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Novel online calculator to predict reduced risk of early recurrence from adjuvant transarterial chemoembolisation for patients with hepatocellular carcinoma

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ABSTRACT

Background The role of adjuvant transarterial chemoembolisation (TACE) to reduce postoperative recurrence varies widely among patients undergoing hepatectomy with curative intent for hepatocellular carcinoma (HCC). Personalised predictive tool to select which patients may benefit from adjuvant TACE is lacking. This study aimed to develop and validate an online calculator for estimating the reduced risk of early recurrence from adjuvant TACE for patients with HCC.

Methods From a multi-institutional database, 2590 eligible patients undergoing curative-intent hepatectomy for HCC were enrolled, and randomly assigned to the training and validation cohorts. Independent predictors of early recurrence within 1 year of surgery were identified in the training cohort, and subsequently used to construct a model and corresponding prediction calculator. The predictive performance of the model was validated using concordance indexes (C-indexes) and calibration curves, and compared with conventional HCC staging systems. The reduced risk of early recurrence when receiving adjuvant TACE was used to estimate the expected benefit from adjuvant TACE.

Results The prediction model was developed by integrating eight factors that were independently associated with risk of early recurrence: alpha-fetoprotein level, maximum tumour size, tumour number, macrovascular and microvascular invasion, satellite nodules, resection margin and adjuvant TACE. The model demonstrated good calibration and discrimination in the training and validation cohorts (C-indexes: 0.799 and 0.778, respectively), and performed better among the whole cohort than four conventional HCC staging systems (C-indexes: 0.797 vs 0.562–0.673, all p<0.001). An online calculator was built to estimate the reduced risk of early recurrence from adjuvant TACE for patients with resected HCC.

Conclusions The proposed calculator can be adopted to assist decision-making for clinicians and patients to determine which patients with resected HCC can significantly benefit from adjuvant TACE.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous studies have indicated that adjuvant transarterial chemoembolisation (TACE) may improve long-term survival in certain subgroups of patients with hepatocellular carcinoma (HCC) after hepatectomy.

⇒ However, these studies did not provide personalised risk assessment or net benefit estimation for individual patients, highlighting the need for a more refined prediction model.

WHAT THIS STUDY ADDS

⇒ This study developed a risk prediction model incorporating eight independent factors associated with early recurrence after hepatectomy for HCC, demonstrating good predictive accuracy and discrimination.

⇒ The model outperformed four commonly used conventional HCC staging systems and facilitated the development of an online calculator to estimate individual patient's reduced risk of early recurrence using adjuvant TACE.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The study's findings may assist clinicians in deciding whether to use adjuvant TACE after hepatectomy for HCC, potentially improving patient outcomes.

⇒ Further research should validate the model with larger cohorts or those from other centres to assess its broader applicability.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most commonly diagnosed cancer of the liver and the fourth leading cause of cancer-related mortality worldwide, with China accounting for over half of the global annual cases and deaths.[1] Hepatectomy is the standard

curative-intent treatment option for appropriately selected patients with localised HCC.[2] However, the high rate of postoperative recurrence, especially early recurrence within the first year after surgery that is most likely due to occult micrometastasis from the original tumour, causes many patients to have a poor prognosis and a high incidence of cancer-specific death.[3 4] Given that survival among patients with recurrence is markedly worse than patients without recurrence, there has been considerable interest in various neoadjuvant and adjuvant treatment approaches to prevent early recurrence following hepatectomy.[5–8] None of these treatment modalities have been widely adopted, however, and none are currently recommended by international guidelines.[9–11] Identification of specific subsets of patients with HCC who are at highest risk of recurrence, and who might preferentially benefit from adjuvant treatment to reduce recurrence, particularly for early recurrence within a short period after surgery, has been a topic of interest.[9 12 13]

Transarterial chemoembolisation (TACE) performed 4–8 weeks after hepatectomy is an adjuvant treatment that has been used to reduce risks of postoperative recurrence and improve long-term prognosis.[14–16] Theoretically, adjuvant TACE can eliminate occult micrometastasis related to the original tumour, or residual tumours left after surgery, thereby preventing early recurrence after surgery.[14 15] However, the impact that adjuvant TACE may play in preventing posthepatectomy recurrence remains controversial. Several single-centre randomised controlled trials (RCTs) reported no benefit, or even decreased survival, using adjuvant TACE.[16–22] These disappointing results may be related to poor selection criteria. To this point, only a recent comprehensive review on adjuvant TACE suggested that patients at high risks of recurrence benefited from adjuvant TACE.[23]

Recently, there has been increasing interest in the development of cancer risk prediction models.[24–26] These models can act as useful decision-making tools in the real-world clinical setting. In particular, such tools may be more reliable than personal clinical judgement about whether any given individual may benefit from adjuvant therapy. Therefore, the goal of the current study was to develop a prediction tool to identify patients with HCC at high risks of early recurrence after curative hepatectomy. In addition, we sought to estimate the degree of risk reduction for early recurrence based on adjuvant TACE utilisation at the individual patient level. To accomplish this goal, we developed an internet browser-based decision calculator to provide clinicians an easy aid to help in the decision-making process about adjuvant TACE after hepatectomy for HCC.

