ORIGINAL ARTICLE

A proposal for T1 subclassification in hepatocellular carcinoma: reappraisal of the AJCC 8th edition

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Abstract

Background In the 8th edition of American Joint Committee on Cancer (AJCC) staging system for hepatocellular carcinoma (HCC), tumor size is not considered in T1 stage. The present study aimed to find out the optimal cutoff for tumor size to further stratify patients with T1 HCC.

Methods Operated HCC patients were identified from the Chang Gung Research Database (CGRD), and the patients with T1bN0M0 tumors were further divided into two groups based on the tumor size. The resulting subgroups were denoted as T1b ($\leq$ cutoff) and T1c ($>$ cutoff). The survivals were compared between T1a/b and T1c as well as T1c and T2.

Results From 2002 to 2018, a total of 2893 patients who underwent surgery for T1N0M0 HCC were identified from the CGRD. After excluding cases who died within 30 days of surgery, Kaplan–Meier survival analysis discovered that T1 tumors $>$ 65 mm (T1c) had survivals similar to those of T2N0M0 tumors. Cox regression multivariate analysis further demonstrated that tumor size $>$ 6.5 cm was an independent poor prognostic indicator for T1 HCC. Sensitivity tests also confirmed that tumors lager than 6.5 cm were significantly more likely to develop both tumor recurrence and liver-specific death after surgery.

Conclusions Our study demonstrated that tumor size would significantly impact the survival outcome of T1 HCC after surgery. Due to significantly worse survival, we proposed a subclassification within T1 HCC, T1c: solitary tumor $>$ 6.5 cm without vascular invasion, to further stratify those patients at risk. Further studies are mandatory to validate our findings.

Keywords Hepatocellular carcinoma · 8th edition of American Joint Committee on Cancer (AJCC) · T1 subclassification · Liver resection · Chang Gung Research Database

Abbreviations

AFP	α-Fetoprotein
aHR	Adjusted HR
AJCC	American Joint Committee on Cancer
ALBI	Albumin–bilirubin
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CGMH	Chang Gung memorial hospital
CGRD	Chang Gung Research Database
CI	Confidence interval
DFS	Disease-free survival
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HCC	Hepatocellular carcinoma
HR	Hazard ratio
ICD-9-CM	International classification of diseases, 9th revision, clinical modification
ICD-10-CM	International classification of diseases, 10th revision, clinical modification
ICD-O-3	International classification of diseases for oncology, 3rd edition
ICG-15	Indocyanine green retention test at 15 min
INR	International normalized ratio
IRB	Institutional Review Board
NLR	Neutrophil-to-lymphocyte ratio
OS	Overall survival
PLR	Platelet-to-lymphocyte ratio
PNI	Prognostic nutritional index
SD	Standard deviation
TACE	Transarterial chemoembolization
TNM	Tumor/node/metastasis
UCSF	University of California San Francisco

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and 6th most common cancer worldwide, with an estimated death of approximately 830,000 worldwide in 2020 [1–4]. In Taiwan, it is the fourth most common cause of cancer death and causes more than 7000 deaths each year [5]. Surgical resection, radiofrequency ablation, and liver transplantation remain the most effective curative therapies in selected patients. However, unlike other solid malignancies, the treatment of HCC must take multiple important factors into considerations. For example, the coexisting underlying liver diseases, such as chronic hepatitis B or C and alcoholic liver disease, had limited the extent and feasibility of liver resection. According to a recent analysis, only around 5–40% of non-cirrhotic HCC patients underwent liver resection, and this percentage was even much lower if the patients have chronic liver disease or overt cirrhosis [6].

Due to heterogeneous disease presentation and poor prognosis, many staging systems thus have been proposed to suggest appropriate treatment and predict survival outcome for patients with HCC. Among them, the American Joint Committee on Cancer (AJCC) Tumor/Node/Metastasis (TNM) staging system is one of the most commonly used staging systems to stratify the prognosis of patients with HCC [7, 8]. The latest edition, 8th edition, was released in December 2016 to further optimize the prognostic capability of the 7th edition [9, 10]. Major vascular invasion, for example, has been upgraded from T3b to T4 in this version. Despite important modifications, however, the newest edition has not stratified the tumors beyond 2 cm based on size. The staging and prognosis of either solitary small or large HCC without vascular invasion, based on this system, are essentially the same. Nevertheless, there were many other studies demonstrating that tumor diameter, in addition to vascular invasion, was also an important prognostic factor for HCC [11–14]. Another recent study even showed that there was an apparent survival difference among stage I HCC patients with different tumor sizes [15]. Patients with larger HCC had significantly higher risks of tumor recurrence and death than those with smaller tumors after liver resection [15]. As a result, it is of urgent needs to reassess the impact of tumor diameter on the outcome of HCC and to enhance the staging system. The current study, by utilizing the data from the Chang Gung Research Database (CGRD), aimed to find out the optimal cutoff for tumor size to further stratify the 8th edition of AJCC TNM staging system [15–18]. To eliminate the potential bias due to different stages and treatment approaches, we examined patients with pathologically proven T1N0M0 HCC who underwent curative intent liver resection.

Materials and methods

Data source

The CGRD, which collected the clinical information from eight Chang Gung memorial hospitals (CGMH) in Taiwan since year 2000, was the primary data source of the current research. With more than 10,070 beds and 500,000 emergency visits each year, the CGRD has accounted for 21.2% of outpatients and 12.4% of inpatients in Taiwan and become an excellent database for various kinds of clinical studies [15–18]. For cancer patients, it contains comprehensive cancer registry maintained in a prospective manner. The information is manually validated with a high completeness rate [19, 20]. Both the International Classification of Diseases, 9th and 10th revision, Clinical Modification (ICD-9-CM and ICD-10-CM) codes and the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) are used in the CGRD. For personal privacy, the individual identity is protected by encryption. The medical information is prospectively digitalized and stored in the CGRD and is amenable for researchers to perform large-scale retrospective analysis.

Study design and population

Figure 1 shows the flow diagram of the current study. The ICD-9-CM code 1550 and ICD-10-CM code C220 were employed to identify HCC patients from the CGRD. Patients who received curative operation from 2002 to 2018 were enrolled as the study population. Those who received non-surgical treatment, who had missing data, or who died within 30 days of surgery were excluded from further analysis. Tumors were staged according to the 8th edition of AJCC TNM staging system in the current study [9, 10]. To explore the optimal cutoff for tumor size, a total of 2876 pathologically proven pT1N0M0 HCC were further identified from the operated cohort.

