B-cell malignancies - A new knowledge hub on the latest research in therapeutic advances

EDUCATIONAL CONTENT AVAILABLE ON THE HUB:

- On-demand Webinars - earn CME credit
- Infographics
- Patient Case Studies
- Currated Research Articles

...and much more

VISIT KNOWLEDGE HUB TODAY

This educational resource has been supported by Eli Lilly.

WILEY

Received: 13 September 2022 | Accepted: 24 September 2022

DOI: 10.1002/jso.27116

RESEARCH ARTICLE

Journal of SURGICAL ONCOLOGY WILEY

TAC score better predicts survival than the BCLC following resection of hepatocellular carcinoma

Henrique A. Lima MD[1,2] | Yutaka Endo MD, PhD[1] | Zorays Moazzam MD[1] | Laura Alaimo MD[1] | Chanza Shaikh MD[1] | Muhammad M. Munir MD[1] | Vivian Resende MD, PhD[2] | Alfredo Guglielmi MD[3] | Hugo P. Marques MD[4] | François Cauchy MD[5] | Vincent Lam MD[6] | George A. Poultsides MD[7] | Irinel Popescu MD[8] | Sorin Alexandrescu MD[8] | Guillaume Martel MD[9] | Itaru Endo MD, PhD[10] | Minoru Kitago MD[11] | Feng Shen MD[12] | Timothy M. Pawlik MD, PhD, MPH, MTS, MBA, FACS, FRACS (Hon)[1]

[1]Department of Surgery, The Ohio State University Wexner Medical Center and James Comprehensive Cancer Center, Columbus, Ohio, USA

[2]School of Medicine, Federal University of Minas Gerais, Belo Horizonte, Brazil

[3]Department of Surgery, University of Verona, Verona, Italy

[4]Department of Surgery, Curry Cabral Hospital, Lisbon, Portugal

[5]Department of Hepatibiliopancreatic Surgery, APHP, Beaujon Hospital, Clichy, France

[6]Department of Surgery, Westmead Hospital, Sydney, New South Wales, Australia

[7]Department of Surgery, Stanford University, Stanford, California, USA

[8]Department of Surgery, Fundeni Clinical Institute, Bucharest, Romania

[9]Department of Surgery, University of Ottawa, Ottawa, Ontario, Canada

[10]School of Medicine, Yokohama City University, Yokohama, Japan

[11]Department of Surgery, Keio University, Tokyo, Japan

[12]Eastern Hepatobiliary Surgery Hospital, Shanghai, China

Correspondence

Timothy M. Pawlik, MD, PhD, MPH, MTS, MBA, FACS, FRACS (Hon), Department of Surgery, The Urban Meyer III and Shelley Meyer Chair for Cancer Research, The Ohio State University, Wexner Medical Center, 395 W, 12th Ave., Suite 670, Columbus, OH, USA.
Email: Tim.Pawlik@osumc.edu

Abstract

Background: Heterogeneity in hepatocellular carcinoma (HCC) still exists within the Barcelona clinic liver cancer (BCLC) subcategories. We developed a simple model to better discriminate and predict prognosis following resection.

Methods: Patients who underwent curative-intent resection for HCC were identified from a multi-institutional database. Predictive factors of survival were identified to develop TAC (tumor burden score [TBS], alpha-fetoprotein [AFP], Child–Pugh CP]) score.

Results: Among 1435 patients, median TBS was 5.1 (interquartile range [IQR]: 3.2–8.1), median AFP was 18.3 ng/ml (IQR 4.0–362.5), and 1391 (96.9%) patients were classified as CP-A. Factors associated with overall survival (OS) included TBS (low: referent; medium: HR 2.26, 95% CI: 1.73–2.96; high: HR = 3.35,

95% CI: 2.22–5.07), AFP (<400 ng/ml: referent; >400 ng/ml: HR = 1.56, 95% CI: 1.27–1.92), and CP (A: referent; B: HR = 1.81, 95% CI: 1.12–2.92) (all $p < 0.05$). A simplified risk score demonstrated superior concordance index, Akaike information criteria, homogeneity, and area under the curve versus BCLC (0.620 vs. 0.541; 5484.655 vs. 5536.454; 60.099 vs. 16.194; 0.62 vs. 0.55, respectively), and further stratified patients within BCLC groups relative to OS (BCLC 0, very low: 86.8%, low: 47.8%) (BCLC A, very low: 79.7%, low: 68.1%, medium: 52.5%, high: 35.6%) (BCLC B, low: 59.8%, medium: 43.7%, high: N/A).

Conclusion: TAC is a simple, holistic score that consistently outperformed BCLC relative to discrimination power and prognostication following resection of HCC.

KEYWORDS

Barcelona clinic liver cancer, hepatocellular carcinoma, multi-institutional database, prognosis, resection, tumor burden score

1 | INTRODUCTION

Adequate staging is important to treat and stratify patients with hepatocellular carcinoma (HCC). To this end, the Barcelona Clinic Liver Cancer (BCLC) system has been widely adopted in the Western world as a means to risk stratify patients, as well as inform treatment strategies related to HCC.[1] Since the BCLC was first introduced in 1999, surgical practices have continually improved, therapeutic interventions have evolved, and selection of patients has become more sophisticated.[2] In turn, despite recent updates, the BCLC algorithm has been criticized for being too restrictive relative to curative-intent treatment recommendations. In particular, liver resection has long been argued to be a viable treatment option for individuals with intermediate-stage HCC, which is a deviation from BCLC recommendations.[3–5] In fact, the latest BCLC update still does not recommend liver resection beyond BCLC 0/A, despite increasing evidence of its feasibility and efficacy in selected patients.[6,7] Moreover, BCLC groups comprise a very heterogeneous population that may derive differential long-term benefits relative to varied treatment strategies. As such, better stratification of patients with intermediate stage HCC remains a topic of great interest to delineate who may most benefit from surgical resection.

Multiple alternative classifications have been proposed, which have either been independent or supplementary to the BCLC system.[8–12] None of these previous classifications have experienced worldwide adoption and an easy-to-use, clinically relevant stratification scheme for patients with intermediate stage HCC remains not defined. For example, BCLC score components are largely based on liver function and arbitrary values for tumor size and number, characterized in a dichotomous manner, that fails to provide a holistic assessment. The latest BCLC update attempted to address these shortcomings by incorporating assessment of liver decompensation (e.g., jaundice, ascites, encephalopathy) independent of the Child–Pugh (CP) with substratification based on the albumin–bilirubin (ALBI) score; in addition, the use of serum alpha-fetoprotein (AFP) was added regardless of tumor burden.[7] In an effort to improve prognostic prediction, the updated BCLC sacrificed simplicity by adding factors to reflect clinical complexity and nuances related to many patients who have HCC.

