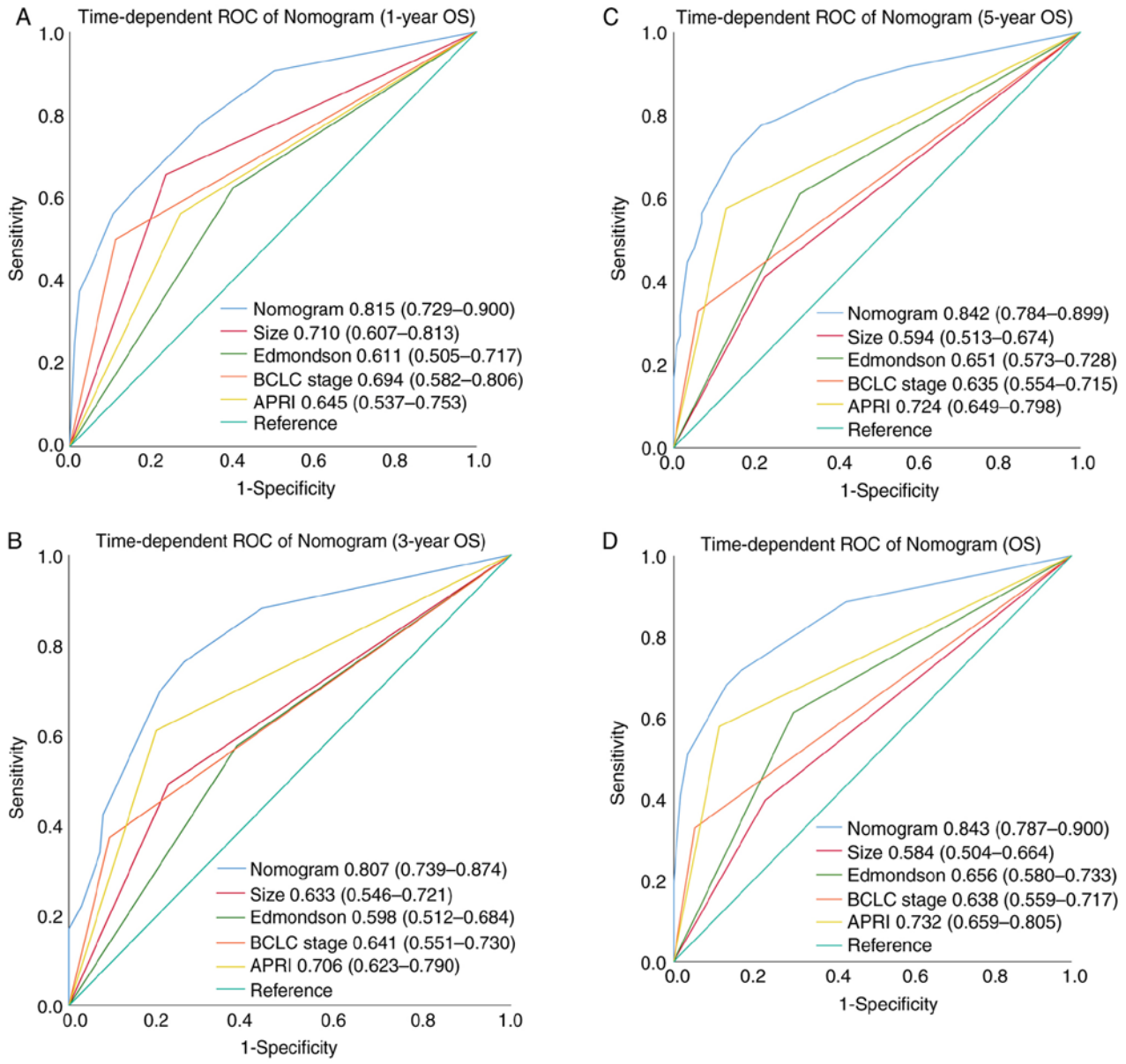

Figure 7. Time-ROC curves at (A) 1-, (B) 3- and (C) 5-years of OS (D) based on the Nomogram, APRI, Tumour size, Edmondson-Steiner grade, and BCLC stage. Time-ROC, Time-dependent receiver operating characteristic; OS, overall survival; APRI, preoperative aspartate aminotransferase-to-platelet ratio index; BCLC, Barcelona Clinic Liver Cancer.

in predicting survival outcome in these patients using the calibration plot and C-index, which was superior to other prognostic factors.

