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Tumor burden score as a new prognostic marker for patients with hepatocellular carcinoma undergoing transarterial chemoembolization

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Abstract

Background and Aim: Size and number are major determinants of tumor burden in hepatocellular carcinoma (HCC). Patients with HCC undergoing transarterial chemoembolization (TACE) have variable outcomes due to heterogeneity of tumor burden. Recently, tumor burden score (TBS) was proposed to evaluate the extent of tumor involvement. However, the prognostic accuracy of TBS has not been well evaluated in HCC. This study aimed to assess its prognostic role in HCC patients undergoing TACE.
Methods: A total of 935 treatment-naïve HCC patients receiving TACE were retrospectively analyzed. Multivariate Cox proportional hazards model was used to determine independent prognostic predictors.
Results: Tumor burden score tended to increase with increasing size and number of tumors in study patients. The Cox model showed that serum creatinine ≥ 1.2 mg/dL (hazard ratio [HR]: 1.296, 95% confidence interval [CI]: 1.077–1.559, $P = 0.006$), serum α-fetoprotein ≥ 400 ng/dL (HR: 2.245, 95% CI: 1.905–2.645, $P < 0.001$), vascular invasion (HR: 1.870, 95% CI: 1.520–2.301, $P < 0.001$), medium TBS (HR: 1.489, 95% CI: 1.206–1.839, $P < 0.001$) and high TBS (HR: 2.563, 95% CI: 1.823–3.602, $P < 0.001$), albumin–bilirubin (ALBI) grade 2–3 (HR: 1.521, 95% CI: 1.291–1.792, $P < 0.001$), and performance status 1 (HR: 1.362, 95% CI: 1.127–1.647, $P < 0.001$) and status 2 (HR: 1.553, 95% CI: 1.237–1.948, $P < 0.001$) were associated with increased mortality. Patients with high TBS had poor overall survival in Barcelona Clinic Liver Cancer stage B/C and different ALBI grades.
Conclusions: Tumor burden score is a feasible new prognostic surrogate marker of tumor burden in HCC and can well discriminate survival in patients undergoing TACE across different baseline characteristics.

Introduction

Hepatocellular carcinoma (HCC) is one of the most common primary liver cancer and caused 800 000 deaths worldwide in 2016.[1] Despite improvement in screening program and treatments, the prognosis of HCC was dismal because a substantially high proportion of patients had large or multiple tumors at diagnosis.[2] Based on current HCC practice guidelines, transarterial chemoembolization (TACE) is the recommended treatment to prolong survival for intermediate stage HCC.[3–5] Notably, TACE can also be performed in patients with early-stage HCC who are unsuitable for curative treatments and even in advanced stage to provide additional survival benefit.[2,6,7] However, patients undergoing TACE may have heterogeneous outcomes due to variable tumor burden and liver functional reserve.[7]

Traditionally, the diameter and number of tumor nodule are determinants of tumor burden in HCC. These two variables were often used as dichotomous variables and incorporated in the staging systems. Importantly, the selection of treatment for HCC relies heavily on the size and number of tumors. One example is that the Milan criteria (single tumor less than 5 cm or two or three nodules smaller than 3 cm) were widely used to evaluate the feasibility of liver transplantation in HCC. The treatment options of patients beyond the Milan criteria could widely vary because of variable

tumor burden. For instance, the prognosis of patients with single tumor and diameter of 7 cm could be quite different from those with three nodules of 5, 4, and 3 cm in diameter. Therefore, it is often difficult to assess the prognosis in patients with variable size and number of tumors. The up-to-7 criteria and up-to-11 criteria were proposed to assess tumor burden in HCC. These two models combine the largest diameter of nodule and number of tumors, with the sum being no more than 7 or 11, but they had apparent shortcomings due to categorical variables of tumor burden.[8,9] Other investigators proposed using the continuum of tumor burden variables as prognostic factors rather than categorical variables and suggested that total tumor diameter and total tumor volume were alternative indicators for tumor burden; still, these two models have some inherent limitations.[10–12]

More recently, Sasaki *et al*. advocated using tumor burden score (TBS) in liver to determine tumor burden in colorectal cancer with liver metastasis undergoing surgical resection.[13] The discriminatory ability of TBS in HCC patients undergoing surgical resection and liver transplantation was reported by independent study groups.[14–16] However, the feasibility and prognostic accuracy of TBS in patients undergoing TACE have not been well evaluated. In this study, we aimed to investigate the prognostic role of TBS in HCC patients undergoing TACE.

Methods

Patients. A prospectively enrolled database based on 935 treatment-naïve HCC patients receiving TACE as primary treatment in Taipei Veterans General Hospital between 2002 and 2016 were retrospectively analyzed. Baseline demographic data and clinical variables such as etiology of liver disease, laboratory data, tumor burden (number and size of tumor, vascular invasion, and TBS), liver functional reserve, performance status, and Barcelona Clinic Liver Cancer (BCLC) stage were recorded at the time of diagnosis. Patients were followed up every 3–6 months until death or dropout from the follow-up. This study was approved by the Institutional Review Board of Taipei Veterans General Hospital. Waiver of consent was obtained, and patient records/information was anonymized and deidentified prior to analysis.

