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Albumin-bilirubin (ALBI) grade-based nomogram to predict tumor recurrence in patients with hepatocellular carcinoma

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ABSTRACT

Background: Tumor recurrence after curative resection is common in hepatocellular carcinoma (HCC), but large-scale long-term prediction on an individual basis has seldom been reported. We aimed to construct an albumin-bilirubin (ALBI) grade-based nomogram to predict tumor recurrence in patients with HCC undergoing surgical resection.

Methods: A total 1038 patients with newly diagnosed HCC undergoing curative resection between 2002 and 2016 were enrolled. Baseline characteristics, tumor status and severity of liver functional reserve were collected. The Cox proportional hazards model was used to predict tumor recurrence and construct the nomogram. The performance of the nomogram was evaluated by the discrimination and calibration tests.

Results: After a mean follow up time of 30 months, 510 (49%) patients developed tumor recurrence. The cumulative recurrence-free survival at 1, 3, 5, and 10 years were 79%, 51%, 38% and 26%, respectively. In the Cox multivariate model, ALBI grade 2–3, multiple tumors, tumor size equal or large than 2 cm, serum α-fetoprotein level equal or greater than 20 ng/ml and total tumor volume equal or larger than 227 cm^3 were independent risk factors associated with tumor recurrence. A nomogram was constructed based on these five variables. Internal validation with 10,380 bootstrapped sample sets had a good concordance of 0.607 (95% of confidence interval: 0.587–0.627). The calibration plots for 1-, 3- and 5-year recurrence-free survival well matched the idealized 45-degree line.

Conclusions: ALBI is a feasible marker for tumor recurrence. This easy-to-use ALBI grade-based nomogram may predict tumor recurrence for individual HCC patient undergoing surgical resection.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignancy and the third leading cause of cancer-related mortality worldwide [1]. The most common etiology of HCC was hepatitis B virus (HBV) infection, hepatitis C (HCV) infection and alcoholism [2,3]. Surgical resection currently remains the best treatment modality for patient with early-stage tumor with well-preserved liver function and provides 5-year survival rate up to 70% [4–6]. However, post-operative tumor recurrence is common and accounts for the main cause of unsatisfactory results after resection [7–10].

Abbreviations: AFP, α-fetoprotein; ALBI, albumin-bilirubin; CI, confidence interval; CT, computed tomography; CTP, Child-Turcotte-Pugh; HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; INR, international normalized ratio; MELD, model for end-stage liver disease; MRI, magnetic resonance imaging; SD, standard deviation.

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Several factors, mainly large and multiple tumors, and underlying liver fibrosis or cirrhosis, were demonstrated to determine post-operative outcomes [7,11–15].

The degree of liver functional reserve plays an important role in prognostic prediction for HCC. The Child-Turcotte-Pugh (CTP) classification has been widely used to assess liver reserve in patients with cirrhosis and is incorporated in many HCC staging systems [16–18]. However, CTP classification has some drawbacks, including arbitrarily defined cutoff points of objective variables and two highly subjective variables (ascites and encephalopathy). The model for end-stage liver disease (MELD) score was used to assess the severity of liver dysfunctional [19]. Notably, as a result of recent international collaboration, the albumin-bilirubin (ALBI) grade, which incorporates serum albumin and albumin only, was proposed as a more objective method to determine liver injury in patients with HCC [20,21]. Also, the ALBI grade has been shown to predict long-term survival in HCC patients undergoing surgical resection [22,23].

Nomograms derived from hazard functions have been applied to a variety of cancers as a straightforward tool to predict survival for patients with malignancies [24–26]. More importantly, nomograms provide the prognosis of cancer patients from group level to individual level [26]. Several studies have used nomogram to predict the prognosis of patients with HCC undergoing different therapies [25,27–29]. However, very few studies with an adequate sample size have specifically focused on recurrence-free survival of HCC patients. We aim to construct an ALBI grade-based nomogram to predict tumor recurrence in a large prospective cohort of HCC patients undergoing surgical resection.

Patients and methods

Patients

Between 2002 and 2016, a total 1038 patients with newly diagnosed HCC undergoing surgical resection were prospectively collected and retrospectively analyzed. Comprehensive baseline information, including patient demographics, etiology of underlying liver disease, tumor status, serum biochemistries, severity of cirrhosis and performance status, was recorded at the time of diagnosis. This study has been approved by the Institutional Review Broad of Taipei Veterans General Hospital. Patient records/information were anonymized and de-identified prior to analysis.

