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ORIGINAL ARTICLE

Total tumor volume predicts survival following liver resection in patients with hepatocellular carcinoma

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Abstract Assessing the prognosis of patients with hepatocellular carcinoma (HCC) by the number and size of tumors is sometimes difficult. The main purpose of the study was to evaluate the prognostic value of total tumor volume (TTV), which combines the two factors, in patients with HCC who underwent liver resection. We retrospectively reviewed 521 HCC patients from January 2001 to December 2008 in our center. Patients were categorized using the tertiles of TTV. The prognostic value of TTV was assessed. With a median follow-up of 116 months, the 1-, 3-, and 5-year overall survival (OS) rates of the patients were 93.1 , 69.9, and 46.3 %, respectively. OS was significantly differed by TTV tertile groups, and higher TTV was associated with shorter OS ($P < 0.001$). Multivariate analysis revealed that TTV was an independent prognostic factor for OS. Larger TTV was significantly associated with higher alpha-fetoprotein level, presence of macrovascular invasion, multiple tumor lesions, larger tumor size, and advanced tumor stages (all $P < 0.05$). Within the first and second tertiles of TTV (TTV ≤ 73.5 cm^3), no significant differences in OS were detected in patients within and beyond Milan criteria ($P = 0.183$). TTV-based Cancer of the Liver Italian Program (CLIP) score gained the lowest Akaike information criterion value, the highest χ^2 value of likelihood ratio test, and the highest *C*-index among the tested staging systems. Our results suggested that TTV is a good indicator of tumor burden in patients with HCC. Further studies are warranted to validate the prognostic value of TTV.

Keywords Total tumor volume · Tumor burden · Hepatocellular carcinoma · Prognosis

Abbreviations

HCC	Hepatocellular carcinoma
LR	Liver resection
TTV	Total tumor volume
HBV	Hepatitis B virus
HCV	Hepatitis C virus
AFP	Alpha-fetoprotein
TNM	Tumor-node-metastasis
BCLC	Barcelona Clinic Liver Cancer stage
CLIP	Cancer of the Liver Italian Program
AIC	Akaike information criterion

Introduction

Hepatocellular carcinoma (HCC) ranks as the fifth most common malignant cancer and the third most frequent cause of cancer leading death worldwide [1, 2]. Chiefly, due to the high prevalence of hepatitis virus infection and alcoholic liver disease, the disease burden of HCC is still quite tremendous [3, 4]. Along with the improvement in the population surveillance program and imaging modalities in the past decades, the

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proportion of patients at early or intermediate stages are expected to increase [5, 6].

Liver resection (LR) is considered as the mainstream treatment option for patients with well-preserved liver function, anatomic resectable lesions, and no evidence of distant metastasis [7–11]. Although liver transplantation removes the tumor lesions and the impaired liver simultaneously, its application is limited by the lack of liver grafts and by huge economic costs [12]. The prognosis of HCC patients largely depends on the interplay of the tumor burden and liver function reserve. Usually, the tumor burden is appraised by the number and size of the tumor nodules. The Milan criteria (solitary HCC diameter≤5 cm or up to three nodules smaller than 3 cm), which was initially proposed by Mazzaferro et al. [13] in 1996, have been accepted as one of the standards selecting the candidates for liver transplantation. And, its prognostic efficacy was later validated in the realm of surgical resection [14]. However, a substantial proportion of HCC patients exceeding the Milan criteria have been found to survive longer than expected after curative liver resection [15]. It therefore seems reasonable to develop a tumor burden assessing parameter that gains optimal prognostic efficacy as well as further reduces unnecessary exclusions due to the strict application of the narrow selection criteria.

Recently, total tumor volume (TTV), which incorporates the number and size of the tumor nodules, has been proven to be a useful parameter to describe tumor burden in HCC patients awaiting liver transplantation [16–18]. However, scarce clinical evidences regarding the prognostic value of TTV in the LR-treated HCC patients have been reported. Lee et al. [19] compared the prognostic ability of Milan criteria and TTV in patients with TTV not more than 65.5 cm^3. But, there have been no studies comprehensively evaluating the prognostic efficacy of TTV in HCC patients who underwent hepatectomy especially for patients with TTV > 65.5 cm^3. We thus performed this retrospective analysis to evaluate the prognostic value of TTV in LR-treated patients.