The heterogeneity in treatment benefit from resection, as well as treatment stratification of patients with HCC, is likely related to differences in tumor morphology, tumor biology, and liver function. As such, we sought to stratify the prognosis of patients with HCC using a simple scoring system composed of tumor burden score (TBS), serum AFP, and CP, which reflect each of these factors, respectively. In particular, TBS has been validated as a simple composite metric of overall tumor size and number[6]; moreover, AFP has been associated with HCC prognosis and CP is the traditional means to assess liver function.[13,14] Therefore, using a large international multi-institutional database, the purpose of the current study was to develop and assess the TAC score relative to long-term prognosis following resection of HCC, as well as characterize the performance of the TAC score to stratify patients with HCC relative to BCLC,[7] Japan Integrated Staging (JIS),[10] and Cancer of the Liver Italian Program (CLIP).[9]

2 | METHODS

2.1 | Study population

Patients who underwent liver resection for HCC between 2000 and 2020 were identified from an international multi-institutional database that included: The Ohio State University Wexner Medical Center, Columbus, OH, USA; Keio University, Tokyo, Japan; Eastern Hepatobiliary Surgery Hospital, Shanghai, China; University of Verona, Verona, Italy; Curry Cabral Hospital, Lisbon, Portugal; HC-UFMG, Federal University of Minas Gerais, Belo Horizonte, Brazil;

APHP, Beaujon Hospital, Clichy, France; Westhead Hospital, Sydney, Australia; Stanford University, Stanford, CA, USA; Fundeni Clinical Institute, Bucharest, Romania; University of Ottawa, Ottawa, Canada; University of Colorado, Denver, Colorado, USA; Yokohama City University, Yokohama, Japan. Patients with missing data, who experienced death within 90-days from surgery, had palliative surgery, or macroscopic residual disease after resection (R2) were excluded. The Institutional Review Board of all institutions approved this study.

2.2 | Variables and definitions

Demographic and preoperative clinicopathologic data included age, sex, comorbidities (Charlson comorbidity index),[15] baseline liver disease, laboratory exams (i.e., platelets, prothrombin international normalized ratio), imaging tumor characteristics (i.e., size and the number), surgical characteristics of liver resection (major resection: ≥3 Couinaud segments),[16] and pathological examination of the specimen. Preoperative liver function was assessed according to the CP classification and tumor staging was defined according to the *AJCC Cancer Staging Manual, 8th edition*.[17] Patients were categorized according to the following staging systems: BCLC,[7] JIS,[10] and CLIP.[9] TBS incorporated maximum tumor size and number of tumors on preoperative imaging into the Pythagorean theorem (TBS^2 = [maximum tumor diameter]^2 + [number of tumors]^2).[18] Patients were categorized as low, medium, or high TBS (cutoff values: 3.36 and 13.74), and as low, or high AFP (cutoff value: 400 ng/ml), as previously defined.[19,20] Non-transplantable recurrence was defined as recurrence beyond the Milan criteria.[21] The primary outcome was 5-year overall survival (OS), defined as the time interval between the date of liver resection to the date of death from any cause, or last follow-up. The secondary outcome was recurrence-free survival (RFS), defined as the time between hepatectomy and recurrence (positive biopsy or suspicious lesion on follow-up imaging).[19] In the postoperative setting, serum tumor markers and imaging studies (ultrasound, computed tomography, and magnetic resonance imaging) were utilized for monitoring. In general, follow-up occurred every 3–4 months in the first 3 years, and every 6 months until the fifth year, then annually.

2.3 | Statistical analysis

Categorical variables were reported as frequencies (%) and compared with the χ^2 test or Fisher exact test. Continuous variables were expressed as median values (interquartile range [IQR]), and compared with Mann–Whitney *U* tests. Survival and recurrence probabilities were compared using a log-rank test and depicted using the Kaplan–Meier curve. Relevant preoperative characteristics were assessed relative to OS through Cox proportional hazard regression analysis with backward exclusion. Variables with $p < 0.05$ were included in the multivariate analysis. The performance of the TAC score was analyzed and compared with the other staging schemas using Harrell's concordance index (C-index), Akaike information criteria (AIC), and homogeneity, measured by the χ^2 test.[22] The impact of various subgroups with the TAC score relative to OS was analyzed using Cox regression; sensitivity analyses (using it as a continuous variable) were also performed. The level of statistical significance was set at $\alpha = 0.05$. All analyses were performed using SPSS software version 28.0 (IBM Corporation) and R version 4.2.0 (R Project for Statistical Computing) statistical packages.

3 | RESULTS

3.1 | Baseline characteristics

Among 1435 patients who met inclusion criteria, median age was 63 years (IQR 54–71) and most patients were male ($n = 1149$, 80.1%) (Table 1). The vast majority of individuals ($n = 1391$, 96.9%) were classified as CP A, while only 44 (3.1%) were CP B. Overall, roughly one-half of patients presented with cirrhosis ($n = 655$, 45.6%); the prevalence of hepatitis B and C was 39.7% ($n = 569$) and 23.5% ($n = 336$), respectively. Median AFP was 18.3 ng/ml (IQR 4.0–362.5); while 1087 (75.7%) patients had a low AFP on presentation, 348 (24.3%) patients had a high AFP. Median tumor size was 4.9 cm (IQR 3.0–8.0) with the majority of patients having a solitary tumor ($n = 1189$, 82.9%). In turn, median TBS was 5.1 (IQR, 3.2–8.1); the majority of patients were categorized as having a medium TBS ($n = 949$, 66.1%), while fewer patients were classified with either low ($n = 390$, 27.2%) or high ($n = 96$, 6.7%) TBS. At the time of surgery, most patients underwent a minor resection ($n = 667$, 64.4%), while a smaller subset underwent a major hepatectomy ($n = 369$, 35.6%). On postoperative pathology, margin status was R0 in the overwhelming majority of patients ($n = 1297$, 91.2%); 854 (60.6%) and 557 (55.0%) patients had a well-or-moderately differentiated tumor and no microvascular invasion, respectively.