Diagnosis and definition

The pre-operative diagnosis of HCC was histologically confirmed or based on the findings of typical radiological features in at least two imaging examinations, including four-phase multidetector contrast-enhanced dynamic computed tomography (CT) scan or magnetic resonance imaging (MRI), or by single positive image along with AFP levels above 400 ng/ml [4]. The CTP classification and MELD score were used to define the severity of chronic liver disease [30,31]. Total tumor volume (TTV) was calculated based on tumor diameter as previously reported [18]. The ALBI score was calculated as the following equation = 0.66 × log10 bilirubin - 0.085 × albumin, where bilirubin is in μmol/L and albumin in g/L. ALBI grade was defined as ALBI grade 1 (score ≤ -2.60), ALBI grade 2 (score more than -2.60 and ≤ -1.39), and ALBI grade 3 (score more than -1.39) [20]. Intrahepatic recurrence was defined as new lesions identified in the remnant liver, whereas extrahepatic recurrence was defined as the emergence of tumor elsewhere outside the liver [32].

Treatment

The criteria for surgical resection patients with HCC were (1) tumor involving no more than three Couinaud segments, (2) CTP class A or B (3) no main portal vein trunk involvement or distant metastases, and (4) absence of other major diseases that may complicate resection [24,33]. After the diagnosis was confirmed, patients were reviewed at our multi-disciplinary HCC board for treatment guidance. Written informed consent was obtained before treatment. The operative procedures have been previously described in detail [34]. The resected liver tissue was sent for gross and microscopic examinations, and the recorded tumor size was based on the largest dimension of the resected specimen. All patients received regular follow up every 2–3 months until death or withdrawal from the study.

Diagnosis of recurrence was based on typical imaging findings in a contrast-enhanced CT scan or MRI associated with an increased serum AFP level. Patients with tumor recurrence were managed with various therapeutic modalities, including re-resection for resectable recurrence, transarterial chemoembolization (TACE) or percutaneous ablation for unresectable intrahepatic recurrence, and systemic chemotherapy, radiotherapy or best supportive care for patients with extrahepatic metastatic disease [17,24]. The treatment decision was based on the pattern of recurrence and liver functional reserve.

Statistics

The chi-square test (two-tailed) or Fisher exact tests were used for categorical data comparison, and the Mann-Whitney ranked sum test was used for continuous data. For the analysis of prognostic predictors, continuous variables were split by the median values and treated as dichotomous covariates. The Kaplan-Meier method with log-rank test was applied to compare the recurrence-free survival. Factors that were significant in the univariate analysis were introduced into multivariate Cox proportional hazards model to determine beta coefficients (BETA) and hazard ratios (HRs). The beta coefficients from the final Cox model were used to construct the nomogram to assess the association of variables with recurrence-free survival after surgical resection. First, prognostic discrimination of the nomogram model was examined by using the concordance indexes. Internal validation with 10 times (10,380) of sample size set of the bootstrapped samples was performed to evaluate the feasibility of nomogram regarding prediction of tumor recurrence. Second, a calibration curve was performed by comparing the means of predicted recurrence-free survival with those with actual tumor recurrence observed by Kaplan-Meier method after grouping patients with quartiles of the nomogram [26]. All statistical analyses were conducted using SAS 9.4 for Windows (SAA Institute INC., Cary, NC, USA) and SPSS for Windows version 21 release (SPSS Inc., Chicago, IL, USA). A p value less than 0.05 was considered statistically significant.

Results

Characteristics of study patients

The baseline demographics of patients undergoing surgical resection are shown in Table 1. The mean age of the study patients was 61 years, and 78% of whom were male. The most common etiology of chronic liver disease was hepatitis B (48%), and approximately 77% of patients were classified as performance status 0. Ninety-four percent of patients were diagnosed as CTP class A, and their mean MELD score was 7.1. The mean ALBI score of patients were -2.65 and about sixty-one percent of patients were

Table 1
Baseline characteristics of patients of hepatocellular carcinoma undergoing surgical resection.

