Original Article

A novel online calculator based on albumin-bilirubin and aspartate transaminase-to-platelet ratio index for predicting postoperative morbidity following hepatectomy for hepatocellular carcinoma

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Background: Identifying patients at high risks of developing postoperative morbidity is important to improve perioperative outcomes. We sought to define the accuracy of two objective and non-invasive serological-based scores, i.e., albumin-bilirubin (ALBI) and aspartate transaminase-to-platelet ratio index (APRI), to predict postoperative morbidity among patients undergoing hepatectomy for hepatocellular carcinoma (HCC), and build up a personalized predictive tool for clinical practice.

Methods: Clinical data of patients who underwent hepatectomy for HCC at 8 hospitals from a multicenter database were retrospectively analyzed. The predictive accuracy of ALBI and APRI relative to 30-day overall and major morbidity were evaluated using area under the receiver operating characteristic curves (AUC). Based on multivariable logistic regression analyses, preoperative and postoperative nomogram models and consequent online calculators were constructed to predict overall and major morbidity, respectively.

Results: Among 2,301 patients, 725 (31.5%) experienced postoperative complications (major morbidity, 35.9%, 260/725). Multivariable analyses identified high ALBI grade (>–2.6) and APRI grade (>1.5) as independent risk factors associated with overall and major morbidity in both preoperative and postoperative prediction models. Two nomogram predictive models and corresponding online calculators that combined ALBI and APRI were subsequently constructed. The AUCs of the preoperative and postoperative models were 0.728 and 0.742 to predict overall morbidity, and 0.739 and 0.713 to predict major morbidity, respectively, which were much higher than those of Child-Pugh score and the model for end-stage liver disease (MELD). Using the bootstrap validation method, the resulting models were internally validated well.

Conclusions: Preoperative ALBI and APRI scores can predict postoperative morbidity following

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hepatectomy for HCC. An easy-to-use online calculator that combined ALBI and APRI was proposed for individually predicting the probabilities of postoperative overall and major morbidity before and immediately after surgery, so as to provide useful information to inform conversations about surgical risks.

Introduction

Hepatocellular carcinoma (HCC) is the fifth common malignancy and the second leading cause of cancer-related death worldwide (1). Hepatectomy is widely accepted as a front-line curative treatment for HCC among appropriately selected patients (2). Improvement in patient selection, surgical techniques and perioperative care have greatly improved the safety of hepatectomy for HCC over the past two decades, including portal vein embolization associating liver partition and portal vein ligation for staged hepatectomy, laparoscopic hepatectomy, and robotic liver resection (2,3). As such, perioperative mortality has been reduced to less than 5% and even zero at some specialized centers (2,4,5). The incidence of postoperative morbidity following hepatectomy for HCC remains high, however, ranging from 20% to 70% (5-9). The occurrence of postoperative morbidity can impair patient recovery, prolong hospital stay, increase hospitalization costs, aggravate patient's physical and mental burden, increase risk of early mortality, even promote tumor recurrence and reduce long-term survival (6,9-11). Actually, long-term postoperative survival after HCC resection remains unsatisfactory due to the high incidence of postoperative recurrence that ranges from 50% to 70% within 5 years after resection (12,13). Thus, understanding risk factors associated with morbidity, and identifying which patients are at high risks of developing morbidity, especially major morbidity, is of great importance to prevent and reduce its occurrence and improve the surgical safety of patients undergoing hepatectomy.

Previous studies demonstrated that some clinical and operative variables were associated with postoperative morbidity following hepatectomy for HCC, including advanced age, obesity, cirrhosis, portal hypertension, insufficient hepatic functional reserve, blood transfusion, and extent of hepatectomy (7-9,14-19). Among these factors, insufficient hepatic functional reserve was recognized as one of the most important risk factors (20-22). Some simple, objective and non-invasive serological-based scores, including albumin-bilirubin (ALBI) and aspartate transaminase (AST) to platelet ratio index (APRI), were established for assessment of hepatic functional reserve (23,24). Although ALBI is based solely on two serological markers, some single-center studies demonstrated that ALBI score was more accurate in predicting overall morbidity compared with Child-Pugh score and model for end-stage liver disease (MELD) (25-27). A single-center study showed that ALBI could be used to predict post-hepatectomy liver failure (PHLF), which is the most representative complication after hepatectomy (28). As for APRI, a few single-center studies with limited sample size also reported that preoperative APRI could be used to predict postoperative morbidity following hepatectomy for HCC (29-32). One previous study also identified that preoperative ALBI and APRI could be used for predicting PHLF for patients with hepatitis B-related HCC (33). In addition, one recent study also reported that the combination of preoperative ALBI and APRI could predict postoperative morbidity for patients undergoing liver surgery after neoadjuvant chemotherapy (34).

By using a large multicenter database, the current study sought to evaluate whether ALBI and APRI were predictive of postoperative 30-day overall and major morbidity among patients who underwent hepatectomy for HCC. Based on multivariable logistic analyses to identify independent risk factors associated with postoperative overall and major morbidity following hepatectomy for HCC, preoperative and postoperative prediction models were built to create preoperative and postoperative nomogram models to predict personalized probability of postoperative morbidity. We present the following article in accordance with the TRIPOD reporting checklist (35) (available at http://dx.doi.org/10.21037/atm-20-1421).

Methods

Patient selection

Patients who underwent open hepatectomy with curative intent for initial HCC between January 2008 to December 2017 at one of eight Chinese hospitals (Zhejiang Provincial People's Hospital, the First Affiliated Hospital of Soochow University, Eastern Hepatobiliary Surgery Hospital, Fuyang People's Hospital, Pu'er People's Hospital, the Fourth Hospital of Harbin, Ziyang First People's Hospital, and Mengchao Hepatobiliary Hospital) were identified. The diagnosis of HCC was confirmed by postoperative pathological examination. Patients were excluded: (I) who were less than 18 years old, (II) who underwent repeat hepatectomy for recurrent HCC, (III) who had combined HCC and cholangiocarcinoma, (IV) who had preoperative anti-tumor treatment, including radiotherapy, transarterial chemoembolization, chemotherapy or portal vein embolization, (V) who had received hepatectomy with concomitant splenectomy, biliary reconstruction, gastrointestinal surgical procedures, or portal-azygous disconnection, and (VI) who had incomplete preoperative medical record or missing variables associated with perioperative outcomes, such as hepatic function tests within 1 week before operation, or incomplete information of postoperative 30-day morbidity (including the type of complications). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of the Eastern Hepatobiliary Surgery Hospital of Shanghai, China (No. EHBHKY2019-K-005) and individual consent for this retrospective analysis was waived.

