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International Validation and Refinement of Oncological Borderline Resectability Criteria for Hepatocellular Carcinoma Using Tumor Burden Score to Predict Survival

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Objective: The aim of this study is to externally validate the original borderline resectability (BR) category for predicting overall survival (OS) in hepatocellular carcinoma (HCC) following resection and to assess whether incorporating the tumor burden score (TBS) and other clinical factors could enhance predictive accuracy.

Background: A recent Japanese expert panel introduced a new HCC classification scheme: resectable (R), borderline resectable 1 (BR1), and borderline resectable 2 (BR2).

Methods: Patients undergoing curative-intent hepatectomy for HCC (2000–2023) were classified as R, BR1, and BR2 using the original BR and a novel TBS-BR category. The TBS-BR category replaces BR's categorical tumor morphology factors with the continuous TBS (TBS^2 = [maximum tumor diameter]^2 + [number of tumors]^2). Multivariable analysis identified oncologic, morphometric, and patient-level factors associated with OS, which were incorporated into an online predictive tool.

Results: Among 1766 patients, the original BR category grouped 1504 (85.2%) as R, 249 (14.1%) as BR1, and 13 (0.7%) as BR2. Utilizing the TBS-BR category, patients were reclassified as TBS-BR R (n = 684, 38.7%), BR1 (n = 1009, 57.1%), and BR2 (n = 73, 4.1%). Both the original and TBS-BR categories correlated with 5-year OS (original: 65.1%, 48.2%, 46.4%; TBS-BR: 70.8%, 58.3%, 40.0%; $P < 0.001$ for both; area under the curve: 0.54 vs 0.58). On multivariable analysis, TBS-BR1 (hazard ratio [HR]: 1.59 [1.20–2.09]; $P = 0.001$), TBS-BR2 (HR: 2.45 [1.47–4.07]; $P < 0.001$, reference: TBS-BR R), American Society of Anesthesiologists (ASA) class >2 (HR: 1.40 [1.09–1.80]; $P = 0.007$), albumin-bilirubin (ALBI) score (HR: 1.51 [1.21–1.88]; $P < 0.001$), and log α-fetoprotein (AFP) (HR: 1.07 [1.03–1.11]; $P < 0.001$) were independently associated with OS. A TBS-BR composite model based on these factors (TBS-BR category, ASA class, ALBI score, and log AFP) was developed and made available online (https://makbn.shinyapps.io/BRHCC/). The model's area under the receiver operating characteristic at 5 years (0.70) outperformed both the original BR (0.57) and Barcelona Clinic Liver Cancer classification (0.64).

Conclusions: The TBS-BR composite model, integrating tumor morphology (TBS), tumor biology (log AFP), overall physical status (ASA class), and liver function (ALBI score) demonstrated superior predictive accuracy for OS compared with the original BR and Barcelona Clinic Liver Cancer classifications.

Keywords: borderline resectablity, hepatectomy, hepatocellular carcinoma, overall survival, tumor burden score

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide,[1] with hepatectomy being the mainstay of curative treatment.[2] However, long-term survival after surgery remains suboptimal with 5-year survival ranging from 20% to 40%.[3] Accurate prognostic tools are essential to guide treatment strategies and optimize postoperative surveillance. A recent consensus from a panel of Japanese experts introduced new resectability criteria for HCC, referred to as the "original borderline resectability (BR) category."[4] These consensus criteria aimed to standardize oncological considerations to determine HCC resectability among patients who were both technically operable and had adequate liver function.[4] This classification addressed the need for clearer guidelines to manage patients eligible for "conversion therapy" and other treatments within the multidisciplinary care of advanced HCC.[4]

The original BR category was based on 3 key factors: tumor morphology (size and number), macroinvasion (including portal vein, hepatic vein, and biliary invasion), and the presence of extrahepatic spread (EHS).[4] The classification scheme categorized HCC resectability into 3 groups: resectable (R), borderline resectable 1 (BR1), and borderline resectable 2 (BR2). R cases are expected to have a significant survival benefit from surgery alone, BR1 cases may benefit from surgery as part of a multidisciplinary approach, while BR2 cases represent an oncological status with uncertain surgical efficacy that requires careful assessment within a multidisciplinary framework. This classification system, developed in 2023, filled a gap in the field as the concept of BR has long been established in pancreatic cancer, wherein invasion of local anatomical structures was a clear predictor of surgical suitability.[5] To date, the concept of BR relative to HCC has only been reported in Japan, highlighting the need for international validation.

The original BR criteria hold potential as a clinically useful tool to predict long-term overall survival (OS) among patients with HCC undergoing hepatectomy. The authors of the original BR category acknowledged the need for further optimization and future updates, taking into account advancements in therapy and further validation studies.[4] To this point, the original BR category utilized categorical tumor morphology data (ie, incremental nominal size and number cutoff values). More recently, our group and others have demonstrated that the tumor burden score (TBS) was a stronger predictor of outcomes among patients with HCC, even outperforming the Barcelona Clinic Liver Cancer (BCLC) staging system.[6] The TBS is a mathematical calculation that combines the maximum tumor size and the number of tumors to predict survival.[7] The TBS is calculated using the Pythagorean theorem to determine the distance from the origin on a Cartesian plane, with the maximum tumor size on the *x*-axis and the number of tumors on the *y*-axis. In the current study, we sought to externally validate the ability of the original BR category to predict OS using an international, multi-institutional database. In addition, we hypothesized that substituting categorical tumor morphology factors with the continuous TBS could enhance the clinical accuracy of the original BR category scheme to predict OS following liver resection of HCC.