Variables	Patients (n = 1038)
Age (years, mean ± SD)	61 ± 13
Male, n (%)	813 (78)
Etiologies of liver disease	
HBV, n (%)	500 (48)
HCV, n (%)	186 (18)
HBV + HCV, n (%)	45 (4)
Alcohol, n (%)	148 (14)
Others, n (%)	159 (16)
Performance status (0/1–2/3-4), n (%)	796/229/13 (77/22/1)
Diabetes mellitus, n (%)	229 (29)
Tumor nodules (single/multiple)	792/246 (76/24)
Maximal tumor diameter ≥ 2 cm, n (%)	916 (88)
Total tumor volume (cm^3), mean ± SD	227 ± 543
Total tumor volume (<227/≥227 cm^3), n (%)	827/211 (80/20)
α-fetoprotein (ng/mL) mean ± SD	8310 ± 80569
α-fetoprotein ≥ 20 ng/ml, n (%)	535 (51%)
Ascites, n (%)	61 (6)
Laboratory values (mean ± SD)	
Alanine transaminase (IU/L)	68 ± 100
Aspartate transaminase (IU/L)	64 ± 78
Albumin (g/L)	36 ± 6.2
Total bilirubin (μmol/L)	26.22 ± 48.18
Platelets (×1,000/μL)	177 ± 80
INR of prothrombin time	1.03 ± 0.1
Estimated GFR ≥ 60 ml/min/1.73m2, n (%)	859 (83)
CTP class (A/B)	977/61 (94/6)
CTP score, mean ± SD	5.3 ± 0.6
ALBI grade (1/2–3), n (%)	633/405 (61/39)
ALBI score, mean ± SD	−2.65 ± 0.44
MELD score, mean ± SD	7.1 ± 2.4
Extent of hepatic resection	
Sub-segmentectomy, n (%)	47 (5)
Segmentectomy, n (%)	268 (26)
Bi-segmentectomy, n (%)	377 (36)
Lobectomy, n (%)	346 (33)

CTP, Child-Turcotte-Pugh score; HBV, hepatitis B virus; HCV, hepatitis C virus; MELD, Model for End-stage liver disease; SD, standard deviation.

classified as ALBI grade 1. Approximately 76% of patients had single tumor, and the majority (88%) of patients had a main tumor diameter 2 cm or more. A higher ALBI score was associated with an increased CTP score ($p < 0.001$ for trend analysis; Fig. 1A). There was a poor correlation between ALBI score and MELD score ($p = 0.196$ for trend analysis; Fig. 1B). All patients had histologically confirmed HCC and were free of disease at the surgical margin.