3.2 | Development of TAC score

On multivariable analysis, after controlling for other competing risk factors, preoperative variables that were independently associated with OS following resection of HCC included presence of cirrhosis (HR 1.48, 95% CI: 1.22–1.81; $p < 0.001$), CP classification (A: referent; B: HR 1.81, 95% CI: 1.12–2.92; $p = 0.015$), AFP level (<400 ng/ml: referent; >400 ng/ml: HR 1.56, 95% CI: 1.27–1.92; $p < 0.001$), and TBS (low: referent; medium: HR 2.26, 95% CI: 1.73–2.96; high: HR 3.35, 95% CI: 2.22–5.07; $p < 0.001$) (Table 2). The β-coefficients of these variables (β low TBS: referent, β medium TBS: 0.815, β high TBS: 1.209; β low AFP: referent, β high AFP: 0.446; β CP-A: referent, β CP-B: 0.593) were used to compose the score based on a simplified point system (TBS low/medium/high = 0/1/2; AFP low/high = 0/1; CP A/B = 0/1, respectively). Subsequently, patients were categorized on a scale ranging from 0 to 4 and classified as "Very Low,"

TABLE 1 Clinicopathologic characteristics of patients

Variables	Overall	TAC score				p Value
		Very low (n = 321, 22.4%)	Low (n = 739, 51.5%)	Medium (n = 331, 23.1%)	High (n = 44, 3.1%)	
Age, years	63 (54–71)	62 (61–64)	64 (63–66)	60 (59–63)	62 (57–68)	0.033
Sex, male	1149 (80.1%)	265 (82.8%)	585 (79.2%)	261 (78.9%)	38 (86.4%)	0.348
ASA PS >2	331 (33.0%)	73 (31.7%)	179 (33.6%)	69 (32.7%)	10 (34.5%)	0.960
CCI ≤9	889 (62.0%)	204 (99.0%)	471 (98.9%)	189 (98.4%)	25 (100.0%)	0.876
Cirrhosis	655 (45.6%)	189 (58.9%)	323 (43.7%)	126 (38.1%)	17 (38.6%)	<0.001
HCV liver infection	336 (23.5%)	106 (33.0%)	178 (24.2%)	46 (14.0%)	6 (13.6%)	<0.001
HBV liver infection	569 (39.7%)	127 (39.6%)	273 (36.9%)	154 (46.5%)	15 (34.1%)	0.025
PLT × 10^3/ul	159 (91–221)	136 (86–181)	162 (89–221)	178 (109–261)	196 (91–282)	<0.001
PT-INR >1.1	166 (13.2%)	35 (12.5%)	80 (12.2%)	41 (14.1%)	10 (27.8%)	0.056
Minimally invasive surgery	217 (15.9%)	89 (29.1%)	104 (14.9%)	24 (7.5%)	0 (0.0%)	<0.001
Major resection	369 (35.6%)	25 (10.5%)	191 (34.7%)	127 (58.5%)	26 (86.7%)	<0.001
Anatomical resection	822 (79.3%)	145 (60.9%)	450 (81.7%)	197 (90.8%)	30 (100.0%)	<0.001
AJCC T stage						<0.001
T1a/1b	165 (11.5%)	108 (33.6%)	44 (6.0%)	12 (3.6%)	1 (2.3%)	
T2/3/4	1,270 (85.5%)	213 (66.4%)	695 (94.0%)	319 (96.4%)	43 (97.7%)	
Liver capsule involvement	390 (35.9%)	65 (26.9%)	206 (37.5%)	107 (40.8%)	12 (38.7%)	0.007
Microvascular invasion	456 (45.0%)	60 (26.3%)	224 (42.4%)	146 (64.6%)	26 (83.9%)	<0.001
Lymphovascular invasion	382 (42.4%)	55 (26.1%)	185 (39.4%)	119 (61.7%)	23 (85.2%)	<0.001
Perineural invasion	23 (5.0%)	3 (2.7%)	13 (5.5%)	3 (2.9%)	4 (33.3%)	<0.001
Margin status						0.188
R1	125 (8.8%)	26 (8.3%)	56 (7.6%)	38 (11.5%)	5 (11.4%)	
R0	1297 (91.2%)	286 (91.7%)	680 (92.4%)	292 (88.5%)	39 (88.6%)	
Grade						<0.001
Well to moderate	854 (60.6%)	216 (69.2%)	481 (66.4%)	140 (42.6%)	17 (38.6%)	
Poor to undifferentiated	555 (39.4%)	96 (30.8%)	243 (33.6%)	189 (57.4%)	27 (61.4%)	

Note: Data are presented as median (IQR) for continuous measures, and *n* (%) for categorical measures.

Abbreviations: AJCC, American Joint Committee on Cancer; ASA PS, American Society of Anesthesiologists Performance Status; CCI, Charlson comorbidity index; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; PLT, platelets; PT-INR, prothrombin international normalized ratio.

"Low," "Medium," "High," and "Very High" relative to risk of long-term mortality.

3.3 | Association of TAC score with clinicopathological features and OS

With a median follow-up of 38 months (IQR 16–67), median and 5-year OS was 96 months (IQR 75.5–116.5) and 65.4%, respectively. Individuals with very low (*n* = 321, 22.4%), low (*n* = 739, 51.5%), medium (*n* = 331, 23.1%), and high (*n* = 44, 3.1%) TAC scores had progressively worse 3-year (88.8%, 81.2%, 68.1%, 59.6%, respectively) and 5-year (81.4%, 66.5%, 51.1%, 32.3%, respectively) OS ($p \leq 0.001$) (Figure 1A,D). A higher TAC score was associated with adverse clinicopathological features, including advanced AJCC T disease, the presence of microvascular, and lymphovascular invasion, as well as poor-to-undifferentiated tumor differentiation (all $p < 0.001$) (Table 1). On multivariable analyses that controlled for pre- and postoperative variables, the TAC score remained independently associated with worse 5-year OS (very low: referent; low: HR 1.57, 95% CI: 1.08–2.28, $p = 0.019$; medium: HR 2.58, 95% CI: 1.71–3.88, $p < 0.001$; high: HR 4.21, 95% CI: 2.19–8.09, $p < 0.001$) (Table 3). In fact, on sensitivity analysis, each unit increase in the TAC score

TABLE 2 Cox regression analysis for preoperative factors associated with overall survival

	Bivariate			Multivariate		
Variable	HR	95% CI	*p* Value	HR	95% CI	*p* Value
Age	1.00	1.00–1.01	0.264	-	-	-
Sex, male	0.84	0.65–1.09	0.187	-	-	-
ASA PS, >II	1.08	0.82–1.42	0.588	-	-	-
CCI ≤9	0.93	0.23–3.74	0.917	-	-	-
PLT × 10^3/ul	1.00	0.99–1.00	0.986	-	-	-
Cirrhosis	1.33	1.10–1.61	0.004	1.48	1.22–1.81	<0.001
HCV liver infection	1.09	0.86–1.40	0.475	-	-	-
HBV liver infection	0.84	0.69–1.02	0.076	-	-	-
Child–Pugh						
A	Ref			Ref		
B	1.93	2.00–3.09	0.007	1.81	1.12–2.92	0.015
AFP (ng/ml)						
<400	Ref			Ref		
>400	1.73	1.14–2.12	<0.001	1.56	1.27–1.92	<0.001
TBS class						
Low	Ref			Ref		
Medium	2.19	1.68–2.86	<0.001	2.26	1.73–2.96	<0.001
High	3.13	2.08–4.69	<0.001	3.35	2.22–5.07	<0.001

Abbreviations: AFP, alpha-fetoprotein; ASA PS, American Society of Anesthesiologists Performance Status; CCI, Charlson comorbidity index; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; PLT, platelets; TBS, tumor burden score.

was independently associated with a 62% higher likelihood of death (HR 1.62; 95% CI: 1.37–1.9, $p < 0.001$).

