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Clinical Studies

Prognosis of advanced hepatocellular carcinoma patients enrolled in clinical trials can be classified by current staging systems

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BACKGROUND: Patients enrolled in clinical trials of advanced hepatocellular carcinoma (HCC) are usually required to have good liver reserve and organ function. However, their outcomes are still highly variable. We aimed to examine whether current staging systems can predict the survival of these highly selected patients.

METHODS: Patients from clinical trials involving first-line anti-angiogenic therapy were assigned to different stage groups using the American Joint Committee on Cancer (AJCC), Barcelona Clinic Liver Cancer (BCLC), China integrated score, Cancer of the Liver Italian Program (CLIP) score, Chinese University Prognostic Index (CUPI), Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire (GETCH), Japan Integrated Staging (JIS) score, Okuda, Tokyo score, and a new staging system recently proposed. Survival prediction by the 10 systems was then compared by both univariate and multivariate analyses.

RESULTS: A total of 157 patients were selected for this study. In univariate analysis, all staging systems can predict patient survival except AJCC, BCLC, and JIS score. Concordance indexes for CLIP score, CUPI, and GETCH (0.752, 0.775, and 0.791, respectively) were significantly higher than those obtained for other staging systems. In multivariate analysis, the CLIP score and CUPI ($P<0.001$ and 0.009, respectively) predicted survival more accurately than did the other tested staging systems. Hepatitis B infection and poor performance status were also associated with poor survival.

CONCLUSION: Several HCC staging systems, especially the CLIP score and CUPI, can predict prognosis of patients who are enrolled in clinical trials of advanced HCC.

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Advanced hepatocellular carcinoma (HCC) had been a disease with no proven treatment until sorafenib was demonstrated to provide survival benefits in two randomised studies in 2007 (Llovet *et al*, 2008; Cheng *et al*, 2009). However, the efficacy of sorafenib is modest. Novel compounds either alone or in combination with sorafenib have been actively explored in phase II or even phase III studies (Hsu *et al*, 2010a, b; Shao *et al*, 2010; Cheng *et al*, 2011).

A staging system that can accurately predict prognosis is crucial for clinical trial designs. For phase II studies, such a system can aid in the selection of a relatively homogeneous yet representative patient population and in the comparison of efficacies across different studies. For phase III studies, such a system can facilitate proper patient stratification and ensure that patient characteristics between treatment arms are balanced. All the commonly used staging systems for HCC were developed in the pre-sorafenib era, and none of them were designed specifically for advanced disease (Okuda *et al*, 1985; The Cancer of the Liver Italian Program investigators, 1998; Chevret *et al*, 1999; Llovet *et al*, 1999; Green *et al*, 2002; Leung *et al*, 2002b; Kudo *et al*, 2003; Tateishi, 2005; Zhang *et al*, 2010). Although a new staging system was proposed by Tournoux-Facon *et al* specifically for patients with HCC in palliative setting (Tournoux-Facon *et al*, 2011), this new system has not been thoroughly compared with staging systems commonly used in East Asia, such as Chinese University Prognostic Index (CUPI), Japan Integrated Staging (JIS) scores, and China integrated score (CIS).

Two prior studies evaluated the ability of commonly used staging systems to predict the prognosis of patients with advanced HCC (Collette *et al*, 2008; Huitzil-Melendez *et al*, 2010). One study found that the Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire (GETCH) predicted patients' prognosis more accurately than did other staging systems at a referral centre in the Unites States. The study did not focus on the clinical trial population (Huitzil-Melendez *et al*, 2010). The other study demonstrated that the Cancer of the Liver Italian Program (CLIP) score more accurately predicted prognosis than Okuda and Barcelona Clinic Liver Cancer (BCLC) for patients who received either supportive care, tamoxifen alone, or tamoxifen in combination with transarterial chemoembolisation (TACE) (Collette *et al*, 2008). This study did not include the GETCH and CUPI staging

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systems for analysis, and the treatment is very different from the current standards. Therefore, it remains unclear which of these commonly used staging systems can most accurately predict the prognosis for patients with advanced HCC who are enrolled in clinical trials.