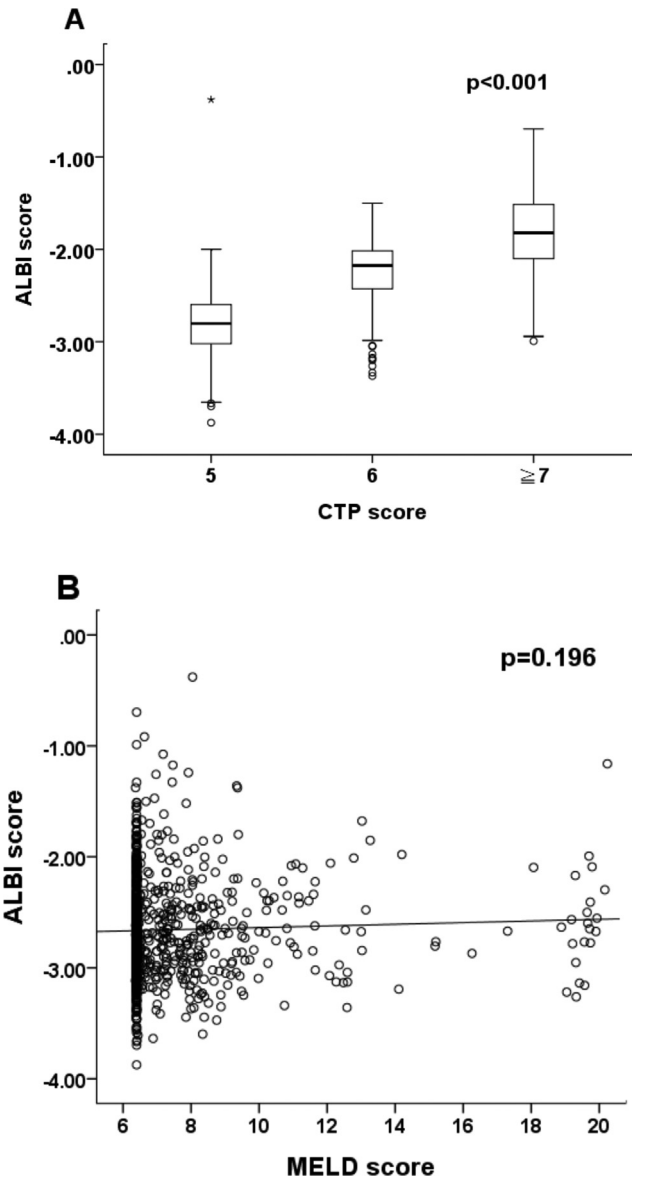

Fig. 1. Correlation of albumin-bilirubin (ALBI) grade between (A) Child-Turcotte-Pugh (CTP) score ($p < 0.001$ for trend), and (B) model for end-stage liver disease (MELD) score ($p = 0.196$ for trend).

Factors associated with tumor recurrence

After a median follow-up of 20 (mean, 30; range, 0–187) months, 510 (49%) patients developed tumor recurrence. Of them, 464 (45%) had intrahepatic and 46 (4%) had extrahepatic recurrence. Post-recurrence treatments were surgical re-resection in 47 (4.5%), radiofrequency ablation in 163 (16%), transarterial chemoembolization in 220 (21%), percutaneous ethanol injection in 10 (1%), sorafenib in 10 (1%), chemotherapy in 15 (1.5%), radiotherapy in 12 (1%) and best supportive care in 33 (3%). The cumulative recurrence-free survival at 1, 3, 5, and 10 years were 79%, 51%, 38% and 26%, respectively. The 1-, 3-, 5- and 10-year recurrence-free survival for patients with ALBI grade 1 was 81%, 54%, 41% and 30%, respectively. For patients with ALBI grade 2–3, the 1-, 3-, 5- and 10-year recurrence-free survival was 77%, 45%, 33% and 20%, respectively ($p = 0.009$, Fig. 2).

In univariate survival analysis, prognostic factors associated with an increased risk of tumor recurrence included hepatitis B, ALBI grade 2–3, multiple tumors, tumor size equal or large than 2 cm, serum α-fetoprotein (AFP) level equal or greater than 20 ng/ml, and total tumor volume equal or larger than 227 cm^3. In the Cox multivariate analysis, ALBI grade 2–3 (BETA 0.228, $p = 0.012$), multiple tumors (BETA 0.311, $p = 0.002$), tumor size equal or large than 2 cm (BETA 0.485, $p = 0.002$), AFP level equal or greater than 20 ng/ml (BETA 0.318, $p = 0.001$) and total tumor volume equal or larger than 227 cm^3 (BETA 0.242, $p = 0.034$) were independent risk factors associated with decreased recurrence-free survival (Table 2).

Construction of the nomogram

Five variables selected in the Cox model were included to build a nomogram. The ratios of calculated BETAs were used to decide the proportional prognostic effect of these variables. Tumor size equal or larger than 2 cm had the largest impact on tumor recurrence in the model and was determined as 10 points. Sequentially, by using the ratios of BETAs between the remaining five variables and tumor

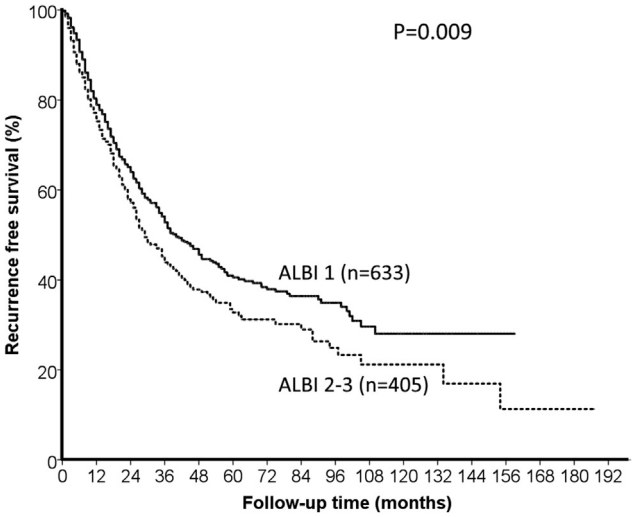

Fig. 2. Recurrence-free survival distribution according to albumin-bilirubin (ALBI) grade. The recurrence-free survival of patients with ALBI grade 1 is better than those with ALBI grade 2–3 ($p = 0.009$).