At present, multiple prognostic indicators for post-operative HCC patients have been identified, but there is a paucity of indicators for patients receiving PATACE. This may be attributed to some factors that affect the clinical outcome of patients with TACE, such as liver function, tumor characteristics and treatment modalities. HCC patients who received PATACE were included in the present study as second-line treatment, in an attempt to avoid the confounders caused by other treatments. In addition, 1.02 as the cut-off value was used of APRI for analysis, which is not in line with the previous studies. For example, the cut-off value of APRI reported by Shen *et al* (26) and Tang *et al* (38) were 0.40 and 0.62, respectively, which were obtained from the ROC curve for patients receiving TACE or liver operations. Moreover, it was also identified that a larger tumor size and a higher BCLC grade were predictive of poorer survival outcomes of patients with HCC patients, consistent with previous studies (17,53,54). It has been established that tumor and clinical features, such as tumor size, tumor number, BCLC stage and MVI, have implications for survival and recurrence of HCC patients, while non-tumor parameters, such as inflammation, viral infection and liver fibrosis, are important in HCC recurrence.

There are certain limitations to the present study. For example, this was a single-center retrospective study, and the majority of participants had an HBV infection background (96%). Therefore, a large-cohort, multi-center study with stratification analysis based on etiology is in demand to validate the findings of the present study. In addition, bias

Table VII. The C-index of nomogram and other predictors in 1-year, 3-year, 5-year DFS and OS.

	Overall survival							Disease-free survival					
Predictors	1-year C-index (95% CI)	P-value	3-year C-index (95% CI)	P-value	5-year C-index (95% CI)	P-value	Predictors`	1-year C-index (95% CI)	P-value	3-year C-index (95% CI)	P-value	5-year C-index (95% CI)	P-value
Nomogram	0.864 (0.792-0.936)	<0.001	0.812 (0.731-0.893)	<0.001	0.783 (0.704-0.862)	<0.001	Nomogram	0.735 (0.636-0.834)	<0.001	0.735 (0.659-0.810)	<0.001	0.686 (0.599-0.774)	<0.001
APRI	0.679 (0.585-0.773)	<0.001	0.671 (0.610-0.732)	<0.001	0.673 (0.622-0.724)	<0.001	APRI	0.602 (0.541-0.663)	<0.001	0.638 (0.561-0.715)	<0.001	0.605 (0.562-0.648)	<0.001
Tumour size	0.709 (0.618-0.799)	<0.001	0.628 (0.567-0.689)	<0.001	0.606 (0.551-0.661)	0.001	Tumour capsule	0.597 (0.540-0.649)	<0.001	0.595 (0.556-0.636)	<0.001	0.592 (0.553-0.631)	<0.001
Edmondson-Steiner grade	0.655 (0.564-0.745)	0.004	0.600 (0.537-0.663)	0.004	0.607 (0.554-0.660)	<0.001	Edmondson-Steiner grade	0.625 (0.566-0.683)	<0.001	0.595 (0.546-0.644)	<0.001	0.595 (0.548-0.642)	<0.001
BCLC stage	0.733 (0.639-0.827)	<0.001	0.636 (0.577-0.695)	<0.001	0.624 (0.575-0.673)	<0.001	BCLC stage	0.626 (0.571-0.681)	<0.001	0.600 (0.557-0.643)	<0.001	0.598 (0.559-0.637)	<0.001

C-index, concordance index; OS, overall survival; DFS, Disease-Free Survival; CI, confidence interval; APRI, aspartate aminotransferase-to-platelet ratio index; BCLC, Barcelona Clinic Liver Cancer.

Table VIII. The AUC of nomogram and other predictors in 1-year, 3-year, 5-year DFS and OS.

