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RESEARCH

Tumor burden score combined with AFP and PIVKA-II (TAP score) to predict the prognosis of hepatocellular carcinoma patients after radical liver resection

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Abstract

Background Our study aimed to combine the morphological behavior (tumor burden score, TBS) and the biological behavior (AFP and PIVKA-II) to predict the prognosis of HCC patients after radical liver resection.

Methods A total of 1766 HCC patients were divided into the training cohort ($n=1079$) and the validation cohort ($n=687$) with a ratio of 6:4. The Kaplan–Meier method was used to analyze the recurrence-free (RFS) and overall survival (OS). The multivariable Cox regression model was established based on the variables screened by the least absolute shrinkage and selection operator (LASSO) regression to identify variables independently associated with recurrence-free survival (RFS) and overall survival (OS). Constructing our prognostic score (TBS-LN(AFP+PIVKA-II) score, TAP score) based on regression coefficients and the predictive ability of the TAP score was compared with Barcelona Clinic Liver Cancer (BCLC) stage.

Results The TAP score had good performance in stratifying RFS ($p<0.001$) and OS ($p<0.001$) in the training cohort and the validation cohort. There still existed significant differences in the intergroup comparisons among three TAP score groups for RFS and OS in the training cohort and the validation cohort. In our LASSO-Cox regression model, the TAP score was independently associated with RFS and OS. The TAP score also outperformed the BCLC stage in predicting RFS (1, 2 and 3 years) and OS (1, 3 and 5 years).

Conclusions The TAP score had good performance in predicting the prognosis of HCC patients after radical liver resection and was superior to the BCLC stage.

Keywords Tumor burden score · Tumor marker · Hepatocellular carcinoma · Liver resection · Prognosis

Introduction

Hepatocellular carcinoma (HCC) is a global health problem, that ranks as the sixth most commonly diagnosed malignancy and the third leading cause of cancer-related mortality worldwide [1]. In some high-incidence countries, such as China and Japan, the incidence and mortality of HCC are gradually decreasing. However, the incidence rates are gradually increasing in some low-incidence countries [2]. For example, in the past two decades, the incidence of HCC has almost tripled in the United States [3]. Some investigators suggested that compared to 2020, the annual new cases of liver cancer will increase by 55%, which is expected to reach 1.4 million in 2040[2]. An estimated 1.3 million patients will die from liver cancer in 2040[2]. Liver resection is a widely accepted curative treatment for patients with

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HCC. However, approximately 50-70% of HCC patients will experience recurrence within 5 years after liver resection, which greatly limited the long-term survival of HCC patients [4, 5].

Many factors contribute to postoperative recurrence in HCC patients following liver resection. The tumor number and tumor size of patients with HCC, which are also known as tumor burden, are commonly used variables to predict the prognosis of patients with HCC after treatment. Recently, the tumor burden score (TBS), which consisted of tumor size and tumor number, was widely confirmed to be a reliable marker for predicting HCC patient's long-term outcomes after liver resection, transplantation, radiofrequency ablation, etc [6–8]. However, TBS cannot fully reflect the biological characteristics of HCC. Some HCC patients with low TBS still exist aggressive tumor behavior and poor long-term outcomes after liver resection.

Alpha-fetoprotein (AFP) and protein induced by vitamin K absence or antagonist II (PIVKA-II) are two widely used tumor markers for the surveillance, diagnosis, and evaluation of treatment responses in patients with HCC. Some investigations have suggested that AFP and PIVKA-II could reflect the tumor biological behavior and predict the prognosis of HCC patients [9, 10]. Many studies also suggested preoperative high AFP level and/or high PIVKA-II level were associated with high incidence of postoperative recurrence and mortality of patients with HCC after liver resection [11, 12]. Some investigators also suggested the combination of TBS and AFP may be predict the prognosis of patients with HCC after liver resection [13, 14]. However, about 30-40% of HCC patients have normal AFP levels (defined as AFP level≤20ng/ml) [15]. In clinical practice, some patients with negative AFP may be positive for PIVKA-II. Some researchers also confirmed that the combination of AFP and PIVKA-II was better than AFP alone for the surveillance and treatment monitoring of HCC [16]. Accordingly, we hypothesized the combination of TBS, AFP and PIVKA-II may be better reflect the tumor behavior and may be a surrogate marker to predict prognosis of patients with HCC after liver resection. To clarify this issue, we carried out this study.

Methods

Patients and follow-up

HCC patients with BCLC 0/A/B who underwent R0 resection between January 2015 and December 2020 at West China Hospital of Sichuan University were retrospectively reviewed. All laboratory tests were performed 1 week before liver resection. After hepatectomy, all patients were regularly followed up every three months during the first two postoperative years and then every six months. Patients who met any of the following criteria were excluded from the study: (1) Lack of AFP or PIVKA-II, or both; (2) Lack of other important information; (3) With other malignant diseases; (4) Ruptured hepatocellular carcinoma; (5) Receive anti-tumor therapy before hepatectomy. Finally, 1766 HCC patients were included in our study (Fig. 1). This study was approved by the ethics committee of West China Hospital.