Preoperative assessment and perioperative care

Preoperative evaluation was performed before surgery at each hospital. Resectability of HCC was assessed by ultrasonography, computed tomography (CT) scan, and/or magnetic resonance imaging (MRI). Preoperative hepatic function was mainly evaluated by biochemistry and Child-Pugh grading at all participating centers, and Child-Pugh grade C was considered an absolute contraindication for hepatectomy. Upper gastrointestinal endoscopy was routinely employed for almost all HCC patients who were scheduled for hepatectomy. Patients older than 60 years and patients with significant co-morbidities were routinely sent for formal cardiopulmonary evaluation in each center. Liver surgery was performed by experienced surgeons in each center. The criteria of hepatectomy for HCC were consistent and constant at all participating centers over the study period (36,37).

Perioperative treatment was generally standardized and consistent at each center. Patients were monitored in the intensive care unit on the first postoperative day before transfer to the general ward, the timing of which was dependent on the patient's condition. Prophylactic broad-spectrum antibiotics were administered intravenously for 1–3 days. Albumin and/or fresh frozen plasma was given if the plasma albumin level was lower than 30 g/L. Blood tests and serologic hepatic function tests were performed 1, 3, 5, and 7 days after operation. All patients underwent chest X-ray examinations on the third postoperative day and ultrasound within the first week after surgery.

Data collection and group division

Medical records were reviewed for the following baseline characteristics and operative variables, which included sex, age, American Society of Anesthesiologists (ASA) score, diabetes mellitus, obesity (body mass index ≥ 30 m^2/kg), hepatitis B surface antigen, anti-hepatitis C virus (HCV), presence/absence of cirrhosis or portal hypertension, preoperative platelets, international normalized ratio (INR), and hepatic function test, tumor's radiological features by preoperative CT or MRI (largest tumor size, tumor number, and gross vascular invasion), intraoperative blood loss, intraoperative blood transfusion, extent of hepatectomy (major or minor), and type of liver resection (anatomical or non-anatomical). The variables that reflected hepatic function including total bilirubin (TB), alanine aminotransferase (ALT), AST and albumin level in the serum were recorded from laboratory tests performed within one week prior to surgery. Basically, TB was measured by diazonium salt method, ALT and AST were measured by enzyme coupling method, and albumin was measured by biuret colorimetric method. Cirrhosis was confirmed by histopathological examination. Portal hypertension was defined by the presence of either esophageal varices or splenomegaly with a low platelet count ($\leq 100 \times 10^9$/L). Major hepatectomy was defined as resection of three or more Couinaud liver segments, and minor hepatectomy as resection of fewer than three segments. Anatomical resection was defined by the Brisbane 2000 nomenclature of liver anatomy (38), while non-anatomical resection included wedge resection or limited resection.

Patients were stratified on the basis of preoperative

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ALBI and APRI scores, as well as Child-Pugh grading and MELD score. The ALBI score was calculated using the following formula: ALBI score = –0.085 × [albumin (g/L)] + 0.66 × $\log_{10}$ [bilirubin (μmol/L)] (24). Using –2.60 as the standardized cut-off value for ALBI score in the firstly proposed study (24), patients were divided into the normal ALBI group (score ≤–2.60, ALBI grade I) and the high ALBI group (score >–2.60, ALBI grade II–III). The APRI score was calculated using the following formula: APRI score = [AST/upper limit of normal)/platelet count (10^9/L)] ×100 (23). Using the commonly-used 1.50 as the cut-off value for APRI score which was used in some previous prognostic studies (23,39), patients were also divided into the normal APRI group (score ≤1.50) and the high APRI group (score >1.50). The calculation of Child-Pugh score included serum albumin, serum bilirubin, prothrombin time, hepatic encephalopathy, and ascites (40). The Child-Pugh grading was defined as grade A (5–6 points); grade B (7–9 points); and grade C (10–15 points). There was no patient with Child-Pugh grade C in this study. The MELD score was calculated by the formula 9.6 × $\log_e$ [creatinine (mg/dL)] + 3.8 × $\log_e$ [bilirubin (mg/dL)] + 11.2 × $\log_e$ (INR) + 6.49 (41).

Study endpoints

The primary endpoint of the study was postoperative 30-day overall morbidity, which was a standardized item recorded within 30 days after surgery. The second endpoint of this study was postoperative 30-day major morbidity defined as Clavien-Dindo grade III-V (42). Postoperative complications (i.e., overall morbidity) included PHLF, intra-abdominal hemorrhage, biliary complications, surgical site infection (SSI), pulmonary, renal, cardiovascular, and other complications. PHLF was defined according to the "50-50 criteria" on or after POD 5 (43). Intra-abdominal hemorrhage was defined as a drop of hemoglobin level >3 g/dL after the end of resection compared with postoperative baseline level and/or any postoperative transfusion of packed red blood cell units for a falling hemoglobin and/or the need for invasive re-intervention (44). SSI within 30 days of surgery was diagnosed according to the Centers for Disease Control and Prevention of the National Nosocomial Infections Surveillance, which could be classified as either incisional (superficial or deep) SSI or organ/space SSI (45). Ascites and pleural effusion that required diuretics or paracentesis were also included as morbidity (46). Bile leak was defined by a bilirubin concentration in the drainage

of more than threefold higher than that in the serum (47). Renal dysfunction was defined as greater than 50% decrease in glomerular filtration rate or doubling of the creatinine level (48). Respiratory complications included pneumonia and pleural effusion. Urinary infection, acute pancreatitis, acute cholangitis and cardiocerebrovascular accident were recorded as other complications.

