A novel preoperative predictive model of 90-day mortality after liver resection for huge hepatocellular carcinoma

Yue Yin[1,2#], Jian-Wen Cheng[1#], Fei-Yu Chen[1#], Xu-Xiao Chen[1], Xin Zhang[1], Ao Huang[1], De-Zhen Guo[1], Yu-Peng Wang[1], Ya Cao[3], Jia Fan[1,4,5], Jian Zhou[1,4,5], Xin-Rong Yang[1]

[1]Department of Liver Surgery and Transplantation, Liver Cancer Institute, Zhongshan Hospital, Fudan University; Key Laboratory of Carcinogenesis and Cancer Invasion (Fudan University), Ministry of Education; Shanghai Key Laboratory of Organ Transplantation, Zhongshan Hospital, Fudan University, Shanghai, China; [2]Department of General Surgery, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; [3]Cancer Research Institute, Central South University; Key Laboratory of Carcinogenesis and Cancer Invasion, Ministry of Education, Changsha, China; [4]Institute of Biomedical Sciences, Fudan University, Shanghai, China; [5]State Key Laboratory of Genetic Engineering, Fudan University, Shanghai, China

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[#]These authors contributed equally to this work.

Correspondence to: Xin-Rong Yang, MD, PhD; Jian Zhou, MD, PhD. Department of Liver Surgery and Transplantation, Liver Cancer Institute, Zhongshan Hospital, Fudan University, 136 Yixueyuan Road, Shanghai 200032, China.

Email: yang.xinrong@zs-hospital.sh.cn; zhou.jian@zs-hospital.sh.cn.

Background: Hepatectomy for huge hepatocellular carcinoma (HCC) (diameter ≥10 cm) is characterized by high mortality. This study aimed to establish a preoperative model to evaluate the risk of postoperative 90-day mortality for huge HCC patients.

Methods: We retrospectively enrolled 1,127 consecutive patients and prospectively enrolled 93 patients with huge HCC who underwent hepatectomy (training cohort, n=798; validation cohort, n=329; prospective cohort, n=93) in our institute. Based on independent preoperative predictors of 90-day mortality, we established a logistic regression model and visualized the model by nomogram.

Results: The 90-day mortality rates were 9.6%, 9.2%, and 10.9% in the training, validation, and prospective cohort. The α-fetoprotein (AFP) level, the prealbumin levels, and the presence of portal vein tumor thrombosis (PVTT) were preoperative independent predictors of 90-day mortality. A logistic regression model, AFP-prealbumin-PVTT score (APP score), was subsequently established and showed good performance in predicting 90-day mortality (training cohort, AUC =0.87; validation cohort, AUC =0.91; prospective cohort, AUC =0.93). Using a cut-off of –1.96, the model could stratify patients into low risk (≤–1.96) and high risk (>–1.96) with different 90-day mortality rates (~30% *vs.* ~2%). Furthermore, the predictive performance for 90-day mortality and overall survival was significantly superior to the Child-Pugh score, the model of end-stage liver disease (MELD) score, and the albumin-bilirubin (ALBI) score.

Conclusions: The APP score can precisely predict postoperative 90-day mortality as well as long-term survival for patients with huge HCC, assisting physician selection of suitable candidates for liver resection and improving the safety and efficacy of surgical treatment.

Keywords: Hepatectomy; huge hepatocellular carcinoma; 90-day mortality; prediction

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Introduction

Hepatocellular carcinoma (HCC) is one of the most prevalent malignancies and the second-leading cause of cancer-related deaths worldwide (1). Huge HCC is defined as HCC with a maximum tumor diameter greater than 10 cm and accounts for 10–20% of newly developed HCC cases (2). Surgical resection is considered a potential curative option for these patients and has been reported to provide a favorable overall survival (OS) in some patients (3,4). Although mortality after liver resection has been dramatically reduced in recent years with advances in surgical techniques and perioperative management (5-7), the postoperative mortality rate of hepatectomy for huge HCC, ranging from 2.7% to 18.1%, is still much higher than the routine liver resection (~1%) (8-10). As the natural history for a patient with advanced HCC is approximately 3–6 months after diagnosis (11), death within 3 months after hepatectomy is regarded as "futile liver resection," which should be avoided because it provides no survival benefit (8,12). Therefore, there is an urgent need to identify patients with huge HCC who have a high risk of postoperative 90-day mortality to optimize the candidate selection for liver resection and avoid futile liver resection (12).

Several models, such as the Child-Pugh score (13), the model for end-stage liver disease (MELD) score (14,15), and the albumin-bilirubin (ALBI) score (16) have been widely applied to evaluate the risk of postoperative outcome for patients with HCC (17-22). However, none of these models were specifically developed to predict the posthepatectomy mortality for HCC. Some other established prediction models are based on intraoperative data or postoperative liver function (23-27), which could not help preoperative decision-making. Furthermore, some preoperative models include patients undergoing hepatectomy for various indications, making the model lack representativeness of a particular patient group (28). Currently, a model to preoperatively evaluate postoperative 90-day mortality in patients with huge HCC is still lacking.

In this study, we aimed to identify the preoperative available parameters that independently influenced postoperative 90-day mortality in patients with huge HCC undergoing hepatectomy and to develop a simple, preoperative risk assessment model for precisely predicting postoperative 90-day mortality for those patients with huge HCC, which may help surgeon select suitable candidates to improve the safety and efficacy for liver resection. We present the following article following the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-7842).

Methods

Patient enrollment

A total of 1,127 consecutive huge HCC patients who underwent liver resection were retrospectively enrolled and divided into two independent cohorts (training cohort, n=798, January 2007 to December 2012 and validation cohort, n=329, January 2013 to December 2014). Furthermore, another independent cohort (prospective cohort, n=93) was prospectively enrolled between March 2019 and March 2020. The inclusion criteria were as follows: (I) liver resection in Zhongshan hospital with complete removal of the tumor; (II) HCC with a maximum tumor diameter greater than or equal to 10 cm. The exclusion criteria were as follows: (I) preoperative distant metastasis; (II) multi-organ removal (except for cholecystectomy).