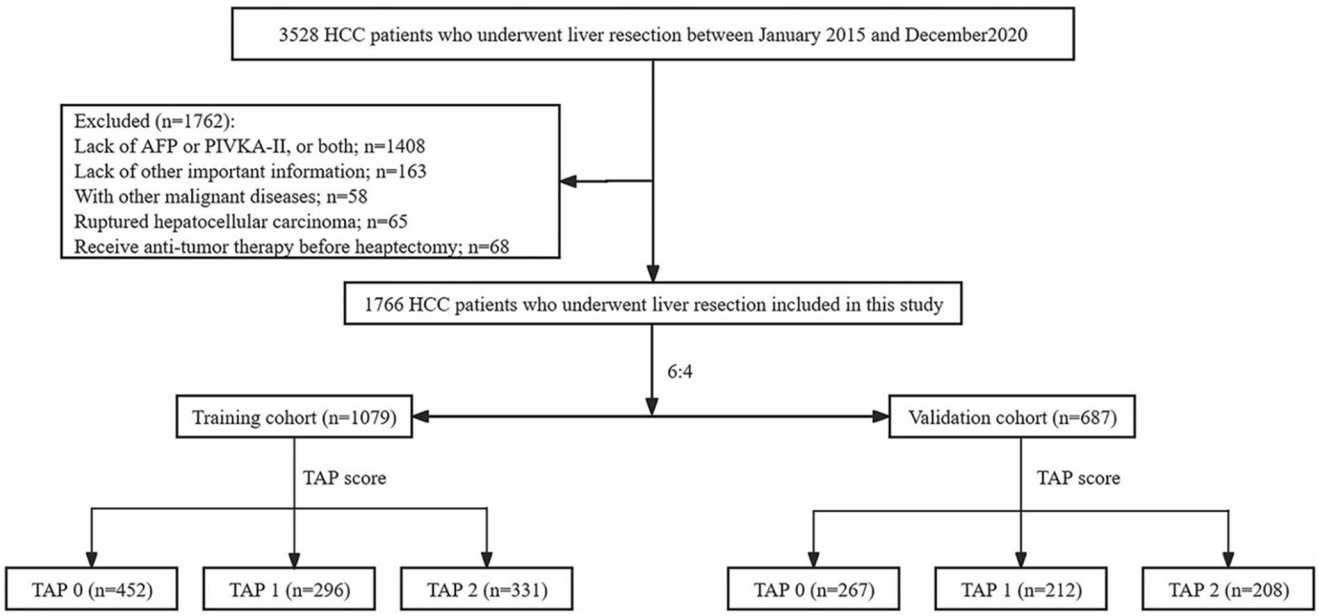

Fig. 1 Study flow chart

Definitions

ALBI grades were classified into three levels (grades I, II, III = ≤–2.60, <–2.60 to ≤–1.39, > −1.39) based on the ALBI score (ALBI score = [(log10 bilirubin (in μmol/L) × 0.66) + (albumin (in g/L) × −0.085)]. The tumor burden score (TBS) was calculated by the following equation: TBS^2 = maximum tumor $size^2$ + $tumor\ number^2$ [17, 18]. The neutrophil to lymphocyte ratio (NLR) was defined as the neutrophil count divided by the lymphocyte count [19]. The platelet to lymphocyte ratio (PLR) was defined as the platelet count divided by the lymphocyte count [19]. The prognostic nutrition index (PNI) was calculated as following formula: serum albumin (g/L) + 5 × lymphocyte count (10^9/L). NLR > 3 and PLR > 150 were considered to indicate high NLR or high PLR respectively [20]. The cut-off value of the PNI was 45, as reported in the literatures [21, 22].

Calculation of the TBS-LN(AFP + PIVKA-II) (TAP) score

The ranges for the sum of AFP and PIVKA-II were very large and were therefore log-transformed in our study for further analyses. The optimal cutoff values of the LN(AFP + PIVKA-II) and the TBS were identified by using the "surv_cutpoint" function from the "survminer" R package. The TAP score was calculated from the β-coefficients of TBS and LN (AFP + PIVKA-II) in the multivariate Cox proportional hazard model. The β-coefficient in the Cox proportional hazards model was multiplied by 2 and rounded (1.00 units) to calculate the TAP score.

Outcomes

Recurrence-free survival (RFS) was the primary outcome and overall survival (OS) was the secondary outcome in our study. RFS was defined as the time from surgery to recurrence or the last follow-up (May 31, 2022). Recurrence after R0 resection was defined as positive imaging results that were compared to the values from the preoperative exam or if they were verified by biopsy or resection. OS was defined as the time from surgery to death from any cause or the last follow-up (May 31, 2022).

Statistics

Patients were divided into a training cohort (n = 1079) and a validation cohort (n = 687) at a ratio of 6:4 for the internal validation by a simple randomization method in the R software. One-way analysis of variance or Kruskal–Wallis test was used to compare differences of continuous variables. The $\chi 2$ test or Fisher's exact test was performed to compare the differences of categorical variables. The Kaplan–Meier method was used to determine recurrence-free (RFS) and overall survival (OS). The multivariable Cox regression model was built using variables screened by the least absolute shrinkage and selection operator (LASSO) regression to identify factors that were independently associated with RFS and OS. The predictive ability of the TAP score was compared with that of the BCLC stage by using Harrell's concordance index (C-index), Akaike information criteria (AIC) and the area under the ROC curve (AUC) [23]. All data analyses were performed using SPSS software version 26.0 and R software version 4.41. P values < 0.05 were considered to indicate statistical significance according to two-tailed tests.

Results

Patient characteristics

A total of 1766 HCC patients were included in our study for the final analysis. We divided HCC patients into the training cohort (n = 1079) and the validation cohort (n = 687) at a ratio of 6:4 for internal validation (Fig. 1). There were no significant differences in the baseline characteristics of patients between the validation and training groups (Table 1, all p > 0.05). Then we identified the cutoff values of the TBS and the LN(AFP + PIVKA-II) based on RFS in the training cohort (Supplementary Fig. S1). The cutoff value of the TBS was 4.1, and more than 4.1 was considered as high-level TBS (Supplementary Fig. S1A). The cutoff value of the LN(AFP + PIVKA-II) was 7.2, and more than 7.2 was considered as high-level LN(AFP + PIVKA-II) (Supplementary Fig. S1B).

Screening independent variables associated with RFS based on the LASSO-Cox proportional hazards regression model

First, we used the LASSO regression to screen for the most likely predictors of RFS (Supplementary Fig. S2). Supplementary Fig. S2A showed the characteristics of the coefficient change of each variable in the LASSO regression model, and the iterative analysis used the 10-fold intersection difference validation method. and when λ was 0.09 (log (λ) = -1.05), a model with excellent performance and the least number of variables was produced (Supplementary Fig. S2B). The variables selected by the LASSO regression include TBS, LN(AFP + PIVKA-II), microvascular invasion (MVI) and satellite nodules. Supplementary Table 1 showed the coefficients of variables screened by the LASSO regression. Then we established the multivariate

Table 1 Clinicopathological characteristics of the training cohort and the validation cohort

Variables	Training cohort ($n=1079$)	Validation cohort ($n=687$)	*P* value
Age, years			0.913
>60y	346(32.1%)	222(32.3%)	
≤60	733(67.9%)	465(67.7%)	
Sex			0.486
Male	924(85.6%)	580(84.4%)	
Female	155(14.4%)	107(15.6%)	
Etiology			0.304
HBV	892(82.7%)	571(83.1%)	
HCV	35(3.2%)	14(2.0%)	
Others	152(14.1%)	102(14.8%)	
ALBI grade			0.443
I	909(84.2%)	588(85.6%)	
II	170(15.8%)	99(14.4%)	
Minimally invasive surgery			
Yes	314(29.1%)	173(25.2%)	0.072
No	765(70.9%)	514(74.8%)	
Tumor burden score	4.2(3.0,6.3)	4.4(3.1,6.5)	0.372
Low, ≤4.1	502(46.5%)	308(44.8%)	0.487
High, >4.1	577(53.5%)	379(55.2%)	
LN(AFP+PIVKA-II)	6.5(5.1,7.7)	6.6(5.1,7.7)	0.369
Low, ≤7.2	698(64.7%)	438(63.8%)	0.690
High, >7.2	381(35.3%)	249(36.2%)	
NLR	2.0(1.5,2.7)	2.0(1.6,2.8)	0.322
Low, ≤3.0	874(81.0%)	556(80.9%)	0.971
High, >3.0	205(19.0%)	131(19.1%)	
PLR	85.5(63.6,118.8)	87.9(65.0,123.0)	0.094
Low, ≤150	943(87.4%)	593(86.3%)	0.512
High, >150	136(12.6%)	94(13.7%)	
PNI	50.9±5.2	50.8±5.1	0.671
Low, ≤45	135(12.5%)	78(11.4%)	0.466
High, >45	944(87.5%)	609(88.6%)	
Max tumor size, >5 cm			0.581
Yes	399(37.0%)	263(38.3%)	
No	680(63.0%)	424(61.7%)	
Single tumor			0.581
Yes	978(90.6%)	628(91.4%)	
No	101(9.4%)	59(8.6%)	
BCLC stage			0.251
0	126(11.7%)	63(9.2%)	
A	881(81.6%)	577(84.0%)	
B	72(6.7%)	47(6.8%)	
Low differentiation			0.077
Yes	99(9.2%)	81(11.8%)	
No	980(90.8%)	606(88.2%)	
Capsular invasion			0.739
Yes	439(40.7%)	285(41.5%)	
No	640(59.3%)	402(58.5%)	
MVI			0.586
Yes	359(33.3%)	220(32.0%)	
No	720(66.7%)	467(68.0%)	
Satellite nodules			0.241
Yes	80(7.4%)	41(6.0%)	
No	999(92.6%)	646((94%)	
Cirrhosis			0.351
Yes	557(51.6%)	339(49.3%)	
No	522(48.4%)	348(50.7%)	

