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## Original Article

# International validation of the Chinese University Prognostic Index for staging of hepatocellular carcinoma: a joint United Kingdom and Hong Kong study

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## Abstract

The outcome of hepatocellular carcinoma (HCC) patients significantly differs between western and eastern population centers. Our group previously developed and validated the Chinese University Prognostic Index (CUPI) for the prognostication of HCC among the Asian HCC patient population. In the current study, we aimed to validate the CUPI using an international cohort of patients with HCC and to compare the CUPI to two widely used staging systems, the Barcelona Clinic Liver Cancer (BCLC) classification and the Cancer of the Liver Italian Program (CLIP). To accomplish this goal, two cohorts of patients were enrolled in the United Kingdom (UK;  $n = 567$ ; 2006–2011) and Hong Kong (HK;  $n = 517$ ; 2007–2012). The baseline clinical data were recorded. The performances of the CUPI, BCLC, and CLIP were compared in terms of a concordance index (C-index) and were evaluated in subgroups of patients according to treatment intent. The results revealed that the median follow-up durations of the UK and HK cohorts were 27.9 and 29.8 months, respectively. The median overall survival of the UK and HK cohorts were 22.9 and 8.6 months, respectively. The CUPI stratified the patients in both cohorts into three risk subgroups corresponding to distinct outcomes. The median overall survival of the CUPI low-, intermediate-, and high-risk subgroups were 3.15, 1.24, and 0.29 years, respectively, in the UK cohort and were 2.07, 0.32, and 0.10 years, respectively, in the HK cohort. For the patients who underwent curative treatment, the prognostic performance did not differ between the three staging systems, and all were suboptimal. For those who underwent palliative treatment, the CUPI displayed the highest C-index, indicating that this staging system was the most informative for both cohorts. In conclusion, the CUPI is applicable to both western and eastern HCC patient populations. The performances of the three staging systems differed according to treatment intent, and the CUPI was demonstrated to be optimal for those undergoing palliative treatment. A more precise staging system for early-stage disease patients is required.

**Key words** Liver neoplasms, staging, international cooperation, therapeutics

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Several staging systems have been developed to stratify the outcome of patients with hepatocellular carcinoma (HCC)<sup>[1-6]</sup>. However, the optimal system remains controversial<sup>[7-13]</sup>. One reason for this controversy stems from the use of a distinct population to develop each staging system. It has been observed that the outcome of HCC differs significantly between western and eastern populations, possibly as a result of different etiologies, ethnicities, or treatment approaches<sup>[14,15]</sup>. Therefore, a staging system that is considered applicable to one region may not be useful for other regions.

Another reason for this controversy is that some staging systems were built purely for determining a prognosis without considering the

treatment modality, whereas others, such as the Barcelona Clinic Liver Cancer (BCLC) classification, were designed to indicate the appropriate treatment modalities<sup>[3]</sup>. However, in daily clinical practice, the BCLC guidelines are not strictly followed by many clinicians. In particular, curative treatments, such as hepatectomy, are frequently offered whenever technically feasible and clinically appropriate rather than as indicated by a precise tumor stage<sup>[16,17]</sup>. This treatment approach might have confounded the comparison between the BCLC staging system and other systems. In addition, previous data suggest that the applicability of staging systems may vary with the treatment modality<sup>[11,18]</sup>. Therefore, it is valuable to determine the performances of different staging systems in populations stratified by curative or palliative treatment.

Previously, our group developed the Chinese University Prognostic Index (CUPI), which aims to maintain the widely used Tumor Node Metastasis (TNM) system except for modifications related to liver dysfunction and several statistically weighted factors<sup>[4]</sup>. This system has been validated in an independent Asian HCC patient population<sup>[12]</sup> but not in a large western population. In the current study, we aimed to validate the CUPI system in an international HCC patient cohort composed of patients recruited from two centers, one eastern and one western, over a similar period of time. Furthermore, we aimed to compare the performance of the CUPI with those of two commonly used systems, the BCLC and the Cancer of the Liver Italian Program (CLIP), and to compare the performances of these staging systems according to the treatment intent.

## Subjects and Methods

### Study cohorts

Two cohorts of patients were recruited. Consecutive patients attending the Joint Hepatoma Clinic at Prince of Wales Hospital, Hong Kong (HK) between January 2007 and December 2011 were recruited as the first cohort. The joint clinic is the primary referral clinic for HCC patients in New Territories East of Hong Kong and serves approximately 2 million patients. Consecutive patients from the Queen Elizabeth University Hospital, Birmingham, the United Kingdom (UK) between June 2006 and March 2012 were recruited as the second cohort. This hospital covers a local population of approximately 5.5 million. The recruitment of patients in both cohorts had obtained approval from the respective ethics committees of both centers. The diagnosis of HCC in both centers was confirmed either by histological evidence when surgery or biopsy had been performed or by radiologic criteria according to the international guidelines for diagnosis of HCC<sup>[19]</sup>.