MATERIALS AND METHODS

Study population

Data on patients who underwent hepatectomy for HCC between January 2010 and December 2020 obtained from a prospectively collected databases of 10 Chinese hospitals were retrospectively analysed. The diagnosis of HCC was confirmed by postoperative pathological examination. The exclusion criteria included patients who (1) were under 18 years of age; (2) had recurrent HCC; (3) received preoperative or other postoperative antitumour therapies including radiotherapy and systemic therapy; (4) underwent hepatectomy with microscopically (R1 resection) or grossly positive margins (R2 resection); (5) had confirmed or highly suspicious residual intrahepatic tumours during the angiography of adjuvant TACE; (6) died within 90 days of surgery; (7) had missing data on essential prognostic variables; (8) were lost to follow-up or non-cancer-specific death within 1 year after surgery. Curative hepatectomy was defined as complete resection of all tumour nodules with microscopically clear margins in the postoperative specimen (R0 resection), and had no residual tumour nodules during the first follow-up after surgery. All patients were randomly assigned to the training and validation cohorts, at a ratio of 7:3, respectively.

Data collection

Baseline characteristics and operative variables were recorded. Baseline characteristics included age, sex, American Society of Anesthesiologists score, obesity, diabetes mellitus, aetiology of liver disease ((hepatitis B virus (HBV), hepatitis C virus (HCV)), cirrhosis, Child-Pugh grading, preoperative alanine aminotransferase, aspartate transaminase and alpha-fetoprotein (AFP) level; tumour factors included maximum tumour size, tumour number, macrovascular invasion, microvascular invasion, satellite nodules, tumour differentiation and tumour encapsulation. Obesity was diagnosed when the body mass index was 30 or higher. Satellite nodules were defined as tumours <1 cm in diameter and were located <1 cm from main tumour. Operative variables included intraoperative blood loss, intraoperative blood transfusion, extent of hepatectomy (major or minor), type of hepatectomy (anatomical or non-anatomical) and width of resections margin. Major hepatectomy was defined as resection of three or more Couinaud segments, while minor hepatectomy was fewer than three Couinaud segments. Anatomical resection was defined by the Brisbane 2000 system, whereas non-anatomical resection included limited or wedge resections.

Adjuvant TACE

The decision to use adjuvant TACE was determined by the individual treating team after consultation with the patient. Given that adjuvant TACE was not standard of care, TACE was recommended and discussed with patients based on a wide array of factors with a goal to improve long-term survival outcomes. Adjuvant TACE was performed within 4~8 weeks after surgery if there were no contraindications to TACE. Generally, the contraindications of adjuvant TACE included poor hepatic dysfunction, uncorrectable coagulopathy and having postoperative major morbidity after HCC resection. A

Table 1 Comparisons of baseline characteristics, operative variables and long-term oncological outcomes between patients who received and did not receive adjuvant TACE in the training cohort

Variables	Total (n=1813)	With adjuvant TACE (n=559)	Without adjuvant TACE (n=1254)	P value
Age >60 years	376 (20.7)	103 (18.4)	273 (21.8)	0.105
Male sex	1597 (88.1)	493 (88.2)	1104 (88.0)	0.925
ASA score >2	217 (12.0)	57 (10.2)	160 (12.8)	0.121
Obesity	46 (2.5)	19 (3.4)	27 (2.2)	0.119
Diabetes mellitus	109 (6.0)	32 (5.7)	77 (6.1)	0.731
HBV (+)	1627 (89.7)	508 (90.9)	1119 (89.2)	0.287
HCV (+)	49 (2.7)	14 (2.5)	35 (2.8)	0.728
Cirrhosis	1367 (75.4)	409 (73.2)	958 (76.4)	0.140
Child-Pugh B	157 (8.7)	36 (6.7)	121 (9.5)	0.057
Preoperative ALT level (U/L)*	35.2 (24.8, 52.6)	42.5 (29.9, 61.3)	32.0 (23.0, 49.0)	0.161
Preoperative AST level (U/L)*	34.0 (25.0, 50.3)	36.4 (28.8, 58.3)	31.8 (24.0, 47.0)	0.130
Preoperative AFP level (ng/mL)				
<20	692 (38.2)	217 (38.8)	475 (37.9)	0.376
20–399	492 (27.1)	154 (27.5)	338 (27.0)	
400–999	166 (9.2)	58 (10.4)	108 (8.6)	
≥1000	463 (25.5)	130 (23.3)	333 (26.6)	
Maximum tumour size (cm)*	5.7±3.7	5.9±3.8	5.6±3.7	0.087
Tumour number				
1	1547 (85.3)	453 (81.0)	1094 (87.2)	0.002
2	142 (7.8)	58 (10.4)	84 (6.7)	
≥3	124 (6.8)	48 (8.6)	76 (6.1)	
Macrovascular invasion	62 (3.4)	31 (5.5)	31 (2.5)	0.001
Microvascular invasion	652 (36.0)	281 (50.3)	371 (29.6)	<0.001
Satellite nodules	321 (17.7)	113 (20.2)	208 (16.6)	0.062
Poor tumour differentiation	1016 (56.0)	444 (79.4)	572 (45.6)	<0.001
Incomplete tumour encapsulation	832 (45.9)	322 (57.6)	510 (40.7)	<0.001
Intraoperative blood loss >400 mL	654 (36.1)	198 (35.4)	456 (36.4)	0.699
Intraoperative blood transfusion	304 (16.8)	89 (15.9)	215 (17.1)	0.519
Major hepatectomy	308 (17.0)	130 (23.3)	178 (14.2)	<0.001
Anatomical resection	446 (24.6)	141 (25.2)	305 (24.3)	0.681
Resection margin <1 cm	816 (45.0)	178 (31.8)	638 (50.9)	<0.001
Period of follow-up, months*	53.3 (37.1, 72.9)	64.0 (45.0, 109.8)	51.0 (30.0, 64.4)	<0.001
Recurrence during the follow-up	999 (55.1)	337 (60.3)	662 (52.8)	0.003
Early recurrence	402 (22.2)	87 (15.6)	315 (25.1)	<0.001
Late recurrence	597 (32.9)	250 (44.7)	347 (27.7)	
Mortality during the follow-up	770 (42.5)	258 (46.2)	512 (40.8)	0.034
Median CSS, 95% CI (months)	109.8 (101.8 to 117.8)	78.0 (69.2 to 86.8)	53.4 (43.1 to 63.7)	<0.001
1-year CSS rate, %	93.5	98.2	91.5	
3-year CSS rate, %	77.8	83.5	75.0	
5-year CSS rate, %	67.1	72.1	65.0	

*Values expressed as mean±SD or median (IQR).
AFP, alpha-fetoprotein; ALT, alanine aminotransferase; ASA, American Society of Anesthesiologists; AST, aspartate transaminase; CSS, cancer-specific survival; HBV, hepatitis B virus; HCV, hepatitis C virus; TACE, transarterial chemoembolisation.