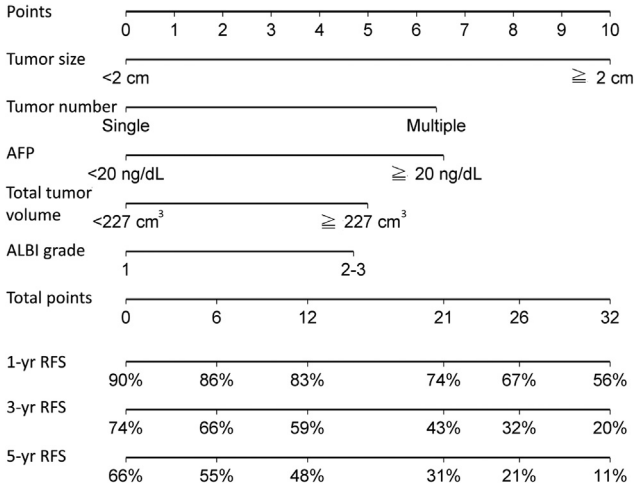

Fig. 3. The composition of nomogram and prediction of tumor recurrence. The nomogram is used by adding up the points identified on the scale of the 5 parameters. The total nomogram point of each patient can be used to predict recurrence-free survival (RFS) at 1, 3 and 5 years on an individual basis.

size equal or larger than 2 cm, 6.6 [calculated as (0.318/0.485) x 10], 6.4, 4.9 and 4.7 points were assigned to AFP equal or greater than 20 ng/ml, multiple tumors, total tumor volume equal or larger than 227 cm^3, and ALB grade 2–3 respectively. Each enrolled patient had one individualized score by adding up the points from these five prognostic variables. The projections from total points (range 0–32) on the scales below indicated the estimated probability of recurrence-free survival at 1, 3 and 5 years (Fig. 3).

Discrimination and calibration of the nomogram

A total 1038 patients were grouped by quartiles of nomogram points. Overall, 87 (9%), 543 (52%), 284 (27%), 122 (12%) patients had nomogram points less than 8 (Q1), between 8 and 17.9 (Q2), between 18 and 23.9 (Q3) and greater than or equal to 24 (Q4), respectively. The predictive accuracy of the nomogram was measured via a concordance index which quantifies the level of concordance between predicted probability and the actual chance of having the event of interest (tumor recurrence). The nomogram had a concordance index of 0.607 [95% of confidence interval (CI), 0.587–0.627] with bootstrapping (B = 10,380). As shown in Fig. 4, the calibration plots for 1-, 3- and 5- year recurrence-free survival well matched the idealized 45-degree line.

Discussion

There are several major findings in this study. First, in this large cohort with 2595 person-years of follow-up, surgical resection resulted in long-term recurrence-free survival of 38% at 5 years and 26% at 10 years. These results are generally consistent with previous studies and confirm that tumor recurrence is a frequent event [9,13]. Second, the ALBI grade is strongly associated with the development of tumor recurrence after surgical resection, indicating this simple biomarker could provide an important prognostic reference for HCC patients. Third, we have constructed an ALBI-based nomogram that can be used for individualized assessment of recurrence-free survival in patients with HCC undergoing surgical resection. This information is crucial for surgical HCC patients in treatment planning and post-treatment follow-up.

We have further analyzed independent risk factors associated with tumour recurrence. In accordance with published studies [34–36], our study showed that the size and number of tumor, serum AFP level, and total tumour volume were linked with higher risk of recurrence after surgical resection. Notably, total tumour volume has been known a surrogate marker of tumour burden and can be used in cancer staging for outcome prediction [18]. Altogether, the extent of tumour involvement, as reflected by these

Table 2
Univariate and multivariate analysis of recurrence-free survival in hepatocellular carcinoma patients undergoing surgical resection.

