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Hong Kong Liver Cancer Staging System Is Associated With Better Performance for Hepatocellular Carcinoma

Special Emphasis on Viral Etiology

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Abstract: Hong Kong Liver Cancer (HKLC) staging system was developed for prognostic and treatment evaluation for hepatocellular carcinoma (HCC) but is not externally validated. We aimed to evaluate and compare HKLC system with Barcelona Clínic Liver Cancer (BCLC) staging system. The prognostic performance, discriminatory ability, and efficacy of treatment recommendations were compared between the BCLC and HKLC systems. Significant differences in survival were found across all stages of BCLC and across stages I to IV of HKLC systems ($P < 0.01$). HKLC system was associated with higher homogeneity in prognostic accuracy. The survival was similar between patients treated according to the HKLC or BCLC system ($P = 0.07$). However, more patients were treated according to HKLC recommendations than to BCLC recommendations (57% vs. 47%, $P < 0.001$). In a hypothetical cohort created by random sampling, patients treated according to the HKLC scheme had better survival compared with patients treated according to the BCLC system ($P < 0.001$).

Subgroup analyses between hepatitis B virus (HBV) and hepatitis C virus (HCV)-related HCC were performed. More HCV-related HCC were at earlier BCLC or HKLC stages (both $P < 0.001$). The HKLC system was more informative with greater homogeneity in predicting survival in both HBV and HCV cohorts. However, HKLC treatment recommendations were associated with better long-term survival only in HBV-related HCC but not in HCV-related HCC ($P < 0.001$ and $P = 0.79$, respectively).

In conclusion, we provided external validation of the HKLC system. Compared with the BCLC system, the HKLC system has better prognostic accuracy and therapeutic efficacy in the entire cohort and in HBV-related HCC but not in HCV-related HCC. Due to high heterogeneity among patients of various etiologies, staging and treatment strategies tailored to specific HCC etiology are required.

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Abbreviations: AASLD = American Association for the Study of Liver Diseases, AFP = α-fetoprotein, AIC = Akaike information criterion, ALT = alanine transaminase, AUC = area under receiver operator characteristic curve, BCLC = Barcelona Clínic Liver Cancer, CI = confidence interval, CLIP = Cancer of the Liver Italian Program, EASL = European Association for the Study of the Liver, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HKLC = Hong Kong Liver Cancer, HR = hazard ratio, IQR = interquartile range, MELD = Model for End-stage Liver Disease, RFS = recurrence-free survival, SD = standard deviation, SR = surgical resection, TACE = transarterial chemoembolization, TIS = Taipei Integrated Scoring System.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related mortality worldwide, with more than 700,000 deaths annually.[1] Despite the enormous global impact and scrupulous endeavors to overcome this malignancy, controversies exist in cancer staging and management planning. At least 10 staging systems have been developed to provide treatment and prognostic information for patients with HCC.[2–4] Originally introduced in 1999, the Barcelona Clínic Liver Cancer (BCLC) staging system offers specific treatment recommendations for each of its distinctive stages.[5] The BCLC system is widely used and has been incorporated in the current European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) HCC management guidelines.[6,7] The BCLC system was created based on several small Western cohorts, and has

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Condensed Abstract: We provide external validation for Hong Kong Liver Cancer (HKLC) system and show that HKLC is associated with better prognostic and therapeutic performance compared with Barcelona Clínic Liver Cancer system in all patients and in patients with hepatitis B- but not in hepatitis C-related hepatocellular carcinoma. Staging and treatment algorithms tailored to specific tumor etiologies are needed.
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been criticized for its lack of universal applicability.[8] The Hong Kong Liver Cancer (HKLC) staging system was proposed recently in response to the challenge, and has been shown to achieve better prognostic ability as well as identifying patients for more aggressive treatment.[9] Despite its proven merits in a Hong Kong cohort, the capabilities of the HKLC system in European population have been challenged.[10]

Considerable geographical variations exist in the prevalence of hepatotropic viral infection. Chronic hepatitis B virus (HBV) is endemic in Asia and Africa, while chronic hepatitis C virus (HCV) is the main etiology of HCC in Japan and Western societies.[11,12] Despite attempts to elucidate clinical differences between HBV- and HCV-related HCC, viral factors are still controversial as an independent prognostic predictor.[13] Characterization of HCC based on the etiologies of background liver injury may provide insights into more comprehensive staging and management strategies of HCC.[14]

