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ORIGINAL ARTICLE

Comparative performances of staging systems for early hepatocellular carcinoma

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Abstract

Background: Several staging systems for patients with hepatocellular carcinoma (HCC) have been proposed, but studies of their prognostic accuracy have yielded conflicting conclusions. Stratifying patients with early HCC is of particular interest because these patients may derive the greatest benefit from intervention, yet no studies have evaluated the comparative performances of staging systems in patients with early HCC.

Methods: A retrospective cohort study was performed using data on 379 patients who underwent liver resection or liver transplantation for HCC at six major hepatobiliary centres in the USA and Europe. The staging systems evaluated were: the Okuda staging system, the International Hepato-Pancreato-Biliary Association (IHPBA) staging system, the Cancer of the Liver Italian Programme (CLIP) score, the Barcelona Clinic Liver Cancer (BCLC) staging system, the Japanese Integrated Staging (JIS) score and the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) staging system, 6th edition. A recently proposed early HCC prognostic score was also evaluated. The discriminative abilities of the staging systems were evaluated using Cox proportional hazards models and the bootstrap-corrected concordance index (*c*).

Results: Overall survival of the cohort was 74% at 3 years and 52% at 5 years, with a median survival of 62 months. Most systems demonstrated poor discriminatory ability ($P > 0.05$ on Cox proportional hazards analysis, $c \approx 0.5$). However, the AJCC/UICC system clearly stratified patients ($P < 0.001$, $c = 0.59$), albeit only into two groups. The early HCC prognostic score also clearly stratified patients ($P < 0.001$, $c = 0.60$) and identified three distinct prognostic groups.

Discussion: The early HCC prognostic score is superior to the AJCC/UICC staging system (6th edition) for predicting the survival of patients with early HCC after liver resection or liver transplantation. Other major HCC staging systems perform poorly in patients with early HCC.

Keywords

hepatocellular carcinoma, staging, surgery, liver resection, liver transplantation

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Introduction

Several staging systems have been proposed for patients with hepatocellular carcinoma (HCC). The Okuda staging system, proposed in 1985, aimed to predict survival in a cohort with relatively advanced HCC undergoing a variety of surgical and non-surgical therapies.[1] As advances in imaging technology have allowed diagnosis of HCC at less advanced stages, several other systems have been proposed in order to more appropriately stratify patients in the modern era. Examples of such systems include clinical staging systems such as the International Hepato-Pancreato-Biliary Association (IHPBA) staging system,[2] the Cancer of the Liver Italian Programme (CLIP) score,[3] and the Barcelona Clinic Liver Cancer (BCLC) staging system.[4,5] Two major pathological staging systems have also been proposed: the Japanese Integrated Staging (JIS) score (which incorporates the Liver Cancer Study Group of Japan [LCSGJ] staging system)[2,6] and the American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) staging system, 6th edition.[7,8] The patient cohorts from which these staging systems were derived varied widely with respect to tumour burden, underlying liver disease and therapeutic strategy. Subsequent studies of their prognostic accuracy have yielded conflicting conclusions depending on the characteristics of the patient cohorts in which they were evaluated.[9–21]

Surgical therapy – either liver resection or liver transplantation – provides the best chance of longterm survival in patients with HCC. Patients whose disease is too advanced to allow one of these treatment modalities may undergo other locoregional or systemic therapies, but generally with inferior results. Additionally, as the incidence of HCC increases in the West and aggressive screening strategies are put into place for at-risk patients, HCC is likely to be diagnosed at earlier stages in more patients. As such, stratifying patients with early HCC is of particular interest, especially to surgeons, because patients with early HCC have the potential to derive the greatest benefit from surgical intervention, follow-up and repeat intervention when indicated. The controversy regarding the appropriate management of patients with early HCC[22–24] makes accurate prognostic stratification of these patients imperative. Yet, no studies have compared HCC staging systems using a cohort composed exclusively of patients with early HCC. Staging system evaluations that include patients with a wide spectrum of HCC disease do not indicate which staging system is most appropriate for use in patients with, specifically, early HCC.

Recently, our group proposed an early HCC prognostic score as a simple and accurate method to predict survival of patients with early HCC.[25] The early HCC prognostic score was derived using population-based data on early HCC patients who underwent liver resection in the USA. However, it has not been externally validated. To this end, we assessed the discriminative accuracy of the early HCC prognostic score in an international cohort of patients who underwent liver resection or liver transplantation. We also evaluated the comparative performances of the major established HCC staging systems as applied to patients with, specifically, early HCC.

Materials and methods

A retrospective cohort study was performed using data on patients who underwent liver resection or liver transplantation for HCC at six major hepatobiliary centres in the USA and Europe between January 1985 and January 2008. This cohort and the data collection process have been described in detail previously.[26] Briefly, data were collected from participating institutions using standardized data entry forms and were subsequently synthesized and analysed at the co-ordinating centre (Johns Hopkins University School of Medicine). All-cause mortality was the endpoint of interest. The 379 patients in the cohort all had early HCC, defined as a solitary tumour nodule $\leq$5 cm in size or two to three tumour nodules all $\leq$3 cm in size and no radiological or pathological evidence of major vascular invasion (i.e. macroscopic invasion of the major branches of the portal vein or hepatic veins) or metastatic disease.