3.4 | Patterns of recurrence

Median and 5-year RFS were 31 months (IQR 26–36) and 38.3%, respectively. Higher TAC score was associated with a greater risk of recurrence, as 3-year (very low: 65.8%, low: 45.7%, medium: 35.1%, high: 26.1%) ($p \le 0.001$) and 5-year (very low: 52.0%, low: 37.3%, medium: 29.5%, high: 26.1%) ($p \le 0.001$). RFS incrementally worsened concomitantly as the TAC score increased (Figure 1C). Among the 761 (53%) patients who experienced recurrence, the incidence incrementally increased with higher TAC scores (very low: 38.1%, low: 52.9%, medium: 64.4%, high: 68.2%, $p < 0.001$). Moreover, TAC scores were associated with different patterns of recurrence. In particular, higher TAC values were associated with larger tumor recurrence, extrahepatic recurrent disease, as well as earlier and non-transplantable recurrence (all $p < 0.001$) (Figure 2 and Supporting Information: Table 1).

3.5 | Comparison of performance

The TAC score performed relatively well in both the training (C-index 0.62, 95% CI: 0.59–0.65) and internal bootstrap validation (0.62, 95% CI: 0.59–0.65). The prognostic performance of the TAC score was compared relative to other staging systems (i.e., CLIP, JIS, AJCC T stage, BCLC). Of note, the TAC score consistently outperformed other prognostic models (AUC: CLIP 0.59, JIS 0.57, AJCC T category 0.57, BCLC 0.55). The TAC score also had a lower AIC value (5484.655) compared with BCLC (5536.454) and the highest homogeneity index (60.099) (both $p < 0.001$). In addition, the predictive ability of the composite TAC score was superior to the performance of any of its individual components (i.e., TBS, AFP, CP) (Table 4).

3.6 | TAC and BCLC

Subsequent analyses were then performed to assess the performance of the TAC score in various subgroups of patients stratified by the BCLC staging system. Of note, the TAC score substratified patients classified as BCLC 0, A, and B relative to long-term outcomes. Specifically, higher TAC scores were associated with a higher risk of death with lower 3-year (BCLC 0, very low: 93.2%, low: 83.6%, $p = 0.007$) (BCLC A, very low: 87.4%, low: 82.8%, medium: 67.7%, high: 65.8%, $p \le 0.001$) (BCLC B, low: 76.6%, medium: 69.9%, high: N/A, $p \le 0.001$) and 5-year (BCLC 0, very low: 86.8%, low: 47.8%, $p = 0.007$) (BCLC A, very low: 79.7%, low: 68.1%, medium: 52.5%, high: 35.6%, $p \le 0.001$) (BCLC B, low: 59.8%, medium: 43.7%, high: N/A, $p \le 0.001$) incrementally decreasing as TAC score increased independent of BCLC classification (Figures 1B and 3).

4 | DISCUSSION

HCC is a primary liver tumor that commonly arises in the context of chronic liver disease and an impaired underlying liver parenchyma.[23] While choice of therapeutic strategies is influenced by the complex interaction between these clinical factors, liver resection, and transplant are often the best curative-intent treatment options.[24] Accurate prognostic stratification is important to assess which patients may benefit the most from a given treatment, as well as inform discussions around long-term outcomes. In this context, the BCLC staging system has been widely adopted in Western countries as a means to guide therapy, as well as determine prognosis based on liver function, tumor size, and tumor number.[1,7] However, despite advances in prognosis and treatment strategies, the recent updated BCLC algorithm still does not recommend hepatic resection as an option for intermediate-stage HCC. In turn, the stratification and prognosis of patients with HCC relative to different disease stages remain a topic of debate.[6,7] In fact, several alternative prognostication systems have been proposed, yet none have been widely adopted. The current study was important because we used a large