MATERIALS AND METHODS

Study Population and Exclusion Criteria

Patients who underwent curative-intent liver resection for HCC between 2000 and 2023 were identified from an international, multi-institutional database. Patients were excluded if they had palliative resection, incomplete follow-up data, or missing values for the original BR category or TBS. The study was approved by the institutional review board of each participating institution.

Variables of Interest, Definitions, and Outcomes

Data were collected on patient demographics including age, sex, the American Society of Anesthesiologists (ASA) physical status classification, body mass index, diabetes, and preoperative cirrhosis status. Tumor staging was based on the 8th edition of the American Joint Committee on Cancer Staging Manual.[8] Laboratory data included preoperative aspartate aminotransferase (IU/L), alanine aminotransferase (IU/L), platelet count ($\times 10^3/\mu L$), albumin-bilirubin (ALBI) score,[9,10] international normalized ratio, and serum α-fetoprotein (AFP) levels (ng/mL). Tumor characteristics, such as maximum diameter and number of liver lesions, were documented along with pathological findings including microvascular and perineural invasion. Details regarding preoperative treatment, such as portal vein embolization, neoadjuvant immunotherapy, or systemic chemotherapy, were also recorded. Surgical variables included surgical approach (open or minimally invasive), extent of hepatectomy (ie, major hepatectomy defined as resection of more than three liver segments according to Couinaud's classification),[11] and whether adjuvant chemotherapy was administered. The TBS, which accounts for both the maximum tumor size and the number of tumors, was calculated using the formula $TBS^2 = (\text{maximum tumor diameter})^2 + (\text{number of tumors})^2$.[6,7]

In the original BR category, the cohort was classified into 3 groups: R, BR1, and BR2.[4] For the R category, tumor factors were defined as a single HCC lesion or multinodular HCC with ≤3 nodules and a maximum tumor diameter of ≤3 cm. Additionally, vascular and bile duct invasion were categorized as: no invasion—absence of macrovascular or bile duct invasion on imaging—and no EHS, which defined the R category. For BR2, the criteria included multinodular HCC with more than 5 nodules and/or any nodule larger than 5 cm in diameter, or vascular and bile duct invasion classified as major invasion, such as invasion of the main portal vein, contralateral portal branches, inferior vena cava, or tumor thrombus extending to the common bile duct. The presence of EHS was also classified under BR2. The BR1 category was defined by tumor conditions falling between the R and BR2 groups, including limited invasion of vascular or bile duct structures. Limited invasion was defined as macrovascular or bile duct invasion that did not extend to major structures, such as the main portal vein, contralateral portal branches, inferior vena cava, or tumor thrombus extending to the common bile duct. Additionally, localized EHS (eg, localized peritoneal dissemination, unilateral adrenal metastasis, or oligometastasis to the lung) was classified as BR1. The database did not fully capture information on localized EHS; therefore, BR1 was defined as having no EHS.

A novel TBS-BR category was created. Specifically, based on the R category tumor morphology definition, which states that for multiple tumors, each tumor must be ≤3 cm in size with a total of ≤3 tumors, the corresponding TBS was 4.24 (ie, 3 tumors, each measuring 3 cm). Considering that the American Association for the Study of Liver Diseases guidelines classify solitary tumors ≤5 cm in diameter as suitable for resection (ie, a TBS approximately of 5), the TBS cutoff for the R category in the TBS-BR classification was simplified to <5.00.[12] Furthermore, the upper limit for the BR1 category included up to 5 tumors, each with a maximum diameter of 5 cm, which corresponded to a TBS of 7.07. Therefore, in the TBS-BR category, the definition of tumor morphology for BR1 was modified to TBS between 5 and 7. The definition of tumor morphology for BR2 was set as TBS ≥7.00. Definitions of factors other than tumor morphology remained unchanged from the original BR category (Supplemental Figure 1, see http://links.lww.com/AOSO/A474).

The primary outcome was OS, defined as the time from the date of curative-intent surgery to the date of death from any cause or the last follow-up, whichever came first.

Statistical Analyses

Continuous variables were presented as medians with interquartile ranges, while categorical variables were expressed as frequencies and percentages. Categorical variables were compared using chi-squared test or Fisher exact test, and continuous variables were assessed using Mann–Whitney *U* test or Kruskal–Wallis test, as appropriate.