Abbreviations: *AFP*, α-fetoprotein; *PIVKA-II*, protein induced by vitamin K deficiency II; *NLR*, neutrophil lymphocyte ratio; *PLR*, platelet lymphocyte ratio; *PNI*, prognostic nutritional index; *BCLC*, Barcelona Clinic Liver Cancer staging system; *AJCC TNM stage, American Joint Committee on Cancer;MVI*, microvascular invasion

* ALBI grades were classified into three levels (grades I, II, III = ≤–2.60, <–2.60 to ≤–1.39, > −1.39) based on the ALBI score (ALBI score = [(log10 bilirubin (in μmol/L) × 0.66) + (albumin (in g/L) × −0.085)]

Cox regression model based on the variables screened by the LASSO regression. In our LASSO-Cox regression model, the variables independently associated with RFS included: TBS (High vs. Low, HR: 1.39, 95%CI:1.11–1.75, $p=0.005$), LN (AFP+PIVKA-II) (High vs. Low, HR: 1.72, 95%CI: 1.38–2.14, $p<0.001$), MVI (Yes vs. No, HR: 1.50, 95%CI: 1.23–1.84, $p<0.001$) and satellite nodules (Yes vs. No, HR: 1.70, 95%CI: 1.26–2.30, $p<0.001$, Table 2). The β-coefficients of TBS and LN(AFP+PIVKA-II) were 0.33 and 0.54 separately (Table 2).

Development of the TAP score

We assigned new scores to the TBS and the LN(AFP+PIVKA-II) based on their β-coefficients (the β-coefficient was multiplied by 2 and rounded (1.00 unit)). As a result, the TBS level and the LN(AFP+PIVKA-II) level were both assigned a score of 0–1 from low to high, respectively. The TAP score was the summation of the TBS score and the LN(AFP+PIVKA-II) score, and the TAP score ranged from 0 to 2. According to our TAP score, we divided the patients in the training group and validation group into three groups separately (Table 3). In the training group, patients in the TAP 0 group were younger ($p<0.001$) but had more hepatitis B infections ($p<0.001$) compared with those in the TPA 1 group and the TAP 2 group. Patients in the TAP 0 group had lower levels of NLR ($p<0.001$) and PLR ($p<0.001$). Compared with those in the TAP 0 group and TAP 1 group, more patients in the TAP 2 group had the liver functional status of ALBI II ($p<0.001$) and had lower levels of PNI ($p=0.008$), fewer patients received minimally invasive surgeries ($p<0.001$). In terms of tumor burden, patients in the TAP 0 group had smaller tumor sizes ($p<0.001$) and larger proportions of single tumor ($p=0.026$) compared with those in the TAP 1 group and the TAP 2 group. Meanwhile, patients in the TAP 0 group had better pathological characteristics

Table 2 Multivariable Cox proportional hazards regression to predict RFS based on LASSO regression

Variables	HR	(95% CI)	*P* value	β-coefficient
Tumor burden score				
Low, ≤4.1	Ref			
High, >4.1	1.39	1.11–1.75	0.005	0.33
LN(AFP+PIVKA-II)				
Low, ≤7.2	Ref			
High, >7.2	1.72	1.38–2.14	<0.001	0.54
MVI				
No	Ref			
Yes	1.50	1.23–1.84	<0.001	0.41
Satellite nodules				
No	Ref			
Yes	1.70	1.26–2.30	<0.001	0.53

(capsular invasion, $p<0.001$; MVI, $p<0.001$; satellite nodules, $p<0.001$), but more patients in the TAP 0 group had cirrhosis ($p<0.001$, Table 3). In the validation group, patients in the TAP 0 group were also younger ($p=0.016$) than those in the TAP 1 group and the TAP 2 group. Patients in the TAP 0 group had lower levels of NLR ($p<0.001$) and PLR ($p<0.001$) and were more likely to receive minimally invasive surgeries ($p<0.001$). In terms of tumor burden, patients in the TAP 0 group had smaller tumor sizes ($p<0.001$) and larger proportions of single tumor ($p=0.016$). patients in the TAP 0 group also had better pathological characteristics (capsular invasion, $p<0.001$; MVI, $p<0.001$; satellite nodules, $p=0.001$), but more patients in the TAP 0 group had cirrhosis ($p<0.001$, Table 3).

Survival analysis based on the TAP score and validation of the TAP score

In the training cohort, the median follow-up time was 38 months. The 5-year RFS rate in the training cohort was 50.2%. The 1-, 2- and 3-year RFS rates in the TAP 0 group were 89.1%, 81.6% and 68.7%, respectively. The 1-, 2- and 3-year RFS rates in the TAP 1 group were 80.6%, 68.9% and 60.1%, respectively. The 1-, 2- and 3-year RFS rates in the TAP 2 group were 61.2%, 48.8% and 42.4%, respectively. In our Kaplan–Meier analysis, the TAP score had good performance in stratifying the RFS ($p<0.001$, Fig. 2A). Meanwhile, there were significant differences in the comparison between groups for RFS (TAP 0 vs., TAP 1, $p<0.001$; TAP 0 vs., TAP 2, $p<0.001$; TAP 1 vs., TAP 2, $p<0.001$, Fig. 2A). In the validation cohort, the median follow-up time was 39 months and the 5-year RFS rate was 50.8%. The 1-, 2- and 3-year RFS rates in the TAP 0 group were 90.6%, 79.5% and 70.8% respectively. The 1-, 2- and 3-year RFS rates in the TAP 1 group were 79.1%, 68.5% and 61.2% respectively. The 1-, 2- and 3-year RFS rates in the TAP 2 group were 67.0%, 50.3% and 43.9% respectively. There still existed significant differences in RFS between the three TAP groups (TAP 0 vs., TAP 1, $p=0.035$; TAP 0 vs., TAP 2, $p<0.001$; TAP 1 vs., TAP 2, $p<0.001$, Fig. 2B).