Materials and methods

Patient selection

From January 2001 to December 2008, 539 patients with HCC as the only primary cancer who underwent curative liver resection (R0 resection) without previous history of treatments at the Department of Abdominal Surgical Oncology, Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, People's Republic of China, were identified. The diagnosis of HCC was determined by the evidence-based clinical guidelines and was confirmed by the pathological examination of the resected specimen. The negative resection margin was validated by the pathological examination. Of them, 18 patients were lost in the follow-up. Thus, finally, a total of 521 patients underwent R0 resection as the initial therapy for HCCs were taken into the study. Clinical data including patient demographics (e.g., age and sex), etiology of underlying liver disease, serum biochemistry, tumor number, tumor size, pathological reports, and liver function reserves were obtained from patients' medical records. Information about tumor staging systems such as the seventh tumor-node-metastasis (TNM) staging of the American Joint Committee on Cancer (AJCC) [20], Cancer of the Liver Italian Program (CLIP) scoring system [21], Barcelona Clinic Liver Cancer (BCLC) staging system [22], and the Okuda staging system [23] for HCC were also collected. Patients' informed consent was not required owing to the retrospective nature of the study.

Treatment

In our institution, the decision of curative intention LR was made by joint discussions. LR was usually considered in patients with (i) anatomically resectable tumors which were assessed by imaging examinations of the tumor size, tumor number, tumor location and vascular involvement; (ii) adequate liver function reserve (Child-Pugh grade A or B); and (iii) less than 25 % retention of indocyanine green 15 min after injection (ICGR-15).

Follow-up

Overall survival time of patients was calculated from the date of surgery to the date of last follow-up or death. The last date of follow-up was August 31, 2015. The follow-up was performed through face-to-face or telephone interview every 3 months in the first 2 years after operation and every 6 months thereafter or when tumor recurrence was highly suspected. At each follow-up visit, the information about physical examination, liver function tests, alpha-fetoprotein (AFP) level test, chest radiography, abdominal ultrasonography (US), contrast-enhanced computer tomography (CT) scans, and (or) liver magnetic resonance imaging (MRI) were obtained.

Definitions

The number and size of tumor nodules were measured by the CT scan in the preoperative evaluation. TTV was calculated as the sum of each tumor nodule volume; the volume of each tumor nodule was calculated as $(4/3) \times 3.14 \times (\text{maximum radius of the tumor nodule in cm})^3$ as previously described [16]. The patients were divided into three subgroups according to the tertiles of TTV (the first tertile <17.1 cm^3, the second tertile 17.1–73.5 cm^3, and the third tertile >73.5 cm^3).

Statistical methods

Continuous variables were expressed as means with standard deviation (SD) or medians with range. Categorical variables were expressed as frequencies with percentages. For group comparisons, chi-squared test or Fisher's exact test (categorical variables) and ANOVA test or Kruskal-Wallis test (continuous variables) were used to compare the differences between subgroups. Cumulative overall survival rates were appraised by the Kaplan-Meier method, and the differences were analyzed by the log rank tests. Significant factors identified in univariate analysis were subsequently enrolled in the multivariate Cox's proportional hazard model. The likelihood ratio related to a Cox's proportional hazard model was used to evaluate the homogeneity within categories of each system [24]. Discrimination for survival data was evaluated using the Harrell's concordance index (*C*-index) [25]. The results of Cox's regression were also presented using the Akaike information criterion (AIC) [26]. Cancer staging system with higher χ^2 value by the likelihood ratio test, higher *C*-index, and lower AIC value was considered to gain superior prognostic ability [26]. A two-tailed $P<0.05$ was considered statistically significant. All statistical analyses were performed using SPSS 11.5 for Windows (SPSS Inc., Chicago, IL) and STATA version 10.0 (STATA Corp., College Station, TX, USA).

Results

The baseline characteristics of the patients

The baseline clinicopathological factors of the patients were summarized in Table 1. Among them, 453 (453/521, 86.9 %) were male patients and 68 (68/521, 13.1 %) were female patients. The mean age of the patients was 54.7 years old. Hepatitis B virus (HBV) was the dominant etiology of the underlying chronic liver disease in the study population (427/521, 81.9 %). Solitary tumor was detected in 442 (442/521, 84.8 %) patients. The maximum diameter of the tumor lesion was 4.7 ± 2.5 cm. The numbers of the patients at Child-Pugh class A and Child-Pugh class B were 509 (509/521, 97.7 %) and 12 (12/521, 2.3 %), respectively.