The patients with T1b tumors were then divided into two groups based on the tumor size, and the cutoff value was set from 3 cm and increased by a 1-cm increment. The resulting subgroups were denoted as T1b ($\leq$ cutoff) and T1c ($>$ cutoff). Kaplan–Meier survival curves were acquired and disease-free survival (DFS) as well as liver-specific overall survival (OS) were analyzed and compared between T1a/b and T1c by log-rank tests. The survivals between T1c and T2N0M0 tumors were also compared. The smallest cutoff with comparable survival outcome between T1c and T2 tumors was designated as the optimal cutoff value. This study was approved by the Institutional Review Boards of CGMH (IRB No.: 202000608B0).
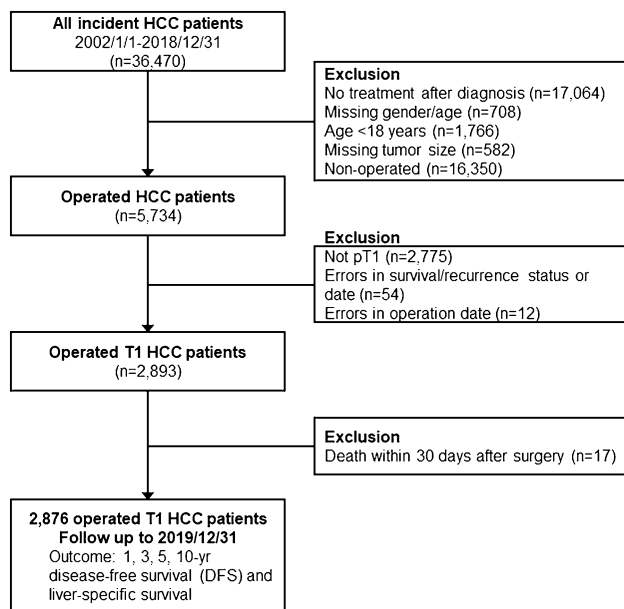
Fig. 1 Flow diagram of the current study. HCC patients diagnosed from 2002 to 2018 were retrieved from the CGRD database ($n = 36,740$). Those who received non-surgical treatment, who had missing data, or who died within 30 days of surgery were excluded from further analysis. The patients with T1bN0M0 tumors were further divided into two groups based on the tumor size, and the cutoff value was set from 3 cm and increased by a 1-cm increment. The disease-free survival (DFS) as well as liver-specific overall survival (OS) were analyzed and compared

Outcome assessment and statistical analysis

DFS and liver-specific OS were used as the primary and secondary outcomes of the current study, respectively. The first date of definite diagnosis for HCC was set as the index date. DFS defined the period between the index date and the date of the first documented clinical recurrence or the end of year 2019. Liver-specific OS spanned the period between the index date and the date of liver-cause mortality or the end of year 2019. The liver-causes included tumor recurrence, metastasis, and complications of decompensated liver cirrhosis.

Kaplan–Meier survival estimation with log-rank test was used to assess the DFS and liver-specific OS. Cox regression multivariate analysis was performed to identify significant prognostic factors associated with disease recurrence or liver-cause mortality for T1 HCC. Five different Cox regression models incorporating multiple prognostic factors were also established as the sensitivity tests to assess the consistency of incremental risks associated with the new subclassification of T1 HCC. The freeware Konstanz information miner (KNIME) and the commercial statistic software STATA (StataCorp. 2019. Stata Statistical Software: release 16. College Station, TX: StataCorp LLC) were employed to

process and analyze the data [21]. All statistics with $p < 0.05$ were regarded as statistically significant.

Results

Patient demographics

We first identified 36,470 patients diagnosed to have HCC from the CGRD. Among them, 5734 patients were operated by liver resection for their HCC. After excluding patients who had more than T1 disease ($n = 2775$), who had erroneous clinical information ($n = 66$), and who died within 30 days of surgery ($n = 17$), a total of 2876 patients were enrolled into our final analysis (Fig. 1). Among these patients who had T1N0M0 HCC, 2172 (75.5%) were male and 1430 (49.7%) were older than 60 years. Hepatitis B virus (HBV) infection remained the most common etiology (48.2%), followed by hepatitis C virus (HCV) infection (24.6%). While nearly half of the patients operated had histologically proven liver cirrhosis, they were mostly (nearly 99%) Child classification A. The mean tumor size was 35.9 mm and the mean alpha-fetoprotein was 2471.8 ng/mL. Nearly 70% of the patients enrolled were categorized as albumin–bilirubin (ALBI) grade 1 and about 75% were either normally nourished or mildly malnourished (Table 1).

Subclassification of T1 HCC

The serial Kaplan–Meier DFS and liver-specific OS curves of T1cN0M0 and T2N0M0 tumors were demonstrated in Supplementary Figs. S1 and S2, respectively. As shown in Fig. S1, when the cutoff was set below 60 mm, the DFS of T1c tumors was still significantly better than that of T2 tumors (all $p < 0.05$). This survival benefit was obliterated when the cutoff was set at 70 mm ($p = 0.055$). Similarly, the liver-specific OS was significantly longer for T1c tumors when the cutoff was below 60 mm (all $p < 0.05$). This advantage was not observed when the cutoff was set at 70 mm ($p = 0.099$) (Supplementary Fig. S2). To obtain an optimal subclassification for T1 HCC, the cutoff value was further examined at 65 mm and the results are shown in Fig. 2. When T1c was designated as tumors > 65 mm, or > 6.5 cm, the DFS and liver specific-OS were not statistically different from those of T2 tumors ($p = 0.062$ and 0.072, respectively). The optimal cutoff value was thus set at 65 mm, and T1 HCC was further subclassified as T1a: solitary tumor ≤ 2 cm with or without vascular invasion, T1b: solitary tumor > 2 cm but ≤ 6.5 cm without vascular invasion, and T1c: solitary tumor > 6.5 cm without vascular invasion. The Kaplan–Meier DFS and liver-specific OS curves of this new subclassification are illustrated in Fig. 3.