Diagnosis and definition. Hepatocellular carcinoma was diagnosed according to the European Association for the Study of the Liver or the American Association for the Study of Liver Diseases HCC practice guidelines.[3,4] Vascular invasion was defined as radiological evidence of tumor invasion to intrahepatic vasculatures, portal trunk, or abdominal great vessels.[17] The albumin–bilirubin (ALBI) score was calculated according to the following formula = $0.66 \times \log_{10}$bilirubin (μmol/L) $- 0.085 \times$ albumin (g/L). The ALBI score was divided into three groups as follows: score ≤ -2.60 (ALBI grade 1), score > -2.60 and ≤ -1.39 (ALBI grade 2), and score > -1.39 (ALBI grade 3).[18–20] The Eastern Cooperative Oncology Group performance scale was used to evaluate performance status.[21]

Tumor burden score. Tumor burden score was defined as the distance from the origin of a Cartesian plane and comprised two variables: maximum tumor size (x-axis) and number of tumors (y-axis) so that TBS^2 = (maximum tumor diameter)^2 + (number of tumors)^2.[13,14] Cutoff values of TBS were determined by the X-tile, a bioinformatic tool produced by Camp *et al*.[22] Patients were divided accordingly into three groups: high TBS (over 13.74), medium TBS (3.36–13.74), and low TBS (less than 3.36) as previously described.[14]

Treatments. Transarterial chemoembolization was performed in patients who had unresectable lesions and were not eligible or unwilling to receive other therapies. The indications of TACE were as follows: (i) no main portal vein trunk involvement, (ii) Child–Turcotte–Pugh (CTP) functional class A or B, (iii) serum creatinine concentration < 1.5 mg/dL, and (iv) absence of distant metastasis.[23] The newly diagnosed patients were discussed in the multidisciplinary HCC board for diagnosis confirmation and treatment recommendation. The benefits and risks of therapeutic information were provided to individual patient according to shared decision-making. Written informed consent was obtained prior to the initiation of treatment. The Seldinger technique of arterial embolization was administered as standard TACE procedure as previously described.[24]

Statistics. All statistical analyses were performed using IBM SPSS STATISTICS for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). Continuous variables were analyzed by the Mann–Whitney rank-sum test, and the chi-squared test or two-tailed Fisher's exact test were used to compare categorical data as appropriate. The overall survival was evaluated by the Kaplan–Meier method with log-rank test. Factors that were significant in the univariate survival analysis were introduced into the multivariate Cox proportional hazards model to determine independent predictors along with their hazard ratios (HRs) and 95% confidence interval (CI). The consequences of the Cox model were expressed with the corrected Akaike information criterion (AICc), which reveals how the model affects the dependent variable (patient survival) and represents an overall assessment of the model.[25,26] The lower the AIC, the more explanatory and informative the model is.[27] For all tests, a P-value < 0.05 was considered statistically significant.

Results

Patient characteristics. The baseline characteristics of HCC patients who received TACE as primary treatment are shown in Table 1. The mean age was 67 years, and the majority (75%) of patients were male. Hepatitis B virus infection is the major etiology of HCC, and about 80% of patients were CTP class A. A total of 331 (35%) patients were ALBI grade 1, 569 (61%) were ALBI grade 2, and 35 (4%) were ALBI grade 3. The mean tumor diameter was 6.3 cm, and 53% of patients had single tumor. In addition, 185 (20%) patients had low TBS, 673 (72%) had medium TBS, and 77 (8%) had high TBS.

Association of tumor burden score with tumor size and number. The distribution of TBS in association with tumor diameter and numbers is shown in Figure 1. For patients with single or multiple nodules, TBS all significantly increased in the

Table 1 Baseline characteristics of patients with hepatocellular carcinoma undergoing transarterial chemoembolization (n = 935)

Variables	n = 935
Age (years), mean ± SD	67 ± 13
Male/female, *n* (%)	704/231 (75/25)
Etiologies of liver disease	
HBV, *n* (%)	393 (42)
HCV, *n* (%)	277 (30)
HBV + HCV, *n* (%)	44 (5)
Others, *n* (%)	221 (23)
Performance status (0/1/2), *n* (%)	591/205/139 (63/22/15)
Diabetes mellitus, *n* (%)	251 (27)
Tumor nodules (single/multiple)	499/436 (53/47)
Maximal tumor diameter ≥ 5 cm, *n* (%)	442 (47)
Tumor diameter, mean ± SD	6.1 ± 4.2
Vascular invasion, *n* (%)	155 (17)
Serum AFP (ng/mL), median (IQR)	41 (9–482)
Serum AFP ≥ 400 ng/mL, *n* (%)	251 (27)
Ascites, *n* (%)	165 (17)
Laboratory values, median (IQR)	
Alanine transaminase (U/L)	47 (31–79)
Albumin (g/L)	37 (33–41)
Total bilirubin (μmol/L)	14.8 (10.3–22.2)
Platelets (1000/μL)	140 (88–205)
INR of prothrombin time (s)	1.06 (1.00–1.13)
Creatinine (mg/dL)	1.0 (0.8–1.2)
CTP class (A/B)	744/191 (80/20)
CTP score, mean ± SD	5.8 ± 0.1
ALBI grade (1/2/3), *n* (%)	331/569/35 (35/61/4)
ALBI score, median (IQR)	−2.37 (−2.73 to −2.01)
MELD score, mean ± SD	8.5 ± 3.5
BCLC stage (0/A/B/C), *n* (%)	32/193/270/440 (3/21/29/47)
Tumor burden score (TBS)	
Low	185 (20)
Medium	673 (72)
High	77 (8)