We further studied the ability of the TAP score to stratify the OS. In the training cohort, the 1-, 3- and 5-year OS rates in the TAP 0 group were 98.0%, 91.8% and 82.2%, respectively. The 1-, 3- and 5-year OS rates in the TAP 1 group were 95.9%, 86.4% and 72.9%, respectively. The 1-, 3- and 5-year OS rates in the TAP 2 group were 86.5%, 68.9% and 58.0%, respectively. We found that the TAP score still had good performance in stratifying the OS by the Kaplan–Meier analysis in our study ($p<0.001$, Fig. 2C). there were still significant differences in the comparison between groups for OS (TAP 0 vs., TAP 1, $p=0.012$; TAP 0 vs., TAP 2, $p<0.001$; TAP 1 vs., TAP 2, $p<0.001$, Fig. 2C). In the validation cohort, the 1-, 3- and 5-year OS rates in the TAP 0 group were 98.5%, 91.5% and 82.1% respectively. The 1-, 3- and 5-year OS rates in the TAP 1 group were 92.0%, 82.1% and 63.3%, respectively. The 1-, 3- and 5-year OS rates in the TAP 2 group were 89.4%, 68.9% and 59.0%, respectively. There still existed significant differences in OS between the three TAP groups (TAP 0 vs., TAP 1, $p<0.001$; TAP 0 vs., TAP 2, $p<0.001$; TAP 1 vs., TAP 2, $p=0.016$, Fig. 2D).

Variables independently associated with RFS and OS based on the TAP score

In the training cohort, we considered the TAP score as a new factor to further complete the multivariate analysis to screen variables independently associated with RFS and OS. In terms of RFS, we first used the LASSO regression to screen the most likely predictor variables associated with RFS. Supplementary Fig. 3A showed the characteristics of the coefficient change of each variable in the LASSO regression model and when λ was 0.07 (log (λ) = -1.15), a model with excellent performance and the least number of variables was produced (Supplementary Fig. 3B). The variables selected by the LASSO regression include TAP score, LN(AFP+PIVKA-II), MVI and satellite nodules. Supplementary Table 2 showed the coefficients of variables screened by the LASSO regression. Then the variables screened by the LASSO regression were included in our multivariable Cox regression model and our LASSO-Cox model showed that the TAP score was an independent factor associated with RFS (TAP 1, HR: 1.47, 95%CI: 1.14–1.89, $p=0.003$; TAP 2, HR: 2.39, 95%CI: 1.89–3.03, $p<0.001$, Table 4). Other variables independently associated with RFS included: MVI (Yes vs. No, HR: 1.51, 95%CI: 1.23–1.84, $p<0.001$) and satellite nodules (Yes vs. No, HR: 1.69, 95%CI: 1.25–2.28, $p=0.001$, Table 4).

Table 3 Characteristics of patients stratified by the TAP score

Variables	Training group ($n=1079$)			*P* value	Validation group ($n=687$)			*P* value
	TAP 0 ($n=452$)	TAP 1 ($n=296$)	TAP 2 ($n=331$)		TAP 0 ($n=267$)	TAP 1 ($n=212$)	TAP 2 ($n=208$)	
Age, years				< 0.001				0.016
> 60y	114(25.2%)	116(39.2%)	116(35.0%)		73(27.3%)	84(39.6%)	65(31.2%)	
≤ 60	338(74.8%)	180(60.8%)	215(65.0%)		194(72.7%)	128(60.4%)	143(68.8%)	
Sex				0.246				0.654
Male	378(83.6%)	260(87.8%)	286(86.4%)		227(85.0%)	175(82.5%)	178(85.6%)	
Female	74(16.4%)	36(12.2%)	45(13.6%)		40(15.0%)	37(17.5%)	30(14.4%)	
Etiology				< 0.001				0.163
HBV	398(88.1%)	227(76.7%)	267(80.7%)		223(83.5%)	181(85.4%)	167(80.3%)	
HCV	15(3.3%)	12(4.0%)	8(2.4%)		9(3.4%)	2(0.9%)	3(1.4%)	
Others	39(8.6%)	57(19.3%)	56(16.9%)		35(13.1%)	29(13.7%)	38(18.3%)	
ALBI grade				< 0.001				0.165
I	393(86.9%)	260(87.8%)	256(77.3%)		233(87.3%)	185(87.3%)	170(81.7%)	
II	59(13.1%)	36(12.2%)	75(22.7%)		34(12.7%)	27(12.7%)	38(18.3%)	
Minimally invasive surgery				< 0.001				< 0.001
Yes	168(37.2%)	81(27.4%)	65(19.6%)		90(33.7%)	45(21.2%)	38(18.3%)	
No	284(62.8%)	215(72.6%)	266(80.4%)		177(66.3%)	167(78.8%)	170(81.7%)	
NLR				< 0.001				< 0.001
Low, ≤ 3.0	395(87.4%)	231(78.0%)	248(74.9%)		238(89.1%)	170(80.2%)	148(71.2%)	
High, > 3.0	57(12.6%)	65(22.0%)	83(25.1%)		29(10.9%)	42(19.8%)	60(28.8%)	
PLR				< 0.001				< 0.001
Low, ≤ 150	428(94.7%)	257(86.8%)	258(77.9%)		248(92.9%)	186(87.7%)	159(76.4%)	
High, > 150	24(5.3%)	39(13.2%)	73)22.1%)		19(7.1%)	26(12.3%)	49(23.6%)	
PNI								0.113
Low, ≤ 45	47(10.4%)	31(10.5%)	57(17.2%)	0.008	22(8.2%)	27(12.7%)	29(13.9%)	
High, > 45	475(89.6%)	265(89.5%)	274(82.8%)		245(91.8%)	185(87.3%)	179(86.1%)	
Max tumor size, >5 cm				< 0.001				< 0.001
Yes	0	156(52.7%)	259(78.2%)		0	97(45.8%)	166(79.8%)	
No	452(100%)	140(47.3%)	72(21.8%)		267(100%)	115(54.2%)	42(20.2%)	
Single tumor				0.026				0.016
Yes	422(93.4%)	260(87.8%)	296(89.4%)		254(95.1%)	191(90.1%)	183(88.0%)	
No	30(6.6%)	36(12.2%)	35(10.6%)		13(4.9%)	21(9.9%)	25(12.0%)	
BCLC stage				< 0.001				< 0.001
0	122(27.0%)	4(1.4%)	0		63(23.6%)	0	0	
A	323(71.5%)	262(88.5%)	296(89.4%)		201(75.3%)	193(91.0%)	183(88.0%)	
B	7(1.5%)	30(10.1%)	35(10.6%)		3(1.1%)	19(9.0%)	25(12.0%)	
Low differentiation				0.088				0.365
Yes	36(8.0%)	23(7.8%)	40(12.1%)		29(10.9%)	22(10.4%)	30(14.4%)	
No	416(92.0%)	273(92.2%)	291(87.9%)		238(89.1%)	190(89.6%)	178(85.6%)	
Capsular invasion				< 0.001				< 0.001
Yes	150(33.2%)	122(41.2%)	167(50.5%)		84(31.5%)	91(42.9%)	110(52.9%)	
No	302(66.8%)	174(58.8%)	164(49.5%)		183(68.5%)	121(57.1%)	98(47.1%)	
MVI				< 0.001				< 0.001
Yes	93(20.6%)	94(31.8%)	172(52.0%)		42(15.7%)	64(30.2%)	114(54.8%)	
No	359(79.4%)	202(68.2%)	159(48.0%)		225(84.3%)	148(69.8%)	94(45.2%)	
Satellite nodules				< 0.001				0.001
Yes	15(3.3%)	28(9.5%)	37(11.2%)		7(2.6%)	11(5.2%)	23(11.1%)	
No	437(96.7%)	268(90.5%)	294(88.8%)		260(97.4%)	201(94.8%)	185(88.9%)	
Cirrhosis				< 0.001				< 0.001
Yes	175(61.3%)	154(48.0%)	193(41.7%)		168(62.9%)	92(43.4%)	79(38.0%)	
No	277(38.7%)	142(52.0%)	138(58.3%)		99(37.1%)	120(56.6%)	129(62.0%)	