The distribution of the TTV

The TTV of the patients was 112.0 ± 222.4 cm^3. The distribution of the patients with reference to the TTV, tumor number, and tumor size was shown in Fig. 1a, b. Adopting the cutoff values as 17.1 and 73.5 cm^3, 174 (33.40 %) patients fell into the first tertile (<17.1 cm^3), 172 (33.01 %) patients fell into the second tertile (17.1–73.5 cm^3), and 175 (33.59 %) patients fell into the third tertile (>73.5 cm^3). We compared the

Table 1 Baseline clinicopathological features of the patients involved in this study

Variable	Value
Age (years)	54.7 ± 11.2[a]
Gender	
Male	453 (86.9 %)[b]
Female	68 (13.1 %)[b]
Etiologies of liver diseases	
HBV only	422 (81.0 %)[b]
HCV only	36 (6.9 %)[b]
HBV and HCV	5 (0.9 %)[b]
Others	58 (11.2 %)[b]
Albumin (g/l)	42.0 ± 16.1[a]
Total bilirubin (μmol/l)	15.6 ± 7.1[a]
Prothrombin time (S)	12.5 ± 1.4[a]
AFP (ng/ml)	25.9 (0.6–111,472.0)[c]
Child-Pugh class	
A	509 (97.7 %)[b]
B	12 (2.3 %)[b]
C	0
Tumor number	
1	442 (84.8 %)[b]
2	30 (5.8 %)[b]
3	22 (4.2 %)[b]
>3	27 (5.2 %)[b]
Tumor size (cm)	4.7 ± 2.5[a]
TTV (cm^3)	112.0 ± 222.4[a]
Macrovascular invasion	
Absent	507 (97.3 %)[b]
Present	14 (2.7 %)[b]
Ascites	
Absent	492 (94.4 %)
Present	29 (5.6 %)
Milan criteria	
Within	313 (60.1 %)[b]
Beyond	209 (39.9 %)[b]
TNM stage	
I	420 (80.6 %)[b]
II	37 (7.1 %)[b]
III	59 (11.3 %)[b]
IV	5 (1.0 %)[b]
BCLC stage	
0	52 (10.0 %)[b]
A	405 (77.7 %)[b]
B	64 (12.3 %)[b]
CLIP score	
0	297 (57.0 %)[b]
1	171 (32.8 %)[b]
2	39 (7.5 %)[b]
3	11 (2.1 %)[b]
4	3 (0.6 %)[b]
Okuda stage	
I	479 (91.9 %)[b]
II	38 (7.3 %)[b]
III	4 (0.8 %)[b]

HBV hepatitis B virus, *HCV* hepatitis C virus, *AFP* alpha-fetoprotein. *TTV* total tumor volume, *TNM* tumor-node-metastasis, *BCLC* Barcelona Clinic Liver Cancer stage, *CLIP* Cancer of the Liver Italian Program

[a] Mean ± standard deviation (SD)

[b] Number (percentage)

[c] Median (range)

