

Huang Yi-Hsiang (Orcid ID: 0000-0001-5241-5425)  
Su Chien-Wei (Orcid ID: 0000-0003-3889-7004)  
Hou Ming-Chih (Orcid ID: 0000-0002-4886-0718)  
Huo Teh-Ia (Orcid ID: 0000-0003-2202-521X)

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

Shu-Yein Ho,<sup>1,2,3</sup> Po-Hong Liu,<sup>3,4</sup> Chia-Yang Hsu,<sup>3,5</sup> Chih-Chieh Ko,<sup>3,6</sup>

Yi-Hsiang Huang,<sup>3,6,7</sup> Chien-Wei Su,<sup>3,6</sup> Rheun-Chuan Lee,<sup>3,8</sup>

Ping-Hsing Tsai,<sup>2</sup> Ming-Chih Hou,<sup>3,6</sup> Teh-Ia Huo<sup>2,3,9</sup>

<sup>1</sup>Division of Gastroenterology and Hepatology, Min-Sheng General Hospital, Taoyuan, Taiwan;

<sup>2</sup>Department of Medical Research, Taipei Veterans General Hospital, Taipei, Taiwan;

<sup>3</sup>Faculty of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan;

<sup>4</sup>Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas, USA;

<sup>5</sup>Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, MI, USA;

<sup>6</sup>Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan;

<sup>7</sup>Institute of Clinical Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan;

<sup>8</sup>Department of Radiology, Taipei Veterans General Hospital, Taipei, Taiwan;

<sup>9</sup>Institute of Pharmacology, National Yang Ming Chiao Tung University, Taipei, Taiwan

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**Correspondence:**

Teh-Ia Huo, MD

Professor of Medicine

Department of Medical Research

Taipei Veterans General Hospital

No. 201, Sec. 2, Shipai Rd., Taipei 11217, Taiwan

Tel: + 886 2 2871 2121

Fax: + 886 2 2873 9318

Email: tihuo@vghtpe.gov.tw

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## **Authorship Statement**

**Guarantor of the article:** Teh-Ia Huo

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

## 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:** TBS tended to increase with increasing size and number of tumors in study patients. The Cox model showed that serum creatinine  $\geq 1.2$  mg/dL (hazard ratio [HR]: 1.296, 95% confidence interval [CI]: 1.077-1.559,  $p=0.006$ ), serum  $\alpha$ -fetoprotein  $\geq 400$  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,  $p<0.001$ ), 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 an increased mortality. Patients with high TBS had poor overall survival in Barcelona Cancer Liver Cancer (BCLC) stage B/C and different ALBI grades.

**Conclusions:** TBS 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.

**Key words:** tumor burden score; hepatocellular carcinoma; transarterial chemoembolization

## Introduction

Hepatocellular carcinoma (HCC) is one of the most common primary liver cancer and caused 800,000 deaths worldwide in 2016.<sup>1</sup> 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.<sup>2</sup> Based on current HCC practice guidelines, transarterial chemoembolization (TACE) is the recommended treatment to prolong survival for intermediate stage HCC.<sup>3-5</sup> Notably, TACE can also be performed in patient with early stage HCC who are unsuitable for curative treatments, and even in advanced stage to provide additional survival benefit.<sup>2, 6, 7</sup> However, patients undergoing TACE may have heterogeneous outcomes due to variable tumor burden and liver functional reserve.<sup>7</sup>

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) was widely used to evaluate the feasibility of liver transplantation in HCC. The treatment options of patients beyond the Milan criteria could widely vary due to 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 cm, 4 cm 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.<sup>8,9</sup> Other investigators proposed using the continuum of tumor burden variables as prognostic factors rather than categorical variables, and suggested that total tumor diameter (TTD) and total tumor volume (TTV) were alternative indicators for tumor burden; still, these two models have some inherent limitations.<sup>10-12</sup>

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.<sup>13</sup> The discriminatory ability of TBS in HCC patients undergoing surgical resection and liver transplantation was reported by independent study groups.<sup>14-16</sup> However, the feasibility and prognostic accuracy of TBS in patients undergoing TACE has 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 to 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, TBS), liver functional reserve, performance status, and Barcelona Cancer Liver Cancer (BCLC) stage were recorded at the time of diagnosis. Patients were followed up every 3-6 months until death or drop-out 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**

HCC was diagnosed according to the European Association for the Study of Liver (EASL) or the American Association for the Study of Liver Disease (AASLD) HCC practice guidelines.<sup>3,4</sup> Vascular invasion was defined as radiological evidence of tumor invasion to intrahepatic vasculatures, portal trunk or abdominal great vessels.<sup>17</sup> The albumin-bilirubin (ALBI) score was calculated according to the following formula =  $0.66 \times \log_{10}\text{bilirubin } (\mu\text{mol/L}) - 0.085 \times \text{albumin (g/L)}$ . The ALBI score was divided into three groups as follow: score  $\leq -2.60$  (ALBI grade 1), score  $> -2.60$  and  $\leq -1.39$  (ALBI grade 2) and score  $> -1.39$  (ALBI grade 3).<sup>18-20</sup> The Eastern Cooperative Oncology Group performance scale was used to evaluate performance status (PS).<sup>21</sup>

### **Tumor burden score (TBS)**

TBS 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  $\text{TBS}^2 = (\text{maximum tumor diameter})^2 + (\text{number of tumors})^2$ .<sup>13,14</sup> Cut-off values of TBS were determined by the X-tile, a bioinformatic tool produced by Camp and colleagues.<sup>22</sup> 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.<sup>14</sup>