The study population was divided into R, BR1, and BR2 groups based on the definitions of the original BR category, and Kaplan–Meier survival curves were generated. The differences among the groups were evaluated using the log-rank test. Subsequently, the TBS-BR category was created, and Kaplan–Meier survival curves were generated with group comparisons made using the log-rank test. The entire cohort was then divided into a training set and a testing set at a ratio of 85:15 (1502 vs 264). A multivariable Cox regression analysis was conducted using the training set based on preoperative data to develop the TBS-BR composite model. To assess the model's ability to predict OS, its performance in the testing set was evaluated using the time-dependent area under the curve (AUC), as well as the area under the receiver operating characteristic (AUROC) curve at 1, 2, 3, 4, and 5 years postoperatively. This model was compared with the BCLC classification and the original BR category. The OS risk stratification of the new predictive model was assessed based on Kaplan–Meier survival curves. An online Shiny application was developed to provide easy access to the TBS-BR composite model. Statistical significance was defined as a P value of <0.05. All statistical analyses were performed using R version 4.3.1.

RESULTS

Study Population

Among 1766 patients who underwent curative-intent surgery for HCC, median age was 67 (59–73) years with 1389 (78.7%) patients being male. A total of 757 (42.9%) patients had an ASA class >2 (Supplemental Table 1, see http://links.lww.com/AOSO/A474). Median body mass index was 25.0 (22.5–28.1) kg/m^2, 513 (29.0%) patients had diabetes, and 794 (45.0%) had preoperative cirrhosis. Median ALBI score was −3.59 (−3.85 to −3.23), and median log AFP was 2.40 (1.21 to 5.09). A total of 696 (39.4%) patients underwent a major hepatectomy. Median tumor size, calculated as the maximum lesion diameter, was 5.00 (3.00 to 8.50) cm with a median tumor number of 1 (1 to 1). Median TBS was 5.10 (3.35 to 8.84). Microvascular invasion was observed in 493 (27.9%) patients, and perineural invasion was present in 108 (6.1%) patients. Adjuvant chemotherapy was administered to 38 (2.2%) patients.

Based on the original BR category definition, among 1766 patients in the analytic cohort, 1504 (85.2%) patients were classified as R, 249 (14.1%) as BR1, and 13 (0.7%) as BR2. Utilizing the novel TBS-BR category, which substituted tumor morphology with TBS (Table 1), patients were classified into TBS-BR R (n = 684, 38.7%), BR1 (n = 1009, 57.1%), and BR2 (n = 73, 4.1%). The proportion of patients with an ASA class >2 increased across the TBS-BR R, BR1, and BR2 groups (36.5%, 45.6%, and 64.4%, respectively; P < 0.001). Median

TABLE 1.

Patient Characteristics of the Overall Population Based on TBS-BR Category

Variable	TBS-BR R (n = 684)	TBS-BR1 (n = 1009)	TBS-BR2 (n = 73)	Overall (N = 1766)	*P*
Age, y, median (IQR)	67.0 (59.0 to 72.0)	67.0 (59.0–74.0)	66.0 (58.3 to 74.0)	67.0 (59.0 to 73.0)	0.660
Male, yes, n (%)	528 (77.2%)	806 (79.9%)	55 (75.3%)	1389 (78.7%)	0.324
ASA class>2, yes, n (%)	250 (36.5%)	460 (45.6%)	47 (64.4%)	757 (42.9%)	<0.001
BMI, kg/m^2, median (IQR)	25.2 (22.8 to 27.8)	24.8 (22.2 to 28.0)	26.5 (24.1 to 31.1)	25.0 (22.5 to 28.1)	<0.001
Diabetes, yes, n (%)	194 (28.4%)	303 (30.0%)	16 (21.9%)	513 (29.0%)	0.320
Cirrhosis, yes, n (%)	387 (56.6%)	364 (36.1%)	43 (58.9%)	794 (45.0%)	<0.001
Platelet, ×10^3/μL, median (IQR)	156 (119 to 201)	202 (150 to 262)	257 (199 to 326)	184 (136 to 243)	<0.001
Albumin, g/L, median (IQR)	41.7 (38.0 to 44.2)	40.2 (37.0 to 43.0)	38.9 (34.0 to 43.0)	41.0 (37.8 to 44.0)	<0.001
Total bilirubin, mg/dL, median (IQR)	0.72 (0.52 to 1.07)	0.60 (0.46 to 0.85)	0.50 (0.39 to 0.90)	0.64 (0.50 to 0.94)	0.013
ALBI score, median (IQR)	−3.62 (−3.86 to −3.28)	−3.57 (−3.84 to −3.21)	−3.56 (−4.01 to −3.13)	−3.59 (−3.85 to −3.23)	0.227
AST, IU/L, median (IQR)	32.0 (23.0 to 52.0)	42.0 (29.0 to 68.0)	45.5 (32.8 to 93.0)	39.0 (25.0 to 61.0)	<0.001
ALT, IU/L, median (IQR)	32.0 (22.0 to 53.8)	38.0 (25.0 to 68.0)	47.5 (28.8 to 73.5)	36.0 (24.0 to 63.0)	<0.001
INR, median (IQR)	1.05 (1.00 to 1.10)	1.05 (1.00 to 1.10)	1.00 (1.00 to 1.10)	1.05 (1.00 to 1.10)	0.803
PVE, yes, n (%)	16 (2.3%)	103 (10.2%)	2 (2.7%)	121 (6.9%)	<0.001
Neoadjuvant chemotherapy, yes, n (%)	3 (0.4%)	4 (0.4%)	0 (0%)	7 (0.4%)	0.926
Neoadjuvant immunotherapy, yes, n (%)	0 (0%)	4 (0.4%)	0 (0%)	4 (0.2%)	0.26
Log AFP, median (IQR)	1.98 (1.14 to 3.81)	2.79 (1.20 to 6.11)	3.59 (1.77 to 6.50)	2.40 (1.21 to 5.09)	<0.001
Tumor number, median (IQR)	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)	<0.001
Tumor size, cm, median (IQR)	3.00 (2.20 to 3.80)	7.00 (5.28 to 11.0)	11.1 (9.00 to 15.0)	5.00 (3.00 to 8.50)	<0.001
TBS, median (IQR)	3.16 (2.51 to 4.03)	7.42 (5.59 to 11.0)	11.1 (9.06 to 15.0)	5.10 (3.35 to 8.84)	<0.001
Microvascular invasion, yes, n (%)	121 (17.7%)	350 (34.7%)	22 (30.1%)	493 (27.9%)	<0.001
Perineural invasion, yes, n (%)	21 (3.1%)	79 (7.8%)	8 (11.0%)	108 (6.1%)	<0.001
AJCC N category, n (%)					
NX	482 (70.5%)	628 (62.2%)	20 (27.4%)	1130 (64.0%)	<0.001
N0	190 (27.8%)	318 (31.5%)	6 (8.2%)	514 (29.1%)	
N1	1 (0.1%)	21 (2.1%)10	2 (2.7%)	24 (1.4%)	
MIS, yes, n (%)	238 (34.8%)	222 (22.0%)	14 (19.2%)	474 (26.8%)	<0.001
Major hepatectomy, yes, n (%)	167 (24.4%)	490 (48.6%)	39 (53.4%)	696 (39.4%)	<0.001
Adjuvant chemotherapy, yes, n (%)	11 (1.6%)	21 (2.1%)	6 (8.2%)	38 (2.2%)	<0.001