Variables	Univariate analysis				Multivariate analysis		
	number	1-year recurrence free survival (%)	3-year recurrence free survival (%)	p	Beta value	hazard ratio	p
Sex (male/female)	813/225	77/78	54/48	0.076			
Age (<61/≥ 61 years)	480/558	77/78	52/47	0.240			
HBV (negative/positive)	404/634	81/76	53/47	0.033	0.163	1.177	0.084
HCV (negative/positive)	781/257	77/80	49/50	0.969			
Alcoholism (no/yes)	878/160	78/75	51/42	0.069			
ALBI grade (1/2–3)	633/405	79/75	53/44	0.009	0.228	1.257	0.012
eGFR (<60/≥ 60 mL/min/1.73m^2)	179/859	81/77	50/49	0.722			
No. of tumor (single/multiple)	792/246	80/71	51/44	<0.001	0.311	1.364	0.002
Tumor size (<2/≥ 2 cm)	122/916	85/76	68/47	<0.001	0.485	1.624	0.002
α-fetoprotein (<20/≥ 20 ng/ml)	504/534	86/69	56/44	<0.001	0.318	1.375	0.001
Total tumor volume (<227/≥ 227 cm^3)	827/211	81/62	52/40	<0.001	0.242	1.273	0.034
Diabetes mellitus (no/yes)	809/229	76/82	49/52	0.369			
Performance status (0/1–2/3-4)	796/229/13	79/73/74	51/43/63	0.065			

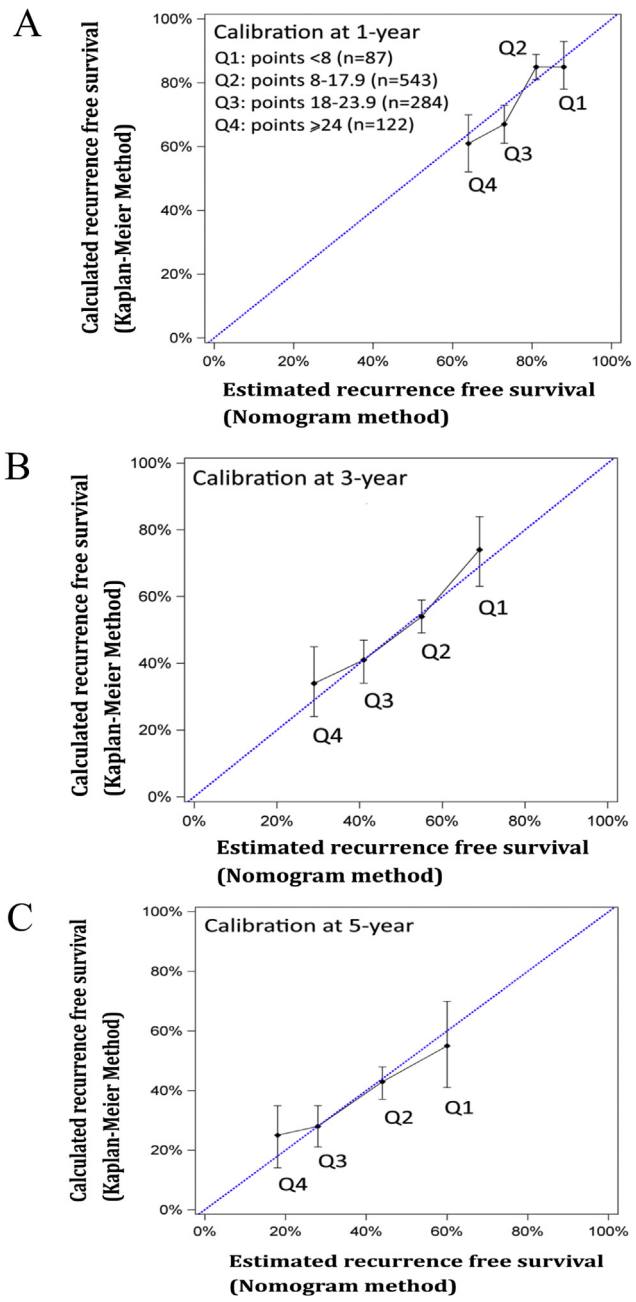

Fig. 4. The calibration of nomogram for 1-, 3-, 5-year recurrence-free survival prediction. The X-axis presents the nomogram-predicted recurrence-free survival and the Y-axis shows the mean recurrence-free survival and 95% confidence interval calculated by the Kaplan-Meier method. Patients were divided into quantiles (Q) to evaluate the accuracy of nomogram (Q1: points < 8, Q2: points 8–17.9, Q3: points 18–23.9, Q4: points ≥ 24). The calibration lines fit along with the 45-degree reference for 1-, 3-, and 5-year recurrence-free survival.

factors, heavily determines the risk of post-resection tumour recurrence.