Table 1 Baseline features of T1 hepatocellular carcinoma patients undergoing liver resection (AJCC 8th version), n (%), n = 2876

Gender	
Female	704 (24.5%)
Male	2172 (75.5%)
Age [mean (SD)] (year)	59.0 (11.2)
Age group	
− 20	2 (0.1%)
21–40	210 (7.3%)
41–60	1234 (42.9%)
61–	1430 (49.7%)
Co-morbidities	
Diabetes	717 (24.9%)
Hypertension	1005 (34.9%)
Chronic hepatitis	
HBV	1385 (48.2%)
HCV	708 (24.6%)
HBV+HCV	142 (4.9%)
Lifestyles	
Cigarette smoking	298 (10.4%)
Alcohol consumption	255 (8.9%)
Betel nut	79 (2.7%)
Child–Turcot–Pugh classification	
A	1464 (98.9%)
B	16 (1.1%)
Cirrhosis	
No	778 (51.0%)
Yes	748 (49.0%)
Tumor size [mean (SD)] (mm)	35.9 (26.7)
Medications	
Anti-HCV/HBV therapy	279 (9.7%)
Metformin	186 (6.5%)
Aspirin	126 (4.4%)

Biochemical profiles	n (%), n = 2876[1]
Alpha-fetoprotein [mean (SD)] (ng/mL)	2471.8 (56,299.0)
ICG-15 [mean (SD)] (%)	9.4 (8.3)
Albumin [mean (SD)] (g/dL)	4.1 (0.5)
Hemoglobin [mean SD)] (g/dL)	13.6 (1.9)
Platelet [mean (SD)] (1000/μL)	175.0 (68.8)
INR [mean (SD)]	1.1 (0.1)
AST (U/L) [mean (SD)]	57.4 (97.2)
ALT (U/L) [mean (SD)]	61.9 (98.7)
Total bilirubin (mg/dL) [mean(SD)]	0.9 (0.6)
ALBI grade	
Grade 1	1629 (69.8%)
Grade 2	676 (29.0%)
Grade 3	27 (1.2%)
PNI	
Normal	1005 (49.0%)
Mild malnutrition	531 (25.9%)
Moderate to severe malnutrition	325 (15.9%)
Serious malnutrition	189 (9.2%)
NLR [mean (SD)]	4.0 (5.4)

Table 1 (continued)

Biochemical profiles	n (%), n = 2876[1]
PLR [mean (SD)]	17.3 (6.9)

[1]Number excluded surgical mortality (30-day mortality)

ALBI albumin–bilirubin grade, *ALT* alanine aminotransferase, *AJCC* American Joint Committee on Cancer, *AST* aspartate aminotransferase, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *ICG-15* indocyanine green retention test at 15 min, *INR* international normalized ratio, *NLR* neutrophil-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *PNI* prognostic nutritional index, *SD* standard deviation

Clinical characteristics of T1c HCC

The newly proposed T1c subgroup was further analyzed and compared with those T1 HCC ≤ 6.5 cm (T1a/b). As shown in Table 2, around 10% (n = 297) of T1 HCC was categorized as T1c. Their mean age of diagnosis was similar to its smaller counterpart, but there were more patients detected at a younger age (≤ 40 years). Of notice, while the incidence of HBV infection was similar between the two groups, there was significantly less HCV-related HCC in T1c group (7.4% vs. 26.6%, $p < 0.001$). There was also much more Child B cirrhosis in T1c HCC (3.2% vs. 0.9%, $p < 0.018$). These larger tumors had significantly higher alpha-fetoprotein, platelet count, aspartate aminotransferase (AST), and neutrophil-to-lymphocyte ratio (NLR) but lower hemoglobin, indocyanine green retention test at 15 min (ICG-15) and platelet-to lymphocyte-ratio (PLR). Although albumin and bilirubin levels were similar between the two groups, the derivative ALBI grades were significantly higher in T1c HCC. The nutritional status in terms of prognostic nutritional index (PNI) was also poorer in T1c HCC.

Surgical outcome and long-term survival of T1 HCC after liver resection

Table 3 summarizes the surgical and oncological outcome of T1 HCC categorized by our new subclassification. The surgical, or 30-day, mortality rate was comparable between the two groups. The median follow-up time was 67.8 months in T1a/b group and 60.5 months in T1c group. More than 50% of T1c developed tumor recurrence after surgery, compared to only 40% in T1a/b ($p < 0.001$). More than 40% of T1c patients were dead at the end of follow-up, with 25.3% attributed to liver cause. On the other hand, only 27% of T1a/b patients were dead during follow-up ($p < 0.001$). As for the pattern of tumor recurrence, local recurrence remained the most common pattern in T1c HCC, but there was also more regional, combined, or distant recurrence in this group ($p < 0.001$). The 1-, 3-, 5-, and

10-year DFS rates were significantly worse in the T1c group (79.1%, 58.9%, 49.6%, and 46.1%, respectively, in T1c and 87.8%, 72.8%, 64.7%, and 58.8%, respectively, in T1a/b, all $p < 0.001$). Similarly, the 1-, 3-, 5-, and 10-year liver-specific survival rates were remarkably lower in T1c than in T1a/b (96.4%, 87.1%, 77.5%, and 69.9%, respectively, in T1c and 98.6%, 94.4%, 88.8%, and 79.2%, respectively, in T1a/b, all $p < 0.01$).

Multivariate analysis of risk factors for tumor recurrence and mortality in T1 HCC

In addition to tumor size > 6.5 cm, age ≥ 65 years, histological cirrhosis, diabetes mellitus, chronic HCV infection, hemoglobin ≤ 10 g/dL, and albumin ≤ 3.5 g/dL were found to be related to tumor recurrence after liver resection for T1 HCC (all $p < 0.05$). HBV infection and administration of antiviral therapy, on the other hand, were associated with less tumor recurrence after surgery. Cox regression multivariate analysis further demonstrated that age ≥ 65 years, histological cirrhosis, and hemoglobin ≤ 10 g/dL, in addition to tumor size > 6.5 cm, were independent prognostic factors for HCC recurrence after surgery (Table 4). Tumors larger than 6.5 cm were 1.61-fold more likely to develop tumor relapse than those smaller than 6.5 cm. Likewise, tumor size > 6.5 cm, histological cirrhosis, and hemoglobin ≤ 10 g/dL were independent predicting factors for liver-specific mortality after liver resection for T1 HCC (all $p < 0.05$) (Table 5). Tumors larger than 6.5 cm had a 1.74-fold risk of liver-specific death after liver resection.