Ethical approval for the use of patient information was obtained from the Zhongshan Hospital Research Ethics Committee (No. B2021-017R). Informed consent was obtained from all patients. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Perioperative management and follow-up

Contrast-enhanced magnetic resonance imaging (MRI) or computed tomography (CT) were routinely performed preoperatively. Solid lesions within the portal vein observed during all phases of intravenous contrast-enhanced CT or MRI, especially with the enhancement of contrast during the arterial phase and washout during the portal venous phase of the procedure, were regarded as portal vein tumor thrombosis (PVTT) (29). The spleen over 9.76 cm in length by the preoperative radiological finding was regarded as splenomegaly (30). Portal hypertension was defined as the presence of either esophageal varices or splenomegaly with a platelet count less than 10^9/L (31). CT volumetry was used to evaluate the volume of the future liver remnant (FLR) in cases with an apparent inadequate FLR. The estimated standard liver volume (SLV) was calculated based on the Urata formula (32). A hepatectomy was only recommended when patients had sufficient future liver remnant. For the patients with a background of liver cirrhosis diagnosed by the MRI, an FLR/SLV ratio >40% was considered to be

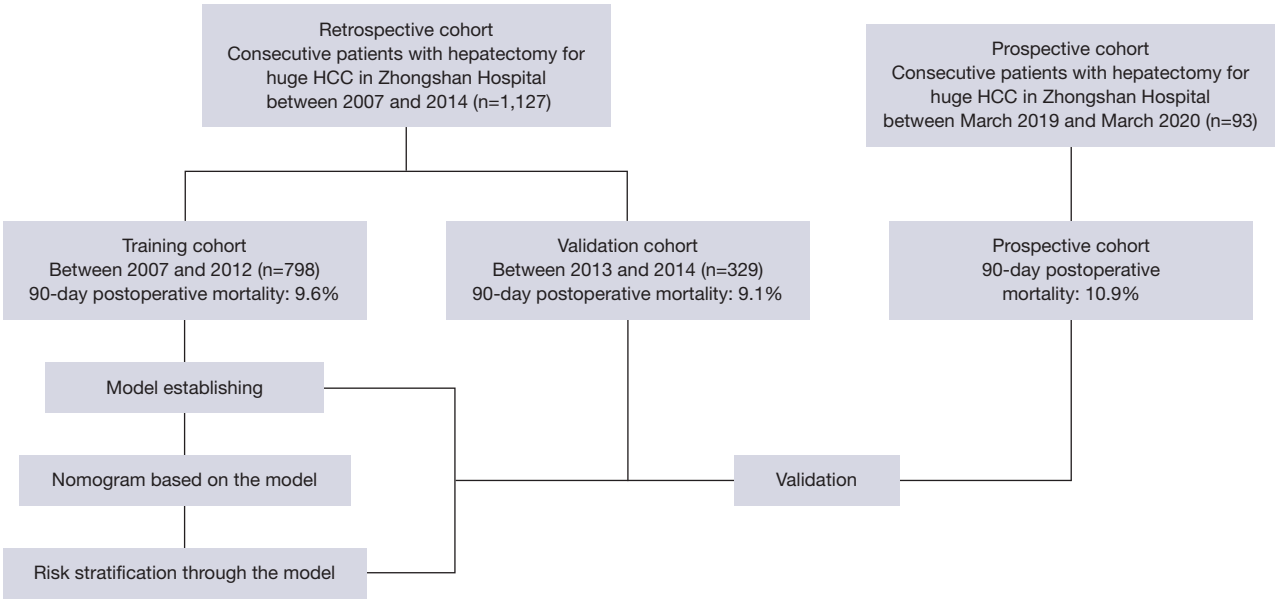

Figure 1 Flow chart for the study design and patients enrollment.

safe for operation, whereas a ratio >30% was considered sufficient in the patients without liver cirrhosis (33). The major hepatectomy was defined as liver resection with more than 3 segments (34). The preoperative Child-Pugh (13), MELD (14), and ALBI (16) scores were also calculated as previously described.

After surgery, regular hepatoprotective dosages and albumin supplementation were administered. Antiviral agents (entecavir) were recommended for all patients with hepatitis B infection. Postoperative complications were categorized according to the Clavien-Dindo Classification (35). Postoperative follow-up examinations were performed monthly for 3 months and every 3 months thereafter. Patients with suitable liver function were recommended to undergo one to three courses of adjuvant transcatheter arterial chemoembolization (TACE; with doxorubicin, cisplatin, 5-fluorouracil, and iodized oil) (36); sorafenib was recommended for patients with PVTT or microvascular invasion. The follow-up was terminated in April 2019 for two retrospective cohorts and in June 2020 for the prospective cohort. The main end-point of this study was 90-day mortality.

Statistical analysis

Statistical analyses were performed using R software (version 3.6.1; https://www.r-project.org/) and GraphPad Prism software (version 7.0; GraphPad Software Inc., San Diego, CA, USA). Categorical variables were compared using the χ^2 test or Fisher's exact test. A nomogram was created based on the results of the multivariate logistic analysis using the rms package. The model was validated using the bootstrap resampling technique in the training and validation cohort. Comparisons of the newly developed model with Child-Pugh, MELD, and ALBI scores were carried out using the receiver operating characteristic curve (ROC curve) and the area under the curve (AUC). The ROC curve and the AUC were derived to assess the performance of the model in the validation and prospective cohort. OS was compared using the log-rank test, and risk factors for survival were identified using the Cox regression method. A two-tailed P value of less than 0.05 was considered significant.

Results

Patient demographics

A total of 1,127 patients were enrolled in this study and divided into the training cohort (n=798) and the validation cohort (n=329). Meanwhile, an additional cohort of 93 patients with huge HCC resection (prospective cohort) was prospectively enrolled for further validation. The study design is shown in *Figure 1*. The characteristics of the training, validation, and prospective cohorts are summarized

in *Table 1* and Table S1. The postoperative 90-day mortality rate was 9.6% (77/798) in the training cohort, 9.2% (30/329) in the validation cohort, and 10.9% (10/93) in the prospective cohort, respectively. All enrolled patients were categorized according to the Child-Pugh A classification. The majority of patients had hepatitis B: 76.1% in the training cohort, 77.8% in the validation cohort, and 73.1% in the prospective cohort.