AFP, α-fetoprotein; ALBI, albumin–bilirubin; BCLC, Barcelona Clinic Liver Cancer; CTP, Child–Turcotte–Pugh; HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalized ratio; IQR, interquartile range; MELD, model for end-stage liver disease; SD, standard deviation; TBS, tumor burden score.

groups of maximum tumor diameter < 3, 3.0–5.0, and 5.1–8.0 cm (all $P < 0.001$). There was no significant difference of TBS in maximum tumor diameter > 8.0 cm of single or multinodular group ($P = 0.632$).

Survival analysis. The median overall survival was 21 months (interquartile range: 8–44 months). The 1-, 3-, and 5-year overall survival rates were 91%, 60%, and 35% respectively for low TBS; 73%, 39%, and 23% respectively for medium TBS; and 46%, 15%, and 5% respectively for high TBS. There was significant survival difference between the three groups (Fig. 2; $P < 0.001$).

In subgroup analysis, for BCLC stage 0/A patients, no significant survival difference was noted between medium and low TBS (Fig. 3a; $P = 0.224$). However, there was significant survival difference between the three TBS score groups for BCLC stage B/C patients. The 1-, 3-, and 5-year survival rates were 80%, 40%, and 19% respectively for low TBS; 70%, 37%, and 21% respectively for medium TBS; and 46%, 15%, and 5% respectively for high TBS (Fig. 3b; $P < 0.001$).

When the survival was stratified by ALBI grade, the 1-, 3-, and 5-year survival rates were 91%, 57%, and 41% respectively for low TBS; 81%, 54%, and 33% respectively for medium TBS; and 49%, 18%, and 0% respectively for high TBS (Fig. 4a; $P < 0.001$) among patients with ALBI grade 1. Consistently, high TBS score had poor overall survival in comparison with medium and low TBS in patients with ALBI grade 2–3. The 1-, 3-, and 5-year survival rates were 91%, 62%, and 33% respectively for low TBS; 68%, 30%, and 17% respectively for medium TBS; and 45%, 13%, and 9% respectively for high TBS (Fig. 4b; $P < 0.001$).

Multivariate Cox proportional hazards model. In univariate analysis, serum creatinine level, presence of ascites, serum α-fetoprotein (AFP) level, presence of vascular invasion, TBS, ALBI grade, and performance status were associated with poor overall survival. Multivariate Cox model showed that serum creatinine ≥ 1.2 mg/dL (HR: 1.296, 95% CI: 1.077–1.559, $P = 0.006$), serum α-fetoprotein ≥ 400 ng/dL (HR: 2.245, 95% CI: 1.905–2.645, $P < 0.001$), vascular invasion (HR: 1.870, 95% CI: 1.520–2.301, $P < 0.001$), medium TBS (HR: 1.489, 95% CI: 1.206–1.839, $P < 0.001$) and high TBS (HR: 2.563, 95% CI: 1.823–3.602, $P < 0.001$), ALBI grade 2–3 (HR: 1.521, 95% CI: 1.291–1.792, $P < 0.001$), and performance status 1 (HR: 1.362, 95% CI: 1.127–1.647, $P < 0.001$) and status 2 (HR: 1.553, 95% CI: 1.237–1.948, $P < 0.001$) were independently associated increased mortality in these patients (Table 2).

In subgroup analysis of BCLC stage B patients, univariate analysis showed that TBS, AFP ≥ 400 ng/mL, diabetes mellitus, and ALBI grade were associated with increased mortality. The multivariate Cox model revealed that high TBS (HR: 1.642, 95% CI: 1.199–2.249, $P = 0.002$), AFP ≥ 400 ng/mL (HR: 1.705, 95% CI: 1.213–2.396, $P = 0.002$), diabetes mellitus (HR: 1.874, 95% CI: 1.322–2.638, $P < 0.001$), and ALBI grade 2–3 (HR: 1.679, 95% CI: 1.256–2.244, $P < 0.001$) were independently associated with decreased survival (Table 3).

The prognostic performance of the up-to-7 criteria, up-to-11 criteria, and TBS was evaluated. Among these three models, TBS had the highest homogeneity and the lowest AICc, suggesting a better prognostic performance to discriminate survival in TACE patients (Table S1).