### Treatment

The patients in both cohorts were examined by their respective multidisciplinary teams. Depending on the tumor extent and liver reserve, the patients were offered treatment, including resection, liver transplantation, local ablation, transarterial treatment, systemic therapy, or supportive care. For the purposes of this study, treatment

modalities, including liver transplantation, surgical resection, and local ablation, were regarded as curative treatments. Other treatments, including transarterial chemoembolization (TACE) or other forms of transarterial therapy, systemic treatment such as sorafenib or clinical trials of targeted agents, and supportive care, were classified as palliative treatments. For patients undergoing transplantation in the UK, the Milan criteria were strictly adhered to, and the patients who received TACE as a “bridge” to transplantation were classified as receiving curative treatment.

### Follow-up

The patients in both the HK and UK cohorts were followed up according to departmental procedures. In general, the patients were followed up every 3 to 6 months after curative treatment, whereas the patients were followed up every 1 to 3 months during or after palliative treatment. The dataset of both cohorts was frozen for analysis on 31 January 2013.

### Statistical analysis

All analyses were performed using SAS<sup>®</sup> version 9.3 (SAS Institute, Inc., Cary, NC, USA). Overall survival (OS) was defined as the duration from diagnosis of HCC to death by any cause or the date of the final follow-up. Survival curves were estimated using the Kaplan-Meier method. Comparison and ranking of the staging systems were performed using Harrell's concordance index (C-index)<sup>[20]</sup>. The C-index is equivalent to the area under the receiver operator characteristic curve. The C-index estimates the proportion of correct predictions (i.e., the proportion of patients with an earlier clinical stage and who experienced longer survival). The C-index varies from 0.5 (no association) to 1.0 (perfect prediction). The C-index and 95% confidence intervals (CIs) of the different staging systems were calculated using the SAS macro program<sup>[21]</sup> and were compared using the bootstrap method with 1,000 replications.

## Results

### Patients' characteristics

A total of 517 patients from the Joint Hepatoma Clinic at Prince of Wales Hospital, HK and 567 patients from the Queen Elizabeth University Hospital, Birmingham, UK were recruited. The baseline characteristics of the patients are shown in **Table 1**. In the HK cohort, hepatitis B virus (HBV) infection was the primary etiology of HCC, but the causes of HCC were heterogeneous in the UK cohort. All patients in the HK cohort were Chinese, whereas 96% of the patients in the UK cohort were Caucasian. The median follow-up durations of the HK and UK cohorts were 29.8 and 27.9 months, respectively. The median OS of the entire HK and UK cohorts was 8.6 and 22.9 months, respectively. Among the patients who underwent curative treatment, the median OS was 54.8 months in the UK cohort but has yet to be determined in the HK cohort. For the patients who underwent palliative treatment, the median OS was 5.5 and 12.7

**Table 1. Baseline characteristics of patients with hepatocellular carcinoma (HCC) in the United Kingdom (UK) and the Hong Kong (HK) cohorts**

Characteristic	UK cohort	HK cohort
Total (cases)	567	517
Age (years)		
Median	64	59
Range	16–88	18–88
Sex (cases)		
Male	458	457
Female	109	60
Etiology [cases (%)]		
HBV	48 (8.5)	415 (80.3)
HCV	92 (16.2)	30 (5.8)
HBV and HCV	0	5 (1.0)
Alcohol	215 (37.9)	0
Others	212 (37.4)	67 (12.9)
Ethnicity [cases (%)]		
Caucasian	548 (96.7)	0
Asian-Oriental	9 (1.5)	517 (100.0)
Others	10 (1.8)	0
ECOG [cases (%)]		
0	151 (26.7)	162 (31.3)
1	283 (49.9)	325 (62.9)
2	114 (20.3)	23 (4.4)
3	16 (2.8)	7 (1.4)
4	3 (0.5)	0
Ascites [cases (%)]	129 (22.8)	134 (25.9)
Symptomatic at presentation [cases (%)]	268 (47.3)	366 (70.8)
First-line treatment [cases (%)]		
Curative treatment	228 (40.2)	92 (17.8)
Hepatectomy	56 (24.6)	59 (64.0)
Liver transplantation	111 (48.7)	0
Locoablative therapy	61 (26.7)	33 (36.0)
Palliative treatment	339 (59.8)	425 (82.2)
TACE or other transarterial therapy	161 (47.5)	125 (29.4)
Systemic therapy (sorafenib, chemotherapy, clinical trial compounds)	74 (21.8)	99 (23.3)
Optimal supportive care	104 (30.7)	201 (47.3)
Bilirubin ( $\mu\text{mol/L}$ )		
Median	16	20
Range	2–503	3–824
Albumin (g/L)		
Median	39	37
Range	23–52	18–34
INR		
Median	1.1	1.12
Range	0.8–4.8	0.87–2.93
ALP (IU/L)		
Median	327	147
Range	74–3,939	38–1,122