	Overall survival							Disease-free survival					
Predictors	1-year AUC (95% CI)	P-value	3-year AUC (95% CI)	P-value	5-year AUC (95% CI)	P-value	Predictors	1-year AUC (95% CI)	P-value	3-year AUC (95% CI)	P-value	5-year AUC (95% CI)	P-value
Nomogram	0.815 (0.729-0.900)	<0.001	0.807 (0.739-0.874)	<0.001	0.842 (0.784-0.899)	<0.001	Nomogram	0.734 (0.657-0.810)	<0.001	0.722 (0.651-0.793)	<0.001	0.756 (0.690-0.821)	<0.001
APRI	0.645 (0.537-0.753)	0.009	0.706 (0.623-0.790)	<0.001	0.724 (0.649-0.798)	<0.001	APRI	0.610 (0.525-0.696)	0.002	0.638 (0.561-0.715)	<0.001	0.651 (0.575-0.726)	<0.001
Tumour size	0.710 (0.607-0.813)	<0.001	0.633 (0.546-0.721)	0.003	0.594 (0.513-0.674)	0.023	Tumour capsule	0.606 (0.519-0.694)	0.015	0.618 (0.541-0.696)	0.004	0.62 (0.543-0.696)	0.004
Edmondson-Steiner grade	0.611 (0.505-0.717)	0.046	0.598 (0.512-0.684)	0.029	0.651 (0.573-0.728)	0.040	Edmondson-Steiner grade	0.637 (0.555-0.720)	0.002	0.597 (0.519-0.676)	0.017	0.620 (0.542-0.699)	0.004
BCLC stage	0.694 (0.582-0.806)	0.001	0.641 (0.551-0.730)	0.002	0.635 (0.554-0.715)	<0.001	BCLC stage	0.636 (0.549-0.723)	0.002	0.604 (0.561-0.715)	0.011	0.598 (0.521-0.676)	0.017

AUC, area under the curve; OS, overall survival; DFS, Disease-Free Survival; CI, confidence interval; APRI, aspartate aminotransferase-to-platelet ratio index; BCLC, Barcelona Clinic Liver Cancer.

Table IX. The AUC of nomogram and other predictors in DFS and OS.

	Overall survival				Disease-free survival		
Predictors	AUC	95% CI	P-value	Predictors	AUC	95% CI	P-value
Nomogram	0.843	0.787-0.900	<0.001	Nomogram	0.776	0.712-0.839	<0.001
APRI	0.732	0.659-0.805	<0.001	APRI	0.681	0.608-0.755	<0.001
Tumour size	0.584	0.504-0.664	0.042	Tumour capsule	0.613	0.536-0.690	0.007
Edmondson-Steiner grade	0.656	0.580-0.733	0.001	Edmondson-Steiner grade	0.604	0.525-0.683	0.013
BCLC stage	0.638	0.559-0.717	<0.001	BCLC stage	0.603	0.526-0.681	0.013

AUC, area under the curve; OS, overall survival; DFS, Disease-Free Survival; CI, confidence interval; APRI, aspartate aminotransferase-to-platelet ratio index; BCLC, Barcelona Clinic Liver Cancer.