Discussion

The diameter of tumor size and numbers of nodules are traditional methods to indicate tumor burden in HCC. However, the use of arbitrary categorical cutoff values of continuous (tumor size) or ordinal (tumor number) may lead to inaccurate prognostic prediction. By using the Pythagorean theorem, TBS was recently proposed to minimize the heterogeneity of size and number of tumor nodules in primary or metastatic liver cancer. Our results indicate that TBS is a useful marker to represent tumor burden and can differentiate overall survival in HCC patients undergoing TACE.

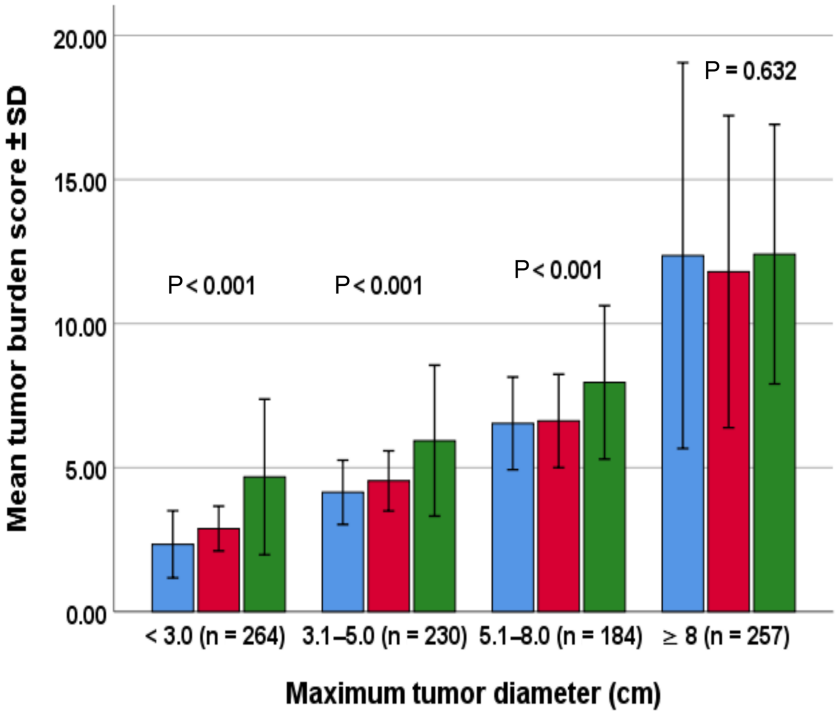

Figure 1 The association of tumor burden score with tumor diameter and numbers. For patients with single or multiple nodules, tumor burden score all significantly increased in the groups of maximum tumor diameter < 3, 3.0–5.0, and 5.1–8.0 cm (all $P < 0.001$), with the exception in tumor diameter > 8.0-cm group ($P = 0.632$). ■, no. of tumor nodule = 1; ■, no. of tumor nodule = 2; ■, no. of tumor nodule ≥ 3.

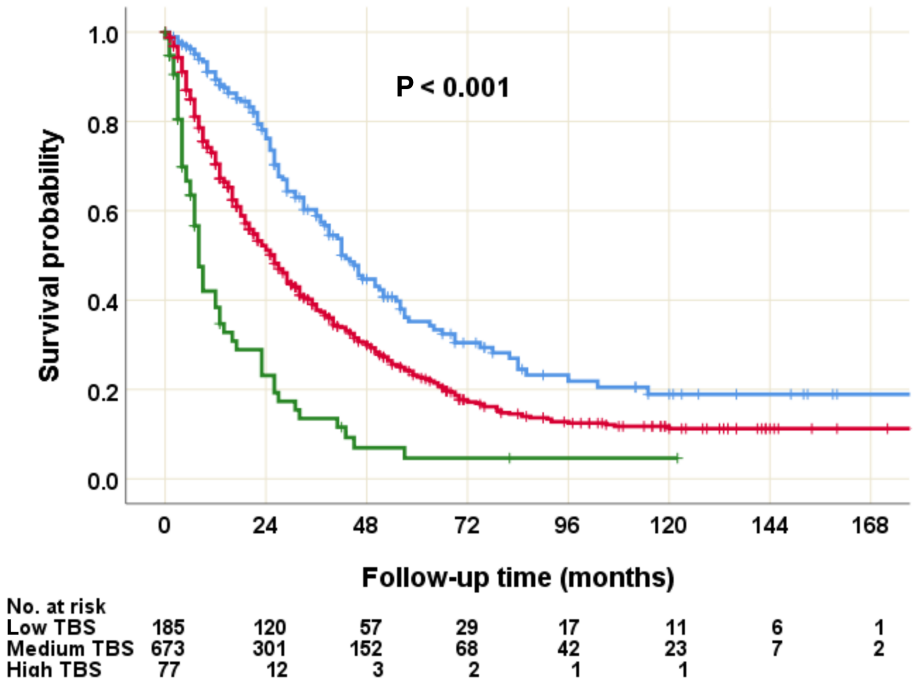

Figure 2 The survival distribution of different tumor burden score (TBS) in hepatocellular carcinoma patients undergoing transarterial chemoembolization. High TBS had decreased overall survival in comparison with medium TBS and low TBS ($P < 0.001$). ┌─, low TBS; ┌─, medium TBS; ┌─, high TBS; ─┼─, low TBS; ─┼─, medium TBS; ─┼─, high TBS.