Preoperative risk factors for postoperative 90-day mortality in the training cohort

The preoperative available clinical indices were used to build up the model. The univariate logistic regression analysis of the training cohort showed that the maximum tumor diameter, PVTT status, prealbumin level, platelet count, total bilirubin level, albumin level, prothrombin time, AFP level, the extent of tumor differentiation, and portal hypertension were statistically significant (*Table 2*). Additionally, the logistic regression analysis revealed that PVTT status was associated with serum prealbumin levels (P=0.010). We included all parameters with a P value less than 0.1 in the multivariate logistic regression analysis, which revealed that preoperative AFP level, prealbumin level, and PVTT status were independent predictors of 90-day mortality after surgery (*Table 3*).

Construction of the APP score for predicting postoperative 90-day mortality

A logistic regression model used these three parameters (prealbumin level, the presence or absence of PVTT, and AFP level) was constructed and derived a linear predictor equation as follows: Linear predictor = (PVTT) × prealbumin × 17.17 + AFP × 2.945 × 10^{-5} + prealbumin × (–26.23), where prealbumin is in g/L, AFP is in ng/mL, and PVTT was assigned a "1" when present or "0" when absent, as determined by preoperative radiological findings. The linear predictor model was named "the AFP-prealbumin-PVTT score (APP score)" and visualized using a nomogram (*Figure 2*).

The AUC of the APP score in predicting 90-day mortality was 0.87 (95% CI, 0.84–0.91) in the training cohort, which was significantly higher than the AUC of the Child–Pugh score (0.55; 95% CI, 0.48–0.62, P<0.001), the MELD score (0.64; 95% CI, 0.57–0.70, P<0.001), and the ALBI score (0.64; 95% CI, 0.57–0.70, P<0.001) (*Figure 3A*). Meanwhile, the optimal cut–off value for the APP score was proposed to be –1.96 using the maximum Youden index, with a sensitivity of 80.5% and a specificity of 80.8% in the training cohort (*Figure 3A*). According to this cut-off value, the APP score could stratify patients in the training cohort into two risk groups for 90-day mortality: low risk (≤–1.96, n=598) and high risk (>–1.96, n=200). The high-risk group had a significantly higher 90-day mortality rate than the low-risk group (31.0% *vs.* 2.5%, P<0.001, *Figure 3B*).

Validation of the APP score in predicting 90-day mortality after hepatectomy

The performance of the APP score in predicting postoperative 90-day mortality was further evaluated. The AUC of the APP score was 0.91 (95% CI, 0.86–0.95) in the validation cohort, which was also superior to the Child-Pugh score (0.59; 95% CI, 0.48–0.71; P<0.001), the MELD score (0.61; 95% CI, 0.50–0.73; P<0.001), and the ALBI score (0.66; 95% CI, 0.56–0.77; P<0.001) (*Figure 3C*). The higher incidence of 90-day mortality was also observed in the high-risk group compared to the low-risk group (validation cohort: 32.0% *vs.* 2.4%, P<0.001; *Figure 3D*). In the prospective cohort, the APP score (AUC =0.93, 95% CI, 0.86–1.00) showed a consistent predictive ability with a higher AUC than the Child-Pugh score (0.53; 95% CI, 0.33–0.73; P<0.001), the MELD score (0.58; 95% CI, 0.41–0.74; P<0.001) and the ALBI score (0.76; 95% CI, 0.58–0.93; P=0.037) (*Figure 3E*). Using the same cut-off value of –1.96, the sensitivity and the specificity of the APP score in predicting 90-day mortality were 80.0% and 82.9% in the validation cohort, and 81.6% and 90.0% in the prospective cohort, respectively. In the prospective cohort, the 90-day mortality rate in the high-risk group was also higher than the low-risk group (37.5% *vs.* 1.4%, P<0.001; *Figure 3F*).

Nevertheless, calibration using bootstrap sampling showed good agreement among the apparent curve, the bias-corrected curve, and the ideal curve in the training and validation cohort (Figure S1). The subgroup analysis in the training and validation cohort indicated that the patients with a higher APP score always had a higher mortality rate regardless of the liver status (cirrhosis), preoperative treatment (TACE), and surgical strategy (anatomical or non-anatomical hepatectomy) (Table S2).

Performance of the APP score in predicting long-term survival for patients with huge HCC after hepatectomy

The median follow-ups were 70.3 months in the training

Table 1 Clinicopathologic characteristics of the training, validation, and prospective cohorts

Characteristics	Training cohort (n=798)	Validation cohort (n=329)	P value	Prospective cohort (n=93)
Gender				
Female	99	49	0.304	15
Male	699	280		78
Age (years)	49.8±11.8	53.1±12.1	<0.001*	54.3±12.3
Tumor diameter (cm)	12.6±2.9	13.2±4.4	0.011*	12.7±2.3
Tumor number				
Single	650	231	<0.001*	73
Multiple	148	98		20
Liver cirrhosis				
No	585	236	0.278	68
Yes	213	93		25
PVTT[§]				
No	618	272	0.060	76
Yes	180	57		17
Splenomegaly				
No	637	266	0.695	77
Yes	161	63		16
Portal Hypertension				
No	738	305	0.896	86
Yes	60	24		7
AFP (ng/mL)	15,778.0±23,407.5	13,648.8±23,052.6	0.163	14,340.2±23,297.5
Prealbumin (g/L)	0.18±0.06	0.18±0.06	0.749	0.17±0.06
HBsAg				
Negative	191	73	0.581	25
Positive	607	256		68
Preoperative TACE				
No	695	296	0.178	83
Yes	103	33		10
Liver resection type				
Non-anatomical	433	177	0.888	46
Anatomical	365	152		47
Major hepatectomy				
No	128	40	0.096	10
Yes	670	289		83

Table 1 *(continued)*

Table 1 *(continued)*

Characteristics	Training cohort (n=798)	Validation cohort (n=329)	P value	Prospective cohort (n=93)
Clavien-Dindo classification				
None or < III	663	280	0.403	80
≥ III	135	49		13
MELD score	2.91±3.06	3.29±2.93	0.058	4.39±2.62
Child-Pugh score	5.11±0.31	5.16±0.37	0.023*	5.02±0.16
ALBI score	–2.65±0.37	–2.63±0.35	0.451	–2.85±0.37

§, among all the patients, 3 patients (2 in the training cohort and 1 in the validation cohort) had histologically proved tumor thrombosis in small branches of portal vein near the tumor (Vp1) but could not be detected by preoperative imaging examinations. *, P<0.05. These 3 patients were not included in the PVTT group. PVTT, portal vein tumor thrombosis; AFP, α-fetoprotein; HBsAg, hepatitis B surface antigen; MELD, model of end-stage liver disease; ALBI, albumin-bilirubin.