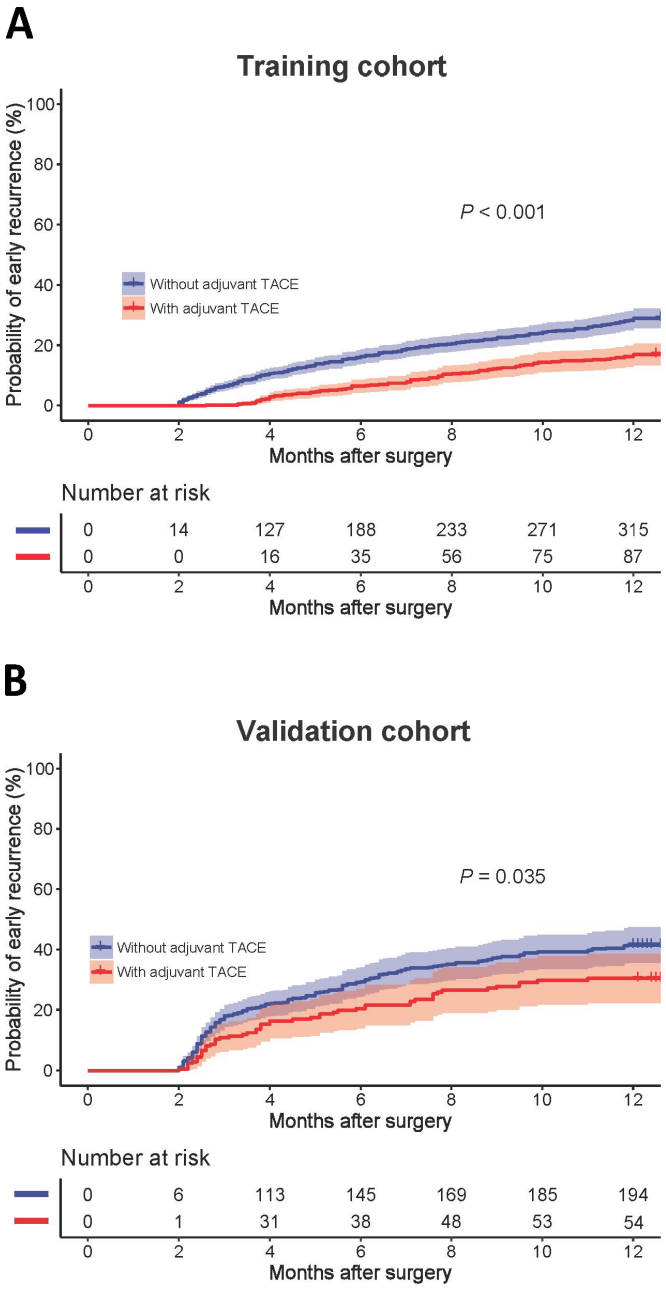

Figure 1 Kaplan-Meier curves of cumulative early recurrence after hepatectomy for hepatocellular carcinoma with or without postoperative adjuvant TACE in the training (A) and validation (B) cohorts. TACE, transarterial chemoembolisation.

vascular catheter was inserted through the femoral artery using the Seldinger technique. Conventional mesenteric arteriography was performed first, and the coeliac artery was catheterised. After assessing the hepatic vascular anatomy, TACE was performed selectively through the left or right hepatic artery, or super-selectively through a tumour-feeding artery if technically feasible. The chemotherapeutic regimens used included three combinations of 5-fluorouracil, mitomycin C, cisplatin, carboplatin, doxorubicin or epirubicin; the embolisation materials used were iodised oil and gelatin sponge cubes, or iodised oil only, which was mixed completely with these chemotherapeutic drugs as an emulsion and injected. The details of the TACE varied at each participating hospital on the amounts and combinations of chemotherapeutic agents used.

Follow-up

After hospital discharge, patients were regularly followed-up at each participating hospital. A standardised postoperative surveillance strategy for recurrence was consistently used at each participating hospital, and included history taking, physical examination, serum AFP level, ultrasonography, contrast-enhanced CT scan or MRI of chest and abdomen at least once every 2~3 months for the first year after surgery, and then once every 3~6 months for the next years. Tumour recurrence was defined as the new appearance of an intrahepatic or extrahepatic tumour nodule, which was diagnosed based on clinical investigation results or confirmed by histology of re-resected tumour samples. When recurrence or distant metastasis was suspected, CT, MRI, angiography, bone scan or positron emission tomography were performed. Once recurrent HCC was confirmed, further treatment decisions by a multidisciplinary team were based on the pattern of recurrent tumour, residual hepatic functional reserve and general condition of patients.