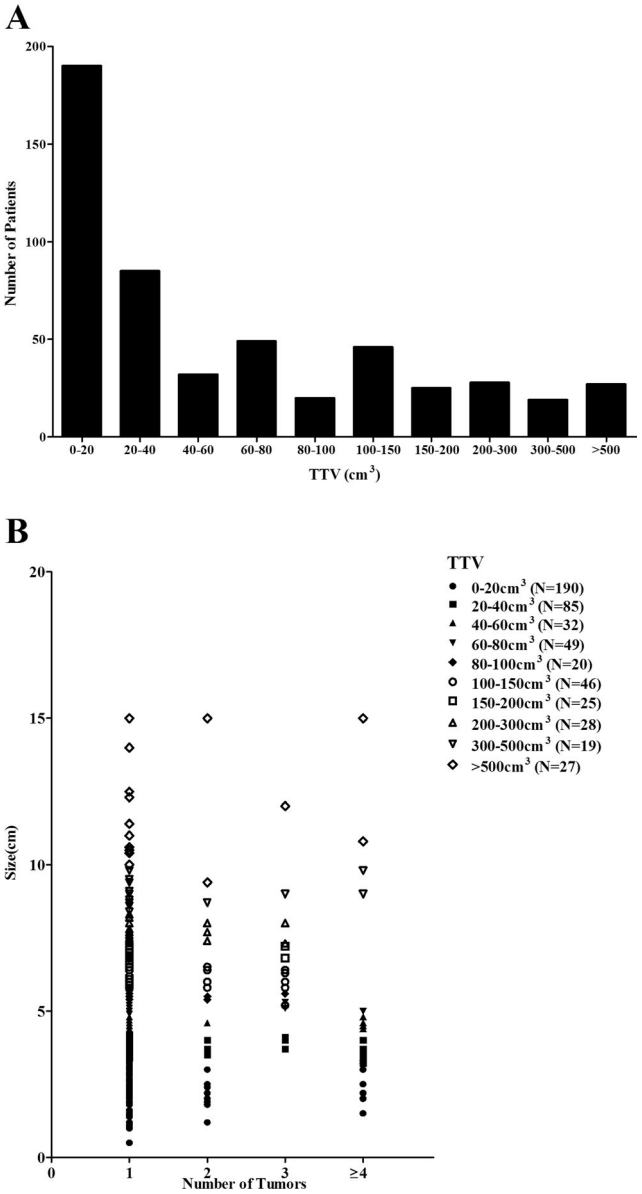

Fig. 1 The distribution of total tumor volume (TTV) of all studied patients (**a**). The distribution of the number and size of tumor lesions of all studied patients when stratified by TTV (**b**)

clinicopathological factors between the three groups. Patients with larger TTV tended to be featured with higher AFP level ($P=0.004$; Table 2), presence of macrovascular invasion ($P=0.026$; Table 2), multiple tumor nodules ($P=0.003$; Table 2), larger tumor size ($P<0.001$; Table 2), advanced TNM stage ($P<0.001$; Table 2), advanced CLIP score ($P<0.001$; Table 2), advanced BCLC stage ($P<0.001$; Table 2), and advanced Okuda stage ($P=0.013$; Table 2).

Prognostic factors for the patients' survival outcome

With a median follow-up of 116 months (range, 80–175 months), the median overall survival (OS) of the patients was 58 months. The 1-, 3-, and 5-year overall survival rates were 93.1, 69.9, and 46.3 %, respectively. The median OS of patients in the first tertile was 69 months, which was significantly longer than that of patients in the second tertile as 60 months ($P=0.005$; Table 3 and Fig. 2). And, the median OS of patients in the second tertile was also significantly longer than that of patients in the third tertile (median OS 60 vs. 40 months, $P<0.001$; Table 3 and Fig. 2). In the univariate analysis, gender as male ($P=0.048$; Table 3), presence of macrovascular invasion ($P<0.001$; Table 3), albumin < 35 g/l ($P<0.001$; Table 3), AFP ≥ 400 ng/ml ($P=0.018$; Table 3), and larger TTV ($P<0.001$; Table 3 and Fig. 2) were significantly associated with inferior survival outcome. These factors were taken into the subsequent Cox multivariate analysis. Compared with patients in the first tertile, the adjusted relative risk for mortality was 1.328 (95 % confidence interval (CI) 1.053–1.675, $P=0.016$) for patients in the second tertile and 1.898 (95 % CI 1.502–2.397, $P<0.001$) for patients in the third tertile. Besides, presence of macrovascular invasion (hazard ratio (HR) = 3.693, 95 % CI 2.140–6.374, $P<0.001$; Table 3), albumin < 35 g/l (HR = 1.957, 95 % CI 1.364–2.809, $P<0.001$; Table 3), and AFP ≥ 400 ng/ml (HR = 1.253, 95 % CI 1.016–1.546, $P=0.035$; Table 3) were identified as the independent prognostic factors regarding the OS.

Comparison of the survival outcome within and beyond the Milan criteria in the first and second TTV tertile groups

Within the first and second tertiles of TTV (TTV ≤ 73.5 cm^3), 312 patients were within Milan criteria and 34 patients were beyond Milan criteria. The median survival time of patients within and beyond the Milan criteria were 66 and 66 months, respectively. No significant difference in overall survival between the above two subgroups was detected ($P=0.183$; Fig. 3).

Evaluation of TTV-based CLIP score

We further appraised the prognostic value of TTV by replacing the "tumor morphology" section of the original CLIP score with the TTV category. In the new system, TTV < 17.1 cm^3 was assigned as score = 0, TTV within the range from 17.1 to 73.5 cm^3 was assigned as score = 1, and TTV > 73.5 cm^3 was assigned as score = 2 (Table 4). Statistically significant differences of OS were found in the pair-wise comparison across the TTV-CLIP scores. The median overall survival time across the TTV-CLIP scores 0–6 were 70.5, 65.5, 50, 41, 32, 20.5, and 15 months, respectively (Fig. 4a). We then compared the prognostic performance of TTV-CLIP score (Fig. 4a), CLIP score (Fig. 4b), TNM staging system (Fig. 4c), BCLC staging system (Fig. 4d), Okuda staging system (Fig. 4e), and Milan criteria (Fig. 4f). TTV-CLIP gained