Statistical analysis

Normally distributed continuous variables were expressed as mean ± standard deviation and non-normally distributed continuous variables as median (range), which were compared by the Student's t-test or the Mann-Whitney U test as appropriate. Categorical variables were expressed as number (n) or proportion (%) and were compared by the χ^2 test or the Fisher's exact test. The incidences of overall and major morbidity were compared between the normal and high ALBI groups, as well as between the normal and high APRI groups. ALBI and APRI's predictive accuracy of overall and major morbidity was assessed by the area under the receiver operating characteristic curve (AUC), which were compared with the Child-Pugh grading and MELD score. Univariable and multivariable analyses were performed to identify independent risk factors associated with overall and major morbidity, respectively. Only significant variables in the univariable analysis (P<0.1) were entered into the multivariable logistic regression model using a forward stepwise variable selection. For multivariable analyses, two models, i.e., pre- and postoperative prediction models, were constructed based on whether those intraoperative variables were enrolled into the model or not. On the basis of the results of multivariable analyses, preoperative and postoperative nomogram models and corresponding web-based calculators for predicting overall and major morbidity were formulated. To assess fit of the nomogram, its predictive performance was tested in the training cohort by discrimination and calibration. The concordance index (C-index) was used to measure the discrimination by calculating the area under the receiver operating characteristic (ROC) curve, while the calibration plot was assessed by employing the Hosmer-Lemeshow test. The predictive performance of the nomograms was also internally validated with 1,000 bootstrap samples and calibration plots. All statistical analysis was performed using SPSS version 25.0 for Windows (SPSS, Chicago, IL, USA) and R 3.5.1 (http://www.r-project.org/). A two-tailed value of P<0.05 was considered as statistically significance.
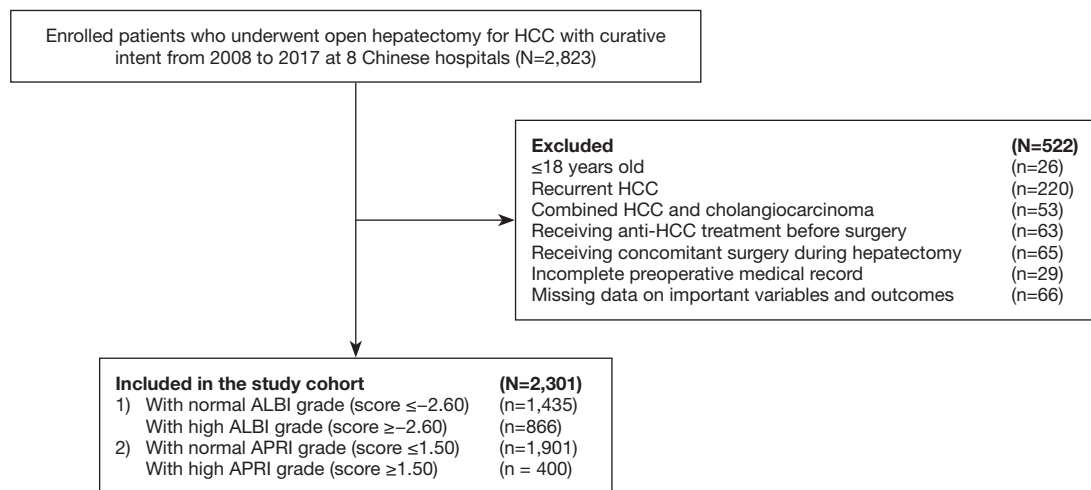
Figure 1 Selection of the study population. HCC, hepatocellular carcinoma; ALBI, albumin-bilirubin; APRI, aspartate transaminase-to-platelet ratio index.

Results

During the study interval, 2,823 patients underwent open hepatectomy with curative intent for HCC in the 8 hospitals in China. Using the inclusion criteria, 2,301 patients were enrolled into the study (*Figure 1*). There were 2,038 men (88.6%) and 263 women (11.4%) with a mean age of 50.9 years (range, 20–83 years). Most patients (90.4%) had hepatitis B and only 62 (2.7%) patients had hepatitis C. In addition, 1,715 (74.5%) patients had cirrhosis and 509 (22.1%) patients had portal hypertension. Overall, 1,435 (62.4%) and 866 (37.6%) patients were categorized into the normal and high ALBI groups; 1,901 (82.6%) and 400 (17.4%) patients were categorized as normal APRI and high APRI, respectively. Baseline characteristics and operative variables were stratified according to the different ALBI and APRI groups (*Table 1*). There were marked differences in many variables between the normal and high ALBI groups, including age, ASA score, Anti-HCV (+), cirrhosis, portal hypertension, preoperative TB, albumin, INR, platelets, ALT and AST levels, Child-Pugh grading, MELD score, largest tumor size, gross vascular invasion, intraoperative blood loss, and intraoperative blood transfusion (all P<0.05). Similarly, significant differences also existed in the normal and high APRI groups, including obesity, HBsAg(+), cirrhosis, portal hypertension, preoperative TB, albumin, INR, platelets, ALT and AST levels, Child-Pugh grading, MELD score, gross vascular invasion, intraoperative blood loss, intraoperative blood transfusion, and extent of hepatectomy (all P<0.05).

Postoperative outcomes

Among the 2,301 patients, 31 (1.3%) and 725 (31.5%) experienced postoperative 30-day mortality and morbidity, respectively. Among the 725 patients with morbidity, 260 (35.9%) and 465 (64.1%) had major or minor complications, respectively. Comparisons of postoperative outcomes between patients in the normal and high ALBI groups, as well as between the normal and high APRI groups are shown in *Table 1*. Of note, there were marked differences in the incidence of overall and major morbidity between the normal and high ALBI groups (26.7% *vs.* 39.5%, and 9.0% *vs.* 15.1%, both P<0.001), as well as between the normal and high APRI groups (29.2% *vs.* 42.3%, P<0.001, and 10.2% *vs.* 16.3%, P=0.001), respectively. Significant differences also existed in the incidences of minor morbidity, mortality, PHLF, pneumonia, SSI, ascites, and pleural effusion between the normal and high ALBI groups (all P<0.01), as well as in the incidences of minor morbidity, mortality, PHLF, intra-abdominal hemorrhage, ascites, and pleural effusion between the normal and high APRI groups (all P<0.05).

Risk factors of overall and major morbidity

Univariable and multivariable logistic regression analyses of preoperative and intraoperative variables identified several factors which were associated with postoperative overall morbidity (*Table 2*). In the preoperative predictive model, ASA score >2, diabetes mellitus, cirrhosis, high ALBI

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Table 1 Comparisons of baseline characteristics, operative variables and postoperative outcomes