Kaplan–Meier estimates of survival[27] and Cox proportional hazards models[28] were used to explore differences in survival among the strata established by six major staging systems: the Okuda staging system;[1] the IHPBA staging system;[2] the CLIP score;[3] the BCLC staging system;[4,5] the JIS score,[6] and the AJCC/UICC staging system (6th edition).[8] In order not to bias the analyses against the clinical staging systems as a result of errors in preoperative assessment, all staging was performed using postoperative data based on pathological review. A previously described early HCC prognostic score[25] was also evaluated. This scoring system allots 1 point each for tumour size > 2 cm, tumour multifocality and the presence of microscopic vascular invasion, and gives a minimum score of 0 and a maximum score of 2 (i.e., patients with scores of 2 and 3 are grouped together). Cox proportional hazards models were stratified by type of surgery (liver resection or liver transplantation). The discriminative abilities of the staging systems were assessed using the bootstrap-corrected concordance index (*c*-statistic), a generalization of the area under the receiver operating characteristic (ROC) curve that quantifies the proportion of all patient pairs for whom the predicted and observed survival outcomes are concordant.[29] A *c*-value of 0.5 indicates no predictive ability compared with chance alone, whereas a value of 1.0 indicates perfect discrimination. All tests of statistical significance were two-sided and statistical significance was established at $\alpha = 0.05$. Statistical analyses were performed using STATA/MP 10.0 for Windows (StataCorp LP, College Station, TX, USA). This study was approved by the Johns Hopkins University School of Medicine Institutional Review Boards.

Results

The cohort used in this analysis consisted of 379 patients, of whom 245 underwent liver resection and 134 underwent liver transplantation. The median ages of the resection and transplantation cohorts were 66 years and 55 years, respectively. Overall, 313

patients were male (83%) and gender distribution was similar in both groups. Viral hepatitis was present in 262 patients (69%), of whom 49 had hepatitis B, 194 had hepatitis C, and 19 had both hepatitis B and C. Alcohol use contributed to liver disease in 140 patients (37%). The median Model for End-stage Liver Disease (MELD) score was 9 in the liver resection group and 10 in the liver transplantation group. Overall, 23% of patients had received prior locoregional therapy (11% of resected patients and 46% of transplanted patients).

Patient and tumour characteristics that are relevant to the staging systems evaluated are described in Table 1. As per the study inclusion criteria, no patients had massive tumours (>50% of liver), major vascular invasion or portal vein thrombosis. About half (49%) the patients who underwent resection and all patients who underwent transplantation had ascites. Most patients had well-compensated cirrhosis, as evidenced by their serum albumin and bilirubin as well as their Child–Pugh classes (81% class A). Although most tumours were >2 cm in size (n = 289, 76%), a significant number in both treatment groups (n = 90, 24%) measured ≤2 cm. Most patients had solitary tumours (n = 332, 88%) and few had multifocal tumours (n = 34 with two tumours, n = 13 with three tumours). Consistent with these results, microvascular invasion was absent in most patients (n = 296, 78%), but present in a minority (n = 83, 22%).

Overall survival of the cohort was 74% at 3 years and 52% at 5 years, with a median survival of 62 months (Table 2, Fig. 1), consistent with the early stage of all tumours and the surgical therapy patients received. Briefly, the ability of the staging systems to stratify patients varied widely. The clinical staging systems demonstrated poor distinction between prognostic groups. The

Table 1 Patient and tumour characteristics for staging systems (n = 379)

Variable	Resection		Transplantation	
	n	%	*n*	%
Number of patients	245		134	
Ascites				
Present	121	49	134	100
Absent	124	51	0	0
Serum albumin				
≥3 g/dl	185	96	90	80
<3 g/dl	8	4	23	20
Serum bilirubin				
≥3 mg/dl	8	4	7	6
<3 mg/dl	214	96	111	94
Serum α-fetoprotein				
≥400 ng/ml	29	13	14	15
<400 ng/ml	195	87	82	85
Child–Pugh class				
Class A	233	95	75	56
Class B	12	5	59	44
Tumour size (all ≤5 cm)				
Size in cm, median, range	3.5	1.0–5.0	2.4	0.5–5.0
Size >2 cm	210	86	79	59
Size ≤2 cm	35	14	55	41
Multifocality				
Yes	15	6	32	24
No	230	94	102	76
Microvascular invasion				
Yes	71	29	12	9
No	174	71	122	91

Table 2 Descriptive survival statistics

Stage/score	3-year, %	5-year, %	Median, months
Overall	74	52	62
Okuda staging system			
A (n = 73)	75	47	56
B (n = 228)	72	51	63
C (n = 3)	67	67	–
IHPBA staging system			
T1 (n = 69)	80	59	82
T2 (n = 284)	72	51	61
T3 (n = 26)	70	51	62
CLIP score			
0 (n = 215)	74	51	61
1 (n = 83)	67	47	56
2 (n = 20)	71	47	46
3 (n = 2)	100	100	92
BCLC staging system			
0 (n = 69)	80	59	82
A1–A3 (n = 263)	71	50	60
A4 (n = 47)	77	55	62
JIS score			
0 (n = 52)	81	65	97
1 (n = 259)	73	49	57
2 (n = 56)	69	57	76
3 (n = 12)	79	47	46
AJCC/UICC staging system			
T1 (n = 256)	80	59	80
T2 (n = 123)	59	38	43
Early HCC prognostic score			
0 (n = 59)	87	67	97
1 (n = 225)	78	55	74
≥2 (n = 95)	56	37	38