Continuous variables: median (IQR); categorical variable: n (%).

AJCC, American Joint Committee on Cancer; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; INR, international normalized ratio; IQR, interquartile range; MIS, minimally invasive surgery; PVE, portal vein embolization.

log AFP also incrementally increased across the TBS-BR R, BR1, and BR2 categories (1.98, 2.79, and 3.59; $P < 0.001$), as did median aspartate aminotransferase (32.0, 42.0, and 45.5 IU/L, respectively; $P < 0.001$) and alanine aminotransferase (32.0, 38.0, and 47.5 IU/L, respectively; $P < 0.001$). Median TBS similarly increased across the TBS-BR R, BR1, and BR2 categories (3.16, 7.42, and 11.1, respectively; $P < 0.001$). The proportion of patients who underwent major hepatectomy increased with TBS-BR R, BR1, and BR2 (24.4%, 48.6%, and 53.4%, respectively; $P < 0.001$), while the proportion of procedures performed using a minimally invasive approach decreased (34.8%, 22.0%, and 19.2%; $P < 0.001$). The use of adjuvant chemotherapy also increased across TBS-BR R, BR1, and BR2 (1.6%, 2.1%, and 8.2%, respectively; $P < 0.001$).

Survival Outcomes Based on Tumor Burden Score-Borderline Resectability Category

The original R, BR1, and BR2 categories were associated with long-term survival among patients undergoing resection of HCC (5-year OS: 65.1%, 48.2%, and 46.4%, respectively; $P < 0.001$) (Supplemental Figure 2A, see http://links.lww.com/AOSO/A474). Similarly, after excluding patients who received any preoperative treatment, survival decreased across R, BR1, and BR2 categories (5-year OS: 67.8%, 57.6%, and 33.3%, respectively; $P < 0.001$) (Supplemental Figure 2B, see http://links.lww.com/AOSO/A474). The proposed novel TBS-BR R, BR1, and BR2 categories were also strongly associated with long-term survival among the entire cohort (5-year OS: 70.8%, 58.3%, and 40.0%, respectively; $P < 0.001$), as well as the cohort excluding individuals who received preoperative treatment (5-year OS: 71.9%, 63.3%, and 50.0%, respectively; $P < 0.001$) (Fig. 1A, B). The overall C-indices based on the original BR (AUC 0.54) or the proposed TBS-BR (AUC 0.58) relative to OS were modest.

Creation of Predictive Model Using Tumor Burden Score-Borderline Resectability Category

The cohort was divided into a training set (n = 1502) and a testing set (n = 264). The training and testing cohorts had similar clinicopathological factors (all $P > 0.05$), except for a higher proportion of cirrhosis in the training cohort (Table 2). On multivariable analysis, TBS-BR1 (hazard ratio [HR]: 1.59 [1.20–2.09]; $P = 0.001$), TBS-BR2 (HR: 2.45 [1.47–4.07]; $P < 0.001$, reference: TBS-BR R), ASA class >2 (HR: 1.40 [1.09–1.80]; $P = 0.007$), ALBI score (HR: 1.51 [1.21–1.88]; $P < 0.001$), and log AFP (HR: 1.07 [1.03–1.11]; $P < 0.001$) were each independently associated with OS (Table 3). Using these factors, a predictive model based on TBS-BR category (TBS-BR composite model) was developed (Supplemental Table 2, see http://links.lww.com/AOSO/A474).