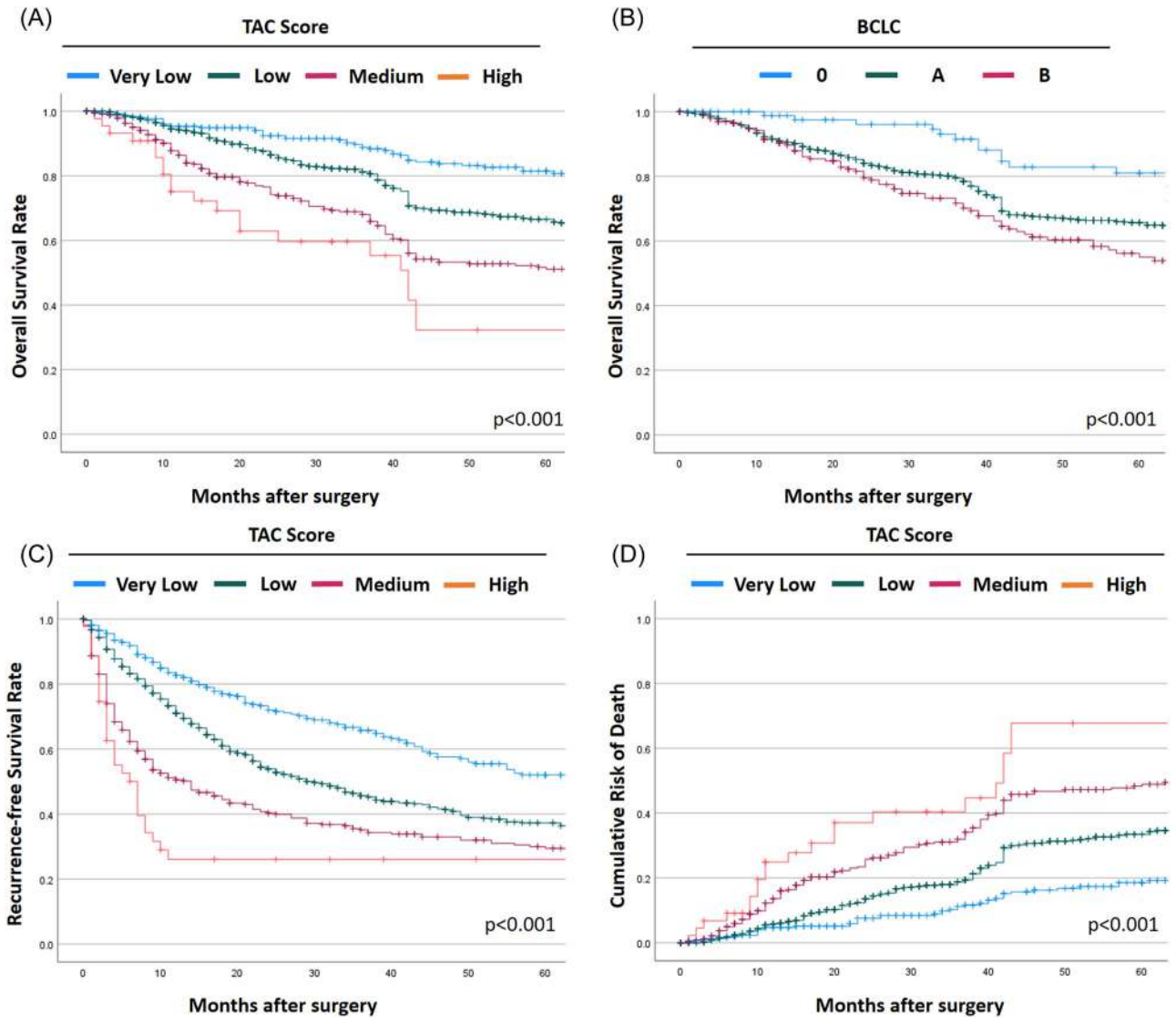

FIGURE 1 Estimated overall survival Kaplan–Meier curves stratified according to the TAC score (A) and the Barcelona clinic liver cancer (BCLC) system (B). Kaplan–Meier curves depict estimated recurrence-free survival (C) and cumulative risk of death (D) according to the TAC score.

multi-institutional database to develop and validate a simple preoperative prognostic model (TAC score) that successfully stratified long-term outcomes among patients with HCC, as well as outperformed the BCLC, AJCC T category, CLIP, and JIS. Of note, patients with higher TAC scores had an incrementally worse prognosis with a 62% higher hazard of death for each TAC unit increase. Moreover, the TAC score was associated with more aggressive patterns of recurrence (i.e., larger, earlier, systemic, and non-transplantable recurrences) and adverse clinicopathologic factors (higher AJCC T disease, presence of lymphovascular, and microvascular invasion, as well as poor-to-undifferentiated tumor grade). Furthermore, the TAC score was able to substratify patients within various BCLC categories, thereby highlighting the heterogeneity within BCLC groups 0/A/B.

The TAC score was developed based on variables that can be easily calculated and routinely assessed in the clinical setting. By incorporating TBS, AFP, and CP, TAC accounted for tumor morphology, biology, and liver function, respectively. TBS is a simple comprehensive continuous metric of tumor burden, which represents an improvement over traditional models that often treat size and number using dichotomous/subjective cut-off values.[18] TBS has been validated as an effective means to summarize overall tumor extent and, in turn, has been a powerful predictor of outcomes following resection of HCC.[6,19] Despite this, TBS has not been widely incorporated into prognostic models related to HCC. The TAC score also utilized serum AFP levels, which have long been recognized to correlate with tumor aggressiveness and, in turn, poor prognosis.[25–27] In fact, Tsilimigras et al.[14] demonstrated a synergistic effect of AFP with TBS to stratify patients with HCC relative to prognosis. In the current study we built off this previous work by combining TBS with AFP and CP classification, which is the most extensively used metric for liver function reserve, to develop a simple integer-based

TABLE 3 Cox regression analysis for factors associated with overall survival

	Bivariate			Multivariate		
Variable	HR	95% CI	*p* Value	HR	95% CI	*p* Value
Cirrhosis	1.33	1.10–1.61	0.004	1.54	1.20–1.97	<0.001
Microvascular invasion	2.20	1.73–2.79	<0.001	1.68	1.30–2.16	<0.001
Perineural invasion	0.66	0.31–1.41	0.282	-	-	-
AJCC T stage						
T1a/1b	Ref					
T2/3/4	1.59	1.13–2.23	0.007	-	-	-
Margin						
R0	Ref					
R1	1.56	1.10–2.19	0.012	-	-	-
Grade						
Well to moderate	Ref					
Poor to undifferentiated	1.44	1.19–1.75	<0.001	1.50	1.15–1.94	0.003
TAC score						
Very low	Ref			Ref		
Low	1.89	1.39–2.56	<0.001	1.57	1.08–2.28	0.018
Medium	3.15	2.29–4.34	<0.001	2.58	1.71–3.88	<0.001
High	4.86	2.92–8.07	<0.001	4.21	2.19–8.09	<0.001

Abbreviations: AJCC, American Joint Committee on Cancer; CI, confidence interval.

prognostic scoring system.[28] CP was used alone rather than including cirrhosis as a separate factor given that these two variables are colinear in nature. In addition, aside from overlapping CP in the assessment of liver status, the term "cirrhosis" can be vague and sometimes difficult to characterize in the preoperative setting with reliability.[29,30] Collectively, the TAC score combines elements of tumor morphology, biology, and liver function to act as a comprehensive scoring schema.

The TAC score performed well compared with other currently used schemas such as CLIP, JIS, AJCC staging, and the BCLC. In fact, TAC demonstrated overall superior prognostic performance following resection of HCC versus all of these aforementioned staging systems with the highest AUC, C-index, and homogeneity. While JIS and CLIP are also composed of simple, easy-to-calculate factors, these staging systems were not primarily designed or validated in cohorts of patients who underwent liver resection. With the expansion of hepatic resection for HCC, other staging systems such as the Model to Estimate Survival for HCC, Model to Estimate Survival in Ambulatory HCC patients, and Hong Kong Liver Cancer score have been developed and proposed in both Eastern or Western cohorts.[8,31,32] Of note, given that the etiology of HCC may differ in Western versus Eastern countries,[33] prognostic scoring systems need to include patients from both geographic locations. To that point, another strength of the current study was the broad, international representation of patients included in the cohort. As such, the TAC score has the advantage of not only being simple to use and having a demonstrably better prognostic performance relative to the CLIP, JIS, and BCLC, but it was also developed and validated in a diverse patient cohort that more likely reflects true clinical practice.