Statistical analysis

The primary end point of the study was early recurrence within 1 year after surgery, which was the prediction end point of the proposed calculator. The secondary end point was cancer-specific survival (CSS), which was defined as the time between the date of surgery and the date of cancer-related death or last follow-up. For patients who did not develop recurrence, the data were censored on the date of death or last follow-up. Categorical variables were expressed as number (proportion, %) and compared using χ^2 test or Fisher's exact test. Continuous variables were expressed as mean±SD or median (IQR) and compared using Student's t-test or Mann-Whitney U test. Apart from maximum tumour size, continuous variables were divided into binaries, tertiles or quartiles as categorical variables based on those commonly used in previous studies.[27–31] Kaplan-Meier curves of cumulative rates of early recurrence and CSS were compared using the log-rank tests. Univariate and multivariate Cox-regression analyses were performed to identify independent predictors of early recurrence. Variables significant at p<0.10 on univariate analysis and the variable 'adjuvant TACE' were entered into multivariate analysis using a forward stepwise variable selection. Based on the results of multivariate analysis, a nomogram was constructed to predict early recurrence probability for an individual patient. To assess fit of the nomogram, the predictive performance was evaluated through discrimination and calibration. Discrimination was summarised using concordance index (C-index), and area under the receiver operating characteristic (ROC) curve, while calibration

Table 2 Univariate and multivariate Cox regression analyses predicting early recurrence in the training cohort

Variables	HR comparison	UV HR (95% CI)	UV p value	MV HR (95% CI)	MV p value*
Age (years)	>60 vs ≤60	1.007 (0.764 to 1.328)	0.959		
Sex	Male vs female	1.168 (0.836 to 1.631)	0.363		
ASA score	>2 vs ≤	1.094 (0.780 to 1.533)	0.603		
Obesity	Yes vs no	1.302 (0.714 to 2.373)	0.389		
Diabetes mellitus	Yes vs no	0.964 (0.600 to 1.549)	0.880		
HBV (+)	Yes vs no	1.217 (0.827 to 1.790)	0.318		
HCV (+)	Yes vs no	0.699 (0.325 to 1.503)	0.359		
Cirrhosis	Yes vs no	1.159 (0.916 to 1.467)	0.218		
Child-Pugh	B vs A	1.216 (0.831 to 1.779)	0.315		
Preoperative ALT level (U/L)	>40 vs ≤40	1.159 (0.953 to 1.411)	0.140		
Preoperative AST level (U/L)	>40 vs ≤40	1.453 (1.161 to 1.820)	0.001	1.057 (0.801 to 1.395)	0.695
Preoperative AFP level (ng/mL)	20–399 vs <20	1.795 (1.314 to 2.453)	<0.001	1.602 (1.138 to 2.255)	0.007
	400–999 vs <20	1.969 (1.283 to 3.022)	0.002	2.023 (1.260 to 3.248)	0.004
	≥1000 vs <20	4.171 (3.114 to 5.585)	<0.001	2.726 (1.964 to 3.783)	<0.001
Maximum tumour size (cm)	Continuous variable	1.187 (1.153 to 1.222)	<0.001	1.594 (1.345 to 1.891)	<0.001
Tumour number	2 vs 1	1.914 (1.312 to 2.792)	0.001	1.645 (1.046 to 2.589)	0.031
	≥3 vs 1	4.546 (3.126 to 6.611)	<0.001	3.138 (1.916 to 5.141)	<0.001
Macrovascular invasion	Yes vs no	4.098 (3.220 to 5.216)	<0.001	3.025 (2.306 to 3.968)	<0.001
Microvascular invasion	Yes vs no	2.597 (2.071 to 3.256)	<0.001	2.266 (1.239 to 4.143)	0.008
Satellite nodules	Yes vs no	2.613 (2.076 to 3.288)	<0.001	1.951 (1.463 to 2.603)	<0.001
Tumour differentiation	Poor vs well/moderate	1.108 (0.884 to 1.389)	0.373		
Incomplete tumour encapsulation	Yes vs no	2.517 (1.939 to 3.267)	<0.001	0.989 (0.686 to 1.427)	0.953
Intraoperative blood loss (mL)	>400 vs ≤400	2.033 (1.623 to 2.546)	<0.001	1.180 (0.859 to 1.624)	0.307
Intraoperative blood transfusion	Yes vs no	2.235 (1.710 to 2.921)	<0.001	1.117 (0.757 to 1.647)	0.577
Extent of hepatectomy	Major vs minor	2.065 (1.579 to 2.700)	<0.001	0.776 (0.540 to 1.114)	0.169
Anatomical resection	Yes vs no	0.780 (0.597 to 1.019)	0.069	0.730 (0.537 to 1.033)	0.089
Resection margin (cm)	<1 vs ≥1	3.475 (2.085 to 5.794)	<0.001	1.563 (1.182 to 2.067)	0.002
Postoperative adjuvant TACE	No vs yes	1.820 (1.401 to 2.365)	<0.001	2.231 (1.700 to 3.167)	<0.001

*Those variables found significant at p<0.1 in univariable analyses were entered into multivariable analyses.
AFP, alpha-fetoprotein; ALT, alanine aminotransferase; ASA, American Society of Anesthesiologists; AST, aspartate transaminase; HBV, hepatitis B virus; HCV, hepatitis C virus; MV, multivariate; TACE, transarterial chemoembolisation; UV, univariate.

was assessed using the Hosmer-Lemeshow test with 1000 bootstrap samples. ROC curve analysis was used to calculate optimal cut-off value that was determined by maximising the Youden index (ie, sensitivity+specificity−1). Accuracy of the prediction model was assessed by sensitivity, specificity, predictive values and likelihood ratios. Predictive performance between the present model and conventional HCC staging systems (including the eighth tumour-node-metastasis classification (TNM), the Cancer of the Liver Italian Programme (CLIP), Milan criteria and Barcelona Clinic Liver Cancer Staging (BCLC)) were compared using ROC curve analysis and decision curve analysis (DCA). A larger area under the curve (AUC) indicated greater discriminatory ability and more accurate performance. As DCA could display true and false positive fractions as functions of various risk thresholds, it was more informative than ROC curves to assess the clinical value of a model.[32] The cohorts were dichotomised into groups of patients deemed to be low and high risk of early recurrence using optimal cut-off value among patients in the training and validation cohorts.