The predictive power of the TBS-BR composite model relative to OS was compared with the original BR and the BCLC classification schemas. The time-dependent AUC for TBS-BR composite model had superior AUCs at all time points after surgery versus the original BR and BCLC classification (Fig. 2). Furthermore, the AUROC curves at each postoperative time point demonstrated that the TBS-BR composite model (1 year: 0.73, 2 years: 0.71, 3 years: 0.73, 4 years: 0.72, 5 years: 0.70) consistently outperformed the original BR (1 year: 0.60, 2 years: 0.58, 3 years: 0.59, 4 years: 0.59, 5 years: 0.57) and BCLC classification (1 year: 0.65, 2 years: 0.64, 3 years: 0.64, 4 years: 0.62, 5 years: 0.64) schemas (Supplemental Figure 3, see http://links.lww.com/AOSO/A474). Based on the predicted risk determined by the TBS-BR composite model, the cohort could be stratified into tertiles relative to survival, demonstrating a strong incremental worsening of long-term outcomes among low, medium, and high-risk groups (5-year OS: 74.1%, 63.0%, and 49.9%; $P < 0.001$) (Fig. 3). Similarly, the TBS-BR composite model stratified recurrence-free survival effectively among the low-, medium-, and high-risk groups, with 5-year recurrence-free survival rates of 55.0%, 47.1%, and 39.0%, respectively ($P < 0.001$) (Supplemental Figure 4, see http://links.lww.com/AOSO/A474). A web-based online tool using the TBS-BR composite model to predict 1-year, 3-year, and 5-year mortality was made available at https://makbn.shinyapps.io/BRHCC/ (Supplemental Figure 5, see http://links.lww.com/AOSO/A474).

DISCUSSION

HCC can be associated with a variable prognosis, emphasizing the need for proper risk stratification after curative-intent liver resection.[3] In 2023, a consensus group of Japanese surgical experts introduced resectability criteria for HCC (the original BR category) that included different oncological considerations.[4] This classification was developed in response to the evolving role of systemic therapy in HCC management.[13,14] Although some treatment guidelines have updated recommendations for systemic therapy,[2,15,16] there is still no clear consensus on the role of surgery in the multidisciplinary treatment of advanced HCC. For example, many global guidelines, such as the BCLC system, generally exclude patients with macroscopic vascular invasion from resection.[2] However, many liver surgeons have

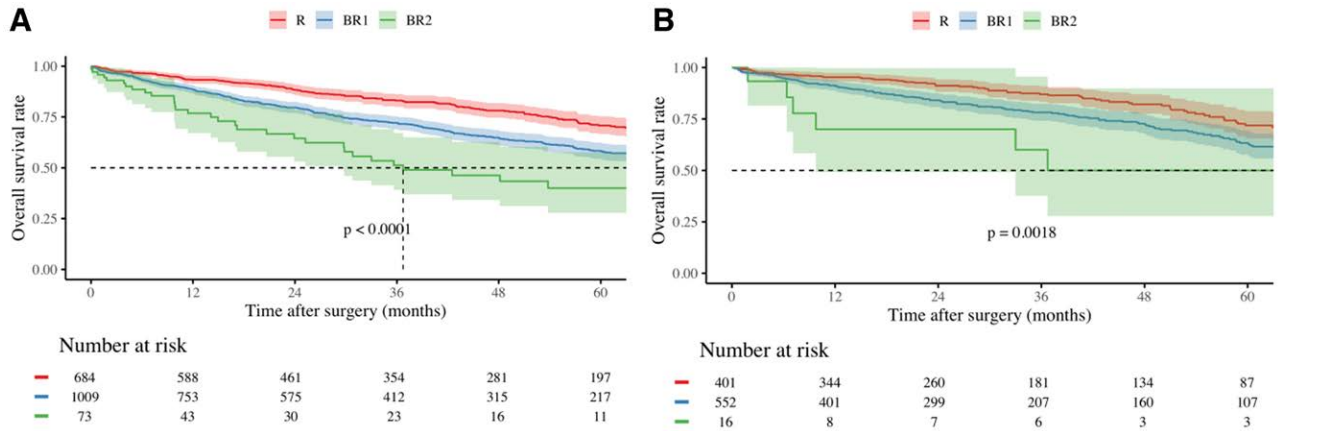

FIGURE 1. Kaplan–Meier curves for overall survival (OS) based on the TBS-BR categories: (A) overall population and (B) limited to surgery cases without preoperative treatment.

TABLE 2.