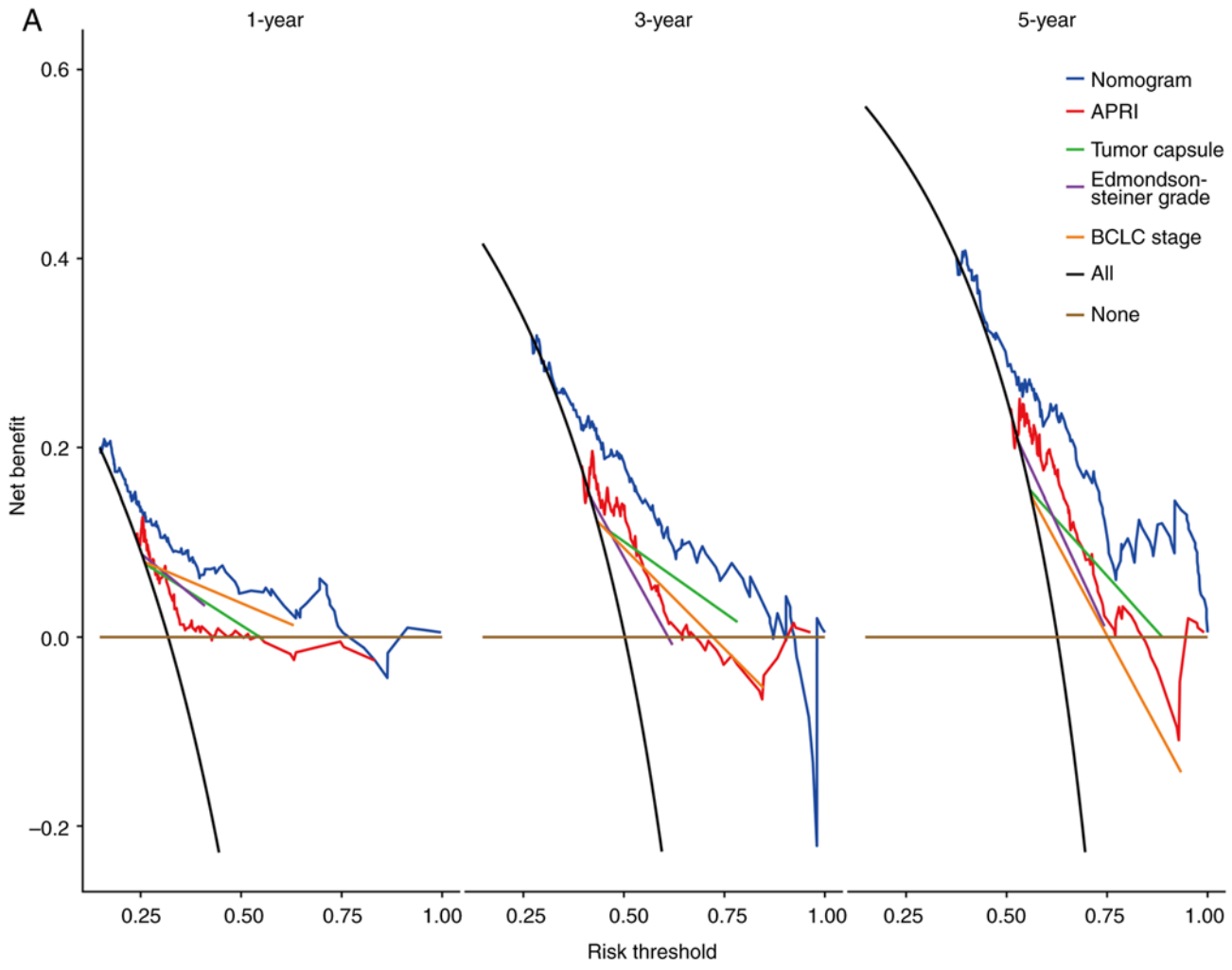

Figure 8. Continued.

may not be completely avoided given that all participants were treated in the same medical center. Moreover, further prospective study is required to validate the results of the present study, in other centers. A control group may also be warranted to reinforce these results. Finally, the present study adopted baseline APRI for analysis, but APRI values were dynamic during follow-up. Thus, it may lead to loss of patient data during follow-up. In conclusion to sum up, the present study identified that APRI has certain clinical value as an independent prognostic factor for DFS and OS of HCC patients receiving PATACE. Combining the APRI and HCC stages, surgeons can improve stratifying of patients into different risk categories, thereby efficiently identifying the high-risk group for improved treatment.