*(To be continued)*

**Table 1. Baseline characteristics of patients with hepatocellular carcinoma (HCC) in the United Kingdom (UK) and the Hong Kong (HK) cohorts (continued)**

Characteristic	UK cohort	HK cohort
AFP ( $\mu\text{g/L}$ )		
Median	28.9	239
Range	0.4–5,690,210	1–3,637,000
Child–Pugh class [cases (%)]		
A	422 (74.4)	351 (67.9)
B	121 (21.4)	139 (26.9)
C	24 (4.2)	27 (5.2)
Vascular invasion [cases (%)]	119 (21.0)	167 (32.3)
Tumor number [cases (%)]		
Unifocal	299 (52.7)	186 (36.0)
Multifocal	268 (47.3)	331 (64.0)
Tumor size (cm)		
Mean	5.8	8.5
Range	0.9–24	0.7–28
Tumor size in locoablative therapy subgroup (cm)	$n = 61$	$n = 33$
Mean $\pm$ SD	$2.4 \pm 0.8$	$4.2 \pm 4.1$
Median	2.4	3.6
Range	1.0–4.8	1.0–5.0

HBV, hepatitis B virus; HCV, hepatitis C virus; ECOG, Eastern Cooperative Oncology Group; TACE, transarterial chemoembolization; INR, international normalized ratio; ALP, alkaline phosphatase; AFP, alpha-fetoprotein; SD, standard deviation.

months in the HK and UK cohorts, respectively.

### Validation of the CUPI in the HK and UK cohorts

The survival data for patients stratified by the CUPI are shown in **Table 2**, and the Kaplan-Meier survival curves are illustrated in **Figure 1**. In both the HK and UK cohorts, the HCC populations were categorized according to the CUPI into three subgroups displaying distinct median OS. In terms of long-term outcome, there was no overlap of the survival curves between each risk subgroup except that there were 6 CUPI high-risk patients in the UK cohort who were long-term survivors. All 6 of these patients received liver transplantation as the first-line treatment.

### Comparison of the staging systems among the UK and HK cohorts

The Kaplan-Meier curves of the patients stratified by the BCLC and CLIP are shown in **Figure 1**. In the UK cohort, the BCLC stage 0/A subgroup exhibited the highest 2-year OS rate (76.9%) compared to the CLIP score 0 (73.3%) and CUPI low-risk subgroups (63.0%). Among the patients displaying the most advanced tumor stage, the CUPI high-risk subgroup displayed the lowest 3-month and 6-month OS rates compared to the CLIP score 4–6 and BCLC stage D subgroups. A similar pattern was observed in the HK cohort.

The BCLC stage 0/A patients exhibited the highest 2-year OS rate (78.7%) compared to the CLIP score 0 (73.7%) and CUPI low-risk patients (50.6%). The 6-month OS rates of the BCLC stage D, CUPI high-risk, and CLIP score 4–6 subgroups were 13.3%, 10.3%, and 17.4%, respectively. The C-indexes of the different staging systems are summarized in **Table 3**. In the UK cohort, the CUPI and CLIP displayed a higher C-index than the BCLC ( $P < 0.001$  in both cases), although the C-index was not different between the CUPI and CLIP. In the HK cohort, the CUPI displayed a higher C-index than the CLIP ( $P = 0.026$ ) but a similar C-index to the BCLC ( $P = 0.234$ ).

### Performance of the staging systems in the curative and palliative treatment subgroups

The survival data for the patients stratified by each tumor staging system according to curative and palliative treatment intent are summarized in **Table 4**, and the Kaplan-Meier survival curves are illustrated in **Figure 2**. In the UK cohort, 228 patients underwent curative treatment. The 2-year OS rates of patients with diseases of BCLC stage 0/A, CLIP score 0, and CUPI low-risk were 83.8%, 82.4%, and 77.9%, respectively. In the HK cohort, 92 patients underwent curative treatment. The 2-year OS rates of patients with diseases of BCLC stage 0/A, CLIP score 0, and CUPI low-risk ranged from 80.5% to 85.6%. Among the patients who underwent curative treatment, the long-term outcomes were not different between early