Variables	Total (N=2,301)	ALBI			APRI		
		The normal group (N=1,435)	The high group (N=866)	P value	The normal group (N=1,901)	The high group (N=400)	P value
Preoperative variables							
Age, years	50.9±10.8	49.8±10.9	52.6±10.4	<0.001	50.8±11.0	51.17±10.0	0.488
Sex, male/female	2,038/263 (88.6/11.4)	1,270/165 (88.5/11.5)	768/98 (88.7/11.3)	0.894	1,694/207 (89.1/10.9)	344/56 (86.0/14.0)	0.075
ASA score >2	290 (12.6)	147 (10.2)	143 (16.5)	<0.001	241 (12.7)	49 (12.3)	0.815
Diabetes mellitus	131 (5.7)	77 (5.4)	54 (6.2)	0.383	107 (5.6)	24 (6.0)	0.771
Obesity (BMI >30 m²/kg)	80 (3.5)	48 (3.3)	32 (3.7)	0.657	59 (3.1)	21 (5.3)	0.033
Anti-HCV (+)	62 (2.7)	27 (1.9)	35 (4.0)	0.002	48 (2.5)	14 (3.5)	0.274
HBsAg (+)	2,079 (90.4)	1,290 (89.9)	789 (91.1)	0.340	1,697 (89.3)	382 (95.5)	<0.001
Cirrhosis	1,715 (74.5)	1,001 (69.8)	714 (82.4)	<0.001	1,372 (72.2)	343 (85.8)	<0.001
Portal hypertension	509 (22.1)	270 (18.8)	239 (27.6)	<0.001	286 (15.0)	223 (55.8)	<0.001
TB level (µmol/L)	14.6±6.4	13.7±5.5	15.9±7.5	<0.001	13.9±6.0	17.6±7.4	<0.001
Albumin level (g/L)	40.5±4.4	43.0±2.9	36.3±2.9	<0.001	40.7±4.3	39.5±4.7	<0.001
INR	1.1±0.1	1.1±0.1	1.1±0.1	<0.001	1.1±0.1	1.1±0.1	<0.001
Platelets level (×10⁹/L)	144.9±69.9	149.4±65.6	137.5±75.9	<0.001	157.82±66.9	83.7±47.7	<0.001
ALT level, U/L	36.0 (4.0–836.6)	35.5 (4.0–467.2)	37.8 (6.0–836.6)	0.092	33.0 (4.0–413.0)	62.5 (14.0–836.6)	<0.001
AST level, U/L	35.0 (6.0–765.7)	33.5 (6.0–335.1)	38.0 (6.0–765.7)	<0.001	31.6 (6.0–159.4)	69.4 (22.0–765.7)	<0.001
Child-Pugh score, A/B	2,104/197 (91.4/8.6)	1,415/20 (98.6/1.4)	689/177 (79.6/20.4)	<0.001	1,785/116 (93.9/6.1)	319/81 (79.8/20.3)	<0.001
MELD score	4.4±2.9	4.0±2.8	4.9±2.9	<0.001	4.1±2.8	5.4±2.9	<0.001
Largest tumor size, cm	6.2±4.0	5.8±3.7	6.7±4.4	<0.001	6.1±4.0	6.3±4.5	0.456
Multiple tumors	421 (18.3)	263 (18.3)	158 (18.2)	0.960	345 (18.1)	76 (19.0)	0.689
Gross vascular invasion	251 (10.9)	139 (9.7)	112 (12.9)	0.016	191 (10.0)	60 (15.0)	0.004
Intraoperative variables							
Intraoperative blood loss	300 (50–8,000)	300 (50–5,000)	350 (50–8,000)	<0.001	300 (50–8,000)	450 (50–8,000)	<0.001
Intraoperative blood transfusion	468 (20.3)	225 (15.7)	224 (25.9)	<0.001	320 (16.8)	129 (32.3)	<0.001
Major hepatectomy	532 (23.1)	299 (20.8)	176 (20.3)	0.768	372 (19.6)	103 (25.8)	0.005
Non-anatomical hepatectomy	1,701 (73.9)	1,049 (73.1)	652 (75.3)	0.247	1,421 (73.8)	300 (74.6)	0.724
Postoperative outcomes							
Postoperative 30-day morbidity	725 (31.5)	383 (26.7)	342 (39.5)	<0.001	556 (29.2)	169 (42.3)	<0.001
Major morbidity	260 (11.3)	129 (9.0)	131 (15.1)	<0.001	195 (10.2)	65 (16.3)	0.001
Minor morbidity	465 (20.2)	254 (17.7)	211 (24.4)	<0.001	361 (19.0)	104 (26.0)	<0.001

Table 1 (continued)

Table 1 *(continued)*

Variables	Total (N=2,301)	ALBI			APRI		
		The normal group (N=1,435)	The high group (N=866)	P value	The normal group (N=1,901)	The high group (N=400)	P value
Perioperative 30-day mortality	31 (1.3)	8 (0.6)	23 (2.6)	<0.001	15 (0.8)	16 (4.0)	<0.001
Type of complications							
PHLF	212 (9.2)	111 (7.7)	101 (11.7)	0.002	158 (8.3)	54 (13.5)	0.001
Intra-abdominal hemorrhage	22 (1.0)	11 (0.8)	11 (1.3)	0.229	13 (0.7)	9 (2.3)	0.008
Bile leak	25 (1.1)	15 (1.0)	10 (1.2)	0.806	20 (1.1)	5 (1.3)	0.790
Pneumonia	45 (2.0)	18 (1.3)	27 (3.1)	0.002	34 (1.8)	11 (2.8)	0.207
Surgical site infection	154 (6.7)	74 (5.2)	80 (9.2)	<0.001	120 (6.3)	34 (8.5)	0.112
Ascites	132 (5.7)	57 (4.0)	75 (8.7)	<0.001	74 (3.9)	58 (14.5)	<0.001
Pleural effusion	462 (20.1)	246 (17.1)	216 (24.9)	<0.001	367 (19.3)	95 (23.8)	0.044
Others	243 (10.6)	133 (9.3)	110 (12.7)	0.009	188 (9.8)	55 (1.8)	0.022
Postoperative hospital stays, days	12.8±6.6	13.6±6.4	12.3±6.9	<0.001	12.6±6.6	14.0±6.7	<0.001

ALBI, albumin-bilirubin grade; ALT, alanine aminotransferase; APRI, aspartate transaminase to platelet ratio index; ASA, American Society of Anesthesiologists; AST, aspartate aminotransferase; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; INR, international normalized ratio; PHLF, post-hepatectomy liver failure; TB, total bilirubin.

grade, high APRI grade and largest tumor size >5 cm were independent risk factors of postoperative overall morbidity. Meanwhile, in the postoperative predictive model, ASA score >2, diabetes mellitus, cirrhosis, high ALBI grade, high APRI grade and intraoperative transfusion, as well as major hepatectomy were identified as independent risk factors of postoperative overall morbidity.

Univariable and multivariable logistic regression analyses of preoperative and intraoperative variables associated with postoperative major morbidity are shown in *Table 3*. Diabetes mellitus, cirrhosis, high ALBI grade, high APRI grade were independent risk factors of postoperative major morbidity in both the preoperative and postoperative prediction models. In addition, intraoperative transfusion and major hepatectomy were identified as independent risk factors of major morbidity in the postoperative model.