To further confirm the validity of our newly proposed T1 subclassfication, sensitivity tests comprising different combinations of variables were conducted and the results are summarized in Table 6. Variables including gender, age, diabetes mellitus (DM), HBV, HCV, NLR, hemoglobin, albumin, antiviral therapy, liver cirrhosis, and ALBI grade, in addition to tumor size > 6.5 cm, were incorporated into 5 different models. The adjusted hazard ratio (aHR) of tumor size > 6.5 cm for either tumor recurrence or liver-specific mortality in the respective models was analyzed and computed. When comparing with smaller tumors, tumors lager than 6.5 cm were significantly more likely to develop both tumor recurrence and liver-specific mortality across all models, with aHR ranging between 1.46 and 1.67 for recurrence and 1.54 and 1.81 for liver-specific mortality.

Discussion

According to the 8th edition of AJCC TNM staging system for HCC, solitary small tumor (< 5 cm) without vascular invasion and solitary huge tumor (> 10 cm) without vascular invasion were all categorized as T1 lesions [9, 10]. As a result, the treatment recommendation and prognosis were deemed to be similar between these two entities. Nevertheless, our recent study demonstrated that in stage I HCC after liver resection, tumors larger than 10 cm had significantly higher risks of tumor recurrence and death than those smaller than 10 cm [15]. Single HCC > 5 cm without vascular invasion, in another study, was found to have a survival rate inferior to that of HCC < 5 cm [12]. There was even another report suggesting that single HCC should be assigned into three different groups according to the tumor size (≤ 5 cm, > 5 and ≤ 8 cm, and > 8 cm, respectively) [13]. Patients with larger HCC, as a result, did not have survival outcome comparable to those with smaller tumors as expected. A recent study further proposed that, due to their similar survivals, the T1b lesions should be integrated with T2 lesions to obtain a modified TNM staging [11]. These studies all indicated that tumor size did significantly impact the outcome of solitary HCC and should be considered in the conventional staging systems. In other words, there should be a subclassification within T1 stage to precisely predict patient outcome. The exact cutoff values, however, are still controversial among different literatures. The current study, by examining one of the largest and most comprehensive clinical databases worldwide, discovered that solitary HCC > 6.5 cm without vascular invasion had a DFS and liver specific-OS similar to those of T2 tumors. Hence, we proposed that T1 HCC can be further classified to accommodate a T1c subcategory: solitary tumor > 6.5 cm without vascular invasion. To further corroborate our findings, we performed Cox regression multivariate analysis and found that tumor size > 6.5 cm was one of the independent prognostic factors for tumor recurrence and liver-specific mortality after liver resection for T1 HCC. By conducting sensitivity tests consisting of different models, we again demonstrated that tumor size did influence the outcome of T1 HCC. All statistics in the sensitivity tests showed the same trend that patients with HCC larger than 6.5 cm had higher risks of recurrence and liver-specific death. This cutoff, coincidentally, corresponded to the criteria suggested by the University of California San Francisco (UCSF) that a solitary HCC larger than 6.5 cm without vascular invasion had significantly worse survivals after orthotopic liver transplantation [22, 23]. Therefore, we believe tumor size > 6.5 cm
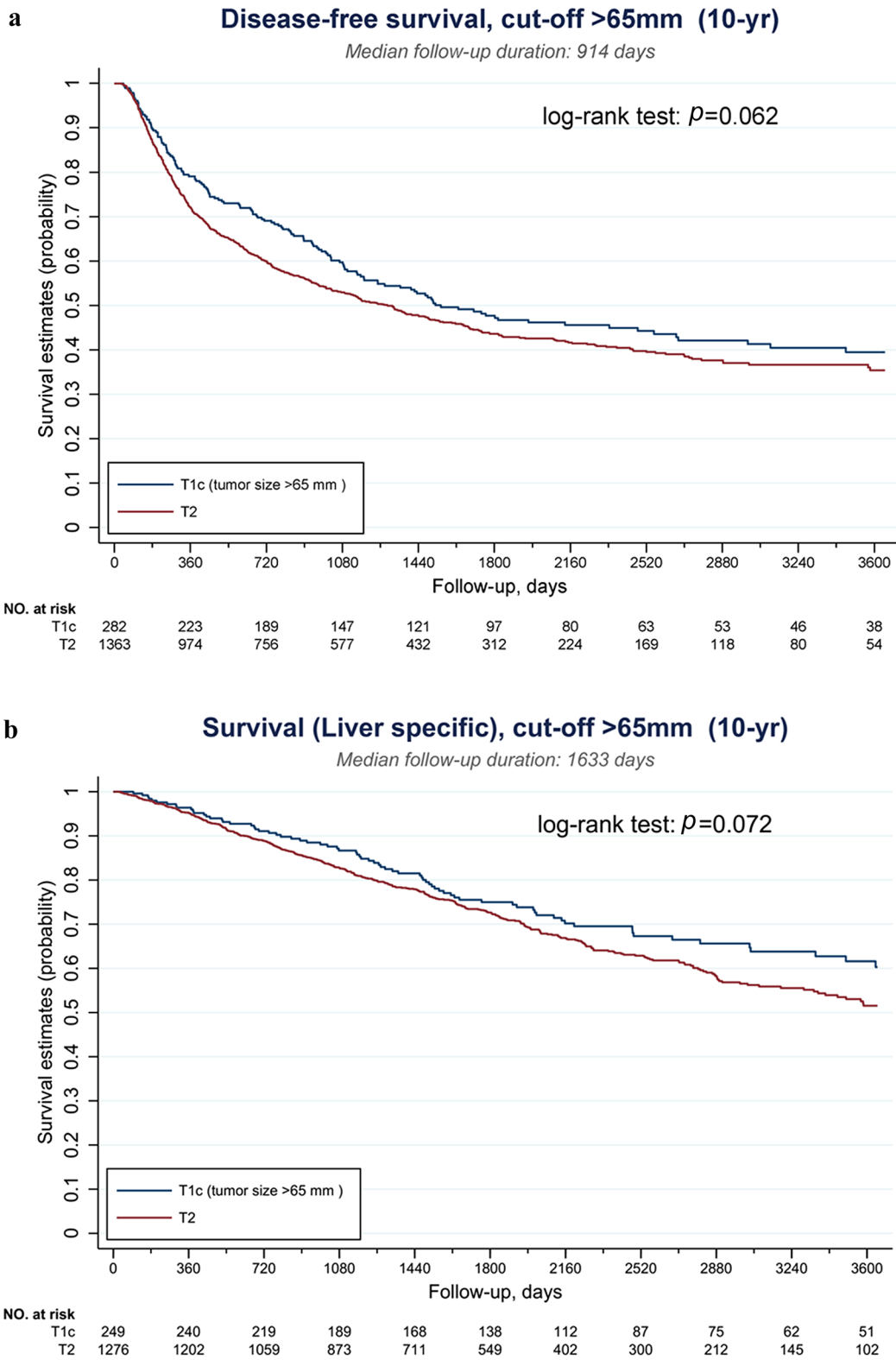
a