**Table 2. Survival of patients according to each tumor staging system in the UK and HK cohorts**

Tumor stage	Number of patients [cases (%)]	Median overall survival (years)	Overall survival rate (%)			
			3-month	6-month	1-year	2-year
<b>UK cohort (n = 567)</b>						
<b>CUPI</b>						
Low-risk	325 (57.3)	3.15 (2.49–4.61)	97.82	91.71	81.20	63.02
Intermediate-risk	197 (34.7)	1.24 (0.88–1.41)	92.84	78.88	55.36	30.55
High-risk	45 (8.0)	0.29 (0.22–0.38)	62.90	27.04	18.93	18.93
<b>BCLC</b>						
0/A	59 (10.4)	4.05 (2.61– n/r)	100.00	96.49	88.75	76.88
B	47 (8.3)	1.90 (1.13–2.57)	93.62	85.00	65.38	47.32
C	420 (74.1)	1.78 (1.50–2.11)	93.74	82.89	67.82	46.80
D	41 (7.2)	0.54 (0.18–0.41)	79.70	52.88	36.18	27.55
<b>CLIP</b>						
0	152 (26.8)	n/r (3.15–n/r)	99.34	95.31	89.48	73.32
1–3	373 (65.8)	1.52 (1.35–1.93)	93.49	82.10	64.42	42.45
4–6	42 (7.4)	0.34 (0.26–0.44)	69.98	33.41	7.59	3.80
<b>HK cohort (n = 517)</b>						
<b>CUPI</b>						
Low-risk	255 (49.3)	2.07 (1.66–2.47)	94.10	85.39	69.88	50.63
Intermediate-risk	191 (37.0)	0.32 (0.27–0.41)	59.80	38.02	19.76	11.04
High-risk	71 (13.7)	0.10 (0.08–0.14)	19.04	10.25	7.32	2.93
<b>BCLC</b>						
0/A	78 (15.0)	3.24 (3.12–n/r)	100.00	98.72	89.09	78.71
B	127 (24.6)	1.52 (1.23–2.23)	94.49	79.48	62.95	42.42
C	282 (54.6)	0.33 (0.26–0.42)	57.66	40.85	24.34	13.01
D	30 (5.8)	0.09 (0.06–0.19)	23.33	13.33	6.67	n/a
<b>CLIP</b>						
0	69 (13.3)	3.38 (2.55–n/r)	100.00	97.08	84.96	73.70
1–3	325 (62.9)	0.88 (0.72–1.11)	81.39	64.53	46.89	30.47
4–6	123 (23.8)	0.15 (0.11–0.19)	28.10	17.36	8.26	2.48

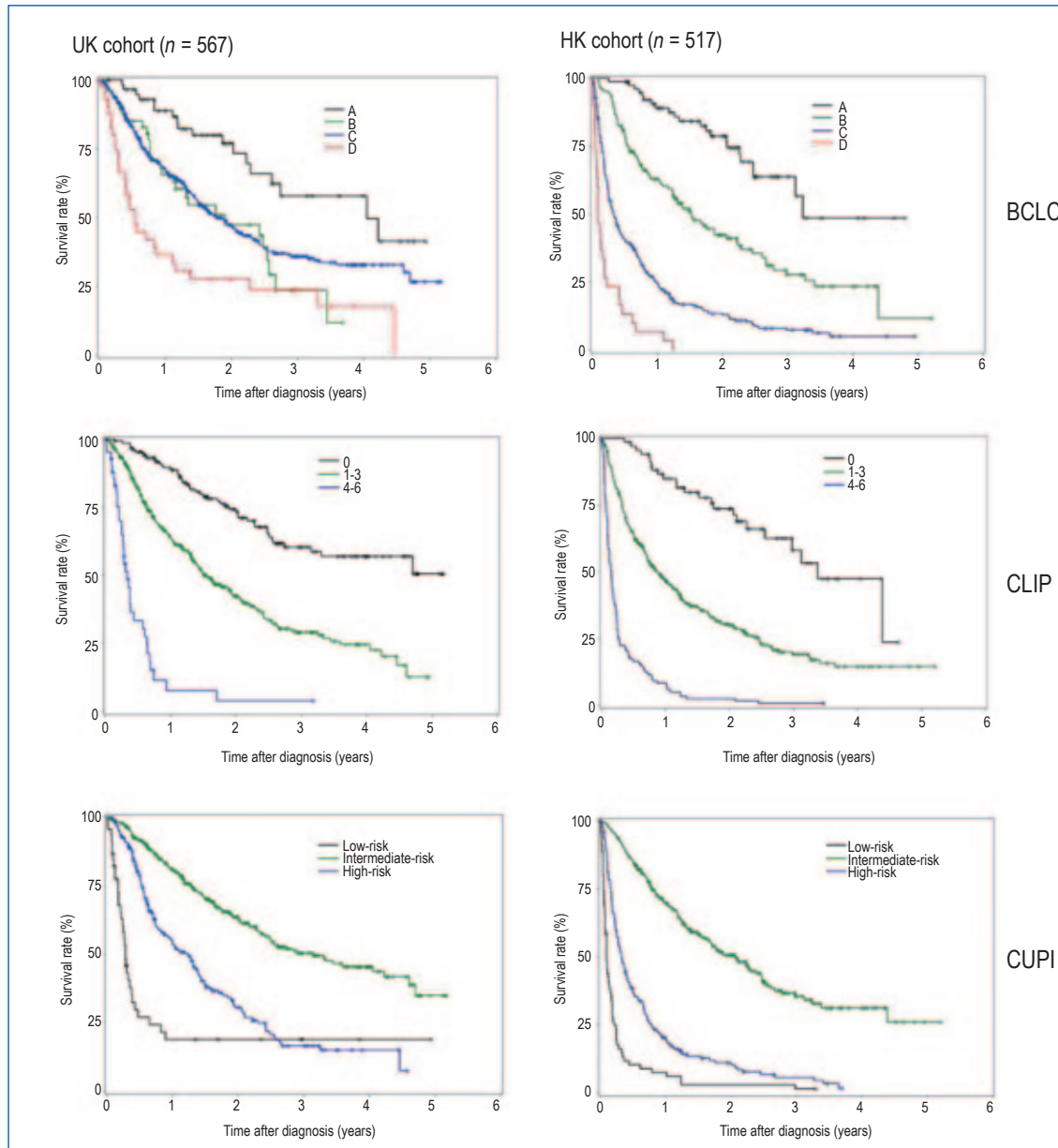
BCLC, Barcelona Clinic Liver Cancer; CLIP, Cancer of the Liver Italian Program; CUPI, Chinese University Prognostic Index; UK, United Kingdom; HK, Hong Kong; n/a, not applicable; n/r, not reached.