Prediction models of overall and major morbidity

The preoperative and postoperative nomogram models to predict overall morbidity were constructed on the basis of independent risk factors as identified by multivariable

analyses in the preoperative and postoperative prediction models. As demonstrated in *Figure 2A,B*, each variable had a corresponding score on the point scale with the total score obtained by adding up the scores to find a point total on the scale, which was then associated with the probability of overall morbidity. Similarly, the preoperative and postoperative nomogram models for predicting major morbidity were constructed as shown in *Figure 2C,D*. Based on these 4 nomogram models, web-based calculators were consequently developed for ease to obtain the probability of overall and major morbidity before or after hepatectomy for HCC. The calibration plots for these four nomograms all showed favorable agreements between prediction by the nomograms and actual observation, as shown in *Figure 3A,B,C,D*. The resulting models were internally validated using the bootstrap validation method which demonstrated good accuracy with the bootstrap-corrected C indices of 0.732 and 0.751 for the preoperative and postoperative prediction of overall morbidity, as well as 0.713 and 0.739 for the preoperative and postoperative prediction of major morbidity, respectively. The calculators are available at: http://www.asapcalculate.top/Cal7_en.html

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Table 2 Univariable and multivariable logistic regression analyses predicting overall morbidity in patients undergoing liver resection for hepatocellular carcinoma

Variables	Univariate logistic regression		Multivariate logistic regression			
			Preoperative prediction model		Postoperative prediction model	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Preoperative variables						
Age >60 years	1.308 (1.057–1.619)	0.013	NS	0.236	NS	0.156
Male	1.038 (0.786–1.371)	0.792				
ASA score >2	1.561 (1.212–2.010)	0.001	1.348 (1.032–1.760)	0.028	1.319 (1.008–1.725)	0.044
Diabetes mellitus	2.110 (1.480–3.009)	<0.001	2.053 (1.414–2.982)	<0.001	2.097 (1.440–3.055)	<0.001
Obesity	0.929 (0.571–1.512)	0.768				
Anti-HCV (+)	1.291 (0.765–2.178)	0.338				
HBsAg (+)	0.933 (0.694–1.252)	0.643				
Cirrhosis	1.960 (1.572–2.443)	<0.001	1.856 (1.478–2.331)	<0.001	1.874 (1.490–2.357)	<0.001
Portal hypertension	1.354 (1.101–1.664)	0.004	NS	0.550	NS	0.933
INR >1.17	1.286 (1.048–1.577)	0.016	NS	0.874	NS	0.948
ALT level >40 U/L	0.930 (0.779–1.111)	0.423				
High ALBI grade	1.793 (1.498–2.145)	<0.001	1.518 (1.260–1.830)	<0.001	1.474 (1.221–1.780)	<0.001
High APRI grade	1.681 (1.346–2.100)	<0.001	1.538 (1.222–1.936)	<0.001	1.359 (1.074–1.720)	0.011
Largest tumor size >5 cm	1.760 (1.470–2.106)	<0.001	1.802 (1.497–2.169)	<0.001	NS	0.432
Multiple tumors	1.018 (0.812–1.278)	0.875				
Gross vascular invasion	1.568 (1.198–2.052)	0.001	NS	0.296	NS	0.708
Intraoperative variables						
Intraoperative blood loss >400 mL	1.983 (1.605–2.451)	<0.001			NS	0.497
Intraoperative blood transfusion	2.112 (1.766–2.526)	<0.001			1.752 (1.445–2.125)	<0.001
Major hepatectomy	1.262 (1.020–1.560)	0.032			1.554 (1.282–1.885)	<0.001
Non-anatomical hepatectomy	1.088 (0.889–1.332)	0.411				

ALBI, albumin-bilirubin grade; ALT, alanine aminotransferase; APRI, aspartate transaminase to platelet ratio index; ASA, American Society of Anesthesiologists; CI, confidence interval; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; INR, international normalized ratio; NS, no significance.

(*Figure 4A,B,C,D*). When users simply input the requested information on the preoperative or postoperative predictors, the probability of postoperative overall and major morbidity can be derived.

Predictive accuracy for overall and major morbidity

The predictive abilities of the preoperative and postoperative nomogram models, Child-Pugh grading, and ALBI, APRI, and MELD scores for overall and major

morbidity among patients with HCC were evaluated by the ROC curves, as shown in *Figure 5A,B*. For predicting overall morbidity, the highest AUC was the postoperative predictive model (AUC: 0.742, 95% CI: 0.720–0.764), followed by the preoperative predictive model (0.728, 0.706–0.751), the ALBI score (0.608, 0.583–0.633), the APRI score (0.559, 0.533–0.584), the MELD score (0.549, 0.524–0.574), and the lowest was the Child-Pugh grading (0.535, 0.510–0.561). As such, the postoperative model had the best predictive accuracy for overall morbidity among

Table 3 Univariable and multivariable logistic regression analyses predicting major morbidity in patients undergoing liver resection for hepatocellular carcinoma

| Variables	Univariate logistic regression		Multivariate logistic regression			
			Preoperative prediction model		Postoperative prediction model	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Preoperative variables						
Age >60 years	1.110 (0.812–1.518)	0.513				
Male	0.988 (0.660–1.480)	0.953				
ASA score >2	1.486 (1.047–2.110)	0.027	NS	0.154	NS	0.182
Diabetes mellitus	1.638 (1.016–2.641)	0.043	1.664 (1.024–2.705)	0.040	1.668 (1.025–2.717)	<0.001
Obesity	0.746 (0.340–1.638)	0.465				
Anti-HCV (+)	1.724 (0.887–3.351)	0.108				
HBsAg (+)	0.763 (0.509–1.142)	0.188				
Cirrhosis	1.775 (1.265–2.491)	0.001	1.639 (1.160–2.317)	0.005	1.647 (1.165–2.328)	0.001
Portal hypertension	1.144 (0.845–1.548)	0.384				
INR >1.17	1.309 (0.979–1.751)	0.070	NS	0.457	NS	0.517
ALT level >40 U/L	1.104 (0.852–1.431)	0.454				
High ALBI grade	1.804 (1.392–2.339)	<0.001	1.565 (1.200–2.040)	0.001	1.531 (1.173–1.999)	0.002
High APRI grade	1.685 (1.244–2.284)	0.001	1.524 (1.116–2.082)	0.008	1.416 (1.030–1.946)	0.008
Largest tumor size >5 cm	1.940 (1.477–2.547)	<0.001	1.890 (1.436–2.488)	<0.001	NS	0.477
Multiple tumors	1.102 (0.795–1.527)	0.559				
Gross vascular invasion	1.265 (0.859–1.862)	0.235				
Intraoperative variables						
Intraoperative blood loss >400 mL	1.616 (1.202–2.172)	0.001			NS	0.681
Intraoperative blood transfusion	1.766 (1.362–2.288)	<0.001			1.388 (1.052–1.832)	0.021
Major hepatectomy	1.522 (1.135–2.042)	0.005			1.725 (1.296–2.295)	<0.001
Non-anatomical hepatectomy	0.911 (0.682–1.217)	0.529				

ALBI, albumin-bilirubin grade; ALT, alanine aminotransferase; APRI, aspartate transaminase to platelet ratio index; ASA, American Society of Anesthesiologists; CI, confidence interval; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; INR, international normalized ratio; NS, no significance.

these 6 indices, while the APRI and ALBI scores had a better predictive accuracy than the Child-Pugh and MELD scores. Similarly, the highest AUC for predicting major morbidity was the postoperative predictive model (AUC: 0.739, 95% CI: 0.709–0.769), followed by the preoperative predictive model (0.713, 0.682–0.745), the ALBI score (0.623, 0.585–0.660), the APRI score (0.587, 0.549–0.624), the MELD score (0.557, 0.520–0.594), and the lowest was the Child-Pugh grading (0.532, 0.493–0.571). The postoperative model also had the best predictive accuracy

for major morbidity among these 6 indices, while the APRI and ALBI scores had a better predictive accuracy than the MELD score and the Child-Pugh grading.