Currently, most clinical trials of advanced HCC use BCLC and Child-Pugh scores to select patients. However, the survival outcomes of these 'well-selected' patients are highly variable. We hypothesised that certain current HCC staging systems can still predict prognosis of these patients, who were enrolled in clinical trials for advanced HCC. The current study was thus conducted to examine the prognosis-predicting performance of 10 staging systems, including the American Joint Committee on Cancer (AJCC; 6th edition) (Green *et al*, 2002), BCLC (Llovet *et al*, 1999), CIS (Zhang *et al*, 2010), CLIP score (The Cancer of the Liver Italian Program investigators, 1998), CUPI (Leung *et al*, 2002b), GETCH (Chevret *et al*, 1999), JIS score (Kudo *et al*, 2003), Okuda (Okuda *et al*, 1985), Tokyo score (Tateishi, 2005), and the staging system proposed by Tournoux-Facon *et al* (2011).

MATERIALS AND METHODS

Study population and variables

All patients who were enrolled in clinical trials that involved first-line systemic therapy for advanced HCC from May 2005 to June 2010 at National Taiwan University Hospital (NTUH), Taipei, Taiwan, were included in this study. All these studies targeted HCC patients with metastatic or locally advanced disease not amenable to loco-regional therapies, including surgery, TACE, and local ablation. All patients were required to have adequate liver reserve and organ function, good performance status, and measurable lesions according to RECIST criteria (version 1.0) (Therasse *et al*, 2000). Treatment regimens included either bevacizumab plus capecitabine, sorafenib plus tegafur/uracil, thalidomide plus tegafur/uracil, sorafenib, or sunitinib (Hsu *et al*, 2010a, b; Cheng *et al*, 2011; Shao *et al*, 2012).

Data regarding patient characteristics, laboratory examination results, and overall survival (OS) were retrieved from the original study records. All patients were assessed following the rules (summarised in Supplementary Table 1) of the AJCC (6th edition) (Green *et al*, 2002), BCLC (Llovet *et al*, 1999), CIS (Zhang *et al*, 2010), CLIP score (The Cancer of the Liver Italian Program investigators, 1998), CUPI (Leung *et al*, 2002b), GETCH (Chevret *et al*, 1999), JIS score (Kudo *et al*, 2003), Okuda (Okuda *et al*, 1985), Tokyo score (Tateishi, 2005), and the staging system proposed by Tournoux-Facon *et al* (2011). This study was approved by the Institute Research Ethical Committee of NTUH.

Statistical methods

Statistical analyses were performed with the SAS statistical software (version 9.1.3, SAS Institute Inc., Cary, NC, USA). In statistical testing, a two-sided *P*-value $\leqslant 0.05$ was considered statistically significant. The prognostic predictions of different staging systems were compared univariately by two methods. First, the Kaplan–Meier method was used to estimate OS. For every staging system, OS was compared between every stage group using the log-rank test. Second, concordance (c) indexes were calculated for all staging systems according to the accuracy of their prediction of OS rankings and then compared with each other.

The Cox's proportional hazard model was utilised to compare the 10 staging systems while adjusting other variables with a potential impact on OS. These variables included treatment regimens, age, gender, hepatitis aetiology (hepatitis B virus (HBV) or hepatitis C virus (HCV)), Karnofsky performance scale, and the presence of prior treatment. Staging systems were compared with one another using a model that involved a stepwise variable selection procedure in which the significance levels for entry and significance levels for stay were set to $\geqslant 0.15$. Values of R^2 and Akaike information criterion (AIC) representing the accuracy of the OS prediction were then calculated for each staging system while adjusting for the confounding variables found by the Cox's model. Higher R^2 or lower AIC mean better prediction of OS.