and advanced diseases in either the UK or HK cohort. The C-index ranged from 0.51 to 0.62 (Table 3), and was not significantly different between the three staging systems.

Alternatively, 339 (59.8%) patients in the UK cohort and 425 (82.2%) in the HK cohort underwent palliative treatment. Among the patients who underwent palliative treatment, there was a significant difference in the median OS between subgroups stratified by the BCLC, CLIP, and CUPI systems (all  $P < 0.001$ ). In terms of short-term outcome, the most notable finding in both cohorts was that the CUPI high-risk subgroup exhibited the worst 3- and 6-month OS rates compared to the BCLC stage D and CLIP score 4–6 subgroups. The 3-month death rates for the CUPI high-risk, BCLC stage D, and CLIP score 4–6 subgroups were 41%, 23%, and 29%, respectively, in the UK cohort and were 79%, 76%, and 71%, respectively, in the HK cohort. Moreover, the CUPI displayed the highest C-index compared with the CLIP and BCLC in both cohorts (Table 3).

## Discussion

The CUPI was originally developed and validated at an Asian center<sup>4,12</sup>, and it had yet to be validated in a western HCC patient population. This is the first study in which the CUPI has been validated in a large cohort of HCC patients diagnosed at a western center. In the UK cohort, the CUPI system stratified HCC patients into three risk subgroups, namely low-, intermediate-, and high-risk subgroups. The low-risk patients exhibited a 2-year OS rate of 63%, whereas those of the intermediate- and high-risk patients were 31% and 19%, respectively. In the HK cohort, although the patients exhibited an overall poorer outcome than the UK cohort, the low-, intermediate- and high-risk subgroups identified using the CUPI displayed similarly distinct median OS of 25.2, 3.8, and 1.0 month, respectively. These survival durations were in accordance with a previous validation study in another HCC patient population at the same center<sup>12</sup>. The robustness of the current dataset and its



**Figure 1.** Kaplan-Meier survival curves of patients with hepatocellular carcinoma (HCC) stratified according to different staging systems in the United Kingdom (UK) and the Hong Kong (HK) cohorts. BCLC, Barcelona Clinic Liver Cancer; CLIP, Cancer of the Liver Italian Program; CUPI, Chinese University Prognostic Index. In the UK cohort, the survival curves of the patients with BCLC stage B and C diseases overlapped. The CLIP and the CUPI stratified patients into different subgroups with distinct median overall survival (OS). In the HK cohort, the BCLC, CLIP, and CUPI staging systems separated the patients into subgroups displaying distinct median OS.

consistency with previous findings suggest that the CUPI staging system is applicable to both western and eastern populations.

Aside from validating the CUPI system, the current results also demonstrate that the CUPI and CLIP displayed higher prognostic performances than the BCLC in the UK cohort, whereas the CUPI was superior in the HK cohort. Although many studies have compared different HCC staging systems<sup>[7-13]</sup>, no previous studies addressed the impact of geographic difference on the performance of these

staging systems. Our current results indicate that the prognostic performances of these three staging systems varied between western and eastern populations. This finding highlights the complexity of the development of a staging system for HCC, in which the prognosis is determined by many factors. In particular, it appears that geographic difference plays a key role in determining the performance of various staging systems. This finding is also in line with recent phase III clinical trials of advanced HCC, which showed that the outcomes of

**Table 3. Concordance indexes (C-index) of the CLIP, CUPI, and BCLC in patients according to geographic region and treatment intent**

Rank	Staging system	C-index	95% CI
UK cohort			
1	CUPI	0.66 <sup>a</sup>	0.64–0.69
2	CLIP	0.65 <sup>a</sup>	0.63–0.67
3	BCLC	0.57	0.55–0.59
UK curative treatment subgroup			
1	CLIP	0.57	0.52–0.63
2	CUPI	0.52	0.60–0.66
3	BCLC	0.51	0.56–0.62
UK palliative treatment subgroup			
1	CUPI	0.69 <sup>a,b</sup>	0.66–0.72
2	CLIP	0.63	0.60–0.66
3	BCLC	0.59	0.57–0.62
HK cohort			
1	CUPI	0.73 <sup>b</sup>	0.71–0.74
2	BCLC	0.71	0.69–0.73
3	CLIP	0.69	0.67–0.71
HK curative treatment subgroup			
1	BCLC	0.63	0.53–0.73
2	CLIP	0.59	0.50–0.67
3	CUPI	0.53	0.49–0.58
HK palliative treatment subgroup			
1	CUPI	0.70 <sup>b,c</sup>	0.68–0.73
2	CLIP	0.66	0.64–0.68
3	BCLC	0.66	0.64–0.68