IHPBA, International Hepato-Pancreato-Biliary Association; CLIP, Cancer of the Liver Italian Programme; BCLC, Barcelona Clinic Liver Cancer; JIS, Japanese Integrated Staging; AJCC/UICC, American Joint Committee on Cancer/International Union Against Cancer, 6th edition; HCC, hepatocellular carcinoma

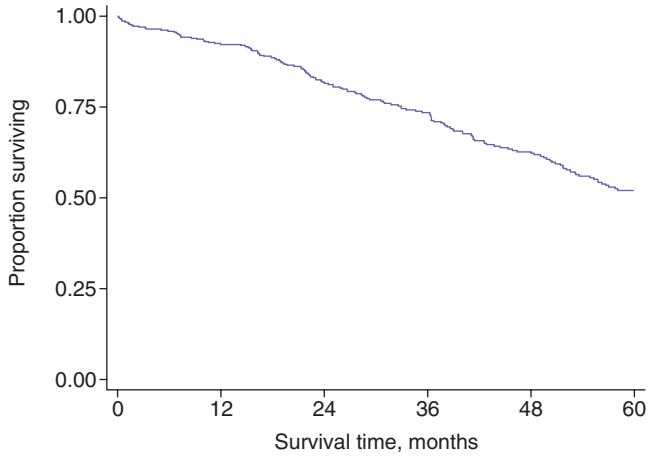

Figure 1 Kaplan–Meier survival estimates, all patients

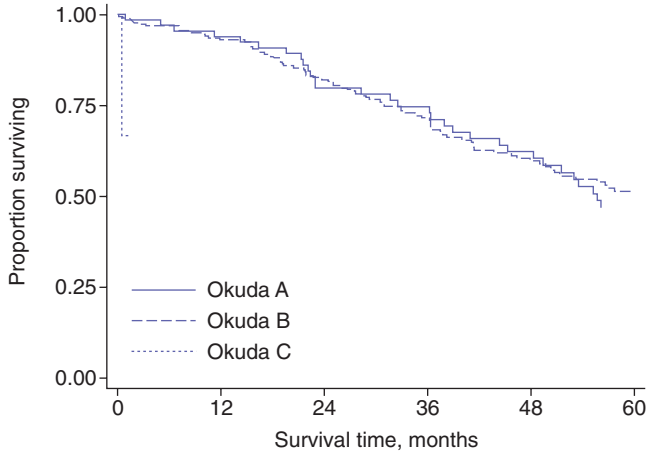

Figure 2 Kaplan–Meier survival estimates, by Okuda stage

Okuda staging system stratified patients into three groups, but the survival curves for the stage A and stage B groups were nearly identical (Fig. 2), and the median survival estimates were also very close (56 vs. 63 months, respectively; Table 2). There was no statistically significant difference between these groups (P = 0.62; Table 3), even after excluding the small (n = 3) Okuda stage C group (P = 0.36). The IHPBA staging system stratified patients into three groups with weak distinctions between them (median survival 82, 61 and 62 months, respectively; Table 2, Fig. 3), and the difference between the groups was not statistically significant (P = 0.62; Table 3). The CLIP score yielded four groups with overlapping survival curves (Fig. 4) and no statistically significant difference between them (P = 0.48; Table 3). There were only two patients in the group with a CLIP score of 3, but excluding them from the analysis did not change this conclusion (P = 0.29). In the BCLC staging system, stages A1–A3 were not further sub-stratified because all patients had well-compensated portal hypertension. For this reason, the BCLC staging system identified three groups with overlapping survival curves (Fig. 5). Stage A4 demonstrated better survival than stages A1–A3 (median survival of 62 vs. 60 months; Table 2), and the difference between the groups was not statistically significant (P = 0.74; Table 3).

The pathological staging systems were similarly analysed. The JIS score yielded four groups with overlapping survival curves (Fig. 6) and a non-monotonic progression of median survival estimates (97, 57, 76 and 46 months, respectively; Table 2). Again, the difference was not statistically significant (P = 0.35; Table 3). By contrast, the AJCC/UICC staging system stratified early HCC patients into two groups with median survival lengths of 80 and 43 months, respectively (Table 2, Fig. 7) and with clear differentiation on Cox proportional hazards analysis (P < 0.001; Table 3). Finally, the early HCC prognostic score yielded three groups with clearly differentiated survival curves (Fig. 8). It also demonstrated the widest range of median survival of any of the evaluated staging systems (97, 74 and 38 months, respectively; Table 2) and a statistically significant difference (P < 0.001).

In all cases, primary modelling of survival was performed by representing the various stage groupings with indicator variables. This approach has the advantage of not assuming a constant incremental effect of advancing tumour stage, but it has the potential drawback of reducing statistical power. To evaluate the possibility that some staging systems failed to demonstrate statistically significant differences between strata as a consequence of our modelling strategy, all systems were also evaluated using models that treated stage as a continuous variable. This approach yielded no changes in any of the conclusions regarding the statistical significance of the differences between strata.