Abbreviations: TAP, tumor burden score (TBS)-LN(AFP + PIVKA-II) score model

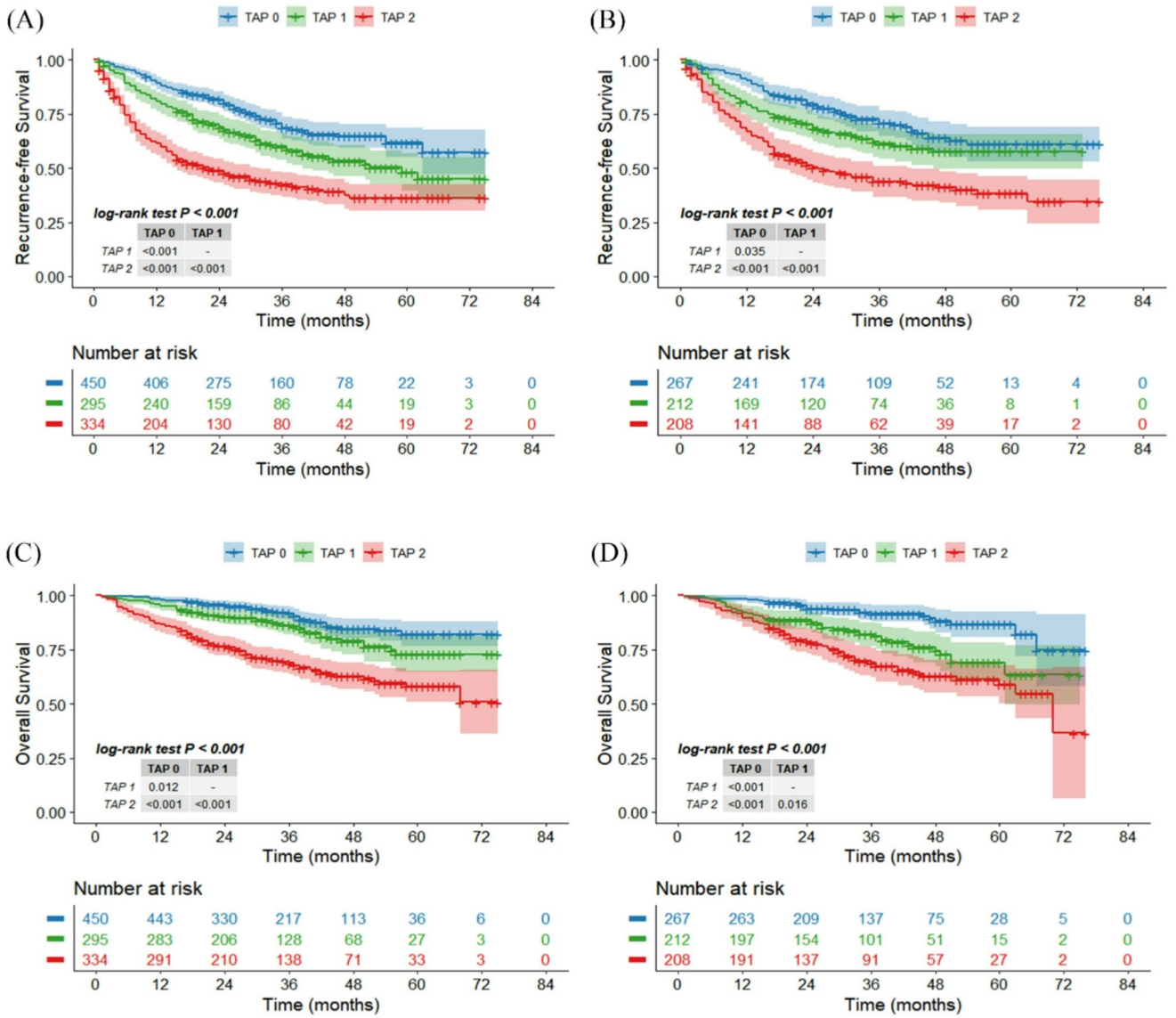

Fig. 2 Survival analysis in the training cohort and the validation cohort. TAP score, tumor burden score (TBS)-LN(AFP+PIVKA-II) score. (**A**) RFS in the training cohort; (**B**) RFS in the validation cohort; (**C**) OS in the training cohort; (**D**) OS in the validation cohort

We further explored the independent factors associated with OS based on the TAP score using the same approach. Supplementary Fig. 3C showed the characteristics of the coefficient change of each variable in the LASSO regression model and when λ was 0.05 (log (λ) = -1.30), a model with excellent performance and the least number of variables was produced (Supplementary Fig. 3D). The variables selected by the LASSO regression include TAP score, LN(AFP+PIVKA-II), ALBI grade, MVI and satellite nodules. Supplementary Table 3 showed the coefficients of variables screened by the LASSO regression. In our LASSO-Cox regression model, the TAP score was still an independent factor associated with OS (TAP 1, HR: 1.51, 95%CI: 1.01–2.27, $p=0.047$; TAP 2, HR: 2.88, 95%CI: 2.01–4.12, $p<0.001$, Table 4). Other variables independently associated with OS included: MVI (Yes vs. No, HR: 1.74, 95%CI: 1.30–2.33, $p<0.001$) and satellite nodules (Yes vs. No, HR: 1.84, 95%CI: 1.24–2.73, $p=0.002$) and ALBI grade (I vs. II, HR: 1.66, 95%CI: 1.20–2.99, $p=0.002$, Table 4).