Currently, the clinical applicability of the HKLC system is uncertain and external validation is still lacking. In addition, to our knowledge, the etiology of underlying liver diseases has not been reported to correlate with HCC staging and treatment algorithm. This study aimed to examine the prognostic accuracy and treatment scheme of the HKLC and BCLC systems in a large HCC cohort. We also assessed possible roles of viral etiologies (HBV and HCV) on the outcomes and prognostic classification in HCC patients.

PATIENTS AND METHODS

Patients

From 2002 to 2013, patients with newly diagnosed HCC admitted to Taipei Veterans General Hospital were retrospectively analyzed. Comprehensive baseline information, including etiologies of underlying liver disease, tumor characteristics, serum biochemistries, and severity of cirrhosis, was recorded. The staging information of the HKLC system was retrospectively determined after a comprehensive chart review. Patients were followed with imaging studies and serum α-fetoprotein (AFP) level every 3–6 months until death or dropout from the follow-up program. Patients receiving liver transplantation were censored at the time of transplantation. The study was approved by the institutional review board of the Taipei Veterans General Hospital and complied with the standards of the Declaration of Helsinki and the current ethical guidelines. Patient consent form was not obtained because of the retrospective nature of this study.

Diagnosis and Definitions

The diagnosis of HCC was confirmed by pathological specimens or according to the criteria from EASL and AASLD HCC management guidelines in force.[6,7,15,16] Total tumor volume and Taipei Integrated Scoring System (TIS) score were calculated based on tumor diameter.[17] Albumin–bilirubin grade was calculated to access the degree of liver dysfunction.[18] Intrahepatic vascular invasion was defined as radiological evidences of vascular invasion in the first-order or smaller branches of portal veins or hepatic veins. Extrahepatic vascular invasion was defined as invasion to main portal trunk or inferior vena cava. HCC patients who were seropositive for hepatitis B surface antigen (HBsAg) while seronegative for anti-HCV antibody and had no history of alcoholism were classified as HBV-related HCC. HCV-related HCC was defined as seropositive for anti-HCV antibody, seronegative for HBsAg, and without history of alcoholism.[13]

TREATMENT

Surgical resection, ablation, and transarterial chemoembolization (TACE) were performed by standard procedures.[19–21] The number of patients receiving sorafenib as the first-line therapy was relatively small (4%) because the drug was reimbursed by the National Health Insurance System in Taiwan only since 2012. Patients were presented to a multidisciplinary HCC board for treatment discussion. Information of therapeutic risks and benefits was comprehensively provided to individual patient. Share decisions were made between patients and clinicians after counseling.

Validation and Prognostic Evaluation of the 2 Staging Systems

To assess prognostic accuracy, the HKLC stage Va was excluded because the survival of these patients was heavily dependent on liver transplantation.[9] Furthermore, only the 5 HKLC main stages were used to compare with the 5 stages of BCLC so that the numbers of parameters were identical. The overall survival was examined by the Kaplan–Meier method with a log-rank test. The prognostic accuracy of the BCLC and HKLC staging systems was compared. Akaike information criterion (AIC) was obtained to reveal how the staging systems correlated with patient survival.[22] Homogeneity was measured by Wald χ^2 generated by the parametric survival analysis.[23] To evaluate the discriminatory abilities for predicting survival at 1-, 3-, and 5-year intervals, the area under the receiver operator characteristic curve (AUC) was calculated and compared for each staging system.[24] In calculating AUC, patients censored before 1, 3, and 5 years were excluded.[25]

Effectiveness of Treatment Algorithms

The efficacy of treatment algorithms of BCLC and HKLC systems was evaluated by comparing the patients who were treated according to treatment recommendations of each BCLC or HKLC stage. Furthermore, the ability of BCLC and HKLC treatment recommendations was also evaluated by creating a hypothetical cohort. Patients who received the recommended treatment(s) according to each stage were automatically enrolled in the hypothetical cohort. Patients who did not receive the recommended treatment(s) were substituted by random sampling from patients with the same BCLC/HKLC dual-classification cohort receiving the recommended treatment(s), assuming patients of the same BCLC/HKLC dual classification shared a similar prognosis.[9] This stratified sampling ensured that the percentages of each BCLC and HKLC stages remained identical to the original cohort. The hypothetical cohorts for HBV-related HCC and HCV-related HCC were also created.