In addition to these factors, ALBI grade can also predict tumour recurrence as demonstrated in our study. Although the CTP classification has been widely used for decades and well correlated with ALBI score (Fig. 1A), there are some advantages of ALBI grade over CTP classification for the evaluation of prognosis in HCC. The CTP system relies on individual parameter that is scored based on arbitrarily defined, pre-determined cutoff points and highly subjective variables [23]. Moreover, not all HCC patients had cirrhosis; some may have normal underlying liver or varying degrees of chronic liver disease [2]. The MELD score is an alternative tool to measure liver functional reserve, but it is mainly used to prioritize cirrhotic patients awaiting liver transplantation and does not necessarily correlate with ALBI score. On the other hand, the ALBI score, which incorporates only serum bilirubin and albumin, is a simple and more objective model for assessing the degree of liver dysfunction in HCC patients [20,23]. The ALBI score may avoid inter-observer variation and could further stratify distinct prognostic subgroups within CTP class A [20]. Thus, the ALBI grade appears to be a promising evidence-based model with good prognostic performance in HCC.

In the current study, we constructed an assessable nomogram from a large patient cohort undergoing surgical resection. The nomogram was employed to generate an easy-to-apply model that can be used for individualized risk estimation for recurrence-free survival after surgical resection. The advantage of using this nomogram is that all variables are ordinary clinical characteristics and no advanced mathematical calculation is required. Earlier studies that used the prognostic nomogram in surgical HCC patients did not incorporate the severity of liver functional reserve into the model [27,29]. Importantly, cirrhosis *per se* has been considered pre-cancerous lesion that may contribute to tumor recurrence after curative resection [27,30]. In the multivariate Cox model, there was 25.7% increased risk of tumor recurrence in patients with ALBI grade 2–3 compared to ALBI grade 1, indicating poor liver functional reserve is associated with decreased recurrence-free survival. These results are consistent with a more recent study [37], and further suggest that genomic instability may occur and contribute to carcinogenesis in cirrhotic background liver. However, the exact mechanism between liver dysfunction, as indicated by the ALBI grade, and tumour recurrence remains unclear.

During a mean follow-up duration of 30 months, 510 (49%) patients had tumor recurrence in this cohort; this number is 102 times the number of predictors used in the nomogram. This feature helps lower the expected error of the predicted probabilities from the Cox model to less than 10% [26]. The concordance index of nomogram was 0.607, which means that if two HCC patients with different nomogram points are selected, the probability that the patient with a higher nomogram score would have tumor recurrence is approximately 61%. Notably, the calibration plots for recurrence-free survival at 1-, 3- and 5- years well matched the idealized 45-degree line, confirming the predictive accuracy of the nomogram. Combining the results of concordance index and calibration plot, this ALBI grade-based nomogram model can be considered a feasible tool to predict tumor recurrence on an individual basis for HCC patients undergoing surgical resection.

This study has a few limitations. First, this was a single-center study where hepatitis B was the predominant cause of HCC. Thus a robust nomogram should be validated externally in different cohorts. Second, all patients in this cohort were treated at a tertiary medical center, therefore referral bias could not be completely avoided. Third, the nomogram was generated from patients receiving surgical resection; it may not be suitable for patients receiving other treatments.

Conclusions

We suggest that the ALBI grade is a feasible predictive marker for tumor recurrence in post-resection HCC. This easy-to-use, user-friendly ALBI grade-based nomogram may predict tumor recurrence for individual HCC patient undergoing surgical resection. External validation is required to determine whether it can be applied to different treatment groups.

Authorship statement

Guarantor of the article: Teh-Ia Huo.

Specific author contributions: S.-Y. Ho and T.-I. Huo performed the research. C.-Y. Hsu and S.-Y. Ho designed the research study and wrote the paper. P.-H. Liu, C.-Y. Hsia, C.-W. Su and S.-Y. Ho collected and analyzed the data. H.-C. Hou and Y.-H. Huang contributed to the design of the study. All authors approved the final version of the manuscript.

Disclosure

There is no conflict of interest for all authors.

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