An internet browser-based software application was programmed in JavaScirpt based on corresponding parameters of the nomogram to provide a prediction model for a given individual patient based on the reduced risk of early recurrence with the use of adjuvant TACE. The reduced risk between two estimates derived from this prediction calculator was the expected benefit from adjuvant TACE, which could be interpreted as the difference in early recurrence probability when a patient did and did not receive adjuvant TACE. The statistical analysis was performed using SPSS V.26.0 and R V.3.5.1 (http://www.

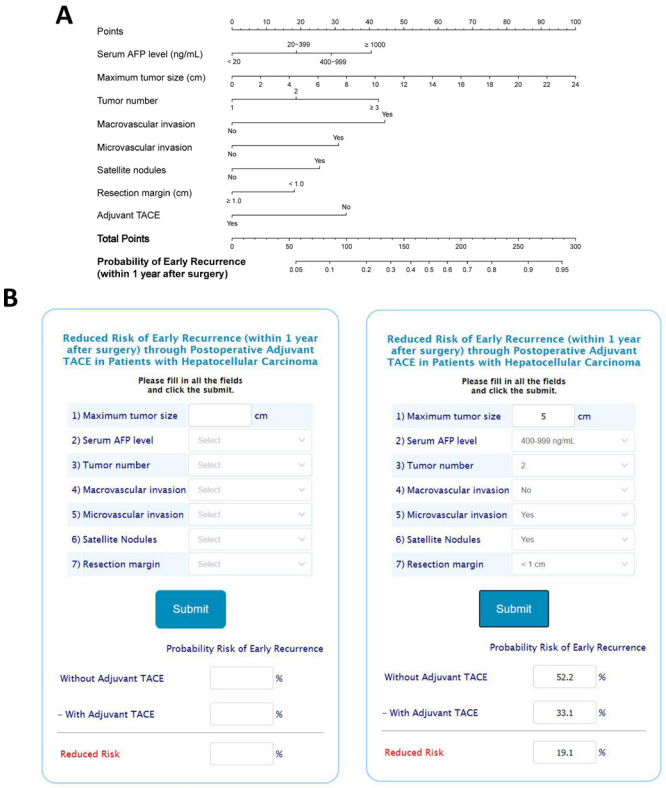

Figure 2 The nomogram prediction model for predicting early recurrence (A) and the corresponding browser-based online calculator (B) (http://asapcalculate.top/Cal9_en.html) to calculate the probabilities of early recurrence both for the situation in which the patient receives or does not receive adjuvant TACE, and the difference between the two estimates is the reduced risk of early recurrence through adjuvant TACE. AFP, alpha-fetoprotein; TACE, transarterial chemoembolisation.

r-project.org/) with packages including 'rms', 'foreign', 'ROCR', 'survival', 'survminer' and 'ggplot'. A two-tailed value of p<0.05 was considered as statistically significant.

RESULTS

Among 2590 patients who underwent curative hepatectomy for HCC and met eligibility criteria, 2276 (87.9%) were males and median age was 51 years (range 20–85 years). Among patients in the overall cohort, 1813 (70%) and 777 (30%) patients were randomly assigned to the training or validation cohorts, respectively (online supplemental figure 1). Baseline characteristics and operative variables for patients in the training and validation cohorts are summarised in online supplemental table 1. In the training cohort, 559 (30.8%) patients underwent adjuvant TACE at a median interval of 33 days (range 21–58 days) after surgery; in contrast, the validation cohort consisted of 206 (26.5%) patients who underwent adjuvant TACE at a median interval of 36 days (range 22–59 days).

Baseline characteristics, operative variables and long-term oncological outcomes of patients in the training cohort were stratified according to receipt of adjuvant

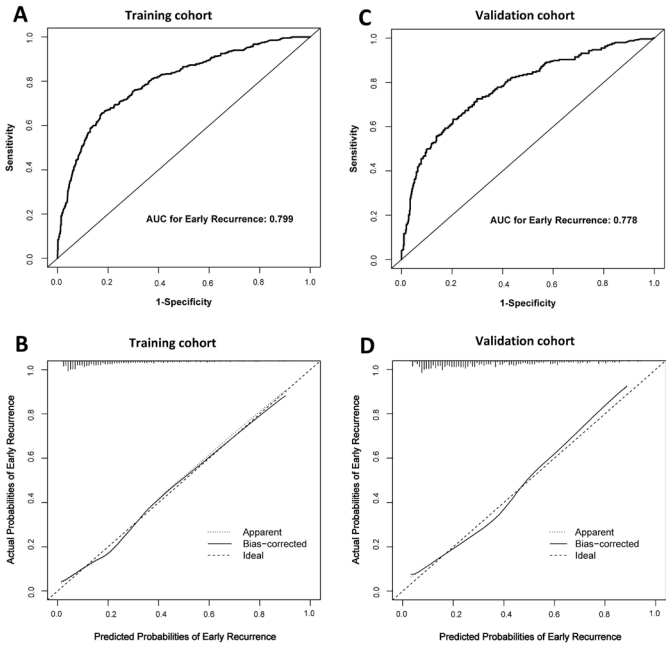

Figure 3 Receiver operating characteristic curves (A, C) and calibration curves (B, D) of the prediction calculator in the training and validation cohorts. AUC, area under the curve.