Table 2 Univariate logistic regression analysis to identify the risk factors for the postoperative 90-day mortality for huge HCC

Clinical feature	OR	95% CI	P value
Gender (male: female)	1.246	0.580–2.675	0.573
Age (year)	0.980	0.961–0.999	0.053
HBsAg (positive: negative)	1.335	0.741–2.406	0.337
Diabetes mellitus (yes: no)	0.770	0.100–10.32	0.986
Tumor diameter (cm)	1.084	1.012–1.161	0.021*
Tumor number (multiple: single)	1.025	0.933–1.126	0.606
PVTT (yes: no)	9.636	5.764–16.109	<0.001*
GGT (U/L)	1.001	0.999–1.003	0.275
Prealbumin (g/L)	<0.001	0.000–0.001	<0.001*
ALT (U/L)	1.000	0.999–1.001	0.890
Platelet count (10^9/L)	0.997	0.993–1.000	0.045
Total bilirubin (μmol/L)	1.02	1.004–1.036	0.013*
Albumin (g/L)	0.941	0.888–0.997	0.039*
Prothrombin time (s)	1.455	1.210–1.750	<0.001*
Creatine (μmol/L)	1.007	0.996–1.018	0.205
AFP (ng/mL)	1.000	1.000–1.001	<0.001*
Tumor differentiation (III–IV: I–II)	2.592	1.610–4.171	<0.001*
Splenomegaly (yes: no)	1.197	0.607–2.360	0.604
Portal hypertension (yes: no)	3.446	1.854–6.404	<0.001*
Major hepatectomy (yes: no)	1.240	0.430–3.600	0.690
Anatomical hepatectomy (yes: no)	1.388	0.931–2.069	0.108

*, P<0.05. HCC, hepatocellular carcinoma; 95% CI, 95% confidential interval; HBsAg, hepatitis B surface antigen; PVTT, portal vein tumor thrombosis; GGT, γ-glutamyl transpeptidase; ALT, Alanine Aminotransferase; AFP, α-fetoprotein.

Table 3 Multivariate logistic regression analysis to identify the risk factors for the postoperative 90-day mortality for huge HCC

Clinical feature	OR	95% CI	P value
AFP (ng/mL)	1.000	1.000–1.001	<0.001*
PVTT (yes: no)	0.709	0.010–4.747	0.453
Prealbumin (g/L)	<0.001	0.000–0.004	<0.001*
Prealbumin × PVTT	2.320×10^{7}	$42.72–1.26\times10^{13}$	0.001*
AFP × PVTT	1.000	1.000–1.000	0.756
AFP × prealbumin	1.000	1.000–1.000	0.960
Age (year)	0.989	0.965–1.014	0.394
Tumor diameter (cm)	1.021	0.940–1.110	0.620
Platelet count (10^9/L)	0.999	0.996–1.003	0.783
Total bilirubin (μmol/L)	1.009	0.995–1.024	0.224
Albumin (g/L)	0.974	0.908–1.045	0.459
Prothrombin time (s)	1.278	0.999–1.641	0.055
Tumor differentiation (III–IV: I–II)	1.650	0.946–2.878	0.078
Portal hypertension (yes: no)	1.624	0.993–5.470	0.052

*, P<0.05. HCC, hepatocellular carcinoma; 95% CI, 95% confidential interval; PVTT, portal vein tumor thrombosis; AFP, α-fetoprotein.

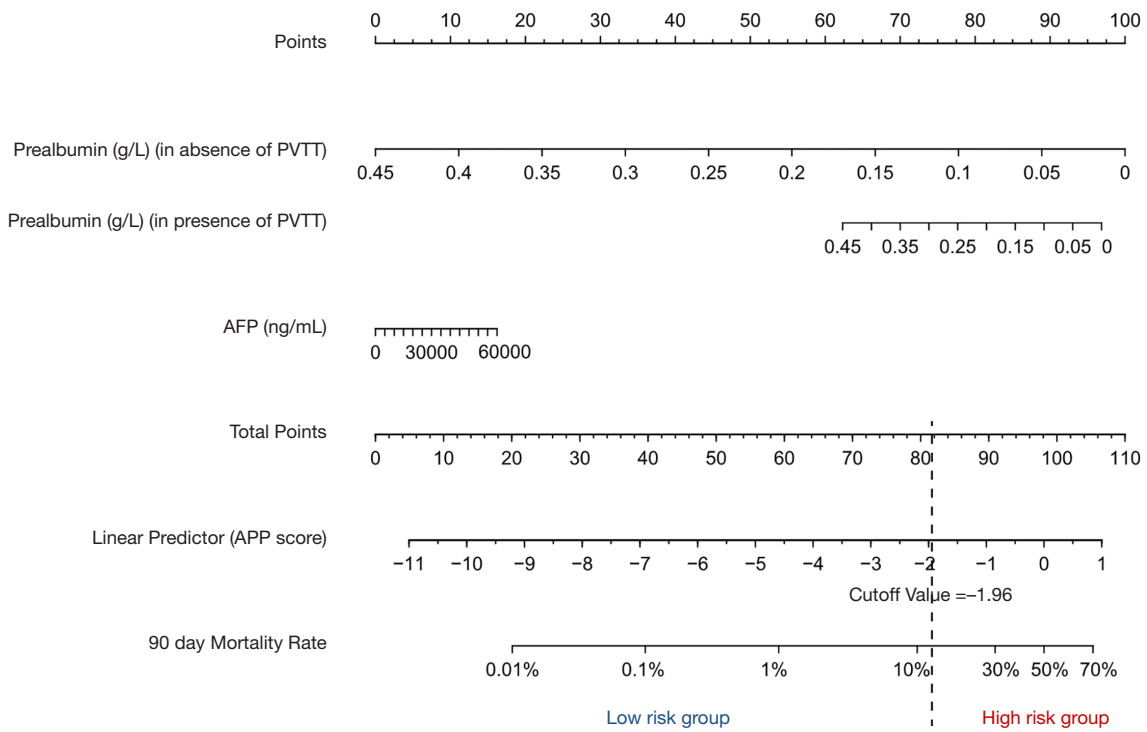

Figure 2 Nomogram for predicting the postoperative 90-day mortality for huge HCC patients. The points of each variable in rows 2 to 4 are added up to the total points presented on the scale in row 5, which corresponds to the linear predictor in row 6 and the 90-day mortality rate in row 7. We named the linear predictor as the AFP-Prealbumin-PVTT score (the APP score), and the patients were stratified into low-risk (≤−1.96) and high risk (>−1.96).