Table 2 Comparison of the clinicopathological characteristics between patients in the TTV tertiles

Variable	Value			*P* value
	First tertile ($n = 174$)	Second tertile ($n = 172$)	Third tertile ($n = 175$)	
Age (years)	54.7 ± 10.6	55.8 ± 11.7	53.5 ± 11.1	0.152[a]
Gender				0.815[b]
Male	149	151	153	
Female	25	21	22	
Albumin (g/l)	41.0 ± 4.8	41.9 ± 5.1	43.0 ± 26.9	0.476[a]
Total bilirubin (μmol/l)	15.8 ± 7.0	15.9 ± 7.3	15.1 ± 6.9	0.534[a]
Prothrombin time (S)	12.5 ± 1.4	12.3 ± 1.0	12.6 ± 1.7	0.328[a]
Child-Pugh class				0.171[c]
A	169	171	169	
B	5	1	6	
AFP (ng/ml)				**0.004**[b]
≥400	37	43	64	
<400	137	129	111	
Tumor number				**0.003**[b]
Solitary	159	146	137	
Multiple	15	26	38	
Tumor size (cm)	2.4 ± 0.6	4.1 ± 0.6	7.5 ± 2.1	**<0.001**[d]
Macrovascular invasion				**0.026**[c]
Absent	173	168	166	
Present	1	4	9	
TNM stage				**<0.001**[c]
I	157	138	125	
II	15	22	0	
III	1	10	48	
IV	1	2	2	
BCLC stage				**<0.001**[b]
0	52	0	0	
A	121	148	136	
B	1	24	39	
CLIP score				**<0.001**[c]
0	120	110	79	
1	50	50	62	
2	4	12	23	
3	0	0	10	
4	0	0	1	
Okuda stage				**0.013**[c]
I	164	164	151	
II	9	7	22	
III	1	1	2	

Significant results were expressed in bold

N number, *AFP* alpha-fetoprotein, *TTV* total tumor volume, *TNM* tumor-node-metastasis, BCLC Barcelona Clinic Liver Cancer stage, CLIP Cancer of the Liver Italian Program

[a] Evaluated by chi-squared test

[b] Evaluated by ANOVA test

[c] Evaluated by Fisher's exact test

[d] Evaluated by Kruskal-Wallis test

Table 3 Univariate analysis and multivariate analysis of the overall survival

			Univariate analysis	Multivariate analysis		
Variable	*N*	Median OS (months)	*P*	HR	95 % CI	*P*
Age (years)			0.566			
≥60	178	58				
<60	343	58				
Gender			**0.048**	0.763	0.569–1.022	0.069
Male	453	58				
Female	68	58				
Macrovascular invasion			**<0.001**	**3.693**	**2.140–6.374**	**<0.001**
Present	14	15				
Absent	507	59				
Total bilirubin (μmol/l)			0.425			
≥17.1	176	58				
<17.1	345	59				
Albumin (g/l)			**<0.001**	**1.957**	**1.364–2.809**	**<0.001**
≥35	488	59				
<35	33	40				
Prothrombin time (S)			0.083			
≥14	483	47				
<14	38	58				
AFP (ng/ml)			**0.018**	**1.253**	**1.016–1.546**	**0.035**
≥400	144	47				
<400	377	61				
TTV (cm^3)						
First tertile (<17.1 cm^3)	174	69	**<0.001**	1		**<0.001**
Second tertile (17.1–73.5 cm^3)	172	60	**0.005**	**1.328**	**1.053–1.675**	**0.016**
Third tertile (>73.5 cm^3)	175	40	**<0.001**	**1.898**	**1.502–2.397**	**<0.001**

Significant results were expressed in bold

N number, *OS* overall survival, *AFP* alpha-fetoprotein, *TTV* total tumor volume, *HR* hazard ratio, *CI* confidence interval