Predictive performance of the TAP score

The Barcelona Clinic Liver Cancer (BCLC) staging system is a typical staging system for HCC, so we compared the ability of the TAP score in predicting RFS and OS with BCLC stage in the training cohort and the validation cohort. In the training cohort, the AUCs for 1-, 2-and 3-year RFS were 0.69 (95%CI: 0.66–0.73), 0.66 (95%CI: 0.63–0.70)

Table 4 Multivariable Cox proportional hazards regression to predict RFS and OS based on TAP score

Variables	HR	(95% CI)	*P* value
RFS			
TAP score			
0	Ref		
1	1.47	1.14–1.89	0.003
2	2.39	1.89–3.03	< 0.001
LN(AFP + PIVKA-II)			
Low, ≤ 7.2	Ref		
High, > 7.2	1.26	0.80–1.99	0.315
MVI			
No	Ref		
Yes	1.51	1.23–1.84	< 0.001
Satellite nodules			
No	Ref		
Yes	1.69	1.25–2.28	0.001
OS			
TAP score			
0	Ref		
1	1.51	1.01–2.27	0.047
2	2.88	2.01–4.12	< 0.001
LN(AFP + PIVKA-II)			
Low, ≤ 7.2	Ref		
High, > 7.2	1.12	0.55–2.33	0.747
MVI			
No	Ref		
Yes	1.74	1.30–2.33	< 0.001
Satellite nodules			
No	Ref		
Yes	1.84	1.24–2.73	0.002
ALBI grade			
I	Ref		
II	1.66	1.20–2.29	0.002

and 0.62 (95%CI: 0.58–0.66) for the TAP score, and the AUCs for 1-, 2-and 3-year RFS were 0.57 (95%CI: 0.55–0.60), 0.57 (95%CI: 0.55–0.60) and 0.54 (95%CI: 0.52–0.57) for the BCLC stage (Fig. 3A/B/C, Supplementary Table 4). Supplementary Fig. S4A showed the time-dependent AUC for RFS (1, 2 and 3 years) between the TAP score and the BCLC stage in the training cohort. The TAP score had a higher C-index (0.64, 95%CI: 0.61–0.66) and a lower AIC (5621.57) in predicting RFS compared with the BCLC stage (C-index, 0.55, 95%CI: 0.53–0.57; AIC: 5676.75) (Supplementary Table 4). As a result, the TAP score outperformed the BCLC stage in predicting RFS in the training cohort. In the validation cohort, the AUCs for 1-, 2-and 3-year RFS were 0.67 (95%CI: 0.62–0.71), 0.65 (95%CI: 0.60–0.69)and 0.61 (95%CI: 0.57–0.66) for the TAP score, and the AUCs for 1-, 2-and 3-year RFS were 0.56 (95%CI: 0.53–0.60), 0.54 (95%CI: 0.51–0.57) and 0.54 (95%CI: 0.51–0.58) for the BCLC stage (Fig. 3D/E/F, Supplementary Table 4). Supplementary Fig. 4B showed the time-dependent AUC for RFS (1, 2 and 3 years) between the TAP score and the BCLC stage in the validation cohort. The TAP score also had a higher C-index 0.62 (95%CI: 0.59–0.65) and a lower AIC (3409.34) in predicting RFS compared with the BCLC stage (C-index, 0.55, 95%: 0.52–0.57; AIC: 3434.13) (Supplementary Table 4) in the validation cohort. The superiority of the TAP score in predicting RFS was also demonstrated in the validation cohort.

We further studied the performance of the TAP score in predicting OS. In the training cohort, the AUCs for 1-, 3- and 5-year OS were 0.73 (95%CI: 0.68–0.79), 0.67 (95%CI: 0.63–0.72) and 0.58 (95%CI: 0.51–0.65) for the TAP score, and the AUCs for 1-, 3- and 5-year OS were 0.56 (95%CI: 0.52–0.61), 0.57 (95%CI: 0.54–0.60) and 0.54 (95%CI: 0.49–0.60) for the BCLC stage (Fig. 4A/B/C, Supplementary Table 4). Supplementary Fig. 4C showed the time-dependent AUC for OS (1, 3 and 5 years) between the TAP score and the BCLC stage in the training cohort. The TAP score had a higher C-index (0.67, 95%CI: 0.63–0.71) and a lower AIC (2615.61) in predicting OS compared with the BCLC stage (C-index, 0.57, 95%CI: 0.54–0.59; AIC: 2656.52) (Supplementary Table 4). So, the TAP score also outperformed the BCLC stage in predicting OS in the training cohort. In the validation cohort, the AUCs for 1-, 3- and 5-year OS were 0.66 (95%CI: 0.59–0.73), 0.66 (95%CI: 0.61–0.72) and 0.62 (95%CI: 0.53–0.70) for the TAP score, and the AUCs for 1-, 3- and 5-year OS were 0.63 (95%CI: 0.57–0.70), 0.59 (95%CI: 0.55–0.63) and 0.60 (95%CI: 0.55–0.65) for the BCLC stage (Fig. 4D/E/F, Supplementary Table 4). Supplementary Fig. 4D showed the time-dependent AUC for OS (1, 3 and 5 years) between the TAP score and the BCLC stage in the validation cohort. The TAP score had a higher C-index (0.65, 95%CI: 0.61–0.70) and a lower AIC (1648.61) in predicting OS compared with the BCLC stage (C-index, 0.59, 95%CI: 0.56–0.62; AIC: 1655.93) (Supplementary Table 4) in the validation cohort. Therefore, the TAP score still outperformed the BCLC stage in predicting OS in the validation cohort.

Discussion

In this study, we confirmed that the TAP score, which consisted of TBS, AFP and PIVKA-II, may be a predictor to predict HCC patient's recurrence and mortality after liver resection. Different from previous investigations, our model included AFP and PIVKA-II two tumor markers, which may be accurately reflect the tumor biological characteristics of HCC patients.