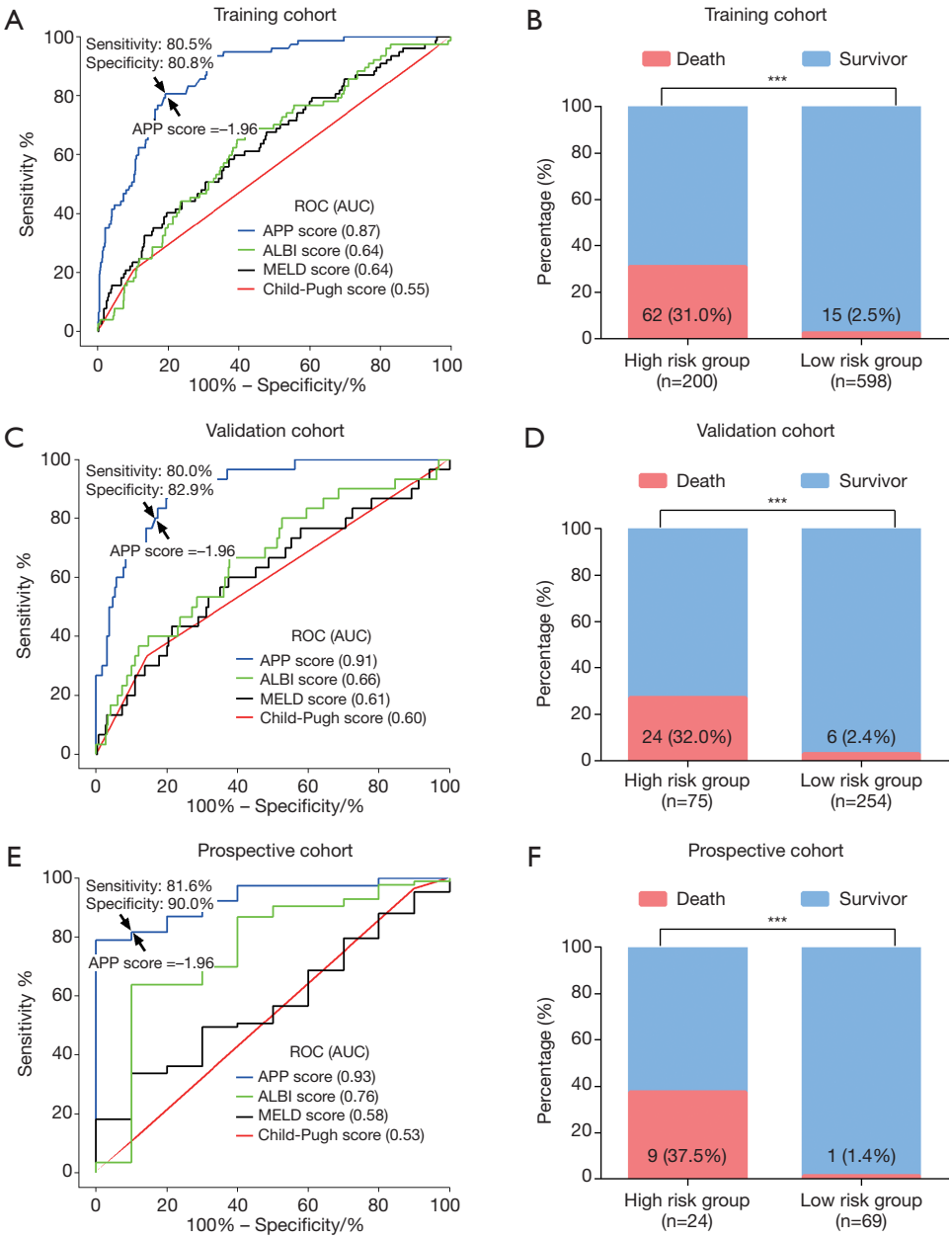

Figure 3 The predictive performance of the APP score for the postoperative 90-day mortality for huge HCC. (A) In the training cohort, the AUC of APP score was significantly larger than the ALBI, MELD score, and Child-Pugh score (all P<0.001). The sensitivity of 80.5% and the specificity of 80.8% was achieved when using the cutoff (APP =–1.96, arrow) derived from the maximum of Youden index. (B) The patients in the high-risk group (APP score >–1.96) had a significantly higher 90-day mortality rate than the low-risk group (APP score ≤–1.96) in the training cohort (31.0% *vs.* 2.5%, P<0.001). (C) In the validation cohort, the AUC of APP score was significantly higher than the ALBI score, MELD score and Child-Pugh score (all P<0.001). With the cutoff derived from the training cohort (arrow), the sensitivity was 80.0% and the specificity was 82.9%. (D) The patients in the high-risk group (APP score >–1.96) had a significant higher 90-day mortality rate than the low-risk group (APP score ≤–1.96) in the validation cohort, (32.0% *vs.* 2.4%, P<0.001). (E) In the prospective cohort, the AUC of APP score was significantly higher than the ALBI score, MELD score and Child-Pugh score (all P<0.001). With the cutoff derived from the training cohort (arrow), the sensitivity was 81.6% and the specificity was 90.0%. (F) The patients in the high-risk group (APP score >–1.96) had a significantly higher 90-day mortality rate than the low-risk group (APP score ≤–1.96) in the prospective cohort (37.5% *vs.* 1.4%, P<0.001). ***, P<0.001.