Conclusions

Accurate prediction of postoperative morbidity, especially before or immediately after surgery, is important to identify patients at high risks so that subsequently timely treatment can be instituted to improve short-term outcomes among

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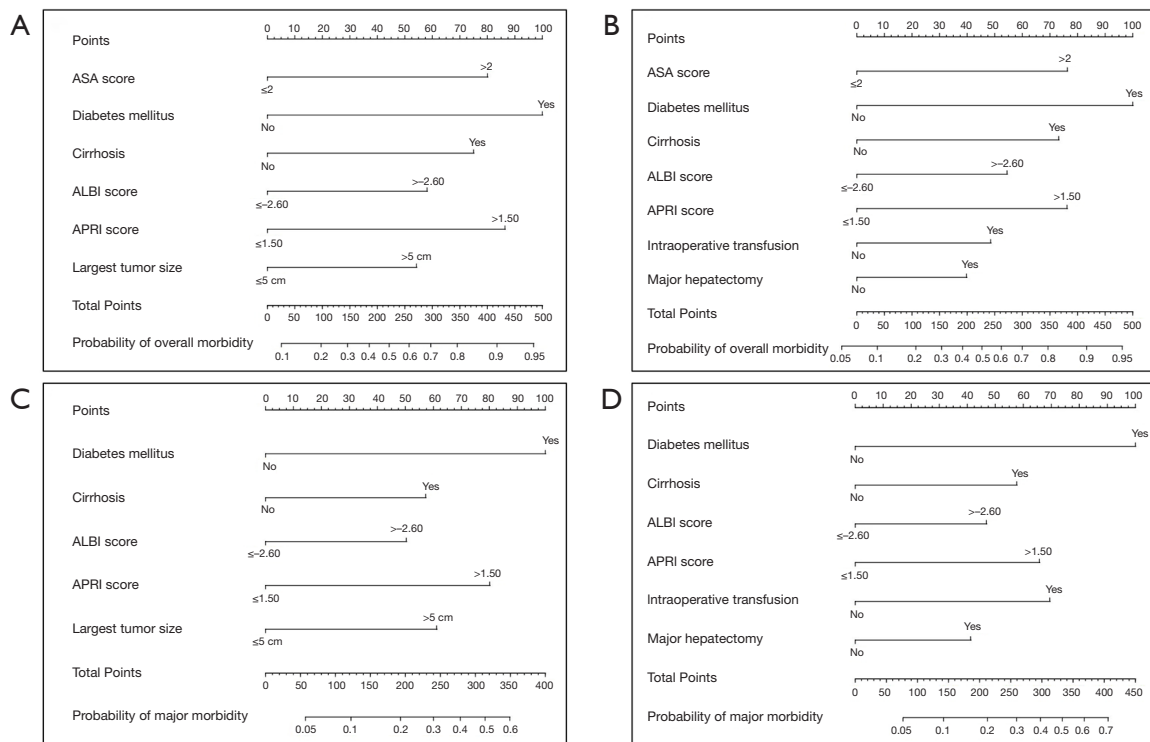
Figure 2 The nomogram models for the prediction of overall morbidity [(A) preoperative and (B) postoperative] and major morbidity [(C) preoperative and (D) postoperative] for patients undergoing hepatectomy for hepatocellular carcinoma.
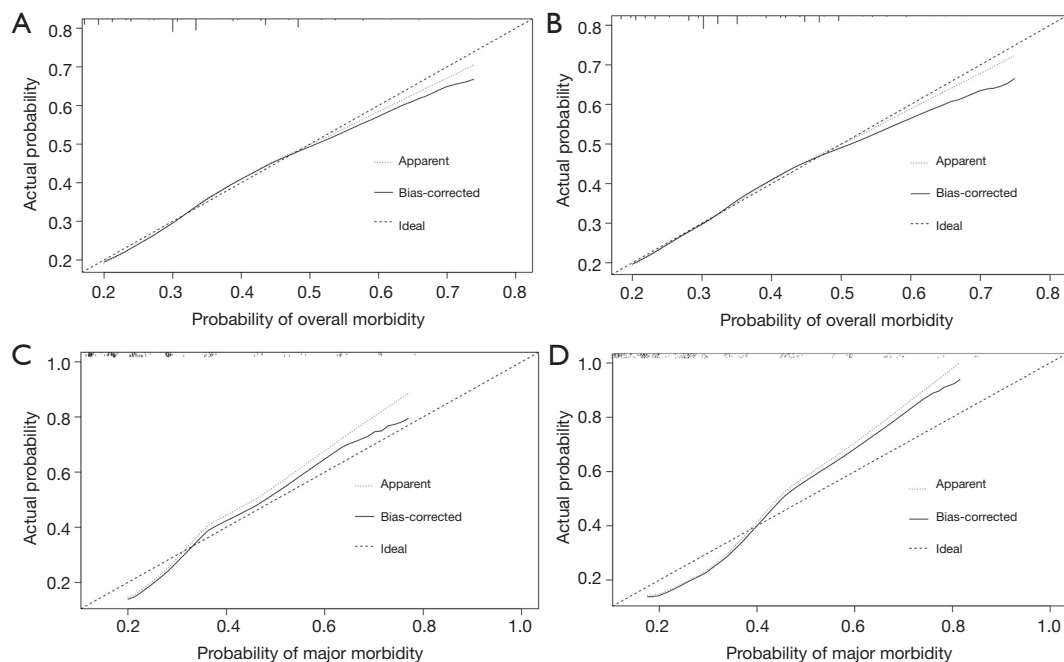
Figure 3 Calibration curves of the nomograms comparing and actual and predicted probabilities of overall and major morbidity, including the predictive performance of preoperative (A) and the postoperative (B) nomograms for predicting overall morbidity, and preoperative (C) and the postoperative (D) nomograms for predicting major morbidity.
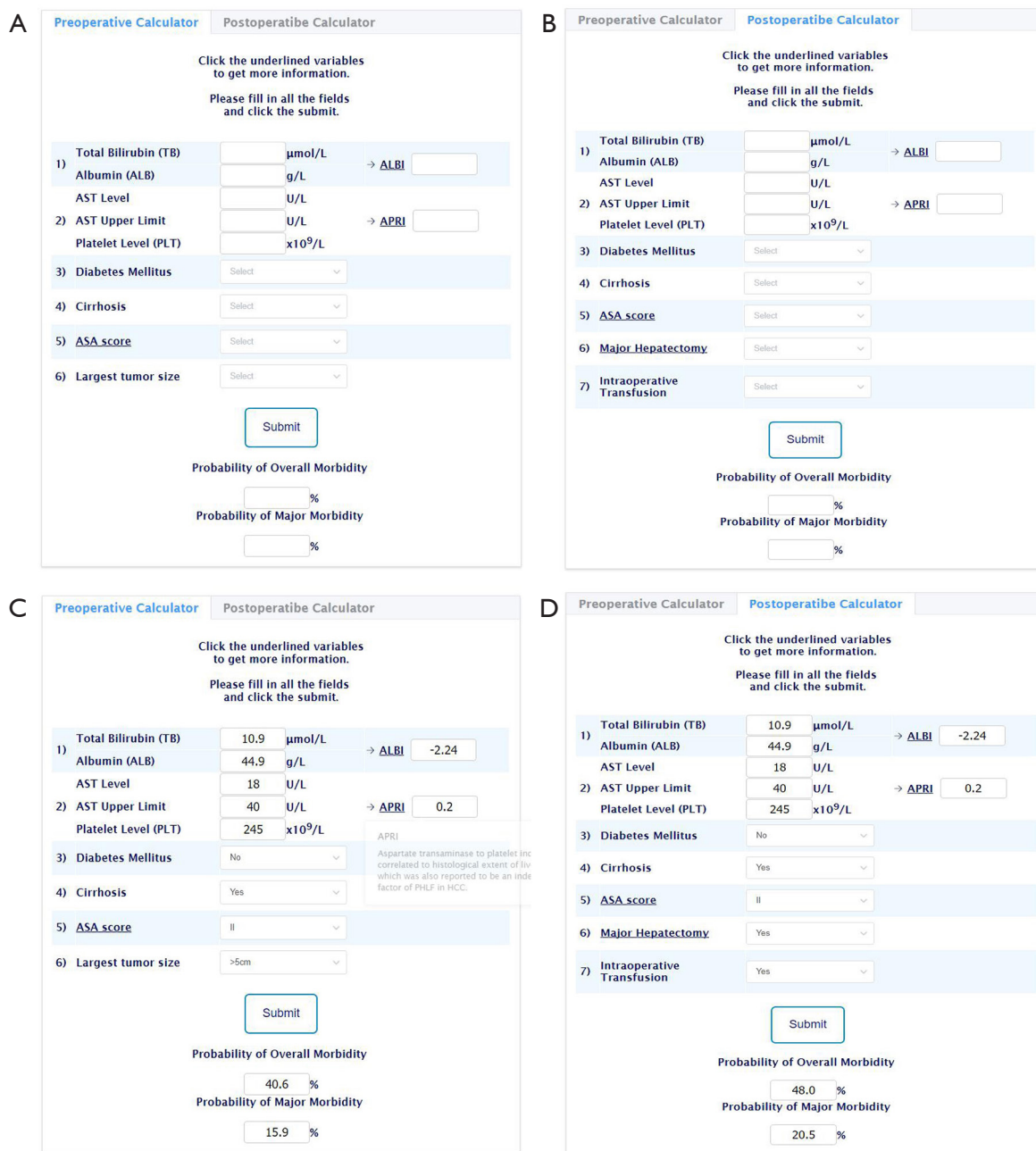
Figure 4 Our Internet browser-based online calculators for the preoperative (A) and postoperative (B) prediction of overall and major morbidity for patients with hepatocellular carcinoma. (http://www.asapcalculate.top/Cal7_en.html). Probabilities of developing overall and major morbidity of a patient who underwent curative hepatectomy for HCC were calculated preoperatively (C) and postoperatively (D), respectively. HCC, hepatocellular carcinoma.