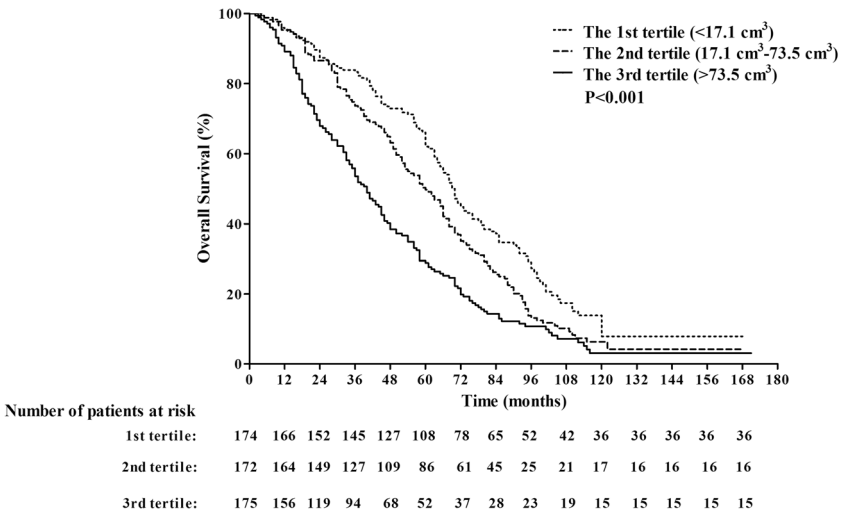

Fig. 2 Kaplan-Meier survival analysis of overall survival (OS) stratified by the tertile of TTV (<17.1 vs. 17.1–73.5 vs. >73.5 cm^3) ($P < 0.001$)

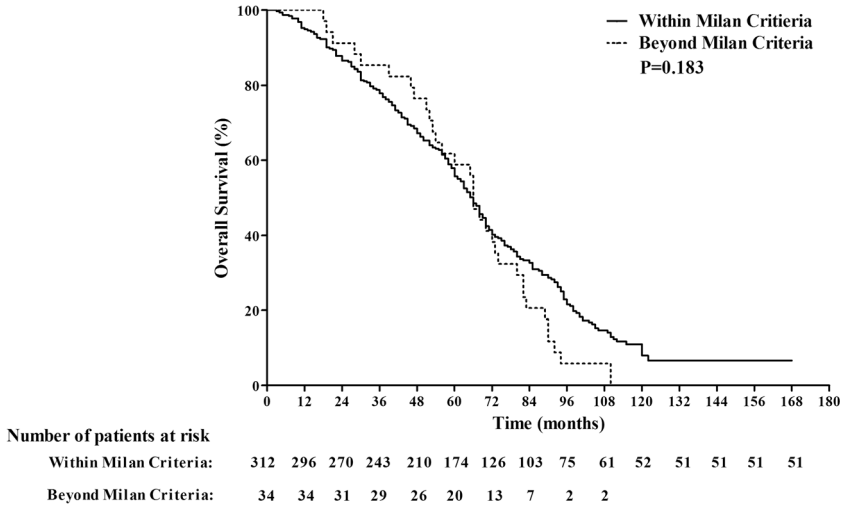

Fig. 3 The comparison of survival distribution between HCC patients within versus beyond the Milan criteria but within the first and second tertiles of TTV (TTV ≤ 73.5 cm^3). No significant difference in long-term outcome between these two groups was detected ($P = 0.183$)

the lowest AIC (AIC = 4932.804), the highest likelihood ratio test (χ^2) as 34.99, and the highest *C*-index as 0.6126 among the seven prognostic scoring systems (Table 5).

Discussion

Few previous studies have extensively evaluated the prognostic value of TTV, which combined the information of tumor number as well as tumor size, in patients receiving liver resection. Our results suggested that patients with larger TTV gained a shorter overall survival than those with smaller TTV. Larger TTV was associated with elevated AFP level, multiple tumors, larger tumor size, presence of macroscopic vascular invasion, and advanced tumor stages. We further incorporated the TTV into the CLIP score and built the TTV-CLIP. The outperformance of TTV-CLIP score in predicting the clinical outcome further upheld the prognostic value of TTV in HCC patients.