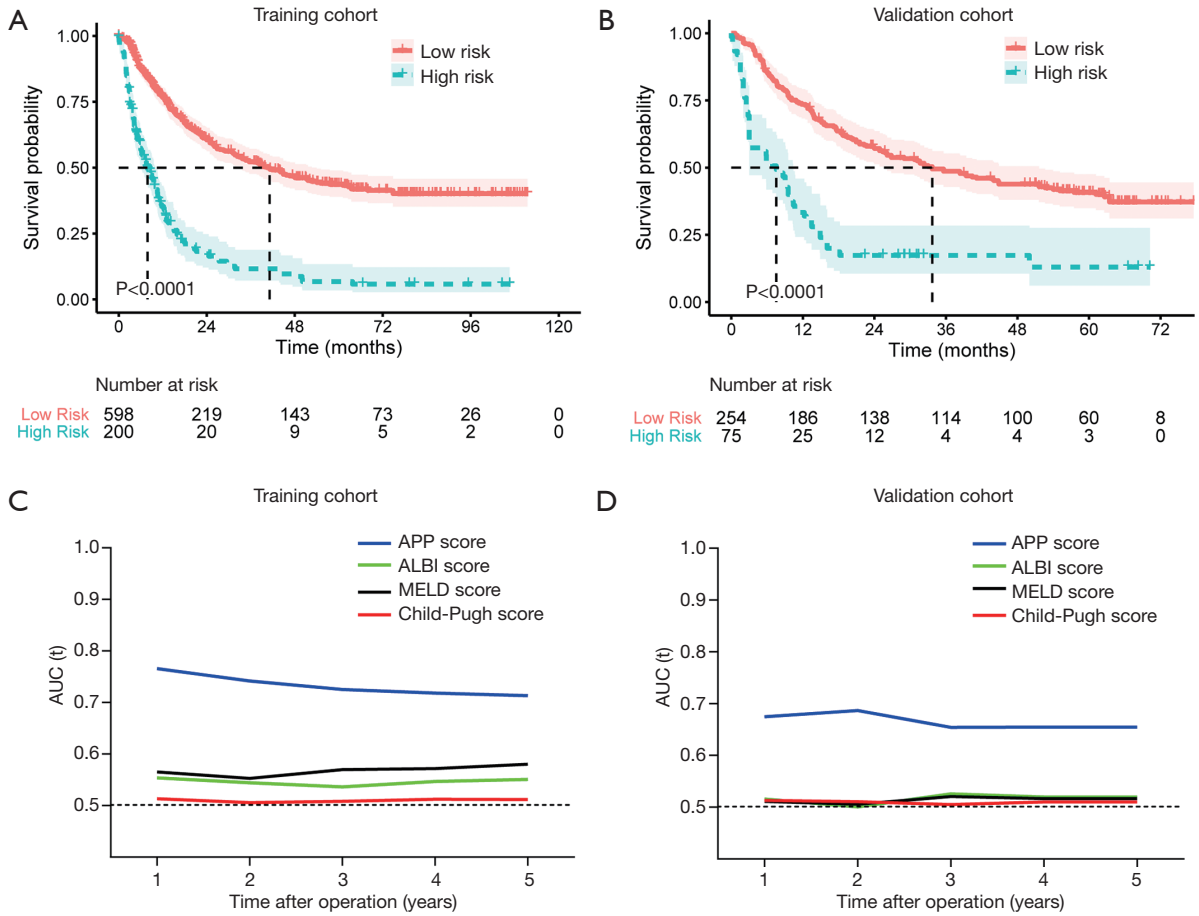

Figure 4 Performance of the nomogram in predicting overall survival for huge HCC undergoing resection. The overall survival (OS) of the patients in the high-risk group (APP score >−1.96) was significantly longer than the low-risk group (APP score ≤−1.96) in both (A) the training cohort (P<0.001), and (B) validation cohort (P<0.001). Time-dependent AUC showed the performance of the APP score, Child-Pugh score, MELD score and ALBI score in predicting OS in (C) the training cohort, and (D) the validation cohort. The AUC of APP score was significantly higher than the ALBI score, MELD score, and Child-Pugh score in predicting 1-, 2-, 3-, 4-, and 5-year OS in the two cohorts (all P<0.001).

cohort (interquartile range: 35.2–104.3 months) and 52.6 months in the validation cohort (interquartile range: 44.1–67.9). Using a threshold of −1.96, the APP score stratified patients into two separate groups with significantly different OS rates in training (median OS: 7.87 *vs.* 41.2 months) and validation cohort (median OS: 7.53 *vs.* 33.7 months) (*Figure 4A,B*). In the multivariate analysis, the APP score was identified as an independent prognostic factor for OS in both the training (HR =3.78, P<0.001) and validation cohorts (HR =2.54, P<0.001) (*Table 4*). In addition, the AUCs of the APP score in predicting OS were significantly higher than those of the Child-Pugh, MELD, and ALBI scores in both the training and validation cohorts (*Figure 4C,D*).

Discussion

Due to advances in surgical technique, preoperative evaluation, and perioperative management, surgical indications for huge HCC tumors have been expanded (7). However, there is still no consensus on the criteria to select patients with huge HCC for surgical treatment to avoid postoperative mortality (37). How to preoperatively evaluate the risk of postoperative 90-day mortality precisely is thus essential to further improve the safety and efficacy of the liver resection for huge HCC (8).