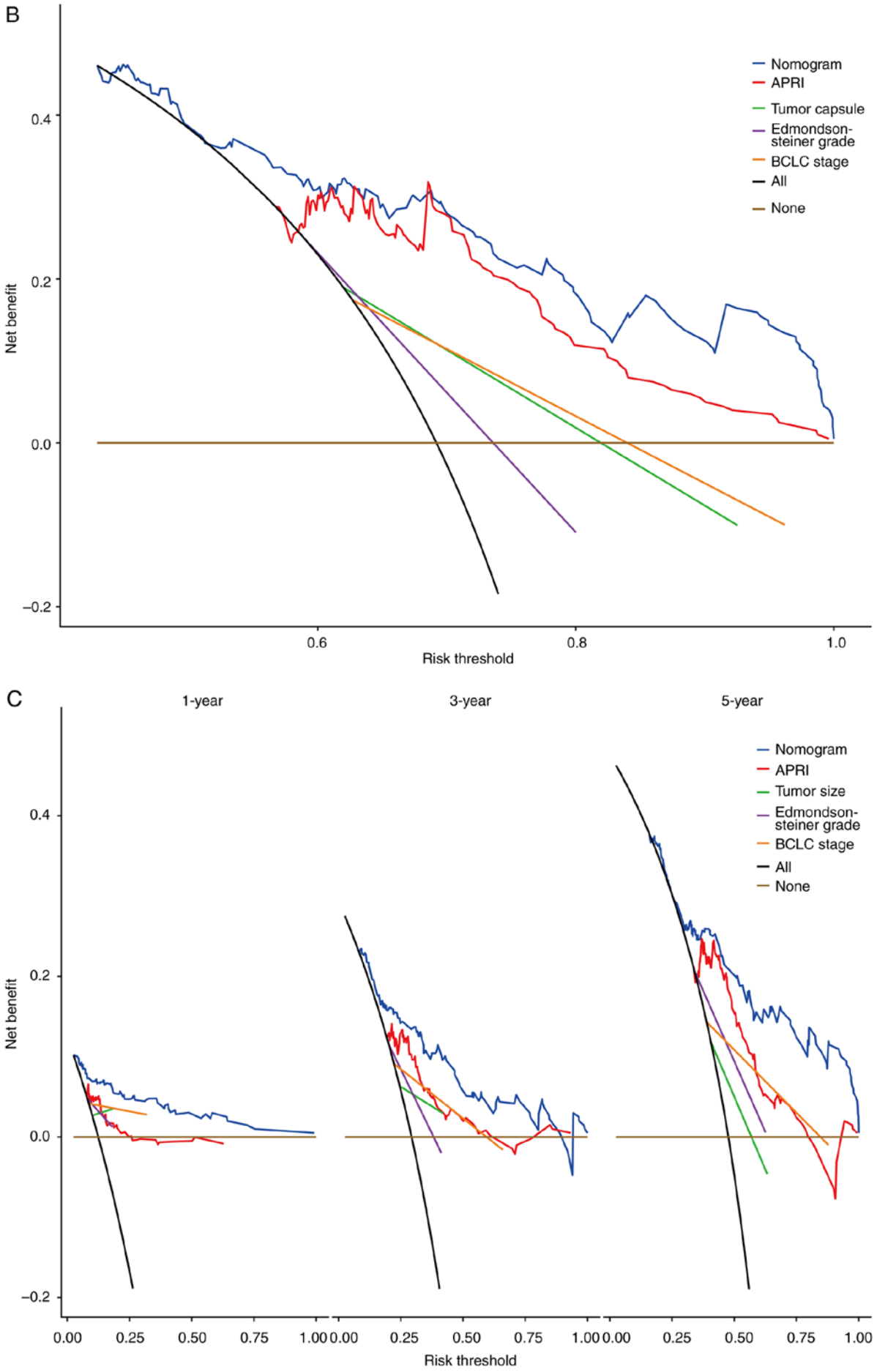

Figure 8. Continued.