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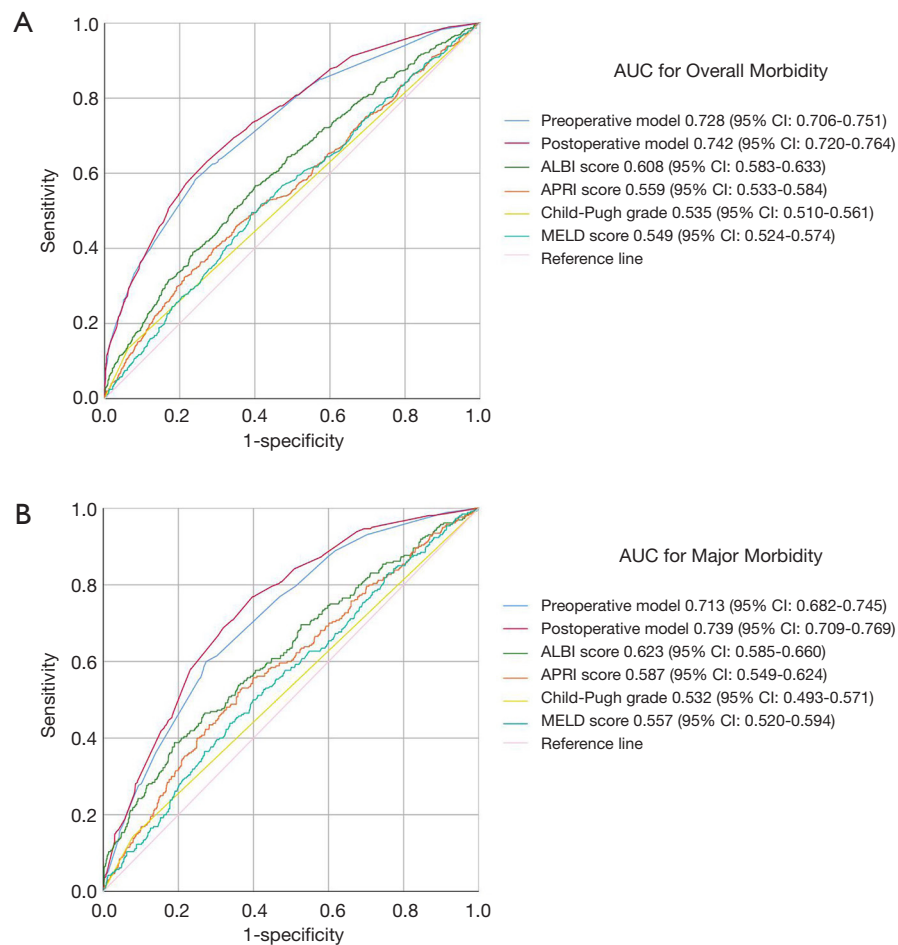
Figure 5 Receiver operating characteristic curves of preoperative and postoperative prediction models, MELD, ALBI, and APRI scores, and Child-Pugh grade for predicting overall morbidity (A) and major morbidity (B). AUC, area under the receiver operating characteristic curve; CI, confidence interval; MELD, model for end-stage liver disease; ALBI, albumin-bilirubin; APRI, aspartate transaminase-to-platelet ratio index.

patients undergoing hepatectomy for HCC. This large multicenter study of 2,301 patients analyzed the impact of two simple and noninvasive biomarker-based scores, i.e., the ALBI and APRI scores, on postoperative morbidity following hepatectomy for HCC. Consistent with previous studies (25-27,29-32,49), the results of the present study demonstrated that both the ALBI and APRI scores had better ability to predict postoperative morbidity than the Child-Pugh grading and MELD score. Furthermore, univariable and multivariable logistic regression analyses identified that, both in the preoperative and postoperative models, high ALBI score (>−2.6) and high APRI score (>1.5) were independent risk factors associated with both overall morbidity and major morbidity after hepatectomy for HCC.