There are several advantages of using TBS as a surrogate marker for tumor burden. Firstly, the calculation of TBS only requires the diameter of the largest tumor and number of tumor nodules in contrast with total tumor diameter and total tumor volume, which require all sizes of tumor nodules. In addition, the formula to calculate these two prognostic tools is also very complex. Secondly, unlike dichotomous approach of the Milan criteria or up-to-7 criteria, TBS is a simple and continuous variable to represent

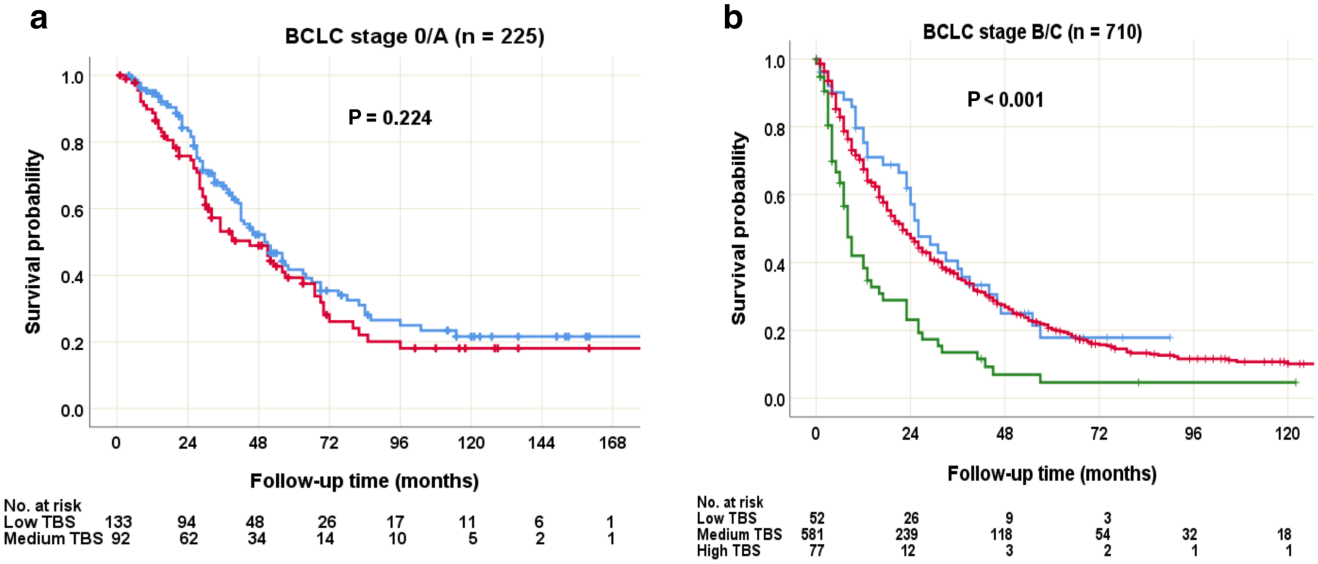

Figure 3 The survival distribution of different tumor burden score (TBS) based on (a) Barcelona Clinic Liver Cancer (BCLC) stage 0/A and (b) BCLC stage B/C. No significant survival different was found between medium TBS and low TBS in BCLC stage O/A ($P = 0.224$). High TBS had increased risk of mortality compared with medium TBS and low TBS in BCLC stage B/C ($P < 0.001$). (a) ⌐, low TBS; ⌐, medium TBS; ┼, low TBS; ┼, medium TBS. (b) ⌐, low TBS; ⌐, medium TBS; ⌐, high TBS; ┼, low TBS; ┼, medium TBS; ┼, high TBS.