Disease-free survival, cut-off >65mm (10-yr)

Median follow-up duration: 914 days

log-rank test: *p*=0.062

Survival estimates (probability)

Follow-up, days

NO. at risk

	0	360	720	1080	1440	1800	2160	2520	2880	3240	3600
T1c	282	223	189	147	121	97	80	63	53	46	38
T2	1363	974	756	577	432	312	224	169	118	80	54

Legend: T1c (tumor size >65 mm) ; T2

b

Survival (Liver specific), cut-off >65mm (10-yr)

Median follow-up duration: 1633 days

log-rank test: *p*=0.072

Survival estimates (probability)

Follow-up, days

NO. at risk

	0	360	720	1080	1440	1800	2160	2520	2880	3240	3600
T1c	249	240	219	189	168	138	112	87	75	62	51
T2	1276	1202	1059	873	711	549	402	300	212	145	102

Legend: T1c (tumor size >65 mm) ; T2

Fig. 2 Survivals of solitary HCC > 6.5 cm were not statistically different from those of T2 tumors. **a** Disease-free survival (DFS) and **b** liver-specific overall survival (OS)
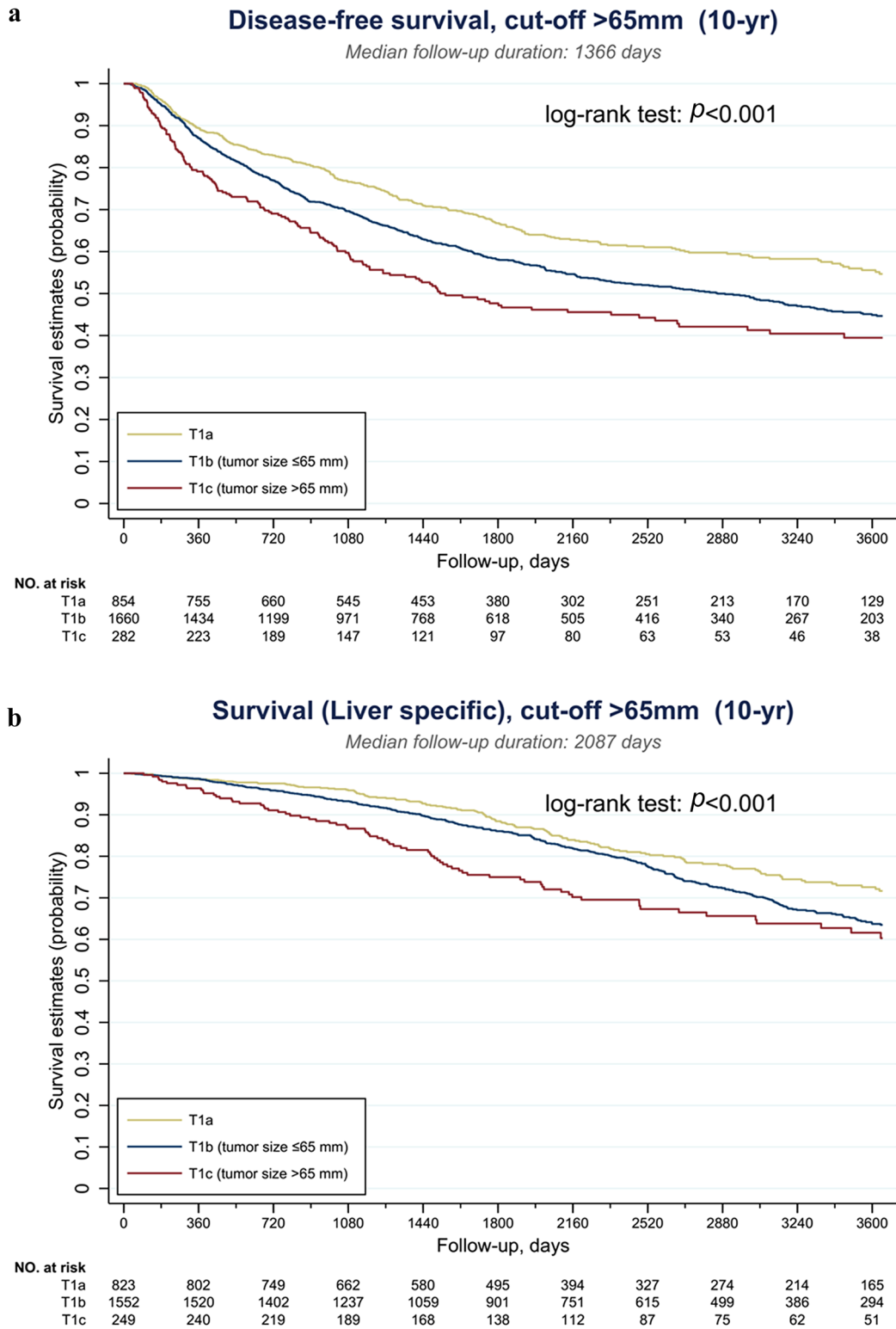
a

b

Fig. 3 Kaplan–Meier survival curves of subclassified T1 HCC. **a** Disease-free survival (DFS) and **b** liver-specific overall survival (OS)

Table 2 Baseline demographic features of T1 hepatocellular carcinoma regarding tumor size, n (%), mean (SD), n = 2876