Finally, the discriminatory abilities of the staging systems were assessed by calculating the bootstrap-corrected c-statistics for each system. Most systems demonstrated poor discriminatory ability, with c-statistics close to 0.5 (Table 3). However, two staging systems – the AJCC/UICC staging system (c = 0.59) and the early HCC prognostic score (c = 0.60) – demonstrated superior discriminatory ability. As noted above, the chief distinction between these systems was that the AJCC/UICC system includes two stages relevant to early HCC, whereas the early HCC prognostic score includes three such groups. Regression analyses and calculation of bootstrap-corrected c-statistics were also performed separately for patients who underwent resection (Table 4) and those who underwent transplantation (Table 5). In these analyses, the AJCC/UICC staging system and the early HCC prognostic score also demonstrated superior discriminatory ability.

Discussion

Several staging systems have been proposed for the prognostic stratification of patients with HCC, but none have been derived[1–4,6–8] or validated[9–21] in a cohort of patients with, specifically, early HCC. Because patients with early HCC are likely to benefit most from surgical therapy, prediction of their prognosis is of special interest and usefulness. In this study, we assessed the comparative performances of several major staging systems for

Table 3 Cox proportional hazards analyses, all patients (n = 379)*

Stage/score	HR	95% CI	*P*-value	*c*-statistic
Okuda staging system				
A (n = 73)	Ref.	–	0.62	0.50
B (n = 228)	0.85	0.58–1.24		
C (n = 3)	1.52	0.20–11.67		
IHPBA staging system				
T1 (n = 69)	Ref.	–	0.62	0.52
T2 (n = 284)	1.11	0.72–1.70		
T3 (n = 26)	1.42	0.71–2.83		
CLIP score				
0 (n = 215)	Ref.	–	0.48	0.51
1 (n = 83)	1.32	0.89–1.94		
2 (n = 20)	1.56	0.70–3.46		
3 (n = 2)	1.45	0.19–10.9		
BCLC staging system				
0 (n = 69)	Ref.	–	0.74	0.51
A1–A3 (n = 263)	1.11	0.72–1.71		
A4 (n = 47)	1.26	0.70–2.29		
JIS score				
0 (n = 52)	Ref.	–	0.35	0.52
1 (n = 259)	1.23	0.76–2.00		
2 (n = 56)	1.53	0.83–2.81		
3 (n = 12)	2.32	0.85–6.36		
AJCC/UICC staging system				
T1 (n = 256)	Ref.	–	<0.001	0.59
T2 (n = 123)	2.17	1.61–2.93		
Early HCC prognostic score				
0 (n = 59)	Ref.	–	<0.001	0.600
1 (n = 225)	1.18	0.72–1.95		
2 (n = 95)	2.46	1.44–4.19		

*All models were stratified by type of surgery to account for differential survival between treatment modalities
HR, hazard ratio; CI, confidence interval; Ref., referent; IHPBA, International Hepato-Pancreato-Biliary Association; CLIP, Cancer of the Liver Italian Programme; BCLC, Barcelona Clinic Liver Cancer; JIS, Japanese Integrated Staging; AJCC/UICC, American Joint Committee on Cancer/International Union Against Cancer, 6th edition; HCC, hepatocellular carcinoma

HCC, focusing on a large international cohort of patients exclusively with early HCC. We found that the AJCC/UICC staging system and the early HCC prognostic score both provided good prognostic discrimination, whereas the other major staging systems performed quite poorly. Surgeons who treat patients with early HCC should be aware that these other staging systems – the Okuda staging system, the IHPBA staging system, the CLIP score, the BCLC staging system and the JIS score – do not appropriately stratify patients with respect to prognosis when applied to subjects with early HCC.

The AJCC/UICC staging system (6th edition) is the most widely used pathological staging system for HCC and has been recommended as the staging system of choice for patients who undergo liver resection or liver transplantation.[30] Indeed, the AJCC/UICC staging system performed well in our analysis, but its chief limitation when applied to patients with early HCC is that it allows identification of only two prognostic strata. By contrast, the early HCC prognostic score, which was developed in a cohort of patients with early HCC,[25] identifies three distinct prognostic strata. The early HCC prognostic score also provides slightly superior discriminatory ability compared with the AJCC/UICC system, as evidenced by the *c*-statistics (0.60 vs. 0.59, respectively). The *c*-statistic for the early HCC prognostic score in the present analysis was identical to that previously reported for a population-based cohort of early HCC patients who underwent liver resection in the USA.[25] The present work is significant in that it externally validates the early HCC prognostic score. It also extends our previous findings by using institutional data (vs. population-based registry data), by including an international cohort of patients, and by including both liver resection and liver transplantation patients.