Table 4 Univariate and multivariate cox regression for the overall survival after the liver resection for huge HCC

Clinical Feature	Training cohort						Validation cohort					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Gender (male: female)	1.19	0.88–1.6	0.266				0.80	0.51–1.24	0.310			
Age (≥60: <60 years)	0.81	0.63–1.05	0.109				0.72	0.49–1.06	0.096			
Diameter (≥12: <12 cm)	1.24	1.02–1.51	0.034*	1.06	0.87–1.29	0.588	1.17	0.85–1.62	0.329			
Number (multiple: single)	1.38	1.1–1.72	0.005*	1.28	1.02–1.60	0.030*	1.59	1.14–2.21	0.006*	1.61	1.15–2.24	0.005*
HBsAg (positive: negative)	1.24	0.98–1.56	0.072				1.41	0.93–2.14	0.105			
Tumor differentiation (III–IV: I–II)	1.74	1.42–2.13	<0.001*	1.45	1.18–1.79	<0.001*	2.32	1.62–3.31	<0.001*	2.08	1.44–3.00	<0.001*
Microvascular invasion (yes: no)	2.20	1.78–2.74	<0.001*	1.62	1.29–2.03	<0.001*	1.99	1.36–2.92	<0.001*	1.58	1.07–2.35	0.023*
Cirrhosis (yes: no)	2.26	1.84–2.76	<0.001*	1.45	1.16–1.8	0.001*	1.22	0.86–1.72	0.26			
The APP score (high risk: low risk)	3.78	3.08–4.64	<0.001*	2.78	2.22–3.49	<0.001*	2.54	1.8–3.58	<0.001*	2.12	1.49–3.01	<0.001*

*, P<0.05. HCC, hepatocellular carcinoma; HR, hazard ratio; 95% CI, 95% confidential interval; AFP, α-fetoprotein; PVTT, portal vein tumor thrombosis.

In this study, three independent risk factors for postoperative 90-day mortality were identified for huge HCC patients: AFP levels, prealbumin levels, and PVTT status. A nomogram model (APP score) was constructed and validated using two independent cohorts to accurately estimate the risk of postoperative 90-day mortality for huge HCC patients before hepatectomy. Moreover, the APP score showed greater predictive value for 90-day mortality and long-term survival than the Child-Pugh, MELD, and ALBI scores. Derived from only three preoperatively available parameters, this nomogram-based model can be easily adapted by surgeons for patient selection and for optimizing treatment for patients with huge HCC in the future.

Postoperative liver failure and tumor recurrence were major contributors to 90-day mortality (38,39), the related preoperative factors were incorporated into the predictive model. Prealbumin levels were reported as an independent predictor of liver failure after hepatectomy (40). With a short half-life (<48 hours) and resistance to interference by extraneous supplements, serum prealbumin is a sensitive marker for liver function (41). AFP levels and PVTT status could reflect tumor status, which widely accepted that a high serum AFP level (42) and the presence of PVTT (43) indicate a poor prognosis for HCC patients. Moreover, the presence of PVTT makes liver resection more technique-demanding (44). For a patient with PVTT, hepatectomy is recommended to *en bloc* removal of the tumor thrombosis or to extract the tumor thrombus through the stump of a portal vein branch. Thus, massive intraoperative bleeding may result because both the portal and hepatic veins are vulnerable to injury during such procedures (45,46).

In the current study, the 90-day mortality in patients with huge HCC accompanied by PVTT was significantly higher than in patients without PVTT (22.8% *vs.* 4.1%, P<0.001). The mortality rates both in the patients with PVTT and without PVTT were consistent with findings from the previous literature (8,9,45,46). The proportion of patients with PVTT might play a major role in the total mortality rate. Intriguingly, an interaction between prealbumin and PVTT was observed in the logistic regression analysis. After analyzing the nomogram, the protective effect of the prealbumin seemed to be obliterated by the presence of PVTT. We speculate that the presence of PVTT could decrease liver blood flow and impair functional liver reserve, leading to a catabolic state and the synthesis of less prealbumin (47), which could explain the interaction between PVTT and prealbumin.

Our model performed well in predicting 90-day mortality for patients with huge HCC who underwent liver resection in the training and validation cohort. Moreover, an independent prospective cohort also confirmed our finding, indicating the robustness of the model. Because some well-established preoperative model had been proven to be effective in predicting the morbidity and mortality after liver resection for HCC (13-16,19,48,49), we compared the APP score with the Child-Pugh, MELD, and ALBI scores. We found that APP score showed improved accuracy compared with three conventional preoperative assessment models (Child-Pugh, MELD, and ALBI scores) in predicting postoperative 90-day mortality of huge HCC patients with liver resection. The poor performance of conventional models may be explained by the fact that they were not specifically designed to assess 90-day mortality or predict fatal tumor recurrence.

The APP score could stratify the candidates of liver resection for huge HCC into two different risk groups for postoperative 90-day mortality. Based on this risk evaluation, we can provide individualized treatment recommendations for these patients. In the whole retrospective cohort, the high-risk group (APP score >–1.96) consisted of only 24.4% of the entire retrospective cohort but accounted for 80.4% of those who died within 90 days after surgery (Figure S2). As postoperative 90-day mortality was greater than 30% in the high-risk group, we do not recommend liver resection for this subgroup; and targeted therapy, TACE, or radiotherapy may be better choices instead. A low incidence of 90-day mortality (~2%) was observed in the low-risk group, similar to that of patients with common HCC who underwent routine hepatectomy (50). Thus, patients with huge HCC categorized in the low-risk group (APP score ≤–1.96) can be considered suitable candidates for hepatectomy. Although the accuracy for predicting the risk of 90-day mortality by the APP score still needs further improvement, we believed that the classification of high- and low-risk groups could be helpful to avoid futile liver resection and choose optimized treatment.

There are a few limitations of this study. The predictive model requires further validation in a larger multicenter study. Meanwhile, our patients were all from China, and most had a history of HBV infection. Therefore, whether the APP score is applicable to patients of a Western nationality with huge HCC should be explored. In addition, indocyanine green tests and ultrasound elastography (FibroScan) were not routinely performed at our institute until 2014. Thus, we did not include these two parameters in the current study.

In conclusion, we established a novel predictive model (the APP score) to precisely predict the risk of postoperative 90-day mortality for patients with huge HCC undergoing hepatectomy. Furthermore, the predictive capability of the APP score in terms of 90-day mortality and OS is superior to the Child-Pugh score, the MELD score, and the ALBI score. The APP score may thus serve as a valuable tool for surgeons to identify suitable candidates for liver resection so as to improve the safety and efficacy of surgical treatments for huge HCC patients.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-7842). The authors have no conflicts of interest to declare. None of the author serves as a current Editorial Team member for this journal.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was

conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethical approval for the use of patient information was obtained from the Zhongshan Hospital Research Ethics Committee (No. B2021-017R). Informed consent was obtained from all patients.