RESULTS

Patient characteristics

A total of 157 patients, with a median age of 56 years, were included in the current study. Patients received one of the following regimens as first-line therapy for advanced HCC: bevacizumab plus capecitabine ($n=20$), sorafenib plus tegafur/uracil ($n=68$), thalidomide plus tegafur/uracil ($n=34$), sorafenib ($n=15$), or sunitinib ($n=20$). The patient characteristics are summarised in Table 1. Eighty-six percentage of patients were male; 75% were seropositive for HBV surface antigen (HBsAg); 16% were seropositive for antibody against HCV (anti-HCV); and 92% had either extrahepatic metastasis or macroscopic vascular invasion. Except for one patient with Child-Pugh B (score = 7) liver reserve, all others were classified to have Child-Pugh A liver reserve. All patients had Karnofsky performance scale indexes $\geqslant 70$; 120 (76%) patients had a Karnofsky performance scale index $\geqslant 90$.

Table 1 Patient characteristics

Variables	Patient number	%
Total	157	100
Median age (range, in years)	56 (24–83)	
Female/male	22/135	14/86
Hepatitis virus		
HBsAg positive	118	75
Anti-HCV positive	25	16
AFP > 400 ng ml^{-1}	93	59
Child-Pugh class		
A	156	99
B[a]	1	1
Sites of disease		
Liver	138	88
Lung	61	39
Bone	11	7
Extrahepatic metastasis or macroscopic vascular invasion		
Any	144	92
Extrahepatic metastasis	98	62
Macroscopic vascular invasion	92	59
Karnofsky performance scale		
70	6	4
80	31	20
90	110	70
100	10	6
Prior treatment for localised disease		
Any	82	52
Surgery	57	36
Local therapy[b]	6	4
TACE	48	31
Mean TACE times	3.3	

Abbreviations: AFP = α-fetoprotein; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; TACE = transcatheter arterial chemoembolisation. [a]The Child-Pugh score was 7. [b]Included percutaneous ethanol injection and radiofrequency ablation.

Patients were classified into stage groups according to 10 staging systems. The distribution of patients among the stage groups is presented in Table 2. As the study focused on patients with advanced HCC enrolled in clinical trials, no patients with early and surgically resectable cases such as AJCC stage I or BCLC stage A were included. Nine (6%) patients had AJCC stage II disease and 11 (7%) patients had BCLC stage B disease. These patients had disease either refractory to TACE or not amenable for TACE owing to hypovascularity. The clinical trials also excluded patients with end-stage disease or severe liver dysfunction. Therefore, none of the patients were classified as CLIP score $\geqslant 5$, BCLC stage D, Okuda stage III, or high risk according to the staging system proposed by Tournoux-Facon *et al*. Interestingly, patients with different CLIP scores were more evenly distributed, with 10%, 20%, 21%, 25%, and 24% of patients having CLIP scores of 0, 1, 2, 3, and 4, respectively.

Table 2 Patient distribution of stage groups

Variables	Patient number	%
AJCC		
II	9	6
III	50	32
IV	98	62
BCLC		
B	11	7
C	146	93
CIS		
0	24	15
1	33	21
2	41	26
3	58	37
4	1	1
CLIP score		
0	15	10
1	32	20
2	33	21
3	39	25
4	38	24
CUPI		
Low risk	48	31
Intermediate risk	80	51
High risk	29	18
GETCH		
Low risk	26	17
Intermediate risk	130	83
High risk	1	1
JIS score		
1	2	1
2	21	13
3	134	85
Okuda		
I	87	55
II	70	45
Tokyo score		
2	23	15
3	6	4
4	37	24
5	87	55
6	4	3
The system of Tournoux-Facon et al		
Low risk	123	78
Intermediate risk	34	22

Abbreviations: AJCC = American Joint Committee on Cancer; BCLC = Barcelona Clinic Liver Cancer; CIS = China integrated score; CLIP = Cancer of the Liver Italian Program; CUPI = Chinese University Prognostic Index; GETCH = Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire; JIS = Japan Integrated Staging Score.