### **Treatments**

TACE was performed in patients who had unresectable lesions and were not eligible or unwilling to receive other therapies. The indications of TACE were: (1) no main portal vein



trunk involvement (2) Child-Turcotte-Pugh (CTP) functional class A or B, (3) serum creatinine concentration < 1.5 mg/dL, and (4) absence of distant metastasis.<sup>23</sup> 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's technique of arterial embolization was administered as standard TACE procedure as previously described.<sup>24</sup>

### **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 ranked sum test, and the Chi-squared test or two-tailed Fisher 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 which 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 (HR) and 95% confidence incidence (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.<sup>25, 26</sup> The lower the AIC, the more explanatory and informative the model is.<sup>27</sup> 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 albumin-bilirubin (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 TBS with tumor size and number**

The distribution of tumor burden score in association with tumor diameter and numbers are shown in Figure 1. For patients with single or multiple nodules, TBS all significantly increased in the groups of maximum tumor diameter < 3 cm, 3.0- 5.0 cm and 5.1-8.0 cm (all  $p < 0.001$ ). There was no significant difference of TBS in maximum tumor diameter > 8.0 cm single or multi-nodular group ( $p = 0.632$ ).

### **Survival analysis**

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

In subgroup analysis, for BCLC stage 0/A patients, no significant survival difference was noted between medium and low TBS (Figure 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%, 19% respectively for low TBS, 70%, 37%, 21% respectively for medium TBS, and 46%, 15%, 5% respectively for high TBS (Figure 3B;  $p < 0.001$ ).

When the survival was stratified by ALBI grade, the 1-, 3-, and 5-year survival rates were 91%, 57%, 41% respectively for low TBS, 81%, 54%, 33% respectively for medium TBS, and 49%, 18%, 0% respectively for high TBS (Figure 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-, 5-year survival rates were 91%, 62%, 33% respectively for low TBS, 68%, 30%, 17% respectively for medium TBS, and 45%, 13%, 9% respectively for high TBS (Figure 4B;  $p < 0.001$ ).

#### **Multivariate Cox proportional hazards model**

In univariate analysis, serum creatinine level, presence of ascites, serum  $\alpha$ -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  $\geq 1.2$  mg/dL (hazard ratio (HR): 1.296, 95% confidence interval [CI]: 1.077-1.559,  $p=0.006$ ), serum  $\alpha$ -fetoprotein  $\geq 400$  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,  $p < 0.001$ ), 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.

In subgroup analysis of BCLC stage B patients, univariate analysis showed that

TBS, AFP  $\geq$  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  $\geq$  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:1.874, 95% CI: 1.322-2.638,  $p<0.001$ ) 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 (Supplementary Table 1).

## 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 cut-off 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.

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 TTD and TTV 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 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.<sup>14-16</sup> 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 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 both in 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.<sup>28</sup> 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.<sup>18, 19</sup> 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,<sup>18, 19, 29, 30</sup> 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.<sup>11, 17</sup> Another consistent finding is that we found that patients with poor performance status had higher risk of mortality in this study.<sup>21</sup>

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.

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Huang Yi-Hsiang (Orcid ID: 0000-0001-5241-5425)  
Su Chien-Wei (Orcid ID: 0000-0003-3889-7004)  
Hou Ming-Chih (Orcid ID: 0000-0002-4886-0718)  
Huo Teh-Ia (Orcid ID: 0000-0003-2202-521X)

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**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 ≥ 5cm, 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 (1,000/μL)	140 (88-205)
INR of prothrombin time (sec)	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)

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ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CTP, Child-Turcotte-Pugh; HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalized ratio; MELD, model for end-stage liver disease; SD, standard deviation

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

Variables	Univariate analysis				Multivariate analysis		
	Number	1-yr survival (%)	3-yr 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 (≥150000/<150000 /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

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ALBI, albumin-bilirubin, AFP, alpha-fetoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus; TBS, tumor burden score

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

Variables	Univariate analysis				Multivariate analysis		
	Number	1-yr survival (%)	3-yr 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 (≥150000/<150000 /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

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ALBI, albumin-bilirubin, AFP, alpha-fetoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus; TBS, tumor burden score

## Figure Legend

**Figure 1.** The association of tumor burden score (TBS) with tumor diameter and numbers. For patients with single or multiple nodules, TBS all significantly increased in the groups of maximum tumor diameter < 3 cm, 3.0- 5.0 cm and 5.1-8.0 cm (all  $p < 0.001$ ), with the exception in tumor diameter > 8.0 cm group ( $p=0.632$ ).

**Figure 2.** The survival distribution of different tumor burden score (TBS) in HCC patients undergoing transarterial chemoembolization (TACE). High TBS had decreased overall survival in comparison with medium TBS and low TBS ( $p < 0.001$ ).

**Figure 3.** The survival distribution of different tumor burden score (TBS) based on (A) BCLC stage 0/A and (B) BCLC stage B/C. No significant survival difference was found between medium TBS and low TBS in BCLC stage 0/A ( $p=0.024$ ). High TBS had increased risk of mortality compared with medium TBS and low TBS in BCLC stage B/C ( $p < 0.001$ ).

**Figure 4.** The survival distribution of different tumor burden score (TBS) based on (A) 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 ( $p < 0.001$ ).