Our results showed that TTV might provide a simplified way to describe the tumor burden and was also a potential parameter in the staging system for HCC. Compared with reporting the tumor burden by the tumor number and size, TTV has several advantages. TTV incorporates the number and size of tumor nodules into one continuous variable. Analyzing a single continuous index may be much simpler than analyzing the size and number of tumor nodule simultaneously. It was observed by someone that patients with multiple nodules but moderate tumor size may gain better clinical prognosis than those of patients with single large tumor [27]. It may be partially explained by the fact that the TTV of the former ones might be smaller than that of the latter ones. Regarding these, reporting the value of TTV instead of the size and number of tumor nodule may describe the tumor burden more accurately. We found that 34 patients in the first and second TTV tertiles were beyond the Milan criteria. The percentage of patients exceeding the Milan criteria but with TTV less than 73.5 cm^3 was as high as 10.9 %, which was higher than the reported 6.5 % by Lee et al. [19] using the cutoff value as 65.5 cm^3. The survival outcome of patients within Milan criteria was comparable with those of the patients beyond Milan criteria but with TTV ≤ 73.5 cm^3. And, distinct difference in the OS was observed between patients with TTV > 73.5 cm^3 and patients with TTV ≤ 73.5 cm^3. The results suggested that the second tertile of TTV (73.5 cm^3) in our study could be used as an expanded criteria selecting

Table 4 Construction of the total tumor volume-based CLIP score (TTV-CLIP)

Parameter	Original CLIP	TTV-CLIP
Tumor morphology	–	–
Single and <50 % liver span	0	–
Multiple and <50 % liver span	1	–
≥50 % liver span	2	–
Total tumor volume (cm^3)	–	–
First tertile (<17.1)	–	0
Second tertile (17.1–73.5)	–	1
Third tertile (>73.5)	–	2
Serum AFP level (ng/ml)	–	–
<400	0	0
≥400	1	1
Macroscopic vascular invasion	–	–
Absent	0	0
Present	1	1
Child-Pugh class		
A	0	0
B	1	1
C	2	2

CLIP:Cancer of the Liver Italian Program, *AFP* alpha-fetoprotein, *TTV* total tumor volume

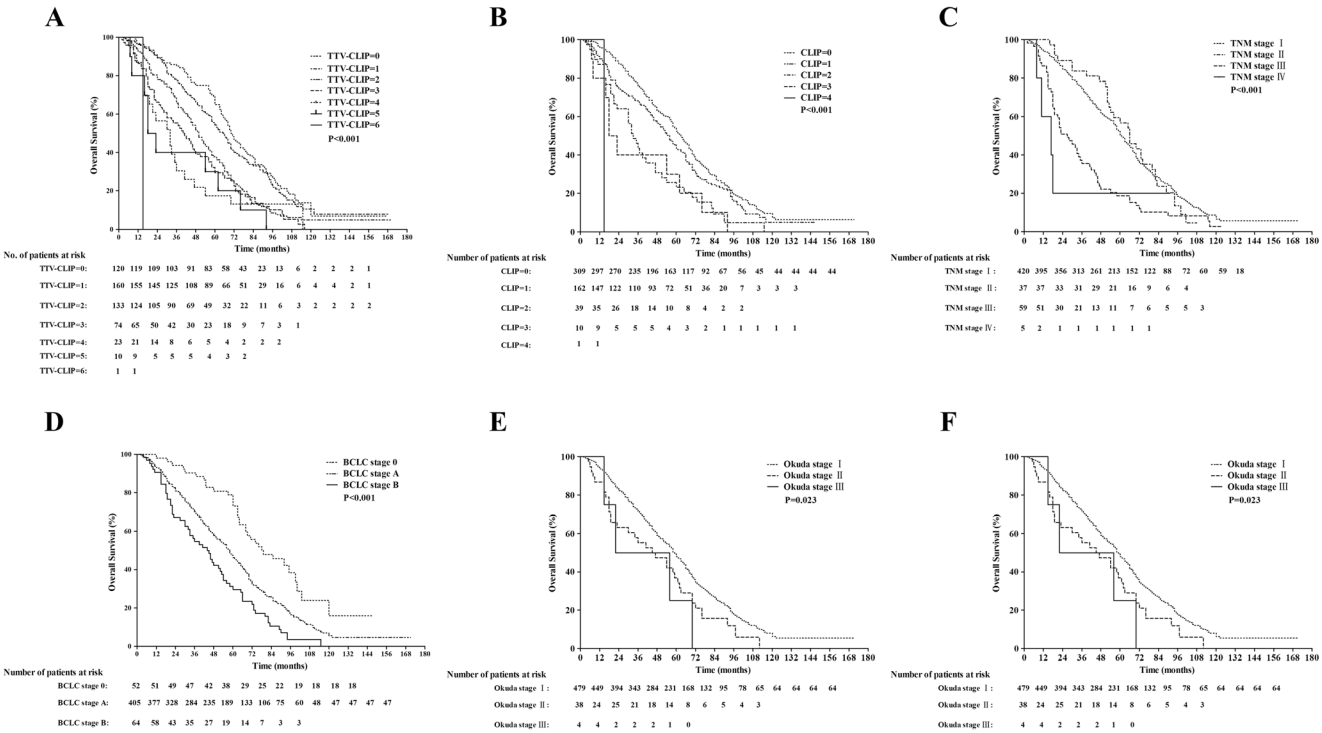

Fig. 4 Comparison of the survival distribution of the TTV-CLIP scoring system (**a**), CLIP scoring system (**b**), TNM staging system (**c**), BCLC staging system (**d**), Okuda staging system (**e**), and Milan criteria (**f**)