Variables	Total n = 2876	T1 ≦ 6.5 cm (T1a/b) n = 2579	T1 > 6.5 cm (T1c) n = 297	p value
Number[a]	2876 (100%)	2579 (89.7%)	297 (10.3%)	
Gender				
Female	704 (24.5%)	638 (24.7%)	66 (22.2%)	0.34
Male	2172 (75.5%)	1941 (75.3%)	231 (77.8%)	
Age	59.0 (11.2)	58.9 (11.0)	59.2 (13.1)	0.71
≤ 20	2 (0.1%)	1 (0.0%)	1 (0.3%)	0.015
21–40	210 (7.3%)	179 (6.9%)	31 (10.4%)	
41–60	1234 (42.9%)	1123 (43.5%)	111 (37.4%)	
≥ 61	1430 (49.7%)	1276 (49.5%)	154 (51.9%)	
Diabetes				
Yes	717 (24.9%)	651 (25.2%)	66 (22.2%)	0.25
Hypertension				
Yes	1005 (34.9%)	887 (34.4%)	118 (39.7%)	0.068
Hepatitis				**< 0.001**
HBV				
Positive	1385 (48.2%)	1255 (48.7%)	130 (43.8%)	
HCV				
Positive	708 (24.6%)	686 (26.6%)	22 (7.4%)	
HBV + HCV				
Positive	142 (4.9%)	126 (4.9%)	16 (5.4%)	
Cigarette smoking				
Yes	298 (10.4%)	274 (10.6%)	24 (8.1%)	0.17
Alcohol				
Yes	255 (8.9%)	229 (8.9%)	26 (8.8%)	0.94
Betel nut				
Yes	79 (2.7%)	69 (2.7%)	10 (3.4%)	0.49
Child–Turcot–Pugh classification				
A	1464 (98.9%)	1342 (99.1%)	122 (96.8%)	0.018
B	16 (1.1%)	12 (0.9%)	4 (3.2%)	
Cirrhosis				
No cirrhosis	778 (51.0%)	678 (48.4%)	100 (79.4%)	< 0.001
Cirrhosis	748 (49.0%)	722 (51.6%)	26 (20.6%)	
Tumor size (Mm)	35.9 (26.7)	28.6 (13.3)	99.3 (29.6)	< 0.001
Medications				
Anti-HCV/HBV therapy	279 (9.7%)	274 (10.6%)	5 (1.7%)	< 0.001
Metformin	186 (6.5%)	174 (6.7%)	12 (4.0%)	0.073
Aspirin	126 (4.4%)	112 (4.3%)	14 (4.7%)	0.77
Biochemical profiles				
Alpha-fetoprotein (ng/mL)	2471.8 (56,299.0)	745.9 (14,201.9)	18,443.7 (174,587.8)	< 0.001
ICG-15 (%)	9.4 (8.3)	9.6 (8.3)	8.3 (8.6)	0.028
Albumin	4.1 (0.5)	4.1 (0.5)	4.0 (0.6)	< 0.001
Hb	13.6 (1.9)	13.7 (1.9)	13.0 (2.1)	< 0.001
Platelet	175.0 (68.8)	169.5 (64.7)	220.0 (83.4)	< 0.001
INR	1.1 (0.1)	1.1 (0.1)	1.1 (0.1)	0.26
AST	57.4 (97.2)	54.7 (92.7)	81.0 (128.0)	< 0.001
ALT	61.9 (98.7)	61.0 (98.7)	70.0 (98.8)	0.15
Total bilirubin	0.9 (0.6)	0.9 (0.5)	0.9 (0.8)	0.57
ALBI grade				
Grade 1	1,629 (69.9%)	1459 (70.8%)	170 (62.7%)	< 0.001
Grade 2	676 (29.0%)	584 (28.3%)	92 (33.9%)	

Table 2 (continued)

Variables	Total $n = 2876$	T1 ≤ 6.5 cm (T1a/b) $n = 2579$	T1 > 6.5 cm (T1c) $n = 297$	p value
Grade 3	27 (1.2%)	18 (0.9%)	9 (3.3%)	
PNI				
Normal	1005 (49.0%)	904 (50.3%)	101 (39.8%)	< 0.001
Mild	531 (25.9%)	463 (25.8%)	68 (26.8%)	
Mod to severe	325 (15.9%)	278 (15.5%)	47 (18.5%)	
Serious	189 (9.2%)	151 (8.4%)	38 (15.0%)	
NLR	4.0 (5.4)	3.8 (4.9)	5.4 (8.1)	< 0.001
PLR	17.3 (6.9)	17.6 (7.1)	14.9 (4.8)	< 0.001

[a]Number excluded surgical mortality (30-day mortality)

ALBI albumin–bilirubin grade, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *Hb* hemoglobin, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *ICG-15* indocyanine green retention test at 15 min, *INR* international normalized ratio, *NLR* neutrophil-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *PNI* prognostic nutritional index, *SD* standard deviation

is an important prognostic factor in T1 HCC and should be considered in the TNM staging system.

Unlike a previous study which claimed that tumor size was not a prominent prognostic indicator in nonvascular invading solitary HCC receiving liver resection, the current study discovered that tumor size > 6.5 cm was indeed a significant prognostic factor among T1 HCC patients undergoing surgery [24]. The inconsistent results may be explained by the different study designs. In the current study, we incrementally divided T1b tumors into two groups and tried to find out a cutoff which could differentiate the new subcategory from the remaining T1 tumors. The resulting T1c subgroup had a survival, not only significantly shorter than the T1a/b tumors, but similarly poor with the T2 tumors. In contrast, the study conducted by Yang et al. divided patients into three groups (≤ 30 mm, 31-50 mm, and > 50 mm) based on tumor size limitations between radiofrequency ablation and liver transplantation [24]. They compared the survival outcome of larger tumors (31-50 mm or > 50 mm) against those of smaller ones (≤ 30 mm). The different cutoffs and analyses may lead to different conclusions. The disparate AJCC versions also rendered these results incomparable. The current study, by adopting the newest 8th edition of AJCC TNM staging system for HCC, is readily available to be applied in the real world clinical practice. Due to inferior survival outcome, the treatment strategy and surveillance protocol should be modified for this subgroup of patients. Adjuvant treatment with either transarterial chemoembolization (TACE) or systemic therapy (tyrosine kinase inhibitors or immune checkpoint inhibitors) could be considered for this subset of patients. Further prospective clinical trials are warranted to establish a more effective treatment protocol for these patients.