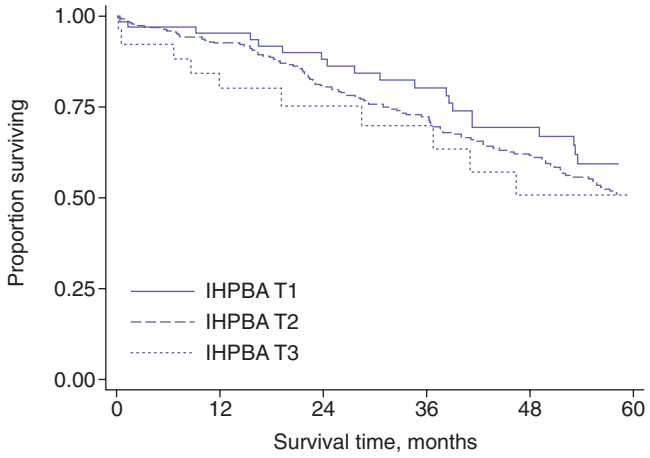

Figure 3 Kaplan–Meier survival estimates, by International Hepato-Pancreato-Biliary Association (IHPBA) T-classification

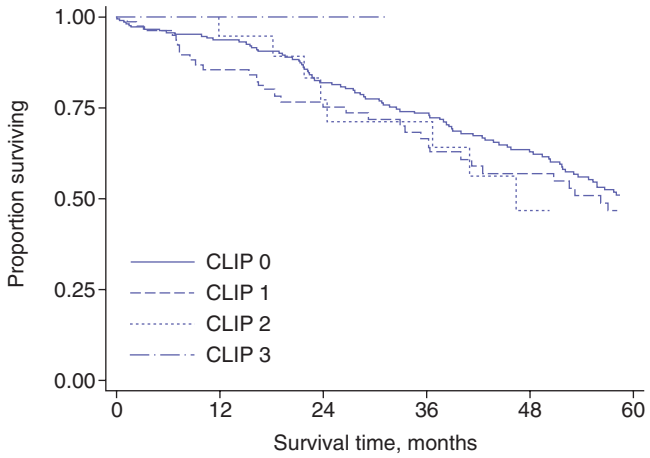

Figure 4 Kaplan–Meier survival estimates, by Cancer of the Liver Italian Programme (CLIP) score

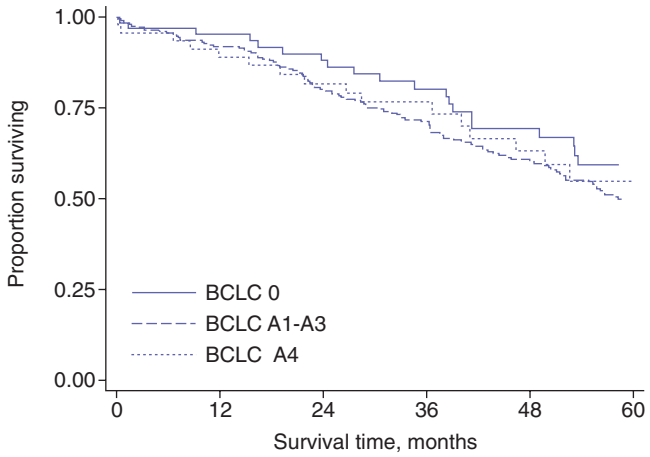

Figure 5 Kaplan–Meier survival estimates, by Barcelona Clinic Liver Cancer (BCLC) stage

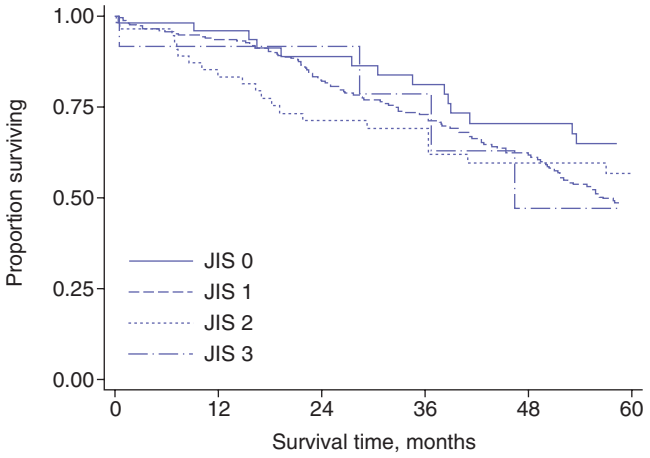

Figure 6 Kaplan–Meier survival estimates, by Japanese Integrated Staging (JIS) score

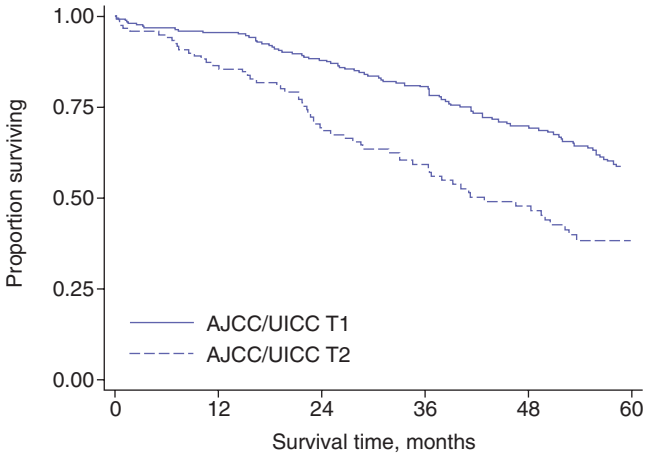

Figure 7 Kaplan–Meier survival estimates, by American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC), 6th edition, T-classification