CI, confidence interval. Other abbreviations as in Table 2. <sup>a</sup> $P < 0.001$  and <sup>c</sup> $P < 0.05$  vs. BCLC; <sup>b</sup> $P < 0.05$  vs. CLIP.

**Table 4. Survival of the patients who underwent either curative or palliative treatment**

Tumor stage	Number of patients [cases (%)]	Median overall survival (years)	Overall survival rate (%)			
			3-month	6-month	1-year	2-year
Curative treatment						
UK cohort (n = 228)						
CUPI						
Low-risk	174 (76.3)	4.70 (4.05–n/r)	97.68	94.14	87.98	77.86
Intermediate-risk	48 (21.1)	2.55 (1.93–4.46)	95.83	93.75	87.35	61.79
High-risk	6 (2.6)	n/r	100.00	100.00	100.00	100.00
BCLC						
O/A	40 (17.5)	4.05 (2.61–n/r)	100.00	94.87	89.67	83.77
B	8 (3.5)	2.55 (1.90–n/r)	100.00	100.00	87.50	72.92
C	169 (74.1)	4.70 (3.25–n/r)	97.01	94.60	88.26	72.64
D	11 (4.8)	4.46 (2.28–4.46)	90.91	81.82	81.82	81.82
CLIP						
0	104 (45.6)	n/r (4.70–n/r)	99.03	96.08	91.94	82.35
1–3	123 (54.0)	3.59 (2.55–4.61)	95.91	92.59	85.80	69.31
4–6	1 (0.4)	0.94	n/a	n/a	n/a	n/a

(To be continued)



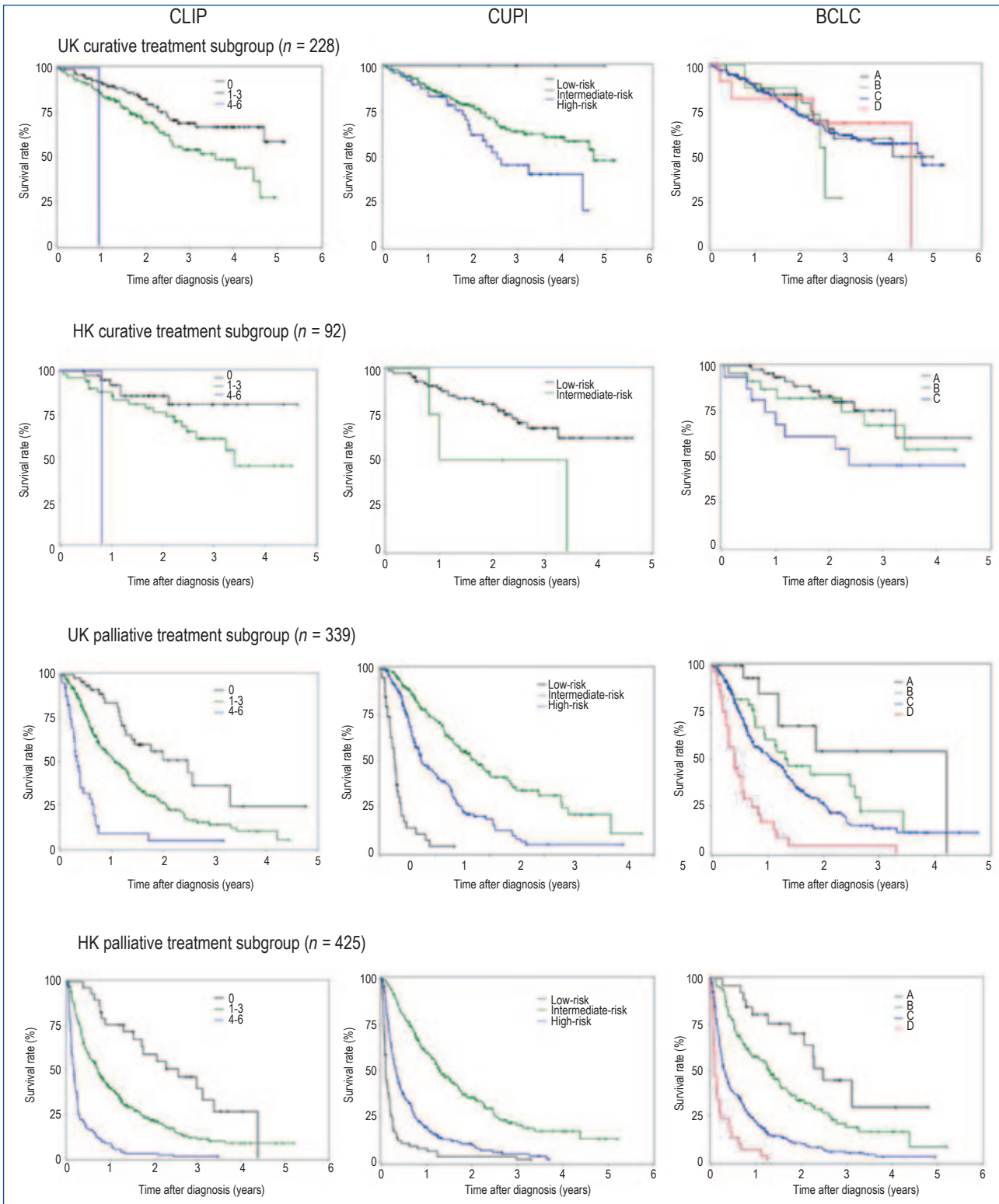
**Table 4. Survival of the patients who underwent either curative or palliative treatment (continued)**