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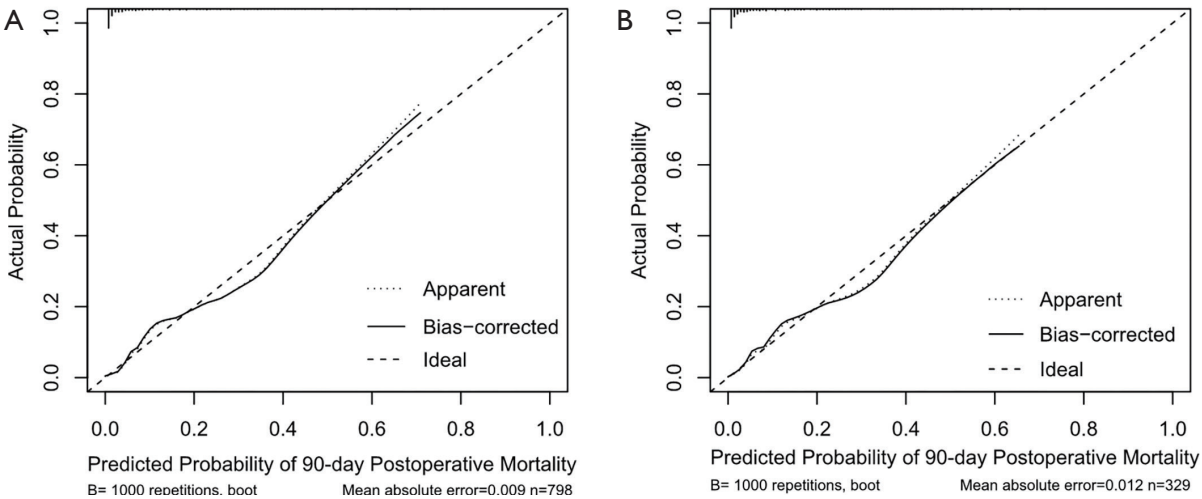

Figure S1 Calibration Curve by bootstrap method of the model. The apparent and the bias-corrected curves showed good agreement with the ideal curve in both (A) training cohort, and (B) validation cohort.

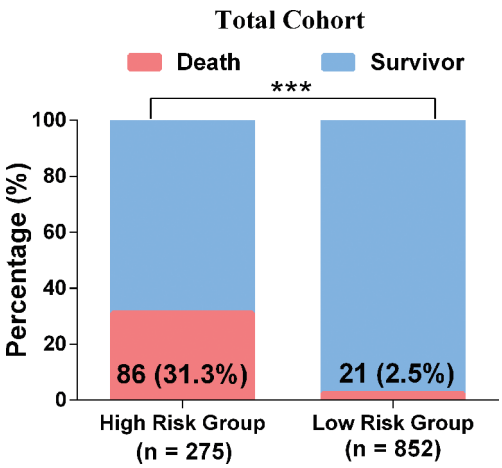

Figure S2 The predictive performance of the APP score for the postoperative 90-day mortality for huge HCC in the entire retrospective cohort. In the entire cohort, the higher incidence of 90-day mortality after hepatectomy was observed in the high-risk group (APP score >–1.96) compared with that of the low-risk group (APP score ≤–1.96), (31.3% *vs.* 2.5%, ***P<0.001).

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Table S1 Detailed clinicopathologic characteristics of the training, validation, and prospective cohorts

Characteristics	Training cohort (n=798)	Validation cohort (n=329)	P value	Prospective cohort (n=93)
Diabetes mellitus				
No	719	294	0.709	82
Yes	79	35		11
Hypertension				
No	744	306	0.892	85
Yes	54	23		8
CNLC staging				
I–II	596	258	0.184	71
III	202	71		22
BCLC staging				
A	494	189	0.164	59
B-C	304	140		34
ALT (U/L)	80.9±228.3	71.0±167.2	0.473	40.7±39.8
Platelet counts (10^9/L)	193.6±77.1	202.1±74.0	0.090	207.9±66.8
TB (μmol/L)	14.0±13.0	13.5±17.4	0.642	13.7±4.9
Albumin (g/L)	39.6±4.2	39.2±3.8	0.096	42.0±4.4
Prothrombin time (s)	12.3±1.2	12.2±1.0	0.093	12.1±0.9
Creatine (μmol/L)	71.6±17.5	71.9±15.8	0.799	73.8±13.7
Blood loss (mL)	473.1±525.0	536.1±597.7	0.059	480.1±621.0
intraoperative transfusion				
No	444	258	0.637	76
Yes	134	71		17
Tumor differentiation				
I–II	563	265	0.001*	67
III–IV	235	64		26
Microvascular Invasion				
No	318	110	0.051	26
Yes	480	219		67

CNLC staging, China liver cancer staging; BCLC staging, Barcelona clinic liver cancer staging; GGT, γ-glutamyl transpeptidase; ALT, alanine aminotransferase; TB, total bilirubin.

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Table S2 The subgroup analysis of APP score in the 90-day mortality in training and validation cohort

Cohort	AUC	95% CI	90-day mortality, n (%)	
			High risk group	Low risk group
Training cohort				
Cirrhosis				
Yes	0.800	0.737–0.863	42 (32.8)	0 (0.0)
No	0.860	0.804–0.917	20 (28.8)	15 (2.9)
Preoperative TACE				
Yes	0.965	0.927–1.00	5 (25.0)	0 (0.0)
No	0.863	0.824–0.902	57 (31.7)	15 (2.9)
Anatomical liver resection				
Yes	0.880	0.836–0.925	37 (35.9)	6 (2.3)
No	0.861	0.803–0.918	25 (25.7)	9 (2.7)
Validation cohort				
Cirrhosis				
Yes	0.885	0.797–0.973	8 (25.8)	1 (1.6)
No	0.918	0.863–0.973	16 (36.4)	5 (2.6)
Preoperative TACE				
Yes	0.906	0.805–1.00	1 (16.7)	0 (0.0)
No	0.905	0.857–0.954	23 (33.3)	6 (2.6)
Anatomical liver resection				
Yes	0.894	0.826–0.962	12 (27.3)	2 (1.9)
No	0.915	0.845–0.984	12 (38.7)	4 (2.7)

AUC, area under curve; 95% CI, 95% confidential interval; TACE, transcatheter arterial chemoembolization.

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