Survival comparisons among stage groups

As of 31 December 2010, 138 (88%) patients had died with a median follow-up time of 35.1 months. Only two patients lost follow-up. The median OS of all patients was 6.6 months (95% confidence interval, 5.3–7.9 months). Kaplan–Meier analysis was utilised to estimate the OS, and the log-rank test was used to univariately compare the survival of every stage group (Figure 1). The CIS ($P<0.001$), CLIP score ($P<0.001$), CUPI ($P<0.001$), GETCH ($P<0.001$), Okuda ($P<0.001$), Tokyo score ($P<0.001$), and the staging system of Tournoux-Facon *et al* ($P<0.001$) differentiated OS by their stage grouping, whereas the AJCC ($P=0.133$), BCLC ($P=0.269$), and JIS score ($P=0.327$) failed to do so. Notably, patients with CIS scores = 2 had better survival than patients with CIS scores = 1.

C indexes were calculated for all the staging systems. The GETCH, CUPI, CLIP score, Okuda, and the staging system proposed by Tournoux-Facon *et al* had the highest c indexes (0.792, 0.775, 0.752, 0.723, and 0.710, respectively), which were not significantly different from one another (Table 3). The AJCC, CIS, and BCLC had the lowest c indexes (0.576, 0.546, and 0.535, respectively, Table 3).

To adjust for variables that were less frequently incorporated into staging systems but may also have a prognostic impact on survival, we analysed all staging systems along with these variables in the multivariate analysis, including treatment regimens, age, gender, serum HBsAg, serum antibody against HCV, Karnofsky performance scale, and the presence of prior treatment for localised disease. In the final model, the CLIP score and CUPI emerged as the most accurate predictors of OS ($P<0.001$ and 0.009, respectively, Table 4). Hepatitis B virus infection and poor performance status were also found to predict poor OS. Adjusting for these two confounding factors, we found that the CLIP score and CUPI yielded the highest R^2 values (0.2938 and 0.1950, respectively) and the lowest AIC (1134.9 and 1155.5, respectively) for predicting OS (Table 3).

DISCUSSION

This study demonstrated that the CLIP score and CUPI can better predict survival of patients with advanced HCC who had been enrolled in clinical trials using anti-angiogenic agents as first-line therapy. This is the first study specifically focusing on such a patient population. The results can be used in the design of future clinical trials for the treatment of advanced HCC. Although all patients were selected by the eligibility criteria of clinical trials to ensure good liver reserve (99% Child-Pugh A) and performance status, these two staging systems could successfully differentiate the survival outcome within their stage groups. Their prognostic prediction was better than other systems as determined by different statistical analyses.

Although the study described here was a retrospective analysis, most items in the staging systems examined were prospectively collected upon patient enrolment in the clinical trials. Survival results were mature and very few patients lost follow-up. However, the results may be biased because the study only included patients from one institute. Nevertheless, such a bias should be limited because the selection criteria used in this study were generally consistent with those commonly used in other clinical trials of systemic therapy for advanced HCC.

Previous studies examined survival of patients with advanced HCC in a heterogeneous patient population. Treatment ranged