In addition to worse survivals, the current study also discovered that T1 HCC > 6.5 cm had less HCV infection and cirrhosis. There were more patients diagnosed at a younger age, too. Since younger HCC patients have been demonstrated to have lower rates of HCV infection and cirrhosis, it may explain the demographic disparities observed [25]. However, it is also likely that the carcinogenesis of T1c HCC is different from that of T1a/b tumors. The non-viral cause, such as fatty liver diseases, might have contributory roles in the pathogenesis of these large tumors. This speculation can be supported by our finding that non-viral cause accounted for more than 54% of T1c HCC in the present study, as compared to only 30% of T1a/b tumors (*p* < 0.001). Further studies are warranted to explore the causal relationships between these associations.

Despite remarkable findings, the current study still has several limitations. First, the current study was generated from the hospital-based database and cancer registry, more descriptive features, such as performance status, postoperative complications, and pathologic details; for example, hepatitis activity index, margin status, and histological grade, were inaccessible. The analysis of these variables was thus lacking. Second, since some T2 lesions, for example, bilobar tumors or more than 3 tumors, may not undergo surgery, the surgical survivals obtained herein may not fully represent the outcome associated with all T2 lesions. This was why we did not propose to upgrade our new "T1c" subcategory into T2 stage (Supplementary Fig. S3). We only intended to find out an optimal size cutoff within the T1 stage to differentiate those patients at risk. As a result, further studies are warranted to examine whether T1c stage should be integrated into T2 stage. Third, as mentioned above, the current study failed to

Table 3 Surgical and oncological outcome of patients with T1 HCC

	T1 HCC $\leq$ 6.5 cm (T1a/b) $n=2593$	T1 HCC $>$ 6.5 cm (T1c) $n=300$	*p* value
Surgical mortality (30 days)	14 (0.5%)	3 (1.0%)	0.32
Recurrence status			
No recurrence	1480 (57.4%)	130 (43.8%)	< 0.001
Recurrence	1035 (40.1%)	152 (51.2%)	
Never disease free	64 (2.5%)	15 (5.1%)	
Follow-up times (months) [Median (IQR)]	67.8 (39.5–105.4)	60.5 (33.0–100)	0.015
Final status			
Alive	1880 (72.9%)	174 (58.6%)	< 0.001
Death—liver cause	495 (19.2%)	75 (25.3%)	
Death—other cause	204 (7.9%)	48 (16.2%)	
	T1 HCC $\leq$ 6.5 cm $n=2515$	T1 HCC $>$ 6.5 cm $n=282$	*p* value
Recurrence pattern			
Local[a]	710 (28.3%)	90 (32.0%)	< 0.001
Regional[b]	53 (2.1%)	14 (5.0%)	
Combined[c]	18 (0.7%)	7 (2.5%)	
Distant	27 (1.1%)	10 (3.6%)	
Death without recurrence	225 (9.0%)	30 (10.7%)	
Disease free survival			
1-year DFS rate	2207 (87.8%)	223 (79.1%)	< 0.001
3-year DFS rate	1832 (72.8%)	166 (58.9%)	< 0.001
5-year DFS rate	1627 (64.7%)	140 (49.6%)	< 0.001
10-year DFS rate	1480 (58.8%)	130 (46.1%)	< 0.001
	T1 HCC $\leq$ 6.5 cm $N=2375$	T1 HCC $>$ 6.5 cm $n=249$	*p* value
Liver-specific survival			
1-year survival rate	2342 (98.6%)	240 (96.4%)	0.008
3-year survival rate	2242 (94.4%)	217 (87.1%)	< 0.001
5-year survival rate	2110 (88.8%)	193 (77.5%)	< 0.001
10-year survival rate	1880 (79.2%)	174 (69.9%)	< 0.001

DFS disease-free survival, *HCC* hepatocellular carcinoma, *IQR* interquartile range

[a]Local recurrence include resection margin/remnant liver or trocar site

[b]Regional recurrence include adjacent organs/regional LNs, or both

[c]Combined recurrence include local and regional recurrence

suggest adequate treatment strategy for T1c lesions. Further well-designed prospective studies targeting at this subset of patients are thus necessary to establish appropriate treatment guidelines. Next, although the potential recall bias could be avoided by prospectively registering the daily clinical data into the CGRD, referral bias was in the meanwhile inevitable, since the CGMHs are the largest tertiary care center in Taiwan [26, 27]. Last but not the least, since the present study was based primarily on data from a single country, the patient population as a result would be rather uniform. The lack of an external validation cohort consisted of different ethnic groups, therefore, would be another drawback of the current study. It would be more convincing if the data can be confirmed by HCC data sets from countries with a more diverse population. Further studies incorporating external validation cohorts are necessary to approve our findings.

Table 4 Univariate and multivariate analyses of risks factors for tumor recurrence after hepatectomy for AJCC 8 T1 hepatocellular carcinoma

Variables	Univariate		Multivariate	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Gender				
Female	1 (reference)			
Male	0.99 (0.87–1.13)	0.922	1.30 (1.00–1.68)	0.050
Age				
< 65 y/o	1 (reference)			
≥ 65 y/o	1.57 (1.40–1.76)	< 0.001	1.26 (1.01–1.58)	0.044*
Tumor size				
≤ 6.5 cm	1 (reference)			
> 6.5 cm	1.45 (1.21–1.73)	< 0.001	1.61 (1.13–2.28)	0.008**
Cirrhosis				
No	1 (reference)			
Yes	1.54 (1.29–1.85)	< 0.001	1.58 (1.26–1.98)	< 0.001***
Diabetes mellitus				
No	1 (reference)			
Yes	1.17 (1.03–1.33)	0.016	1.00 (0.79–1.26)	0.975
Hypertension				
No	1 (reference)			
Yes	1.06 (0.94–1.19)	0.323		
Alcohol				
No	1 (reference)			
Yes	0.90 (0.72–1.12)	0.342		
HBs Ag				
Negative	1 (reference)		0.82 (0.63–1.06)	0.132
Positive	0.70 (0.63–0.79)	< 0.001		
Hepatitis C virus				
Negative	1 (reference)			
Positive	1.41 (1.25–1.58)	< 0.001	1.24 (0.95–1.61)	0.110
Hemoglobin				
> 10 (g/dL)	1 (reference)			
≤ 10	1.66 (1.29–2.12)	< 0.001	1.78 (1.15–2.75)	0.010**
INR				
≤ 1.4	1 (reference)			
> 1.4	0.90 (0.41–1.97)	0.791		
Albumin				
> 3.5 (g/dL)	1 (reference)			
≤ 3.5	1.50 (1.27–1.77)	< 0.001	1.02 (0.71–1.47)	0.896
α-Fetoprotein				
≤ 400 (ng/mL)	1 (reference)			
> 400	1.07 (0.88–1.29)	0.514	1.11 (0.80–1.53)	0.527
Antiviral therapy in HBV or HCV infection				
No	1 (reference)			
Yes	0.68 (0.55–0.86)	0.001	0.74 (0.52–1.06)	0.102
NLR (continuous variables)	1.00 (0.99–1.01)	0.986		