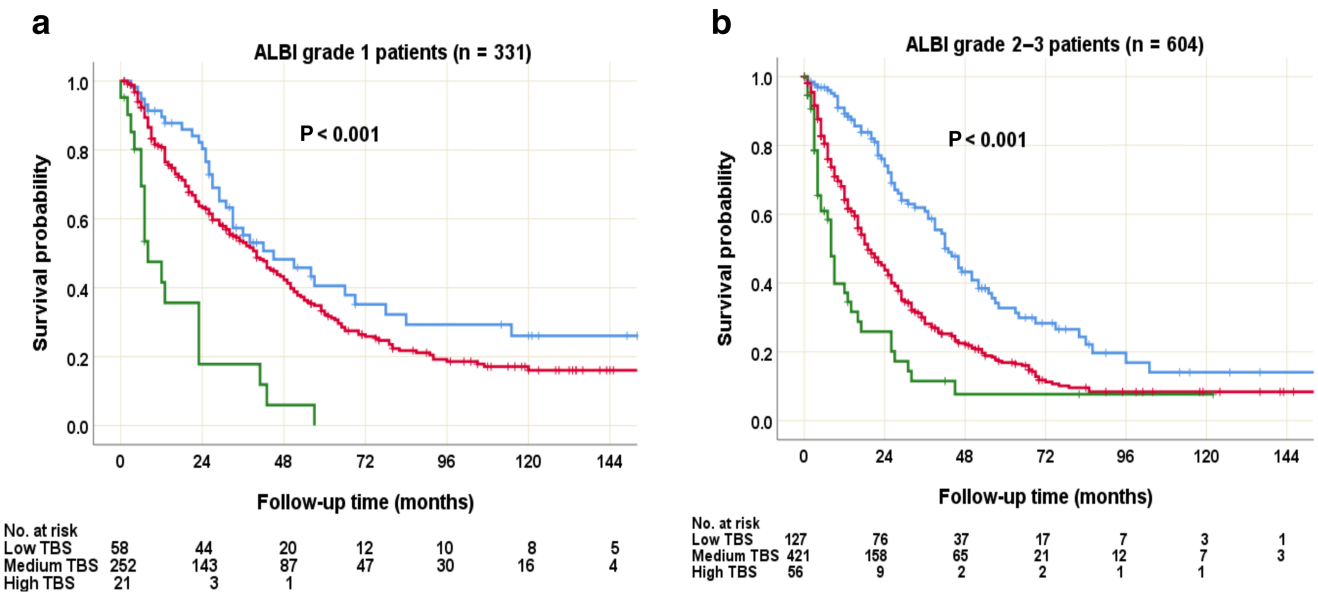

Figure 4 The survival distribution of different tumor burden score (TBS) based on (a) albumin–bilirubin (ALBI) grade 1 and (b) ALBI grade 2–3 patients. There were significant survival differences between different TBS groups in ALBI grade 1 ($P < 0.001$) and grade 2–3 patients ($P < 0.001$). (a) ⌐, low TBS; ⌐, medium TBS; ⌐, high TBS; ┼, low TBS; ┼, medium TBS; ┼, high TBS. (b) ⌐, low TBS; ⌐, medium TBS; ⌐, high TBS; ┼, low TBS; ┼, medium TBS; ┼, high TBS.

the extent of tumor involvement in liver. Notably, our results show that TBS had the highest homogeneity and the lowest AICc compared with these two criteria. In addition, TBS can be conveniently categorized into different risk groups to predict the outcome more specifically. Thirdly, there is a clear dose–response relationship between TBS and the long-term survival for different patient groups in our study. In multivariate Cox analysis, patients with higher TBS had increased risk of mortality compared with medium TBS and low TBS. These results are consistent with previous studies.[14–16] Our results further support the idea that TBS can be used as an independent prognostic predictor to assess tumor burden and outcome in these patients.

In addition to the predictive power for the entire cohort, the prognostic value of TBS was also confirmed in patients with

Table 2 Univariate and multivariate analysis of overall survival in patients undergoing transarterial chemoembolization (n = 935)

Variables	Number	Univariate analysis			Multivariate analysis		
		1-year survival (%)	3-year survival (%)	*P*	HR	95% CI	*P*
Age (< 65/≥ 65 years)	388/547	71/77	42/41	0.968			
Sex (male/female)	704/231	74/76	39/49	0.865			
HBV (negative/positive)	498/437	76/73	43/40	0.968			
HCV (negative/positive)	614/321	71/81	39/46	0.133			
Platelet (≥ 150 000/< 150 000/μL)	424/511	66/81	36/46	0.004			
Creatinine (< 1.2/≥ 1.2 mg/dL)	721/214	76/71	44/32	0.005	1.296	1.077–1.559	0.006
Ascites (absent/present)	770/165	78/59	44/29	< 0.001			
Serum AFP (< 400/≥ 400 ng/mL)	684/251	82/54	49/20	< 0.001	2.245	1.905–2.645	< 0.001
Vascular invasion (no/yes)	780/155	81/43	45/22	< 0.001	1.870	1.520–2.301	< 0.001
Diabetes mellitus (no/yes)	684/251	75/74	43/37	0.239			
TBS							
Low	185	91	60		1		
Medium	673	73	39	< 0.001	1.489	1.206–1.839	< 0.001
High	77	46	15	< 0.001	2.563	1.823–3.602	< 0.001
ALBI							
Grade 1	331	81	52		1		
Grade 2–3	604	71	35	< 0.001	1.521	1.291–1.792	< 0.001
Performance status							
0	591	82	48	< 0.001	1		
1	205	64	31	< 0.001	1.362	1.127–1.647	< 0.001
2	139	59	25	< 0.001	1.553	1.237–1.948	< 0.001

AFP, α-fetoprotein; ALBI, albumin–bilirubin; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; TBS, tumor burden score.