While likely multifactorial, the reason for the superior performance of the TAC score may be partially due to its role as a surrogate of adverse clinicopathological factors. Of note, patients with a higher TAC score were at a much higher likelihood to have more advanced T-disease, as well as the presence of lymphovascular and microvascular invasion, as well as poor-to-undifferentiated tumors (Table 1). Furthermore, the TAC score was also strongly associated with patterns of recurrence with RFS incrementally worsening with higher TAC scores (Figure 1). Recurrence is a major concern in resected HCC as a considerable number of patients will go on to develop non-transplantable recurrences, the main obstacle to the long-term success of primary liver resection.[34] Of note, the proportion of individuals who suffered a larger, earlier, systemic and non-transplantable recurrence incrementally increased with TAC scores (Figure 2, Supporting Information: Table 1). These results were consistent with a bimodal distribution of HCC recurrence, whereby early recurrence often correlates to residual tumor cells, while late recurrence originates from new multicentric carcinogenesis (i.e., de novo carcinogenesis).[25] The integration of tumor morphology, biology, and liver function in the TAC score may provide a better understanding of the anticipated disease course and natural history of HCC following initial resection. Therefore, the TAC prognostic model may provide insight to inform preoperative decision-making process relative to the anticipated benefit of HCC resection.

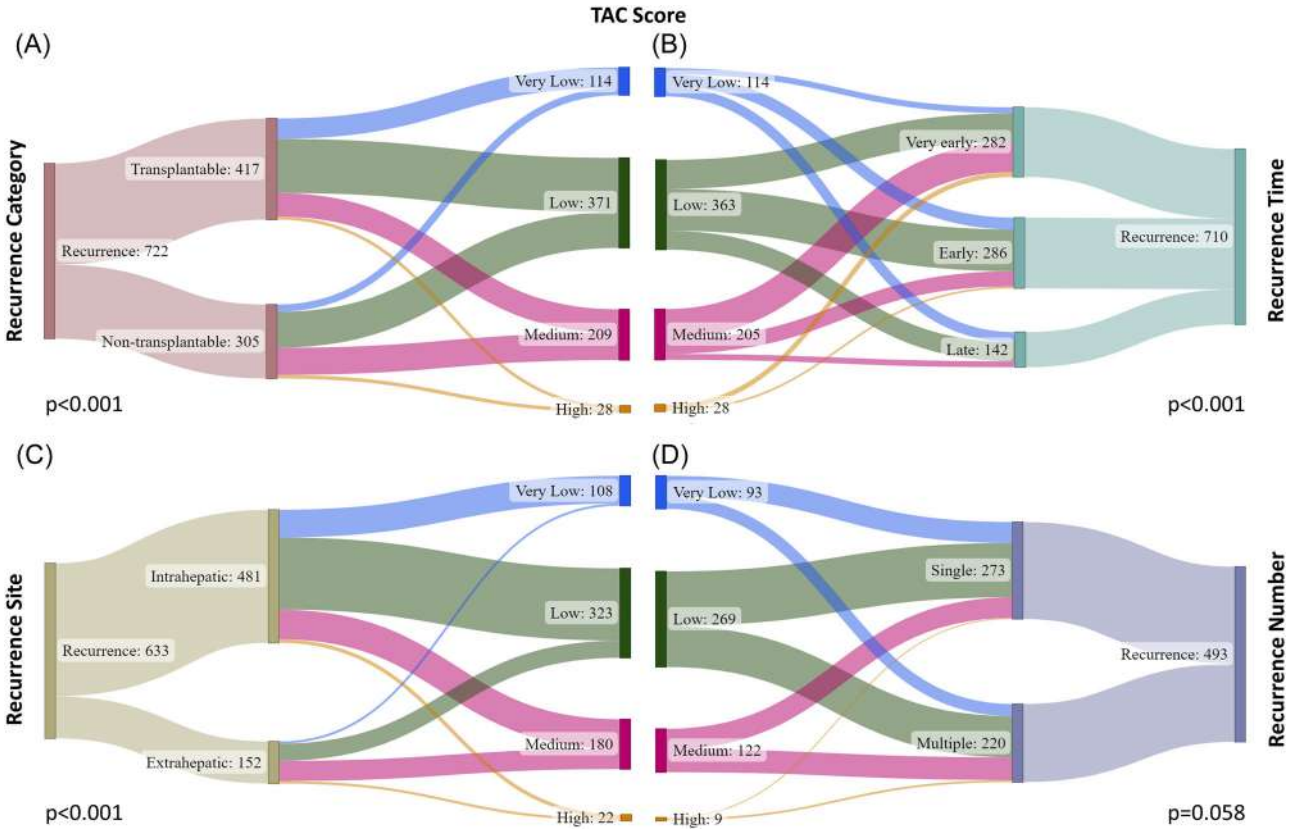

FIGURE 2 Sankey diagrams depicting patterns of recurrence according to the TAC score and recurrence category (A), time (B), site (C), and number (D)

TABLE 4 Comparison of predictive accuracy performance of the TAC Score, the Barcelona clinic liver cancer (BCLC) staging system, and others

System	Akaike information criterion	Homogeneity (χ^2)	C-index	95% CI
TAC score	5484.655	60.099	0.620	0.592–0.647
CLIP	5037.548	37.126	0.597	0.560–0.624
JIS	5061.988	26.493	0.578	0.553–0.603
AJCC T stage	5503.796	37.954	0.577	0.550–0.604
BCLC	5536.454	16.194	0.541	0.521–0.561
Components of the TAC score				
Imaging TBS class	5509.918	40.124	0.586	0.562–0.609
AFP >400 ng/ml	5528.074	27.614	0.568	0.544–0.592
Child–Pugh	5542.910	2.306	0.534	0.512–0.555

Abbreviations: AFP, alpha-fetoprotein; AJCC, American Joint Committee on Cancer, 8th edition; BCLC, Barcelona clinic liver cancer; CI, confidence interval; CLIP, Cancer of the Liver Italian Program; JIS, Japan Integrated Score; TBS, tumor burden score.