Tumor stage	Number of patients [cases (%)]	Median overall survival (years)	Overall survival rate (%)			
			3-month	6-month	1-year	2-year
<b>HK cohort (n = 92)</b>						
<b>CUPI</b>						
Low-risk	88 (95.7)	n/r	97.73	95.43	89.26	80.54
Intermediate-risk	4 (4.3)	2.21 (0.81–3.41)	100.00	100.00	100.00	75.00
High-risk	0	n/a	n/a	n/a	n/a	n/a
<b>BCLC</b>						
0/A	52 (56.5)	n/r	100.00	100.00	93.65	83.24
B	24 (26.1)	n/r	95.83	91.48	86.90	82.08
C	16 (17.4)	2.38 (1.00–n/r)	93.75	87.50	74.48	60.94
D	0	n/a	n/a	n/a	n/a	n/a
<b>CLIP</b>						
0	40 (43.5)	n/r	100.00	97.44	91.93	85.59
1–3	51 (55.4)	3.41 (2.66–n/r)	96.08	94.12	87.74	76.04
4–6	1 (1.1)	0.81	100.00	100.00	0	0
<b>Palliative treatment</b>						
<b>UK cohort (n = 39)</b>						
<b>CUPI</b>						
Low-risk	151 (44.5)	1.76 (1.35–2.33)	97.99	88.79	72.51	42.43
Intermediate-risk	149 (44.0)	0.75 (0.64–1.05)	91.87	73.77	43.39	18.15
High-risk	39 (11.5)	0.27 (0.18–0.31)	56.81	13.43	3.36	n/a
<b>BCLC</b>						
0/A	19 (5.6)	4.22 (1.19–4.22)	100.00	100.00	84.85	54.30
B	39 (11.5)	1.35 (0.93–2.57)	92.31	81.90	60.43	41.78
C	251 (74.0)	1.05 (0.81–1.32)	91.53	74.61	52.56	26.11
D	30 (8.9)	0.40 (0.28–0.57)	75.52	41.20	16.48	4.12
<b>CLIP</b>						
0	48 (14.2)	2.49 (1.38–3.31)	100.00	93.66	83.67	50.58
1–3	250 (73.8)	1.06 (0.88–1.05)	92.30	76.65	52.45	26.35
4–6	41 (12.0)	0.34 (0.26–0.44)	69.21	31.47	8.39	4.20
<b>HK cohort (n = 425)</b>						
<b>CUPI</b>						
Low-risk	167 (39.3)	1.30 (1.11–1.66)	92.17	80.05	59.76	35.15
Intermediate-risk	187 (44.0)	0.32 (0.26–0.85)	58.93	36.68	18.53	10.05
High-risk	71 (16.7)	0.10 (0.08–0.14)	19.04	10.25	7.32	2.93
<b>BCLC</b>						
0/A	26 (6.1)	2.48 (2.06–n/r)	100.00	96.15	80.38	69.98
B	103 (24.2)	1.26 (0.88–1.66)	94.17	76.69	57.52	33.59
C	266 (62.6)	0.30 (0.25–0.37)	55.61	38.21	21.58	10.18
D	30 (7.1)	0.09 (0.06–0.19)	23.33	13.33	6.67	0
<b>CLIP</b>						
0	29 (6.8)	2.55 (1.53–3.38)	100.00	96.55	75.56	58.95
1–3	274 (64.5)	0.70 (0.57–0.85)	78.63	58.94	39.32	21.58
4–6	122 (28.7)	0.15 (0.11–0.19)	27.50	16.67	8.33	2.50

Abbreviations as in Table 2.

HCC differ significantly between western and eastern centers<sup>[22–24]</sup>. The primary reasons for the geographic impact on the performance of these staging systems remain unclear: it is possible that differences in etiology, the availability of a screening program, and variations in

treatment approach may account for this phenomenon. Regardless of the underlying reasons, it is evident that geographic difference needs to be considered during the development of a universal staging system to accurately predict the prognosis of HCC patients globally.