Table 3 Univariate and multivariate analysis of overall survival in BCLC stage B HCC patients undergoing TACE (n = 270)

Variables	Number	Univariate analysis			Multivariate analysis		
		1-year survival (%)	3-year survival (%)	*P*	HR	95% CI	*P*
Age (< 65/≥ 65 years)	106/164	88/82	53/40	0.806			
Sex (male/female)	220/50	85/81	45/46	0.908			
HBV (negative/positive)	129/141	87/82	55/35	0.790			
HCV (negative/positive)	191/79	81/91	40/56	0.822			
Platelet (≥ 150 000/< 150 000/μL)	132/138	84/84	41/48	0.980			
Creatinine (< 1.2/≥ 1.2 mg/dL)	213/57	84/84	46/38	0.872			
Ascites (absent/present)	253/17	84/81	45/49	0.721			
Serum AFP (< 400/≥ 400 ng/mL)	211/59	87/71	49/28	< 0.001	1.705	1.213–2.396	0.002
Vascular invasion (no/yes)	201/69	84/50	45/50	0.493			
Diabetes mellitus (no/yes)	205/65	84/84	50/25	< 0.001	1.874	1.322–2.638	< 0.001
TBS							
Medium	201	86	51		1		
High	69	79	28	0.002	1.642	1.199–2.249	0.002
ALBI							
Grade 1	121	89	58		1		
Grade 2–3	149	80	33	< 0.001	1.679	1.256–2.244	< 0.001

AFP, α-fetoprotein; ALBI, albumin–bilirubin; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; TACE, transarterial chemoembolization; TBS, tumor burden score.

different baseline characteristics. In subgroup analysis based on the BCLC stage, patients with high TBS had the worst outcome in BCLC stage B/C group. Notably, the reason why TBS did not play a significant role in early or very early BCLC stage is probably due to relatively small sample size and very small tumor burden in this subgroup. In addition, in subgroup analysis of BCLC stage B patients, patients with high TBS were associated with increased risk of mortality in the Cox model. Alternatively, when the ALBI grade was considered, TBS can stratify the survival in both ALBI grade 1 and grade 2–3 patients. These findings

further indicate the independent role of TBS in predicting patient outcome in BCLC stage B/C and different ALBI grades.

The severity of liver functional reserve has also been shown an important determinant in the management HCC. The CTP classification and MELD score are used to evaluate the severity of liver injury. However, these two models were reported to have some shortcomings.[28] Recently, ALBI grade is a simple and objective indicator to assess the severity of liver damage in HCC patients and has been validated by several research groups.[18,19] Our study reveals that patients with ALBI grade 2–3 had 45% increased risk of mortality compared with ALBI grade 1 in the multivariate Cox analysis. These results are mostly consistent with other study groups[18,19,29,30] and confirm that ALBI grade is an indispensable tool to evaluate liver functional reserve in HCC patients.

Serum AFP level and vascular invasion were also reported to closely associate with tumor burden in HCC. Our results show that serum AFP and vascular invasion were independent prognostic indicators in the multivariate analysis. Several research groups consistently showed that these two predictors may predict overall survival in HCC patients.[11,17] Another consistent finding is that we found that patients with poor performance status had higher risk of mortality in this study.[21]

There are a few limitations in this study. Firstly, our findings are based on a single medical center in Asia where hepatitis B is the predominant etiology of chronic liver disease. External validation is required before our findings can be applied to Western countries where hepatitis C and alcoholism are more often seen. Secondly, TBS is a simple and easy tool to evaluate tumor burden. However, the diameter of the largest nodule and number of tumors express the same statistical power. For example, patient with a 5-cm nodule and three 1-cm nodules may have the same outcome compared with all four 5-cm nodules. Thirdly, the selection of TACE was based on the decision of multidisciplinary team and may not strictly adhere to the BCLC staging treatment recommendation.

In conclusion, we confirm that TBS tends to increase with increasing size and number of tumors and can discriminate overall survival in patients undergoing TACE. In addition, the discriminatory ability of TBS for outcome prediction is independent of BCLC stage B/C and ALBI grades. TBS is a simple and useful prognostic tool and requires further study to demonstrate its feasibility in different clinical settings.

References

1 Liu Z, Jiang Y, Yuan H *et al*. The trends in incidence of primary liver cancer caused by specific etiologies: results from the Global Burden of Disease Study 2016 and implications for liver cancer prevention. *J. Hepatol.* 2019; **70**: 674–83.

2 Xu L, Peng ZW, Chen MS *et al*. Prognostic nomogram for patients with unresectable hepatocellular carcinoma after transcatheter arterial chemoembolization. *J. Hepatol.* 2015; **63**: 122–30.

3 Heimbach JK, Kulik LM, Finn RS *et al*. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology* 2018; **67**: 358–80.

4 European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. *J. Hepatol.* 2018; **69**: 182–236.

5 Facciorusso A, Mariani L, Sposito C *et al*. Drug-eluting beads *versus* conventional chemoembolization for the treatment of unresectable hepatocellular carcinoma. *J. Gastroenterol. Hepatol.* 2016; **31**: 645–53.

6 Bargellini I, Sacco R, Bozzi E *et al*. Transarterial chemoembolization in very early and early-stage hepatocellular carcinoma patients excluded from curative treatment: a prospective cohort study. *Eur. J. Radiol.* 2012; **81**: 1173–8.

7 Wang Q, Xia D, Bai W *et al*. Development of a prognostic score for recommended tace candidates with hepatocellular carcinoma: a multicentre observational study. *J. Hepatol.* 2019; **70**: 893–903.