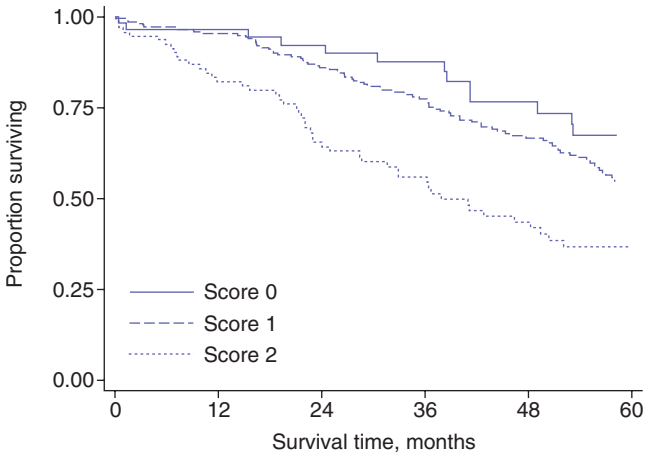

Figure 8 Kaplan–Meier survival estimates, by early hepatocellular carcinoma prognostic score

Table 4 Cox proportional hazards analyses, liver resection (n = 245)

Stage/score	HR	95% CI	*P*-value	*c*-statistic
Okuda staging system				
A (n = 73)	Ref.	–	0.02	0.49
B (n = 116)	0.84	0.57–1.22		
C (n = 2)	119	7.09–1993		
IHPBA staging system				
T1 (n = 30)	Ref.	–	0.92	0.48
T2 (n = 205)	0.96	0.58–1.60		
T3 (n = 10)	0.82	0.30–2.22		
CLIP score				
0 (n = 180)	Ref.	–	0.45	0.51
1 (n = 41)	1.20	0.76–1.88		
2 (n = 3)	2.34	0.57–9.57		
3 (n = 0)	–	–		
BCLC staging system				
0 (n = 30)	Ref.	–	0.87	0.49
A1–A3 (n = 200)	0.97	0.58–1.61		
A4 (n = 15)	0.80	0.33–1.94		
JIS score				
0 (n = 29)	Ref.	–	0.65	0.51
1 (n = 197)	0.93	0.56–1.54		
2 (n = 17)	1.30	0.61–2.79		
3 (n = 2)	2.23	0.29–16.9		
AJCC/UICC staging system				
T1 (n = 164)	Ref.	–	<0.001	0.59
T2 (n = 81)	2.14	1.53–3.00		
Early HCC prognostic score				
0 (n = 25)	Ref.	–	0.001	0.58
1 (n = 146)	1.04	0.56–1.90		
2 (n = 74)	2.01	1.07–3.79		

HR, hazard ratio; CI, confidence interval; Ref., referent; IHPBA, International Hepato-Pancreato-Biliary Association; CLIP, Cancer of the Liver Italian Programme; BCLC, Barcelona Clinic Liver Cancer; JIS, Japanese Integrated Staging; AJCC/UICC, American Joint Committee on Cancer/International Union Against Cancer, 6th edition; HCC, hepatocellular carcinoma

Both the AJCC/UICC staging system and the early HCC prognostic score were developed based on rigorous analyses of clinicopathological data from patients with resected HCC.[7,25] The main difference between the approaches taken by these two systems is that the early HCC prognostic score allows patients with solitary tumours to be stratified with respect to both tumour size (>2 cm vs. ≤2 cm) and the presence of microvascular invasion, whereas the AJCC/UICC system does not consider size to be a prognostic factor for solitary tumours. A recent analysis evaluated a modified version of the AJCC/UICC staging system (6th edition) that: (i) further stratifies solitary tumours without microvascular invasion based on a 2-cm size cut-off, and (ii) further stratifies multifocal tumours of ≤5 cm in size (T2) based on the presence or absence of macroscopic vascular invasion.[31] That study found that such modification enhanced the predictive ability of the standard AJCC/UICC staging system (6th edition).[31] Interestingly, the approach taken was similar (although not identical) to that proposed in the early HCC prognostic score, which also recognizes the additional prognostic impact of tumour size >2 cm for both solitary and multifocal tumours and the additional prognostic impact of microvascular invasion in multifocal tumours.

Previous studies that have failed to find prognostic value in a 2-cm size cut-off for solitary tumours may have included too few patients with small tumours.[2,7,9] Data on Japanese patients,[18] however, demonstrated the prognostic value of a 2-cm cut-off, perhaps because of the higher proportion of patients diagnosed in the early stages, and the 2-cm cut-off is an important component of the LCSGJ staging system[2] and, consequently, the JIS score.[6] In the present study, 24% of patients had tumours ≤2 cm in size and