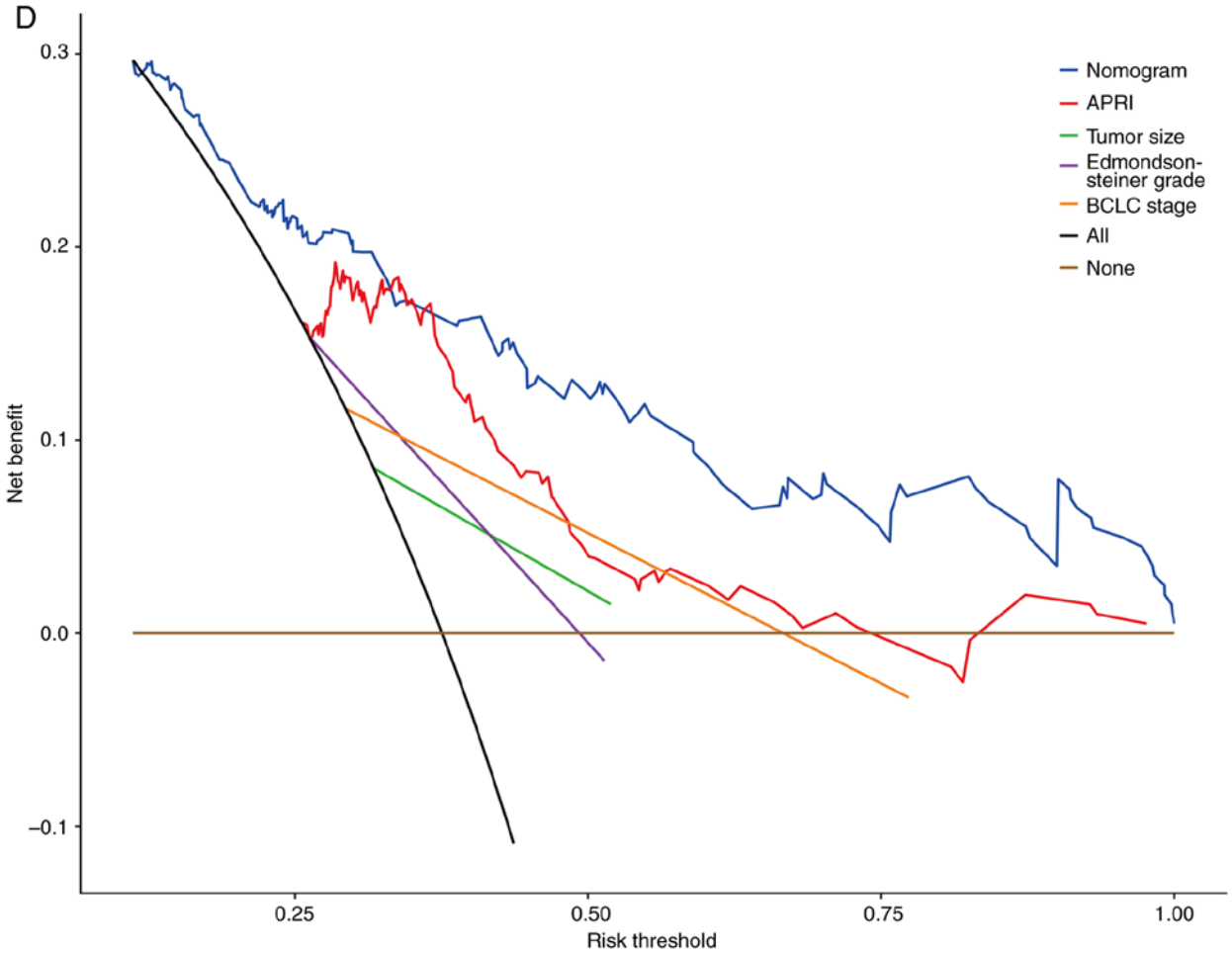

Figure 8. DCA of the APRI-based nomogram and other predictors for (A and B) 1-, 3- and 5-year DFS, and DFS and (C and D) 1-, 3- and 5-year OS, and OS. The x-axis and the y-axis represent threshold predicted probability and net benefit, respectively. Each predictor had a line with a corresponding color. Nomograms based on APRI show a greater net benefit with a wider range of threshold probabilities than other predictors. DCA, Decision curve analysis; APRI, preoperative aspartate aminotransferase-to-platelet ratio index; DFS, disease-free survival; OS, overall survival.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

QHS, NNZ, JBH, YXY and YFZ conceptualized and designed the study. XPY, BWS and LZ acquired, analyzed and interpreted the data. QHS, NNZ and JBH drafted the manuscript. QHS, YXY and YFZ critically revised the manuscript for important intellectual content. QHS and YFZ confirm the authenticity of all the raw data. All authors have made a significant contribution to the present study, and have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved (approval no. B2021-322) by the Second Hospital of Nanjing ethics committee (Nanjing, China). All patients enrolled in this study signed an informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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