8 Wang YY, Zhong JH, Xu HF *et al*. A modified staging of early and intermediate hepatocellular carcinoma based on single tumour >7 cm and multiple tumours beyond up-to-seven criteria. *Aliment. Pharmacol. Ther.* 2019; **49**: 202–10.

9 Hu KS, Tang B, Yuan J *et al*. A new substage classification strategy for Barcelona Clinic Liver Cancer stage B patients with hepatocellular carcinoma. *J. Gastroenterol. Hepatol.* 2019; **34**: 1984–91.

10 Lai Q, Avolio AW, Manzia TM *et al*. Combination of biological and morphological parameters for the selection of patients with hepatocellular carcinoma waiting for liver transplantation. *Clin. Transplant.* 2012; **26**: E125–31.

11 Huo TI, Hsu CY, Huang YH *et al*. Prognostic prediction across a gradient of total tumor volume in patients with hepatocellular carcinoma undergoing locoregional therapy. *BMC Gastroenterol.* 2010; **10**: 146.

12 Kim JH, Shim JH, Lee HC *et al*. New intermediate-stage subclassification for patients with hepatocellular carcinoma treated with transarterial chemoembolization. *Liver Int.* 2017; **37**: 1861–8.

13 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**: 132–41.

14 Tsilimigras DI, Moris D, Hyer JM *et al*. Hepatocellular carcinoma tumour burden score to stratify prognosis after resection. *Br. J. Surg.* 2020; **107**: 854–64.

15 Moris D, Shaw BI, McElroy L, Barbas AS. Using hepatocellular carcinoma tumor burden score to stratify prognosis after liver transplantation. *Cancers (Basel)* 2020; **12**: 3372.

16 Vitale A, Lai Q, Farinati F *et al*. Utility of tumor burden score to stratify prognosis of patients with hepatocellular cancer: results of 4759 cases from ITA.LI.CA study group. *J. Gastrointest. Surg.* 2018; **22**: 859–71.

17 Lee YH, Hsu CY, Huang YH *et al*. Vascular invasion in hepatocellular carcinoma: prevalence, determinants and prognostic impact. *J. Clin. Gastroenterol.* 2014; **48**: 734–41.

18 Johnson PJ, Berhane S, Kagebayashi C *et al*. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach—the ALBI grade. *J. Clin. Oncol.* 2015; **33**: 550–8.

19 Ho SY, Hsu CY, Liu PH *et al*. Albumin-bilirubin grade-based nomogram of the BCLC system for personalized prognostic prediction in hepatocellular carcinoma. *Liver Int.* 2020; **40**: 205–14.

20 Chan AW, Chong CC, Mo FK *et al*. Incorporating albumin–bilirubin grade into the Cancer of the Liver Italian Program system for hepatocellular carcinoma. *J. Gastroenterol. Hepatol.* 2017; **32**: 221–8.

21 Hsu CY, Lee YH, Hsia CY *et al*. Performance status in patients with hepatocellular carcinoma: determinants, prognostic impact, and ability to improve the barcelona clinic liver cancer system. *Hepatology* 2013; **57**: 112–9.

22 Camp RL, Dolled-Filhart M, Rimm DL. X-tile: a new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization. *Clin. Cancer Res.* 2004; **10**: 7252–9.

23 Huo TI, Wu JC, Huang YH *et al*. Acute renal failure after transarterial chemoembolization for hepatocellular carcinoma: a retrospective study of the incidence, risk factors, clinical course and long-term outcome. *Aliment. Pharmacol. Ther.* 2004; **19**: 999–1007.

24 Hsu CY, Huang YH, Su CW *et al*. Renal failure in patients with hepatocellular carcinoma and ascites undergoing transarterial chemoembolization. *Liver Int.* 2010; **30**: 77–84.
25 Hosmer DW, Hosmer T, Le Cessie S, Lemeshow S. A comparison of goodness-of-fit tests for the logistic regression model. *Stat. Med.* 1997; **16**: 965–80.
26 Feinstein AR. Clinical biostatistics. XVI. The process of prognostic stratification. 2. *Clin. Pharmacol. Ther.* 1972; **13**: 609–24.
27 Forster MR. Key concepts in model selection: performance and generalizability. *J Math Psychol.* 2000; **44**: 205–31.
28 Ho S-Y, Hsu C-Y, Liu P-H *et al*. Survival of patients with hepatocellular carcinoma in renal insufficiency: prognostic role of albumin-bilirubin grade. *Cancer* 2020; **12**: 1130.
29 Huo TI. ALBI grade as a new player in hepatocellular carcinoma. *J. Chin. Med. Assoc.* 2019; **82**: 1.
30 Tada T, Kumada T, Toyoda H *et al*. Impact of albumin–bilirubin grade on survival in patients with hepatocellular carcinoma who received sorafenib: an analysis using time-dependent receiver operating characteristic. *J. Gastroenterol. Hepatol.* 2019; **34**: 1066–73.

Supporting information

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

Table S1. Comparison of the prognostic performance among up-to-7 criteria, up-to-11 criteria and TBS in HCC patients undergoing TACE (n = 935).