Table 5 Cox proportional hazards analyses, liver transplantation (n = 134)*

Stage/score	HR	95% CI	*P*-value	*c*-statistic
IHPBA staging system				
T1 (n = 39)	Ref.	–	0.15	0.56
T2 (n = 79)	1.36	0.63–2.96		
T3 (n = 16)	2.82	1.04–7.67		
CLIP score				
0 (n = 35)	Ref.	–	0.60	0.54
1 (n = 42)	1.77	0.75–4.18		
2 (n = 17)	1.63	0.56–4.69		
3 (n = 2)	1.69	0.21–13.6		
BCLC staging system				
0 (n = 39)	Ref.	–	0.28	0.54
A1–A3 (n = 63)	1.34	0.60–3.00		
A4 (n = 32)	2.02	0.84–4.84		
JIS score				
0 (n = 23)	Ref.	–	0.07	0.52
1 (n = 62)	3.78	1.11–12.9		
2 (n = 39)	3.22	0.91–11.4		
3 (n = 10)	5.11	1.13–23.1		
AJCC/UICC staging system				
T1 (n = 92)	Ref.	–	0.02	0.58
T2 (n = 42)	2.29	1.19–4.42		
Early HCC prognostic score				
0 (n = 34)	Ref.	–	0.01	0.60
1 (n = 79)	1.39	0.59–3.28		
2 (n = 21)	4.24	1.58–11.3		

*The Okuda staging system was omitted because observations in stages A (n = 0) and C (n = 1) were too few
HR, hazard ratio; CI, confidence interval; Ref., referent; IHPBA, International Hepato-Pancreato-Biliary Association; CLIP, Cancer of the Liver Italian Programme; BCLC, Barcelona Clinic Liver Cancer; JIS, Japanese Integrated Staging; AJCC/UICC, American Joint Committee on Cancer/International Union Against Cancer, 6th edition; HCC, hepatocellular carcinoma

this factor probably explains part of the advantage of the early HCC prognostic score over the AJCC/UICC staging system in this cohort with early HCC.

Strengths of the present analysis include the fact that its data were gathered from a large, international cohort. The cohort included both liver resection and liver transplantation patients, which allows the results to be generalized to both groups. The accuracy of clinical staging systems may be limited both by the staging systems themselves and by inaccuracies in the data used to stage patients. For example, the imaging modality used or the progression of the tumour during the interval between imaging and surgery may decrease the apparent accuracy of a clinical staging system. Because we based all staging on pathological data, our analysis assumed the best possible performance of the clinical staging systems under circumstances of completely accurate data on tumour number and size. Several limitations should also be considered. The absence of certain data precluded some patients from being assigned a CLIP score or Okuda stage, which may have affected the assessment of these systems' predictive abilities. Additionally, data limitations prevented the sub-stratification of BCLC stages A1–A3. However, because stage A4 demonstrated better survival than stages A1–A3, further sub-stratification would still have resulted in at least one of the stages A1, A2 or A3 indicating worse survival than stage A4. As such, the BCLC staging system would still have demonstrated considerable drawbacks in this cohort. Finally, because data were retrospectively acquired from several institutions, pathological review was not standardized.

In summary, both the AJCC/UICC staging system (6th edition) and the early HCC prognostic score allow stratification of patients with early HCC undergoing liver resection or liver transplantation. Other major staging systems perform inadequately in this group of patients. We recommend the early HCC prognostic score for use in studies that focus on patients with early HCC undergoing liver resection or liver transplantation.

Conflicts of interest

None declared.