The BCLC staging system classifies patients into different treatment/prognostic groups (i.e., 0/A/B/C/D), yet individuals within these groups can still have a very heterogeneous prognosis and derive vastly different benefits from the same therapeutic intervention.[1,24] For example, many surgeons believe that there is a role for hepatic resection among intermediate stage HCC.[4,35] However, the updated BCLC treatment algorithm still does not recommend liver resection beyond early-stage HCC, even in selected individuals.[6,7] Interestingly, stratification of patients using the TAC score highlighted the heterogeneity in prognosis among patients subclassified into the BCLC stages 0, A, and B stages. In particular, the TAC score noted a wide array of survival outcomes among patients in each of the different BCLC stage categories, suggesting that selected patients in each subgroup may benefit more from resection than other

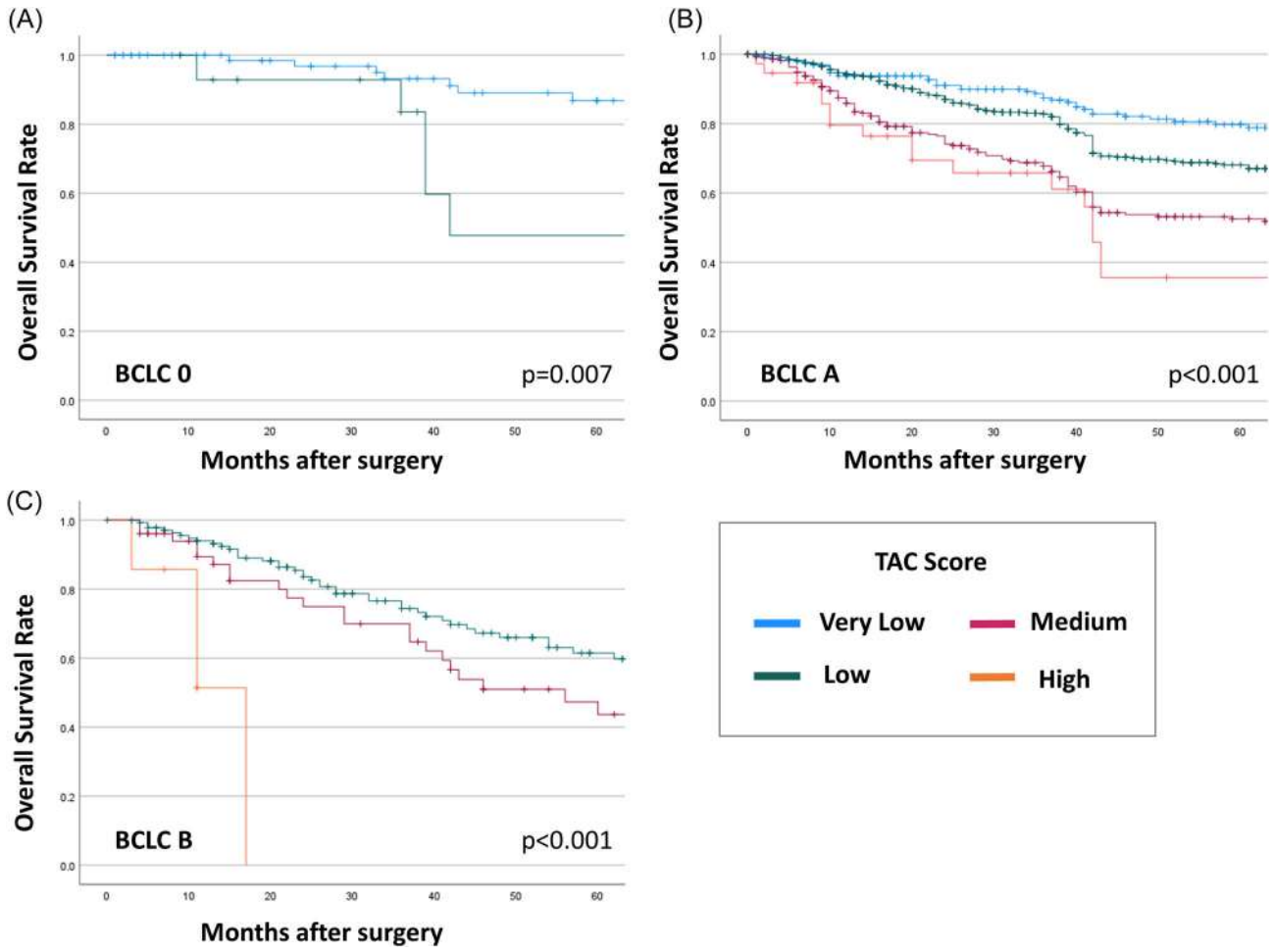

FIGURE 3 Estimated overall survival Kaplan–Meier curves stratified according to the TAC score among BCLC 0 (A), BCLC A (B), and BCLC B (C) patients. BCLC, Barcelona clinic liver cancer.

patients. While the BCLC algorithm restricted surgery to only patients with early-stage disease, the TAC score identified a subset of BCLC B patients with a 5-year OS of 59.8%. These results were in line with previous data from the literature that supported the feasibility and applicability of liver resection even among intermediate-stage patients.[6,36] Collectively, the data strongly suggested that the TAC score can provide an effective manner in which to better discriminate long-term survival of patients following resection of HCC, helping to determine which patients may benefit the most from hepatectomy.

Data from this study should be interpreted taking into account several limitations. Although the international multi-institutional cohort was a strength, differences in surgical techniques, patient selection, and compliance with surveillance protocols among institutions may have impacted the findings. In addition, the retrospective design of study may have resulted in selection bias, as well as residual bias within the analyses. The current study also included only patients who underwent curative-intent liver resection. Therefore, the prognostic ability of TAC cannot be generalized to nonsurgical candidates.

In conclusion, the TAC score was a simple, yet holistic composite prognostic tool that included readily available clinical parameters. Developed and validated using a large, multi-international cohort, the TAC score demonstrated very good prognostic performance that outperformed BCLC, as well as several other traditional prognostic scoring systems. Moreover, the TAC score was able to substratify patients within different BCLC categories (i.e., 0/A/B/C) to discriminate prognosis further, thereby highlighting the residual prognostic heterogeneity within each BCLC category. The TAC score may provide surgeons an accurate, easy-to-use prognostic tool to refine estimates related to long-term survival following resection of HCC to help inform which treatment strategies may survive patients best.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Timothy M. Pawlik https://orcid.org/0000-0002-7994-9870