TACE and are summarised in table 1. At the time of censoring, 999 (55.1%) patients had developed recurrence for a cumulative incidence of early recurrence within 1 year after surgery being 22.2% (402/1813). Compared with patients who did not receive adjuvant TACE, patients who received adjuvant TACE had a lower cumulative incidence of early recurrence in the training cohort (15.6% vs 25.1%, p<0.001) and in the validation cohort (26.2% vs 34.6%, p=0.035) (figure 1). CSS also differed among patients who did and did not receive adjuvant TACE in both training and validation cohorts (online supplemental figure 2).

Predictors of early recurrence

Univariate and multivariate Cox regression analyses to predict early HCC recurrence in the training cohort are shown in table 2. Independent predictors of early recurrence included preoperative AFP level (≥1000 vs 400–999 vs 20–399 vs <20 ng/mL), maximum tumour size as a continuous variable, tumour number (≥3 vs 2 vs 1), macrovascular invasion (yes vs no), microvascular invasion (yes vs no), satellite nodules (yes vs no), resection margin (<1.0 vs ≥1.0 cm) and receipt of adjuvant TACE (no vs yes).

Development of prediction calculator

A prediction model integrating these eight factors that were independently associated with early recurrence was constructed (figure 2A). Each variable was assigned a score on a point scale. By adding up all the scores and locating the total score on the scale, a straight line could be drawn perpendicularly downwards to ascertain the probability of early recurrence. To facilitate ease and convenience of use, an internet browser-based calculator

Table 3 Accuracy of the prediction calculator for predicting the probability of early recurrence

Performance index	Training cohort	Validation cohort
Area under ROC curve, C-index*	0.799 (0.780 to 0.818)	0.778 (0.747 to 0.807)
R^2	0.302	0.285
Optimal cut-off score†	124	124
Sensitivity, %*	65.7 (60.8 to 70.3)	63.3 (57.0 to 69.3)
Specificity, %*	82.4 (80.3 to 84.3)	79.6 (75.9 to 82.9)
Positive predictive value, %*	51.5 (48.2 to 54.8)	59.2 (54.5 to 63.8)
Negative predictive value, %*	89.4 (88.0 to 90.6)	82.2 (79.6 to 84.6)
Positive likelihood ratio*	3.72 (3.3 to 4.4)	3.10 (2.6 to 3.8)
Negative likelihood ratio*	0.42 (0.4 to 0.5)	0.46 (0.4 to 0.5)

*Value with 95% CI.
†According to the result from the training cohort.
C-index, concordance index; ROC, receiver operating characteristic.

was built based on the nomogram prediction model formula to calculate the probabilities of early recurrence among patients who did and did not receive adjuvant TACE. The difference between the two estimates was deemed the overall risk reduction of early recurrence due to use of adjuvant TACE (figure 2B). The corresponding scores and formula to calculate early recurrence probability are provided in online supplemental table 2. The online calculator is available for free at: http://asapcalculate.top/Cal9_en.html. After the user inputs information related to the independent risk factors, the probability of early recurrence relative to receipt of adjuvant TACE, as well as the reduced risk of early recurrence associated with the use of adjuvant TACE are automatically generated and displayed.

Validation of prediction calculator

The calculator risk prediction demonstrated good predictive performance to estimate the probability of early HCC recurrence with a C-index of 0.799 (95% CI 0.780 to 0.818) in the training cohort (figure 3A). The calibration plot of the nomogram model fitted well and demonstrated good agreement between the prediction and actual observation for the probability of early recurrence (figure 3B). As shown in table 3, the optimal cut-off score for the proposed calculator was 124 with the corresponding probability of early recurrence being 34.2%; the sensitivity, specificity, positive predictive value and negative predictive value were 65.7%, 82.4%, 51.5% and 89.4%, respectively.

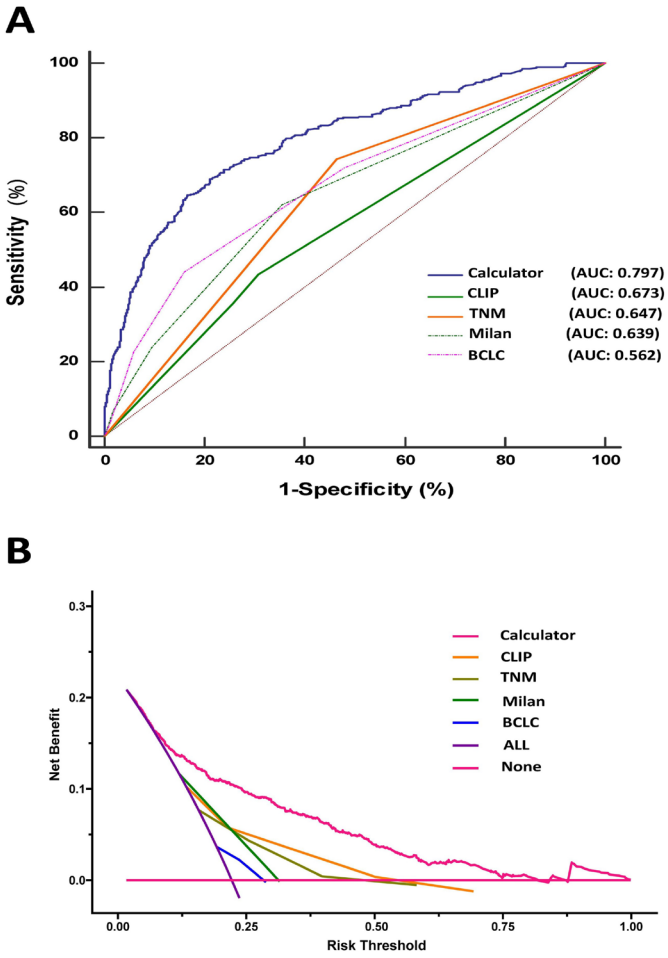

Figure 4 Receiver operating characteristic curves (A) and decision curves (B) of the prediction calculator and other conventional staging systems for the prediction of early recurrence in the whole cohort. AUC, area under the curve; BCLC, Barcelona Clinic Liver Cancer Staging; CLIP, the Cancer of the Liver Italian Programme; TNM, Tumor-Node-Metastasis classification.