Patient Characteristics of the Training Set and Testing Set

Variable	Testing Set (n = 264)	Training Set (n = 1502)	Overall (N = 1766)	*P*
Age, y, median (IQR)	66.0 (59.0 to 74.3)	67.0 (59.0 to 73.0)	67.0 (59.0 to 73.0)	0.315
Male, yes, n (%)	209 (79.2%)	1180 (78.6%)	1389 (78.7%)	0.889
ASA class >2, yes, n (%)	110 (41.7%)	647 (43.1%)	757 (42.9%)	0.839
BMI, kg/m^2, median (IQR)	24.4 (22.0 to 27.5)	25.1 (22.6 to 28.2)	25.0 (22.5 to 28.1)	0.084
Diabetes, yes, n (%)	69 (26.1%)	444 (29.6%)	513 (29.0%)	0.285
Cirrhosis, yes, n (%)	100 (37.9%)	694 (46.2%)	794 (45.0%)	0.011
Platelet, ×10^3/μL, median (IQR)	182 (136 to 244)	184 (137 to 243)	184 (136 to 243)	0.384
Albumin, g/L, median (IQR)	41.0 (38.0 to 44.0)	41.0 (37.7 to 44.0)	41.0 (37.8 to 44.0)	0.828
Total bilirubin, mg/dL, median (IQR)	0.70 (0.48 to 0.94)	0.63 (0.50 to 0.93)	0.64 (0.50 to 0.94)	0.870
ALBI score, median (IQR)	−3.58 (−3.80 to −3.22)	−3.59 (−3.86 to −3.23)	−3.59 (−3.85 to −3.23)	0.525
AST, IU/L, median (IQR)	36.0 (24.0 to 56.0)	39.0 (26.0 to 63.0)	39.0 (25.0 to 61.0)	0.283
ALT, IU/L, median (IQR)	34.0 (22.0 to 56.0)	37.0 (24.0 to 65.0)	36.0 (24.0 to 63.0)	0.122
INR, median (IQR)	1.06 (1.00 to 1.10)	1.05 (1.00 to 1.10)	1.05 (1.00 to 1.10)	0.681
PVE, yes, n (%)	15 (5.7%)	106 (7.1%)	121 (6.9%)	0.485
Neoadjuvant chemotherapy, yes, n (%)	1 (0.4%)	6 (0.4%)	7 (0.4%)	1.000
Neoadjuvant immunotherapy, yes, n (%)	1 (0.4%)	3 (0.2%)	4 (0.2%)	1.000
Log AFP, median (IQR)	2.12 (1.10 to 5.17)	2.43 (1.25 to 5.03)	2.40 (1.21 to 5.09)	0.831
Tumor number, median (IQR)	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)	0.652
Tumor size, cm, median (IQR)	4.70 (3.00 to 8.00)	5.00 (3.10 to 8.50)	5.00 (3.00 to 8.50)	0.791
TBS, median (IQR)	5.01 (3.16 to 8.93)	5.10 (3.44 to 8.83)	5.10 (3.35 to 8.84)	0.832
Microvascular invasion, yes, n (%)	75 (28.4%)	418 (27.8%)	493 (27.9%)	0.060
Perineural invasion, yes, n (%)	15 (5.7%)	93 (6.2%)	108 (6.1%)	0.605
AJCC N category, n (%)				
NX	168 (63.6%)	962 (64.0%)	1130 (64.0%)	0.293
N0	81 (30.7%)	433 (28.8%)	514 (29.1%)	
N1	1 (0.4%)	23 (1.5%)	24 (1.4%)	
Minimally invasive Surgery, yes, n (%)	72 (27.3%)	402 (26.8%)	474 (26.8%)	0.915
Major hepatectomy, yes, n (%)	95 (36.0%)	601 (40.0%)	696 (39.4%)	0.243
Adjuvant chemotherapy, yes, n (%)	7 (2.7%)	31 (2.1%)	38 (2.2%)	0.700
TBS-BR category, n (%)				
TBS-BR R	111 (42.0%)	573 (38.1%)	684 (38.7%)	0.485
TBS-BR1	143 (54.2%)	866 (57.7%)	1009 (57.1%)	
TBS-BR2	10 (3.8%)	63 (4.2%)	73 (4.1%)	

Continuous variables: median (IQR); categorical variable: n (%).

AJCC, American Joint Committee on Cancer; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; INR, international normalized ratio; IQR, interquartile range; PVE, portal vein embolization.

TABLE 3.

Univariate and Multivariable Cox Regression Analysis for Overall Survival Prediction

	Univariate		Multivariable	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
TBS-BR category (ref: TBS-BR R)				
TBS-BR1	1.63 (1.34–1.99)	<0.001	1.59 (1.20–2.09)	0.001
TBS-BR2	2.64 (1.78–3.91)	<0.001	2.45 (1.47–4.07)	<0.001
Age	1.01 (1.00–1.02)	0.020	1.01 (0.99–1.02)	0.202
Male, yes (ref: female)	1.09 (0.88–1.36)	0.430	1.19 (0.89–1.60)	0.235
BMI, kg/m^2	1.00 (0.98–1.02)	0.842	0.98 (0.96–1.01)	0.258
Diabetes, yes	1.27 (1.04–1.54)	0.022	1.21 (0.92–1.59)	0.175
Major hepatectomy, yes	1.19 (0.99–1.43)	0.060	1.08 (0.85–1.38)	0.531
ASA class>2, yes	1.36 (1.13–1.63)	0.001	1.40 (1.09–1.80)	0.007
ALBI score	1.44 (1.19–1.75)	<0.001	1.51 (1.21–1.88)	<0.001
Log AFP	1.07 (1.04–1.11)	<0.001	1.07 (1.03–1.11)	<0.001