REFERENCES

1. Bruix J, Sherman M, Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. *Hepatology*. 2005;42(5):1208-1236.
2. Guro H, Cho JY, Han HS, Yoon YS, Choi Y, Periyasamy M. Current status of laparoscopic liver resection for hepatocellular carcinoma. *Clin Mol Hepatol*. 2016;22(2):212-218.
3. Yamazaki S, Takayama T. Management strategies to minimize mortality in liver resection for hepatocellular carcinoma. *Jpn J Clin Oncol*. 2017;47(10):899-908.
4. Hyun MH, Lee YS, Kim JH, et al. Hepatic resection compared to chemoembolization in intermediate- to advanced-stage hepatocellular carcinoma: a meta-analysis of high-quality studies. *Hepatology*. 2018;68(3):977-993.
5. Zhaohui Z, Shunli S, Bin C, et al. Hepatic resection provides survival benefit for selected intermediate-stage (BCLC-B) hepatocellular carcinoma patients. *Cancer Res Treat*. 2019;51(1):65-72.
6. Tsilimigras DI, Bagante F, Moris D, et al. Recurrence patterns and outcomes after resection of hepatocellular carcinoma within and beyond the barcelona clinic liver cancer criteria. *Ann Surg Oncol*. 2020;27(7):2321-2331.
7. Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. *J Hepatol*. 2022;76(3):681-693.
8. Liu PH, Hsu CY, Hsia CY, et al. Proposal and validation of a new model to estimate survival for hepatocellular carcinoma patients. *Eur J Cancer*. 2016;63:25-33.
9. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients: the cancer of the liver Italian program (CLIP) investigators. *Hepatology*. 1998;28(3):751-755.
10. Kudo M, Chung H, Haji S, et al. Validation of a new prognostic staging system for hepatocellular carcinoma: the JIS score compared with the CLIP score. *Hepatology*. 2004;40(6):1396-1405.
11. Bolondi L, Burroughs A, Dufour JF, et al. Heterogeneity of patients with intermediate (BCLC B) hepatocellular carcinoma: proposal for a subclassification to facilitate treatment decisions. *Semin Liver Dis*. 2012;32(4):348-359.
12. Kudo M, Arizumi T, Ueshima K, Sakurai T, Kitano M, Nishida N. Subclassification of BCLC B stage hepatocellular carcinoma and treatment strategies: proposal of modified bolondi's subclassification (Kinki criteria). *Dig Dis*. 2015;33(6):751-758.
13. Chen HL, Chen YH, Du L, Song YP, Zhu B. Elevated serum alpha-fetoprotein levels are associated with poor prognosis of hepatocellular carcinoma after surgical resection: a systematic review and meta-analysis. *Arab J Gastroenterol*. 2021;22(1):12-22.
14. Tsilimigras DI, Hyer JM, Diaz A, et al. Synergistic impact of alpha-fetoprotein and tumor burden on long-term outcomes following curative-intent resection of hepatocellular carcinoma. *Cancers*. 2021;13(4):747.
15. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383.
16. Strasberg SM. Nomenclature of hepatic anatomy and resections: a review of the Brisbane 2000 system. *J Hepatobiliary Pancreat Surg*. 2005;12(5):351-355.
17. Amin MB, Greene FL, Edge SB, et al. The eighth edition AJCC cancer staging manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin*. 2017;67(2):93-99.
18. Sasaki K, Morioka D, Conci S, et al. The tumor burden score: a new "metro-ticket" prognostic tool for colorectal liver metastases based on tumor size and number of tumors. *Ann Surg*. 2018;267(1):132-141.
19. Tsilimigras DI, Moris D, Hyer JM, et al. Hepatocellular carcinoma tumour burden score to stratify prognosis after resection. *Br J Surg*. 2020;107(7):854-864.
20. Yang SL, Liu LP, Yang S, et al. Preoperative serum α-fetoprotein and prognosis after hepatectomy for hepatocellular carcinoma. *Br J Surg*. 2016;103(6):716-724.
21. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med*. 1996;334(11):693-699.
22. Pourhoseingholi MA, Hajizadeh E, Moghimi Dehkordi B, Safaee A, Abadi A, Zali MR. Comparing Cox regression and parametric models for survival of patients with gastric carcinoma. *Asian Pac J Cancer Prev*. 2007;8(3):412-416.
23. Llovet JM, Kelley RK, Villanueva A, et al. Hepatocellular carcinoma. *Nat Rev Dis Primers*. 2021;7(1):6.
24. European Association for the Study of the Liver, European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol*. 2018;69(1):182-236.
25. Ding HF, Zhang XF, Bagante F, et al. Prediction of tumor recurrence by α-fetoprotein model after curative resection for hepatocellular carcinoma. *Eur J Surg Oncol*. 2021;47(3 pt B):660-666.
26. Santambrogio R, Opocher E, Costa M, et al. Hepatic resection for "BCLC stage A" hepatocellular carcinoma. The prognostic role of alpha-fetoprotein. *Ann Surg Oncol*. 2012;19(2):426-434.
27. Hsu CY, Liu PH, Lee YH, et al. Using serum α-fetoprotein for prognostic prediction in patients with hepatocellular carcinoma: what is the most optimal cutoff? *PLoS One*. 2015;10(3):e0118825.
28. Peng Y, Qi X, Guo X. Child-Pugh versus MELD score for the assessment of prognosis in liver cirrhosis: a systematic review and meta-analysis of obserfvational studies. *Medicine*. 2016;95(8):e2877.
29. Bruix J, Gores GJ, Mazzaferro V. Hepatocellular carcinoma: clinical frontiers and perspectives. *Gut*. 2014;63(5):844-855.
30. Rajakannu M, Coilly A, Adam R, Samuel D, Vibert E. Prospective validation of transient elastography for staging liver fibrosis in patients undergoing hepatectomy and liver transplantation. *J Hepatol*. 2017;S0168-8278(17):32214-32216.
31. Yang JD, Kim WR, Park KW, et al. Model to estimate survival in ambulatory patients with hepatocellular carcinoma. *Hepatology*. 2012;56(2):614-621.
32. Yau T, Tang VY, Yao TJ, Fan ST, Lo CM, Poon RT. Development of Hong Kong liver cancer staging system with treatment stratification for patients with hepatocellular carcinoma. *Gastroenterology*. 2014;146(7):1691-7000.
33. Yim SY, Seo YS, Jung CH, et al. The management and prognosis of patients with hepatocellular carcinoma: what has changed in 20 years? *Liver Int*. 2016;36(3):445-453.
34. Seo CG, Yim SY, Um SH, et al. Survival according to recurrence patterns after resection for transplantable hepatocellular carcinoma in HBV endemic area: appraisal of liver transplantation strategy. *Clin Res Hepatol Gastroenterol*. 2020;44(4):532-542.
35. Vitale A, Burra P, Frigo AC, et al. Italian Liver Cancer (ITA.LI.CA) Group. Survival benefit of liver resection for patients with hepatocellular carcinoma across different barcelona clinic liver cancer stages: a multicentre study. *J Hepatol*. 2015;62(3):617-624.
36. Torzilli G, Belghiti J, Kokudo N, et al. A snapshot of the effective indications and results of surgery for hepatocellular carcinoma in tertiary referral centers: is it adherent to the EASL/AASLD

recommendations?: an observational study of the HCC East-West study group. *Ann Surg*. 2013;257(5):929-937.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Lima HA, Endo Y, Moazzam Z, et al. TAC score better predicts survival than the BCLC following resection of hepatocellular carcinoma. *J Surg Oncol*. 2023;127:374-384. doi:10.1002/jso.27116