In the validation cohort, the proposed calculator performed equally well as the training cohort with a C-index of 0.778 (95% CI 0.747 to 0.807) (figure 3C) and a good-fit calibration plot (figure 3D). The sensitivity, specificity, positive predictive value and negative predictive value in predicting early recurrence in the validation cohort were 63.3%, 79.6%, 59.2% and 82.2%, respectively (table 3).

Performance comparisons

The predictive performance between the proposed calculator and the four commonly used conventional HCC staging systems was then compared using ROC curves and DCA analysis among all 2590 patients in the entire cohort (figure 4). The C-index of the prediction calculator was 0.797 (95% CI 0.781 to 0.813), which was markedly superior to the eighth TNM classification (C-index: 0.647, 95% CI 0.625 to 0.669), the CLIP staging (C-index: 0.673, 95% CI 0.650 to 0.694), the Milan criteria (C-index: 0.639, 95% CI 0.617 to 0.662) and the BCLC staging (C-index:

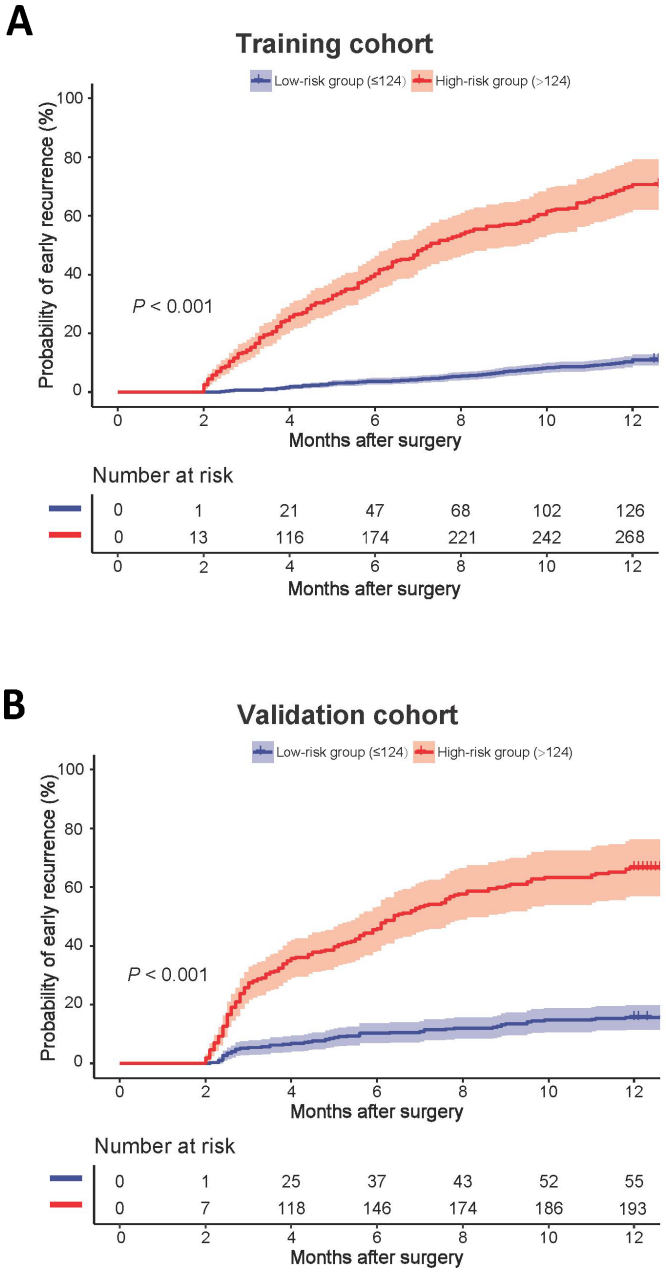

Figure 5 Kaplan-Meier curves of cumulative early recurrence between the high-risk and low-risk groups according to the prediction calculator in the training (A) and validation cohorts (B).

0.562, 95% CI 0.539 to 0.585) (all p<0.001). DCA curves revealed that the prediction calculator was the highest within the risk threshold range, suggesting that the nomogram model was better at predicting the benefit of TACE than the four commonly used conventional HCC staging systems.

Stratification of risk groups

According to an optimal cut-off score of 124 to predict early recurrence, patients were divided into two groups: a high-risk group (nomogram score >124) and a low-risk group (nomogram score ≤124). Marked differences in the actual cumulative rates of early recurrence between the high-risk and low-risk groups were noted; the actual cumulative rates of early recurrence among patients at high risk of early recurrence in both training and validation cohorts were much higher than those individuals classified as low risk (both p<0.001) (figure 5). The cumulative CSS among patients at high risk of early recurrence in both training and validation cohorts was also higher than patients classified as low risk (both p<0.001) (online supplemental figure 3).