candidates receiving hepatectomy. Further studies are warranted to validate the prognostic efficacy of the criteria.

Patients with larger TTV predisposed to have AFP ≥ 400 ng/ml and macroscopic vascular invasion. Elevated AFP level and macroscopic vascular invasion were proved to be adverse prognostic indicators in our analysis, which were also consistent with previous studies [28, 29]. AFP level has long been regarded as being closely linked with the aggressive behavior of the tumor cells as well as the disease progression process [29]. And, several studies revealed that AFP concentrations often increase concomitantly with the augment of tumor burden [30]. Since TTV can be used to rating the tumor burden, it is quite possible that a larger TTV is expected to be more often associated with elevated AFP level. Besides, it is also assumed that larger tumors are often accompanied with the higher incidence of vascular invasion and presence of satellite nodules [27]. The close relationship between larger TTV and adverse clinicopathological features further defended the prognostic value of TTV.

CLIP score was initially derived from a retrospective cohort study of 435 patients and was then externally validated in a lot of studies [21, 31]. In our study, two of the components of CLIP score, including AFP level and presence of macroscopic vascular invasion, both obtained statistical significance in the multivariate analysis for OS. The original CLIP score has an inherent defect as the scale for "tumor morphology" is relatively subjective, without specific size criteria. Therefore, its objectivity and reliability in predicting outcomes may be

Table 5 Comparison of prognostic performance of the tumor prognostic systems in patients with hepatocellular carcinoma

	Likelihood ratio test (χ^2)	AIC	*C*-index
TTV-CLIP (0/1/2/3/4/5/6)	45.91	4921.875	0.6126
CLIP (0/1/2/3/4)	20.57	4947.218	0.5612
BCLC (0/A/B)	27.59	4940.199	0.5572
TNM (I/II/III/IV)	20.53	4947.264	0.5492
Okuda (I/II/III)	6.28	4961.505	0.5182
TTV (first/second/third tertiles)	36.83	4930.963	0.6001
Milan (within/beyond)	27.65	4940.141	0.5730

Higher likelihood ratio χ^2 test values, *C* index and lower Akaike information criterion, were associated with better performance of the score or stage

TTV total tumor volume, *TNM* tumor-node-metastasis, *BCLC* Barcelona Clinic Liver Cancer stage, *CLIP* Cancer of the Liver Italian Program, *AIC* Akaike information criterion, *C-index* Harrell's concordance index

somehow compromised [32]. We thus replaced the tumor morphology section with TTV in the modified CLIP score system. The TTV-based CLIP score gained a better prognostic ability than that of the original CLIP score, TNM staging system, Okuda staging system, BCLC staging system, TTV tertile category, and Milan criteria. Further external validation studies are warranted to establish the value of TTV-CLIP score.

This study has a few potential limitations. First of all, the retrospective nature of the study may be susceptible to the selection bias and recalling bias. Secondly, as HBV is the predominant etiology of HCC in China, the results of the study may have more implication for HBV-dominant areas. Our results should still be interpreted with caution in areas where other etiologies such as HCV, alcohol liver disease, and non-alcoholic fatty liver disease predominate. Thirdly, the calculation of TTV is based on the assumption that all tumor nodules are spherical. In fact, many tumor lesions were irregularly shaped. In order to enhance the applicability of our results in the surgeon's preoperative evaluation, the value of radius was measured by the preoperative CT scan, which might be somehow different from the actual values. In addition, our study chiefly focused on patients who underwent liver resection. It should be reminded that before entering into the clinical practice, the prognostic values of TTV and TTV-CLIP scores need more external validations.

Conclusions

TTV is a good parameter measuring the tumor burden of HCC. Patients with TTV ≤ 73.5 cm^3 may gain more survival benefits from liver resection. And, the TTV-CLIP score may provide a good prognostic performance for LR-treated HCC patients.

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Compliance with ethical standards

Conflicts of interest None

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