References

1. Okuda K, Ohtsuki T, Obata H, Tomimatsu M, Okazaki N, Hasegawa H *et al*. (1985) Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. *Cancer* 56:918–928.
2. Makuuchi M, Belghiti J, Belli G, Fan ST, Lau JW, Ringe B *et al*. (2003) IHPBA concordant classification of primary liver cancer: working group report. *J Hepatobiliary Pancreat Surg* 10:26–30.
3. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients: the Cancer of the Liver Italian Program (CLIP) investigators. *Hepatology* 28:751–755.
4. Llovet JM, Bru C, Bruix J. (1999) Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis* 19:329–338.
5. Bruix J, Boix L, Sala M, Llovet JM. (2004) Focus on hepatocellular carcinoma. *Cancer Cell* 5:215–219.
6. Kudo M, Chung H, Osaki Y. (2003) Prognostic staging system for hepatocellular carcinoma (CLIP score): its value and limitations, and a proposal for a new staging system, the Japan Integrated Staging Score (JIS score). *J Gastroenterol* 38:207–215.
7. Vauthey JN, Lauwers GY, Esnaola NF, Do KA, Belghiti J, Mirza N *et al*. (2002) Simplified staging for hepatocellular carcinoma. *J Clin Oncol* 20:1527–1536.
8. Greene FL, Page DL, Fleming ID, Fritz A, Balch CM, Haller DG, Morrow M. (2002) *AJCC Cancer Staging Manual*, 6 edn, Springer-Verlag, New York.
9. Poon RT, Fan ST. (2003) Evaluation of the new AJCC/UICC staging system for hepatocellular carcinoma after hepatic resection in Chinese patients. *Surg Oncol Clin N Am* 12:35–50.
10. Marrero JA, Fontana RJ, Barrat A, Askari F, Conjeevaram HS, Su GL, Lok AS. (2005) Prognosis of hepatocellular carcinoma: comparison of 7 staging systems in an American cohort. *Hepatology* 41:707–716.
11. Nanashima A, Omagari K, Tobinaga S, Shibata K, Sumida Y, Mine M *et al*. (2005) Comparative study of survival of patients with hepatocellular carcinoma predicted by different staging systems using multivariate analysis. Eur *J Surg Oncol* 31:882–890.
12. Grieco A, Pompili M, Caminiti G, Miele L, Covino M, Alfei B *et al*. (2005) Prognostic factors for survival in patients with early-intermediate hepatocellular carcinoma undergoing non-surgical therapy: comparison of Okuda, CLIP, and BCLC staging systems in a single Italian centre. *Gut* 54:411–418.
13. Tateishi R, Yoshida H, Shiina S, Imamura H, Hasegawa K, Teratani T *et al*. (2005) Proposal of a new prognostic model for hepatocellular carcinoma: an analysis of 403 patients. *Gut* 54:419–425.
14. Toyoda H, Kumada T, Kiriyama S, Sone Y, Tanikawa M, Hisanaga Y *et al*. (2005) Comparison of the usefulness of three staging systems for hepatocellular carcinoma (CLIP, BCLC, and JIS) in Japan. *Am J Gastroenterol* 100:1764–1771.
15. Cillo U, Vitale A, Grigoletto F, Farinati F, Brolese A, Zanus G *et al*. (2006) Prospective validation of the Barcelona Clinic Liver Cancer staging system. *J Hepatol* 44:723–731.
16. Chen TW, Chu CM, Yu JC, Chen CJ, Chan DC, Liu YC, Hsieh CB. (2007) Comparison of clinical staging systems in predicting survival of hepatocellular carcinoma patients receiving major or minor hepatectomy. *Eur J Surg Oncol* 33:480–487.
17. Kondo K, Chijiiwa K, Nagano M, Hiyoshi M, Kai M, Maehara N *et al*. (2007) Comparison of seven prognostic staging systems in patients who undergo hepatectomy for hepatocellular carcinoma. *Hepatogastroenterology* 54:1534–1538.
18. Minagawa M, Ikai I, Matsuyama Y, Yamaoka Y, Makuuchi M. (2007) Staging of hepatocellular carcinoma: assessment of the Japanese TNM and AJCC/UICC TNM systems in a cohort of 13,772 patients in Japan. *Ann Surg* 245:909–922.
19. Lu W, Dong J, Huang Z, Guo D, Liu Y, Shi S. (2008) Comparison of four current staging systems for Chinese patients with hepatocellular carcinoma undergoing curative resection: Okuda, CLIP, TNM and CUPI. *J Gastroenterol Hepatol* 23:1874–1878.
20. Vauthey JN, Ribero D, Abdalla EK, Jonas S, Bharat A, Schumacher G *et al*. (2007) Outcomes of liver transplantation in 490 patients with hepatocellular carcinoma: validation of a uniform staging after surgical treatment. *J Am Coll Surg* 204:1016–1027; discussion 1027–1018.
21. Guglielmi A, Ruzzenente A, Pachera S, Valdegamberi A, Sandri M, D'Onofrio M, Iacono C. (2008) Comparison of seven staging systems in cirrhotic patients with hepatocellular carcinoma in a cohort of patients who underwent radiofrequency ablation with complete response. *Am J Gastroenterol* 103:597–604.
22. Arii S, Yamaoka Y, Futagawa S, Inoue K, Kobayashi K, Kojiro M *et al*. (2000) Results of surgical and nonsurgical treatment for small-sized hepatocellular carcinomas: a retrospective and nationwide survey in Japan. The Liver Cancer Study Group of Japan. *Hepatology* 32:1224–1229.
23. Llovet JM, Bruix J, Gores GJ. (2000) Surgical resection versus transplantation for early hepatocellular carcinoma: clues for the best strategy. *Hepatology* 31:1019–1021.
24. El-Serag HB, Marrero JA, Rudolph L, Reddy KR. (2008) Diagnosis and treatment of hepatocellular carcinoma. *Gastroenterology* 134:1752–1763.
25. Nathan H, Schulick RD, Choti MA, Pawlik TM. (2009) Predictors of survival after resection of early hepatocellular carcinoma. *Ann Surg* 249:799–805.
26. Bellavance EC, Lumpkins KM, Mentha G, Marques HP, Capussotti L, Pulitano C *et al*. (2008) Surgical management of early-stage hepatocellular carcinoma: resection or transplantation? *J Gastrointest Surg* 12:1699–1708.
27. Kaplan EL, Meier P. (1958) Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 53:457–481.
28. Cox DR. (1972) Regression models and life-tables. *J Royal Stat Soc B* 34:187–220.
29. Harrell FE, Jr., Lee KL, Mark DB. (1996) Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 15:361–387.
30. Henderson J, Sherman M, Tavill A, Abecassis M, Chejfec G, Gramlich T. (2003) AHPBA/AJCC consensus conference on staging of hepatocellular carcinoma: consensus statement. *HPB (Oxford)* 5:243–250.
31. Kee KM, Wang JH, Lee CM, Chen CL, Changchien CS, Hu TH *et al*. (2007) Validation of clinical AJCC/UICC TNM staging system for hepatocellular carcinoma: analysis of 5,613 cases from a medical center in southern Taiwan. *Int J Cancer* 120:2650–2655.