The covariates with significant statistics and with important clinical implications were put into the multivariate Cox regressions

CI confidence interval, *HBs Ag* hepatitis B surface antigen, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *HR* hazard ration, *INR* international normalized ratio

Table 5 Univariate and multivariate analyses of risks factors for liver-specific mortality after hepatectomy for AJCC 8 T1 hepatocellular carcinoma

Variables	Univariate		Multivariate (selected)	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Gender				
Female	1 (reference)			
Male	0.92 (0.76–1.11)	0.368	1.04 (0.70–1.55)	0.845
Age				
<65 y/o	1 (reference)			
≥65 y/o	1.97 (1.67–2.33)	<0.001	1.33 (0.93–1.91)	0.119
Tumor size				
≤6.5 cm	1 (reference)			
>6.5 cm	1.51 (1.17–1.95)	0.001	1.74 (1.02–2.96)	0.043*
Cirrhosis				
No	1 (reference)			
Yes	1.56 (1.17–2.10)	0.003	1.71 (1.19–2.45)	0.004**
Diabetes mellitus				
No	1 (reference)			
Yes	1.34 (1.11–1.61)	0.002	0.86 (0.58–1.26)	0.428
Alcohol				
No	1 (reference)			
Yes	1.13 (0.81–1.57)	0.459		
HBs Ag				
Negative	1 (reference)			
Positive	0.67 (0.57–0.79)	<0.001	0.86 (0.57–1.30)	0.479
Hepatitis C virus negative	1 (reference)			
Positive	1.36 (1.15–1.62)	<0.001	1.25 (0.82–1.89)	0.301
Hemoglobin				
>10 (g/dL)	1 (reference)			
≤10	2.30 (1.64–3.23)	<0.001	2.96 (1.69–5.18)	<0.001***
INR				
≤1.4	1 (reference)			
>1.4	0.95 (0.35–2.60)	0.926		
Albumin				
>3.5 (g/dL)	1 (reference)			
≤3.5	1.64 (1.30–2.08)	<0.001	1.24 (0.75–2.06)	0.405
α-Fetoprotein				
≤400 (ng/mL))	1 (reference)			
>400	0.99 (0.75–1.31)	0.932	1.06 (0.63–1.79)	0.817
Antiviral therapy in HBV or HCV infection				
No	1 (reference)		0.70 (0.39 1.27)	0.240
Yes	0.71 (0.51–0.99)	0.043		
NLR (continuous variables)	0.99 (0.98–1.01)	0.425		

The covariates with significant statistics and with important clinical implications were put into the multivariate Cox regressions

CI confidence interval, *HBs Ag* hepatitis B surface antigen, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *HR* hazard ration, *INR* international normalized ratio

Conclusions

Our CGRD-based study demonstrated that tumor size would significantly impact the survival outcome of T1 HCC after surgery. Solitary tumor >6.5 cm without vascular invasion, after serial analysis, was found to have a survival similar to that of T2 HCC. As a result, we proposed a subclassification

Table 6 Sensitivity tests

Models	Tumor recurrence		Liver-specific mortality	
	aHR[b] (95% CI)	*p* value	aHR[b] (95% CI)	*p* value
Model 1: Tumor size[a], gender, age, DM, HBV, HCV, NLR	1.46 (1.21–1.77)	< 0.001	1.54 (1.18–2.01)	0.001
Model 2: Tumor size[a], cirrhosis, AFP, Hb	1.67 (1.20–2.32)	0.002	1.80 (1.09–2.99)	0.022
Model 3: Tumor size[a], cirrhosis, AFP, Hb, gender, age, DM, HBV, HCV, anti-HBV/ HCV therapy	1.61 (1.15–2.27)	0.006	1.81 (1.08–3.03)	0.023
Model 4: Tumor size[a], cirrhosis, AFP, Hb, gender, age, DM, HBV, HCV, anti-HBV/ HCV therapy, ALBI	1.61 (1.13–2.28)	0.008	1.74 (1.02–2.96)	0.043
Model 5: Tumor size[a], cirrhosis, AFP, Hb, gender, age, DM, HBV, HCV, anti-HBV/ HCV therapy, albumin	1.60 (1.13–2.26)	0.009	1.73 (1.02–2.94)	0.042

ALBI albumin–bilirubin grade, *AFP* alpha-fetoprotein, *aHR* adjusted hazard ration, *CI* confidence interval, *DM* diabetes mellitus, *Hb* hemoglobin, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *INR* international normalized ratio, *NLR* neutrophil-to-lymphocyte ratio

[a]Tumor size > 6.5 cm vs. ≤ 6.5 cm

[b]aHR of tumor size > 6.5 cm as computed in different models

within T1 HCC, T1c: solitary tumor > 6.5 cm without vascular invasion, to further stratify those patients at risk. Due to significantly higher risks of recurrence and death, adjuvant treatment should be considered for this subset of T1 HCC. Further studies are mandatory to validate our findings.

Declarations

Conflict of interest Chao-Wei Lee, Hsin-I Tsai, Ming-Chin Yu, Chih-Chi Wang, Wei-Chen Lee, Ta-Sen Yeh, Chun-Nan Yeh, Cheng-Yu Lin, Tony Kuo, and Hsing-Yu Chen have no conflicts of interest or financial ties to disclose.

Ethics approval and consent to participate This study was approved by the Institutional Review Boards (CGMH IRB No: 202000608B0).of CGMH. For retrospective study, informed consent was waived according to our institutional guideline.

Consent to publish Not applicable.

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