BMI, body mass index; CI, confidence interval.

long recognized that certain patients, not traditionally considered surgical candidates, may still benefit from resection. Recent studies have highlighted the importance of the extent of portal vein invasion, suggesting that it may be inappropriate to categorically exclude patients with macrovascular invasion from surgery.[17] The BR paradigm addressed this gap by stratifying patients relative to resectability based on macroinvasion into the portal vein, hepatic vein, bile duct, and EHS on preoperative imaging. The concept of BR had not been investigated or validated in an international cohort, nor did the original BR category incorporate more updated means to measure overall tumor burden. The current study was important because we externally validated the original BR classification scheme for HCC using an international multi-institutional cohort. Perhaps

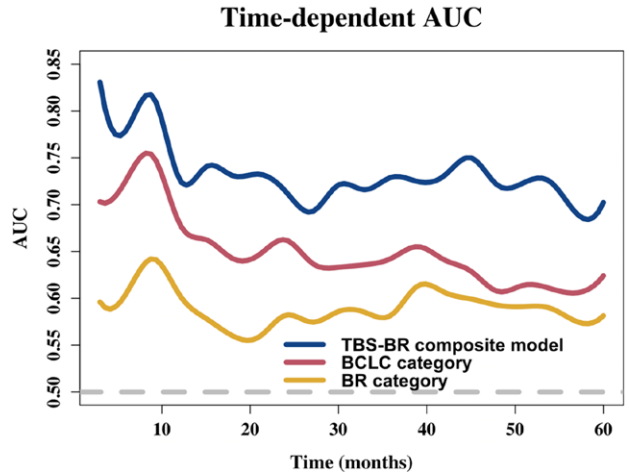

FIGURE 2. Comparison of time-dependent AUC between TBS-BR composite model, BCLC category, and BR category.

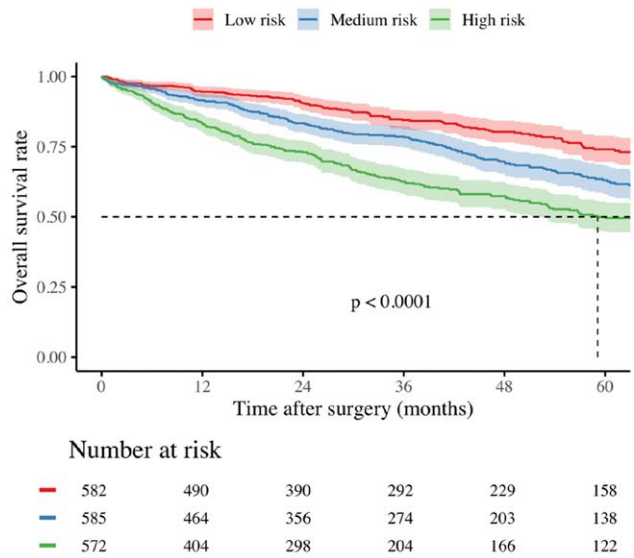

FIGURE 3. Stratification of overall survival by TBS-BR composite model using Kaplan–Meier analysis.

more importantly, we provided an updated model that incorporated TBS, a validated continuous score of tumor burden;[6,7] of note, the revised TBS-BR category had an enhanced ability to predict OS. Furthermore, combining TBS-BR category with other preoperative variables such as ASA class, ALBI score, and log AFP into a composite score provided a tool to predict OS after HCC resection that was better than both the original BR category and BCLC staging system. The tool was made available as an online calculator to facilitate its use in the clinical setting (https://makbn.shinyapps.io/BRHCC/).

Previous studies aimed at identifying prognostic factors following curative-intent hepatectomy for HCC primarily focused on pre- and postoperative pathological factors.[18–20] The BR paradigm, however, sought to stratify resectability relative to morphologic and anatomic factors akin to pancreatic cancer and colorectal liver metastasis. First introduced in 2006 by Varadhachary et al,[21] the term "BR" is generally used to describe a type of cancer that is technically resectable but has a high risk of incomplete resection or early recurrence after surgery.[22] For example, borderline resectable pancreatic cancer has become recognized as a clinical entity with specific definitions and therapeutic and prognostic implications.[23,24] Similarly, the concept of BR has been applied to patients with colorectal liver metastases,[25–28] in which patients with borderline resectable disease are generally treated with preoperative chemotherapy.[25,29] Traditionally, the concept of BR has not been applied to HCC, in part because of the limited effective systemic therapeutic options.[30] Sorafenib, among the first "effective" systemic therapy for HCC, did not lead to tumor shrinkage and survival prolongation was marginal.[31] More recently, however, the introduction of more effective drugs like lenvatinib,[32] along with immunotherapies and immuno checkpoint inhibitors such as pembrolizumab and nivolumab,[33] has prompted reconsideration of preoperative therapy for advanced HCC. In particular, there is an emerging need to classify patients with borderline resectable HCC to identify individuals who may benefit from multidisciplinary treatment strategies including preoperative systemic therapy. Numerous clinical trials are underway to assess the safety and feasibility of combining immune checkpoint inhibitors with tyrosine kinase inhibitors for advanced HCC.[34]