DISCUSSION

Postoperative adjuvant therapies predominantly act by eliminating microvascular disease that originated from primary tumour or residual foci left after resection for malignant tumours.[33 34] Adjuvant TACE may be more suitable for patients who are most likely to develop early recurrence after hepatectomy for HCC. Several recent RCTs and systematic reviews have indicated that adjuvant TACE was associated with improvement in long-term survival only in subsets of patients with one or more high-risk characteristics of HCC recurrence, but not for patients with no high-risk features.[21–23 35–37] Therefore, prediction of individual patient risk to develop postoperative recurrence is of great importance in decision-making as to whether to use adjuvant TACE for patients with HCC. The current study aimed to identify the personalised net benefit, that is, the reduce risk of early recurrence associated with the use of adjuvant TACE for an individual patient undergoing hepatectomy for HCC using a prediction model based on eight independent factors. The model demonstrated good discrimination and calibration, with C-indices >0.75 in both training and validation cohorts. Based on this nomogram formula, a proposed online calculator was created to estimate the probabilities of early recurrence for patients with HCC relative to receipt of adjuvant TACE or not, as well as the difference between the two estimates being the expected benefit from adjuvant TACE. In addition, patients could be stratified into risk groups relative to early recurrence based on the calculator, which was also able to categorise patient risk of CSS. To our knowledge, this is the first prediction model to estimate the reduced risk of early recurrence from adjuvant TACE among individual patients undergoing hepatectomy for HCC. These data may help clinicians in decisions-making about the potential role of adjuvant TACE among patients undergoing hepatectomy for HCC.

Several RCTs have previously indicated that a subgroup of patients with HCC may benefit from adjuvant TACE;[18 19 21 22] in particular, patients with more than one specific risk factors associated with recurrence may derive a benefit. Risk factors included tumour size >5 cm,[21] presence of microvascular invasion,[21 22] multiple tumours[21] and HCC with macrovascular invasion.[18 19] In our previous meta-analysis which included 24 studies with 6977 patients with HCC, the pooled analysis demonstrated that adjuvant TACE was associated

with an improved recurrence-free survival in patients with multinodular HCC (HR 0.31, p<0.01), microvascular invasion (HR 0.67, p<0.01) and portal vein tumour thrombus (HR 0.58, p<0.01).[23] Previous studies failed, however, to consider the weight and relevance of each of these specific risk factors with recurrence; in turn, previous reports failed to estimate the net benefit of adjuvant TACE for an individual patient. Thus, customised survival prediction models are necessary to provide prognostication for an individual patient, as previous studies were unable to guide recommendations based on coarse groupings of large numbers of heterogeneous patients. Furthermore, by estimating prognostic probability solely based on HCC staging, previous data were not refined enough for an individual patient. Data from the current study illustrated how our proposed calculator could better be predicted based on predictive factors than the four commonly used conventional staging systems.

Clinical prediction nomograms and calculators are becoming increasingly used as prognostic devices in oncology and medicine to predict cancer prevention, risks and treatment outcomes.[38] With the ability to generate an individual probability of a clinical event by integrating diverse prognostic and determinant variables, nomograms and calculators meet our desire for biologically and clinically integrated models and fulfil our drive towards personalised medicine. Rapid computation through user-friendly digital interfaces, together with increased accuracy, and more easily understood prognoses compared with conventional staging, allow for seamless incorporation of nomogram-derived prognosis to aid clinical decision making. Although prediction models can never substitute for evidence coming from large-scale RCTs, these tools are useful adjuncts to help decision-making in clinical situations in which data from RCTs are not available, and the optimal treatment management remains controversial. As more specific patient and tumour information becomes routinely available in the future, such as genetic information and molecular tumour markers, the use of predictive models will become increasingly used to improve patient stratification, and personalised decision-making relative to an individual patient for adjuvant therapies. As the proposed model can also be used to predict adjuvant TACE in some patients resulting in either no benefit or only a small improvement, for example, in patients with a solitary small HCC or tumours without any macrovascular and microvascular invasion, a specific threshold at which adjuvant TACE should be recommended is still hard to define. In the 'real-world' clinical setting, the final decision on whether to use adjuvant TACE should be based on a joint decision between clinicians and patients after careful discussion on the pros and cons of adjuvant therapy. In the future, other regression modelling techniques, including those using artificial intelligence and machine learning, will also be explored to determine whether the predictive accuracy can further be improved.[39–41] The final decision on whether to use adjuvant TACE should be based on the net potential prognostic benefit as estimated by the prediction model and on specific patient preferences and quality of life considerations.

There are several limitations of the current study. As a retrospective observational study, some variables could not be standardised or identified, such as techniques of hepatectomy and specifics of adjuvant TACE. In addition, enrolled patients all came from China and most of them had a background of HBV infection (nearly 90% both in the training and validation cohorts). Whether the model can be applied to predominantly patients with HCV-related HCC in Western countries needs further studies. Due to data limitation and for simplicity and applicability of the model, the specifics of adjuvant TACE were also not further explored to include chemotherapy types and chemotherapy cycles and numbers, as well as patients' liver function status at their first follow-up. Finally, the impact of tumour immune-related indicators and molecular tumour markers on recurrence of HCC were not considered. Future efforts to test the model performance using an external validation with large cohorts or those cohorts coming from other centres, especially from the West, should be made.

In conclusion, a risk prediction model that incorporated eight independent risk factors associated with early recurrence after hepatectomy for HCC was constructed and validated. The model had good predictive accuracy and discrimination, which were superior to four commonly used conventional HCC staging systems. The risk groupings of early recurrence determined by this calculator were able to differentiate patient's CSS. The proposed calculator helped to easily determine an estimation of an individual patient of the reduced risk of early recurrence by using adjuvant TACE. This tool may assist clinicians in decision-making whether to use adjuvant TACE after hepatectomy for HCC.

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