AFP is the mostly commonly used tumor marker for patients with HCC in our clinical practice. However, in up to 40% of HCC patients, the serum AFP level may be in normal. Moreover, in the worldwide, the incidence of

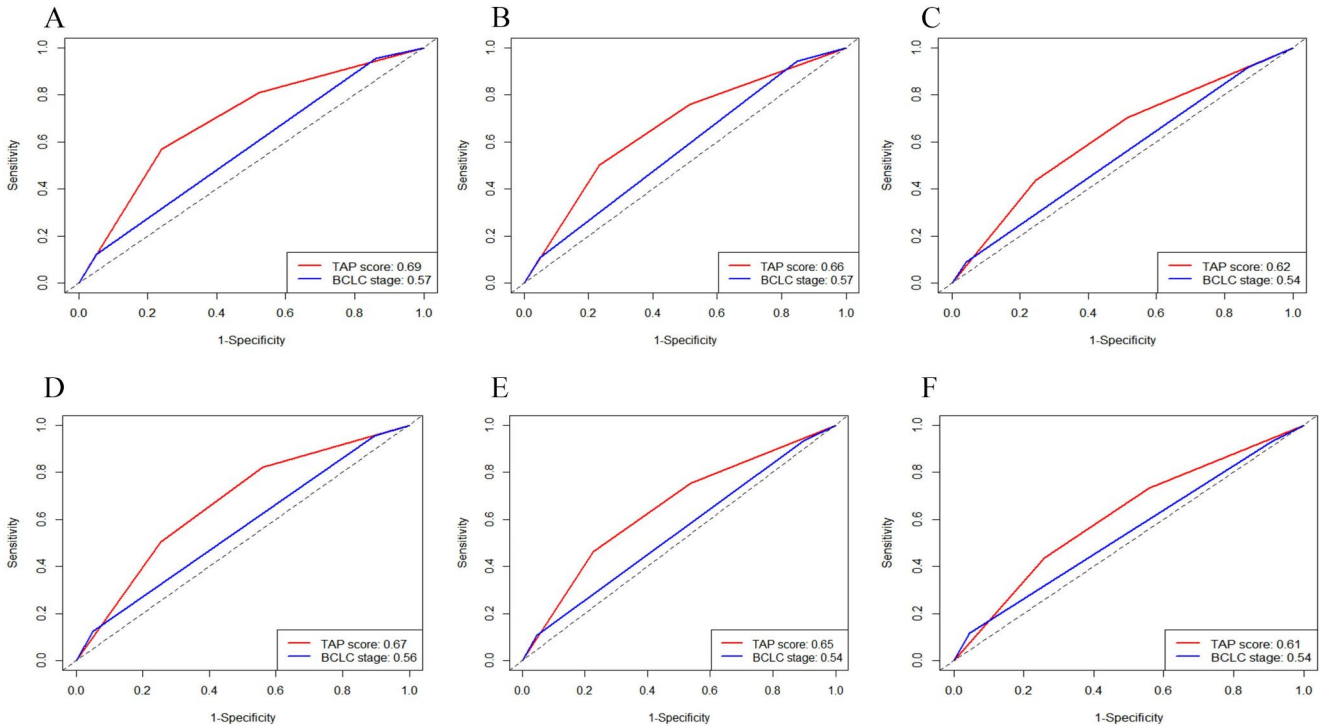

Fig. 3 The comparison of the predictive ability in RFS of the TAP score with the BCLC stage in the training cohort and the validation cohort. Training cohort: (**A**) 1-year RFS; (**B**) 2-year RFS; (**C**) 3-year RFS; Validation cohort: (**D**) 1-year RFS; (**E**) 2-year RFS; (**F**) 3-year RFS

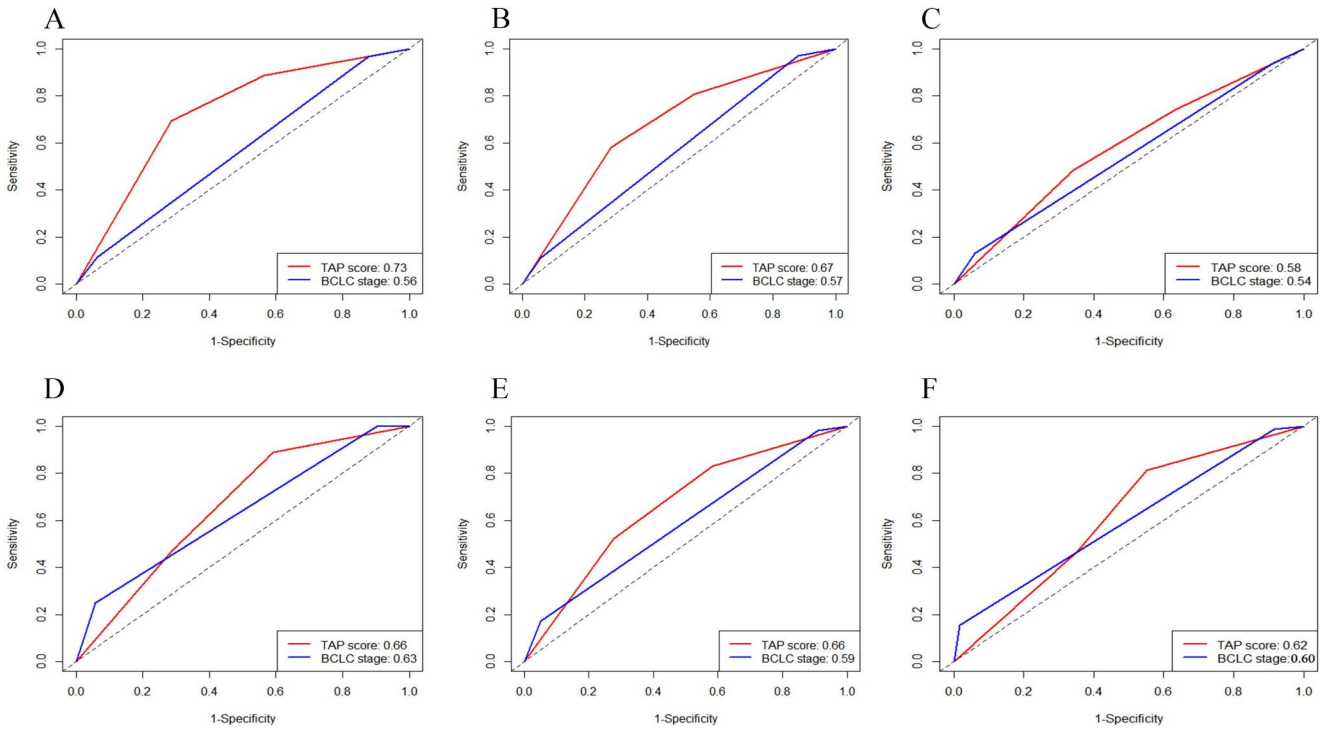

Fig. 4 The comparison of the predictive ability in OS of the TAP score with the BCLC stage in the training cohort and the validation cohort. Training cohort: (**A**) 1-year OS; (**B**) 3-year OS; (**C**) 5-year OS; Validation cohort: (**A**) 1-year OS; (**B**) 3-year OS; (**C**) 5-year OS

AFP-negative HCC is increasing because of the proportion of nonviral-related HCC cases is increasing in some countries [10]. PIVKA- II and AFP had complementary effects on the diagnosis of HCC. Some investigators even confirmed that patients with metabolic dysfunction-associated steatosis liver disease / metabolic dysfunction-associated steatohepatitis-related HCC have a high percentage of PIVKA- II positivity [10, 24]. Previous studies revealed not only high preoperative AFP level, but also high preoperative PIVKA- II level were associated with aggressive tumor biological characteristics, such as presence of MVI, poor tumor differentiation and so on [9, 25, 26]. Li et al. [27] showed PIVKA- II was potential marker for diagnosis of portal vein thrombus. Ma et al. conformed high Ki67 expression was observed in HCC patients with high PIVKA-II levels which indicated a more aggressive tumor phenotype [28]. Wang et al. even suggested preoperative PIVKA-II positivity, but not preoperative AFP positivity was an independent risk factor to predict early recurrence of patients with HCC after liver resection [29]. Therefore, combining the status of AFP and PIVKA- II may be able to more accurately distinguish HCC patients' outcomes after liver resection. Our study also confirmed the predictive ability of TAP score was better than the BCLC stage.