**Figure 2.** Kaplan-Meier survival curves of HCC patients in the UK and HK cohorts according to treatment intent. Among the patients who underwent curative treatment, the three staging systems could not stratify their outcome in a satisfactory manner as evidenced by the overlapping survival curves of both the UK and HK cohorts. Compared to the patients who underwent curative treatment, the performances of the three staging systems more appropriately stratified the outcome of the patients who underwent palliative treatment.

At present, the BCLC system has been recommended by some authorities as the standard HCC staging system in all regions<sup>[25]</sup>. This system was initially constructed to guide treatment for specific subgroups of patients and was subsequently used to estimate the prognosis of the respective subgroup of patients when treated with the recommended treatment modality. The BCLC has been previously reported to be an informative system for the prognostication of HCC at centers in which the BCLC guidelines are followed<sup>[7,26]</sup>. However, in real-world practice, the BCLC treatment algorithm is not frequently referred to by clinicians, which is exemplified in the current study, as a proportion of the patients of a BCLC stage other than 0 or A achieved long-term survival after undergoing curative treatment. For example, the BCLC stage D patients were only considered for supportive care according to the BCLC system, but 11 patients with BCLC stage D disease in the UK cohort exhibited long-term survival after liver transplantation. In addition, according to the BCLC treatment guidelines, BCLC stage C disease should only be treated with sorafenib or clinical trial therapies using systemic agents, but a high proportion of patients with BCLC stage C disease in both cohorts underwent surgical resection and exhibited long-term survival. Another limitation of the BCLC staging system was that patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 1 were grouped into the BCLC stage C category even in the absence of extra-hepatic disease. In both the UK and HK cohorts, many patients were grouped into BCLC stage C category because of their ECOG performance status of 1. However, these subgroups of patients were potential candidates for an aggressive treatment modality, such as surgery or TACE. Thus, the prognostic performance of the BCLC system may be undermined by the results of the current study.

The current study also demonstrated that the performance of the existing staging systems is strongly influenced by the treatment intent. The overall performance of all three staging systems was suboptimal for the prediction of the OS among the patients who underwent curative treatment compared to those who underwent palliative treatment. This difference is likely because the disease behavior and the aims of the staging systems differ significantly between the curative and palliative treatment subgroups. For patients who are scheduled to undergo curative treatment, the most important aim of a staging system should be the determination of risk for recurrence, thereby predicting long-term survival. On the other hand, for patients with extensive tumors and advanced liver disease who are unsuitable for curative treatment, the primary aim of a staging system should be the accurate prediction of short-term survival so that patients with terminal disease are precluded from complex trial procedures or aggressive treatment<sup>[27]</sup>. The results of the current

study support the concept of separate staging systems to estimate the prognosis of patients undergoing either curative or palliative treatment. For the former, Vauthey *et al.*<sup>[28]</sup> have described the use of a modified TNM system to identify long-term survivors or patients who are at risk of relapse. For patients with advanced disease, our current results demonstrate that the CUPI was the most informative staging system for both cohorts. In particular, the CUPI high-risk subgroup displayed the shortest 3- and 6-month OS rates in the palliative treatment subgroup, regardless of the geographic region. Currently, although most clinical trials of novel systemic agents for HCC require clinical investigators to exclude patients when their median OS is expected to be shorter than 3 months, such a decision involves the subjective and empirical judgment of these clinicians. In fact, recent studies reported that more than 30% of patients may survive longer than 3 months even when they meet the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trials' exclusion criteria<sup>[29]</sup>. Using the CUPI system, clinical investigators could more accurately identify the patients with terminal disease and preclude them from unnecessary trial procedures.

There are several caveats to this study. First, there is significant heterogeneity among the HCC populations in different geographic regions. The current study populations may not be fully representative of patients outside of the UK and HK. This concern is lessened by similar findings presented following recent studies conducted by the US and Asian centers<sup>[8,10]</sup>. Second, the proportion of patients undergoing curative treatment, especially resection and transplantation, was higher in the UK cohort. This difference is likely a result of some patients being diagnosed at an earlier stage due to surveillance in the UK but not in HK. Therefore, extrapolating these results to centers with different proportions of treatment modalities should be performed with caution. Third, both the UK and HK cohorts contained a small proportion of BCLC stage 0/A disease patients. Validation of these results at other centers using a higher proportion of patients with early BCLC stage disease is warranted.

In conclusion, the current study shows that the CUPI is applicable to patients with HCC treated at both western and Asian centers, displaying particular strength in the prognostication of patients with advanced disease. Treatment intent has a significant impact on the performance of the current staging systems, and the BCLC, CLIP, and CUPI systems are suboptimal in the prognostication of patients who undergo curative treatment. We propose that two separate systems are required for patients undergoing either curative or palliative treatment.

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