The concept of BR was initially proposed by a Japanese consensus panel to shift the focus from merely classifying tumors as "resectable" to evaluating whether surgery is oncologically justified.[4] A separate report suggested that the use of the BR1 category may help to select patients with advanced HCC for multidisciplinary combination therapy.[35] While treatment strategies for HCC expand, the BR paradigm for HCC may play an increasingly important role, similar to its established use in pancreatic cancer and colorectal liver metastasis.[5] While the original BR category demonstrated the potential to risk-stratify patients relative to OS, it may be somewhat inadequate. In fact, in the current study, while we did validate the original BR scheme by demonstrating stratification of OS according to R, BR1, and BR2, the original BR category had an AUC of only 0.54. As such, we sought to enhance the BR definitions by using TBS. TBS was initially proposed by our own group as a "metro-ticket" prognostic tool for patients with colorectal liver metastasis, incorporating tumor size and number of tumors.[7] TBS has since been validated as a strong prognostic tool to stratify patients with both primary and secondary liver tumors, including HCC.[6,36,37] The modification of BR to TBS-BR allowed for the assessment of tumor burden as continuous rather than a noncontinuous variable. The incorporation of TBS in the risk assessment of patients undergoing transplantation had demonstrated a similar improvement in model accuracy.[38]

While superior as a predictive tool compared with the original BR category, the TBS-BR model had a performance that was still only modest. Effective stratification of patients with HCC requires a more nuanced approach that addresses resectability based on anatomy (technical resectability), tumor biology (oncological resectability), and the patient's overall condition (liver function and physical status). Given this, we sought to augment the TBS-BR model (tumor morphology) with the addition of log AFP (tumor biology), as well as ALBI score (liver function) and ASA class (overall physical status) based on the multivariable analysis. In turn, this TBS-BR-based composite model had the best AUROC curves at each postoperative time point (1 year: 0.73, 2 years: 0.71, 3 years: 0.73, 4 years: 0.72, 5 years: 0.70) compared with the original BR category (1 year: 0.60, 2 years: 0.58, 3 years: 0.59, 4 years: 0.59, 5 years: 0.57) and BCLC classification (1 year: 0.65, 2 years: 0.64, 3 years: 0.64, 4 years: 0.62, 5 years: 0.64) schemas (Supplemental Figure 2, see http://links.lww.com/AOSO/A474). Collectively, that data demonstrated that combining technical, oncologic, liver function, and patient factors into a composite score provided the best prognostic discrimination. In turn, the tool was made available as an online calculator to facilitate its use in the clinical setting.

Several limitations should be considered when interpreting the results of the current study. Although the use of a multi-institutional international database improved the generalizability

of the findings, variations in surgical protocols, techniques, treatments, and preoperative imaging across different institutions and countries may have introduced bias. Additionally, the original BR definition categorized any single HCC as R disease; in this study, we simplified the definition of tumor morphology by using TBS instead of distinguishing between single and multiple tumors. Future studies should evaluate the importance of TBS relative to single versus multiple tumors. While the AUROC value of 0.7 for the TBS-BR composite model may appear modest compared to traditional predictive models, it is important to emphasize that the primary significance of this model lies in its ability to refine and operationalize the concept of BR for HCC. Unlike conventional OS prediction tools, the TBS-BR composite model integrates tumor morphology, tumor biology, liver function, and overall physical status, providing a clinically meaningful framework for guiding surgical decision-making within a multidisciplinary treatment paradigm. Therefore, this study does not represent "just another attempt" at OS stratification but rather a fundamental advancement of the BR concept, redefining oncological resectability in HCC. Importantly, even in the era of multidisciplinary care, surgery remains the ultimate curative option for HCC, and the inclusion of BR2 patients in the TBS-BR framework underscores its utility in guiding treatment decisions across all levels of disease severity, including the most challenging cases. Given the evolving nature of HCC treatments and multidisciplinary approaches, prediction models will need to be periodically reviewed and revised for relevance and accuracy.

In conclusion, the BR scheme for HCC may be an important oncologic concept to evaluate "oncologic resectability" especially within the context of the evolving role of systemic therapy combined with resection for advanced HCC. The BR scheme incorporated tumor morphology, macroinvasion to the portal vein, hepatic vein, and bile duct, as well as EHS. Using TBS to model tumor morphology as a continuous variable, the proposed TBS-BR model further enhanced the predictive accuracy of OS following resection of HCC. In addition, the TBS-BR composite model, which included tumor morphology (TBS), tumor biology (log AFP), overall physical status (ASA class), and liver function (ALBI score) demonstrated a better predictive power for OS compared with either the original BR category or BCLC classifications system.

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