Based on independent risk factors (including both ALBI and APRI) obtained from multivariable analyses, we constructed preoperative and postoperative nomogram models to predict overall morbidity and major morbidity, respectively. These nomogram models could help surgeons to accurately predict the probabilities of morbidity among patients before or immediately after surgery and provide useful information to inform conversations about surgical risks. Furthermore, to facilitate their use in clinical practice, we developed corresponding online calculators to make it easy to obtain personalized probabilities of overall morbidity and major morbidity in patients with HCC.

In the present study, the primary endpoints that fascinate us are postoperative 30-day, rather than 90-day, overall

and major morbidity, most of which occurred during hospitalization of hepatectomy. Numerous studies have demonstrated that the occurrence of postoperative 30-day morbidity was independently associated with long-term recurrence and survival after curative resection for HCC (6,9,50). Furthermore, postoperative 30-day morbidity is closely related to the re-admission rate after discharge, which is also an important evaluation index of medical quality. How to more precisely predict, so as to effectively prevent and decrease the occurrence of postoperative 30-day morbidity, is one of key issues to improve short- and long-term prognosis for patients undergoing hepatectomy for HCC. Of course, the attempt to predict postoperative 90-day morbidity is also an interesting research topic, which, in our opinion, can also be achieved by the use of nomogram models.

The ALBI and APRI scores are non-invasive, simple and entirely objective scores which are derived from routine laboratory results. In the current study, the ALBI and APRI scores (although each grade contains only two biochemical variables) have better discriminatory ability than the Child-Pugh grading and MELD score (although each grade contains 3–5 variables) to predict postoperative overall and major morbidity among patients undergoing hepatectomy for HCC. As such, more variables included in the prediction model do not necessarily translate into a more accurate predictive ability. The ALBI score consists of only bilirubin and albumin and APRI consists of only AST and platelets, both of which eliminate the need for subjective variables that are contained in the Child-Pugh grading.

Apart from the ALBI and APRI scores, there are other independent risk factors which are known to be associated with postoperative morbidity. Diabetes mellitus, a metabolic disorder characterized by hyperglycemia, compromises the ability of the liver to regenerate and is particularly associated with poor prognosis after hepatic ischaemia-reperfusion injury (51). In numerous previously reported studies, diabetes mellitus were shown to have a negative impact on short-term outcomes in patients undergoing hepatectomy (19,52-54). In the present study, diabetes mellitus was also noted to be an important risk factor associated with postoperative morbidity (either overall or major) in both the preoperative and postoperative prediction models. Additionally, in this study, largest tumor size >5 cm was an independent risk factor of postoperative morbidity in the preoperative prediction model, while major hepatectomy and intraoperative blood transfusion were two independent risk factors of postoperative

morbidity in the postoperative prediction model. There was a positive correlation between tumor size, extent of hepatectomy and postoperative morbidity: the larger the tumor size, the higher the probability of performing major hepatectomy, and the higher the probability of development of postoperative morbidity. As for the relationship of blood transfusion and postoperative morbidity, previous studies showed that intraoperative blood transfusion may have immunosuppressive effects on the body and thus hinder postoperative hepatic function recovery, as well as increase the incidence of infectious complications (including SSI, pulmonary infection, etc.), which could be one of the potential causes of postoperative overall or major morbidity (55). Perhaps due to the increased effect on the prediction of postoperative morbidity from intraoperative blood transfusion, the prediction ability of the postoperative model was more accurate than that of the preoperative model.

Admittedly, accurate prediction of postoperative overall morbidity is not so easy, because there are so many types of postoperative complications following hepatectomy, including PHLF, bile leak, SSI, ascites, pleural effusion, etc. Although there are common predictive factors for some types of complications, more often the predictive factors are different for most types of complication. In turn, the choice of predictive factors for predicting all postoperative complications is very important but difficult. Enrolling more predictive factors may make the model more accurate, but it will also make the model not simple enough and limit its promotion value in clinical practice. In this study, we used independent predictive factors obtained from multivariable analysis, and developed an online calculator through the formula obtained by the multivariable logistic regression model. This approach could not only effectively control the number of predictors, but also guarantees the different predictive capabilities of each predictor in the predictive model. Therefore, in our study, both of the C-indexes of the preoperative and postoperative prediction models exceeded 0.70, which were much higher than the Child-Pugh and MELD scores (all C-indexes <0.55).

There are several limitations in the present study. The retrospective study design had inherent defects. The majority of patients in the present study have underlying liver diseases related to hepatitis B virus, while the etiology in most western countries and Japan is predominantly HCV. Thus, results from the current study may not be applicable to HCC patients with different etiologies. Surgeons' skill and perioperative care in different hospitals are also likely to

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be a heterogeneous factor, although the surgical procedure have been standardized. Lastly, although we constructed and internally validated these two predictive nomogram models, external validation for these two models is unavailable due to the lack of an external validation cohort. Future studies should aim to validate the efficacy and applicability of the proposed novel online models using external cohorts of patients with HCC. We are now collecting cases in our clinic and one prospective validation study is under way. We also hope that more centers, especially from the West, will be able to employ and validate our online calculators in the future.

In conclusion, the present study demonstrated that the ALBI and APRI scores are useful predictors of postoperative 30-day overall and major morbidity in patients undergoing hepatectomy for HCC. Preoperative and postoperative prediction models that combined ALBI and APRI were developed into online calculators, which could help clinicians easily and accurately to predict the probability of postoperative overall and major morbidity among patients with HCC before or immediately after hepatectomy, so as to provide useful information to inform conversations about surgical risks.

Acknowledgments

Footnote

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). The study was approved by the Institutional Review Board of the Eastern Hepatobiliary Surgery Hospital of Shanghai, China (No. EHBHKY2019-K-005) and individual consent for this retrospective analysis was waived.

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