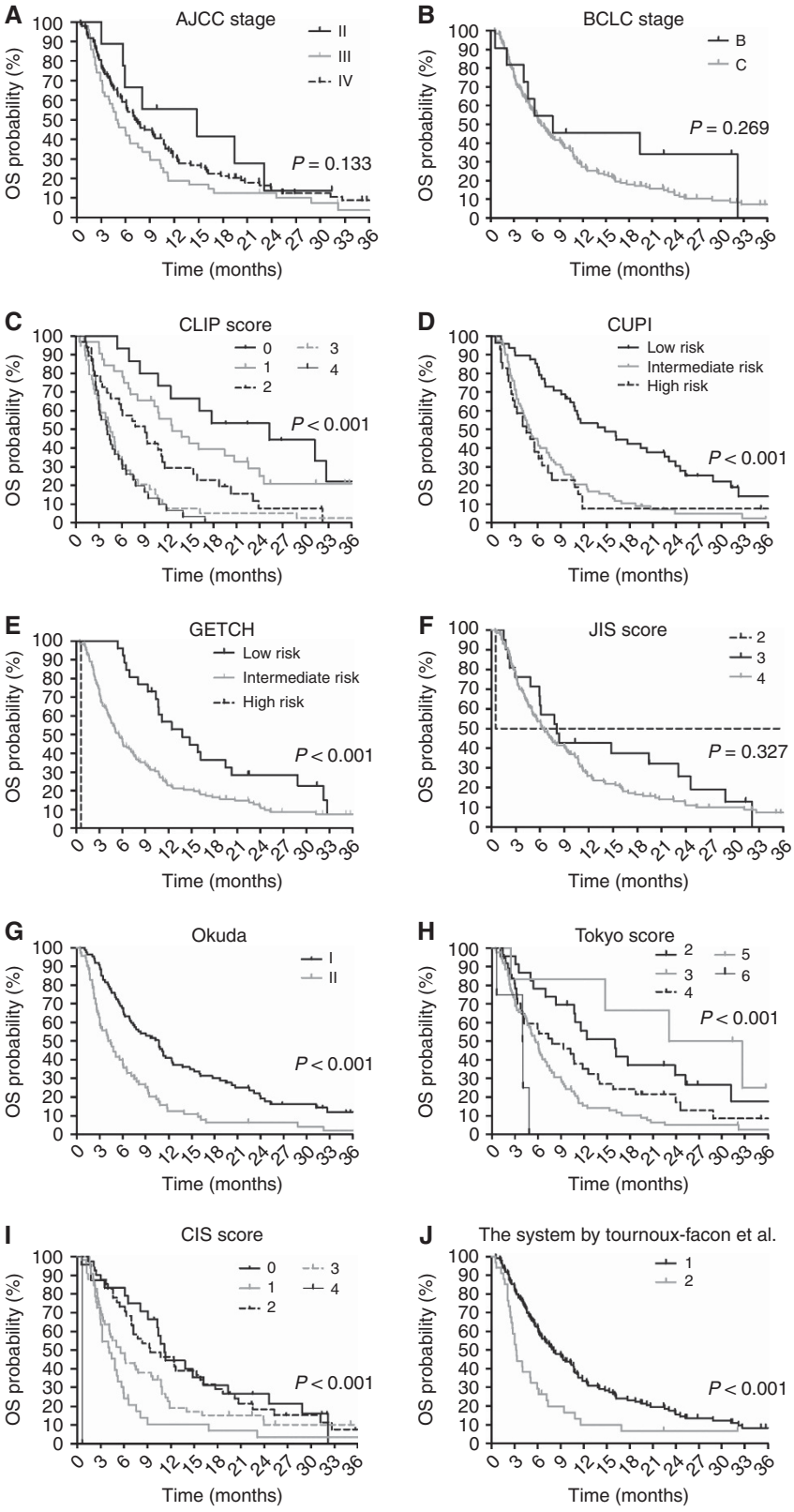

Figure 1 Kaplan–Meier analysis of overall survival (OS) by every stage group. (**A**) American Joint Committee on Cancer (AJCC), (**B**) Barcelona Clinic Liver Cancer (BCLC), (**C**) Okuda, (**D**) Cancer of the Liver Italian Program (CLIP) score, (**E**) Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire (GETCH), (**F**) Chinese University Prognostic Index (CUPI), (**G**) Japan Integrated Staging (JIS) Score, (**H**) Tokyo score, (**I**) China integrated score (CIS), and (**J**) the system proposed by Tournoux-Facon *et al* *P*-values by log-rank test.