Unlike in some previous studies, we used the sum of AFP and PIVKA- II to represent HCC patient's biological behavior [12, 30]. However, some studies only focused on the secretion status of AFP and PIVKA- II [12, 30]. For example, Chon et al. [30] confirmed that the prognosis of HCC patients who were positive for both AFP and PIVKA-II had a worse prognosis than those who were negative for both or had only one positive. In Chon et al.'s study, they considered AFP levels≥20ng/ml as AFP positive, whereas PVIKA- II levels≥40 mAU/mL as PVIKA- II positive [30]. This study didn't concern the detail level of these two tumor markers [30]. But, in the clinical practice, the prognosis of HCC patients was not only related to the secretion status of tumor markers, but also associated with the detail level of tumor markers. Ma et al. [31] confirmed the preoperative serum AFP level was an independent risk factor for postoperative recurrence and mortality. HCC patients with an AFP level≤20 ng/mL had the best prognosis after liver resection, then followed by patients with an AFP level 20-400ng/mL, and patients with an AFP level>400 ng/mL had the worst prognosis [30]. Accordingly, when using tumor markers to predict HCC patient's prognosis, we should considerate both the secretion status and detail levels. Lee et al. [32] even suggested AFP plus PIVKA-II gave reliable information regarding the tumor biology of far advanced HCC. AFP plus PIVKA-II≤300 may serve as selection criteria for liver transplantation for patients advanced HCC [31]. Moreover, there were large ranges of both AFP and PVIKA- II among patients with HCC. Sometimes, this difference may be more than 10,000-fold. However, small differences do not have a significant impact on patient outcomes. Accordingly, in this study, log-transformed on AFP and PVIKA- II were used to reduce the expected skewness.

Previous studies often converted tumor diameter and tumor number into binary variables to represent the tumor burden of HCC patients [33, 34]. However, some investigators suggested it will weaken the prognostic power of tumor size and tumor number [17, 35]. Recently, Sasaki et al. [17] proposed the TBS, which included tumor size and tumor number, to represent patient's tumor burden. A lot of studies have confirmed TBS was a reliable predictor for patients with HCC after liver transplantation, liver resection, radiofrequency ablation and so on. However, TBS can only reflect patient's tumor burden, but cannot fully reflect the biological behavior of patients with HCC. Some patients with high TBS may still have a better prognosis, while some patients with low TBS still have a worse prognosis. Previous studies have confirmed that TBS combined with AFP can better predict the prognosis of patients with HCC than TBS alone. But unlike these studies, the TAP score included TBS, AFP and PVIKA- II, which may give us a better picture of tumor biology. To the best of our knowledge, this is the first study to combine TBS, AFP and PVIKA- II to predict HCC patient's prognosis after liver resection.

In clinical practice, the TAP score may have the ability to subclassify the prognosis of early and intermediate-stage HCC patients after liver resection, which may help surgeons to make more individualized treatment decisions. For example, patients with huge HCC are in BCLC stage A and surgical treatment is preferred according to guideline recommendations, but this group of patients actually have a worse prognosis after surgery compared to patients with small hepatocellular carcinomas in BCLC stage A [36]. According to our TAP score, patients with huge HCC may belong to TAP 2 group. In the era of increasing interest in preoperative neoadjuvant therapy for hepatocellular carcinoma. HCC patients who belong to BCLC stage A but have a TAP score of 2 may be possible candidates for preoperative neoadjuvant therapy, which may make surgeons more careful in making surgical decisions for patients with huge HCC. For HCC patients in BCLC stage B, surgical resection remains the preferred treatment strategy for some patients. The TAP score may also subclassify HCC patients in BCLC stage B, which may be possible to screen patients who are best suitable for undergoing surgery.

It is also noting that the cutoff values are closely associated with the characteristic of the study cohort. In our study, the cutoff value of TBS was the same as our previous study. But as far as we know, there was no relevant study reporting the cutoff value of LN(AFP+PIVKA-II). Thus, the cutoff

values in our study needs to be further validate or adjust in a large multicenter cohort in the future.

There are also some limitations in this study. First, this was a single-center retrospective study, and due to the retrospective nature of our study, the elective bias which could influence the result was unavoidable. For example, patients lacked of relevant information were excluded. But this study was a large sample study, therefore, the TAP score still has a good predictive power for patients with HCC after liver resection. But the TAP score still needs to be validated in prospective multicenter studies. Second, unlike AFP, some centers didn't routinely test PVIKA- II to HCC patients, which will limit the use of TAP score. However, with the change of the etiology of HCC in many centers, an increasing number of HCC patients with negative AFP will be diagnosed [10]. Many studies have also demonstrated that preoperative PIVKA-II is associated with pathological features and prognosis of HCC patients after liver resection. Moreover, in our study, in APF-negative patients, patients with PIVKA-II positive had worse survival outcomes than those with PIVKA-II negative. Thus, it's very necessary to make routine monitoring (e.g. preoperative examinations, monitoring during postoperative follow-ups) of PIVKA in the diagnosis, treatment evaluation and monitoring of patients with HCC. Third, in the current study, we didn't include patients with BCLC stage C HCC. Many studies have confirmed macrovascular invasion was a strong risk factor for postoperative recurrence and mortality in patients with HCC independent of tumor burden [37, 38]. Accordingly, whether the TAP score was useful for patients with BCLC stage C HCC needs further study. Last, the main etiology of HCC is HBV in China, so most of the patients in our study were infected with hepatitis B. Although a small proportion of patients with HCC due to other causes were included in our study, a large study cohort which excludes HBV-related HCC patients is necessary to validate our results.

In conclusion, our study suggested TAP score, which consisted of TBS, AFP and PVIKA- II was a surrogate prognostic marker for patients with HCC after liver resection.

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Author contributions Z.C.Q, C.L and T.F.W proposed this study. Z. C. Q, W. Y. W, J. L. D, W. L. Q, C. W. C and Y. Q. X collected the data. Z. C. Q and W. Y. W analyzed the data. Z. C. Q and W. Y. W wrote the manuscript. J. Y. S, C. L and T. F. W revised and reviewed the manuscript.

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Data availability The corresponding author will, upon reasonable request, share the datasets used and/or analyzed in the present research.

Declarations

Ethical approval The West China Hospital's Ethics Committee gave its approval to this study. The committee decided not to require informed consent because the study was retrospective.

Competing interests The authors declare no competing interests.

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