Table 3 Concordance indexes, R^2 and AIC of staging systems for their prediction of overall survival

	Concordance index	R^2	AIC
GETCH	0.792	0.1134	1170.6
CUPI	0.775	0.1950	1155.5
CLIP score	0.752	0.2938	1134.9
Okuda	0.723	0.1577	1162.6
The system of Tournoux-Facon *et al*	0.710	0.0922	1183.1
Tokyo score	0.678	0.1710	1160.1
JIS score	0.584	0.0502	1181.4
BCLC	0.576	0.0507	1190.1
CIS	0.546	0.0467	1183.5
AJCC	0.535	0.0429	1182.6

Abbreviations: AIC = Akaike information criterion; AJCC = American Joint Committee on Cancer; BCLC = Barcelona Clinic Liver Cancer; CIS = China integrated score; CLIP = Cancer of the Liver Italian Program; CUPI = Chinese University Prognostic Index; GETCH = Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire; JIS = Japan Integrated Staging Score.

Table 4 Final Cox's proportional hazards model[a] for best staging systems to predict overall survival

Variables	*P*-value	Hazard ratio	95% CI
HBsAg (+)	0.016	1.652	1.099–2.484
Karnofsky performance scale	0.024	0.969	0.944–0.996
CUPI	0.004	1.853	1.215–2.828
CLIP score	<0.001	1.671	1.371–2.037

Abbreviations: CI = confidence interval; CLIP = Cancer of the Liver Italian Program; CUPI = Chinese University Prognostic Index; HBsAg = hepatitis B virus surface antigen. [a]Co-variables included for variable selection were treatment regimens, age, gender, HBsAg, antibody against hepatitis C virus, Karnofsky performance scale, the presence of prior treatment for localised disease and all the 10 staging systems studied.

from supportive care, TACE, cytotoxic chemotherapy, to targeted therapy (Collette *et al*, 2008; Huitzil-Melendez *et al*, 2010; Lin *et al*, 2012), and patients may not all have been enrolled in clinical trials. These studies found that CLIP score, CUPI, or GETCH can better differentiate prognosis of these patients. Among them, our prior study found CLIP score as a better staging system for patients who received various systemic treatment for advanced HCC (Lin *et al*, 2012). In the current study, we focused on a patient population that is more relevant to current practice. The results demonstrated that the CLIP score and CUPI emerged as the best systems for predicting OS after adjusting for other potential prognostic factors that are not included in most staging systems. Above all, CLIP could be considered a pivotal stratification factor in clinical trial designs because it was repeatedly demonstrated to predict prognosis of patients enrolled in clinical trials, regardless the treatment regimens.

In addition to the CLIP and CUPI, we found that viral aetiology was a prognostic factor in the multivariate analyses, which is consistent with other reports (Leung *et al*, 2002a; Cantarini *et al*, 2006; Chen *et al*, 2006; Shao *et al*, 2011). Positive HBsAg was associated with poorer survival (Cantarini *et al*, 2006; Chen *et al*, 2006; Shao *et al*, 2011). As HCC resulting from different aetiological factors can have different carcinogenesis and molecular signatures (Okabe *et al*, 2000; Laurent-Puig *et al*, 2001; Iizuka *et al*, 2002; Moinzadeh *et al*, 2005), it is not surprising that aetiology should have an impact on prognosis of patients with HCC. On the contrary, several potential prognostic predictors were not identified by the current analysis because some of them (e.g., α-fetoprotein) were incorporated into the staging systems, while others were homogenous (e.g., all but one of our patients had Child-Pugh A status) in the entire study population.

In conclusion, our study indicates that several current HCC staging systems, especially CLIP score and CUPI, can predict survival of a highly selected patient cohort consisting of patients who were enrolled in clinical trials of advanced HCC. These two staging systems should be considered when selecting eligibility criteria and/or setting the stratification for randomisation to ensure an optimal clinical trial design.

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