Statistics

The Mann–Whitney *U* test was used to compare continuous variables. The 2-tailed χ^2 test and Fisher exact test were employed to compare categorical data. For survival analysis, the proportionality assumption was assessed graphically and by a test based on Schoenfeld residuals. When proportionality was rejected, parametric survival analysis was employed.[26] Statistical analyses were conducted with IBM SPSS version 21 for Windows (IBM, Armonk, NY) and SAS version 9.4 for Windows (SAS Institute Inc., Cary, NC). Statistical significance was set as P value less than 0.05 in a 2-tailed test.

RESULTS

Characteristics and Survival of Study Patients

During the study period, a total of 3,182 patients were identified. The majority of the patients were male (77%) with a median age of 65 years (Table 1). After excluding mixed etiologies of underlying liver diseases, hepatitis B and C were found to be the only cause of liver disease in 1292 (41%) and 726 (23%) of patients, respectively. About 62% of patients had single tumor, and nearly 44% of patients had tumor diameter >5 cm. The median total tumor volume was 48 cm^3. Intrahepatic and extrahepatic vascular invasions were noted in 418 (13%) and 388 (12%) of patients, respectively.

Briefly, resection, ablation, TACE, and systemic therapies were performed in 29%, 19%, 28%, and 10% of the patients, respectively. The median follow-up duration of the entire cohort was 17 months. Significant differences in survival distributions were found across all stages of BCLC and between stages I and IV of HKLC systems (all $P < 0.01$ except between HKLC stage IV and stage V, Figure 1). The numbers and survivals of each BCLC or HKLC stage are shown in Table 2.

Characteristics and Survival Between HBV- and HCV-Related HCC

The comparison of clinical characteristics between HBV- and HCV-related HCC is shown in Table 3. Patients with HBV-related HCC had higher rates of vascular invasion compared with patients with HCV-related HCC ($P < 0.01$). Patients with HBV-related HCC were more likely to receive resection but were less likely to undergo ablation or TACE (all $P < 0.001$). The overall survival was similar between HBV and HCV cohorts ($P = 0.53$).

From staging perspectives, more patients with HCV-related HCC had earlier stages of tumor (BCLC stage 0 or A, and HKLC stage I or II, both $P < 0.001$). The treatments the patients received also differed between HBV and HCV cohorts, both in earlier or later stages of diseases (all $P < 0.01$). HBV-related HCC was associated with better overall survival compared with HCV-related HCC in patients with BCLC stage 0 or A HCC ($P = 0.008$). There was a trend toward better survival in HBV patients with HKLC stage I or II HCC compared with HCV patients of the same HKLC stages ($P = 0.05$). Otherwise, the overall survival was similar between HBV and HCV cohorts in later stages of HCC (BCLC stages B, C, or D, and HKLC stages III, IV, or V).

Prognostic Performance of BCLC and HKLC Staging Systems

The prognostic performance of BCLC and HKLC staging systems was evaluated with homogeneity and AIC methods (Table 4). In all patient cohorts, HKLC offered higher homogeneity (Wald χ^2) and lower AIC value compared with BCLC. In both HBV-related HCC and HCV-related HCC cohorts, the HKLC system was still consistently associated with higher homogeneity and lower AIC value compared with the BCLC system.

The discriminatory abilities for mortality at 1-, 3-, and 5-year intervals of BCLC and HKLC systems were validated by the AUC method (Table 5). The discriminatory ability was higher for HKLC compared with BCLC at 1-year and 3-year intervals (both $P < 0.05$). In the subgroup analysis for HBV-related HCC, the discriminatory ability was also higher for

TABLE 1. Demographics and Staging Parameters of HCC Cohort

Variables	All Patients (n = 3182)
Age (yr, median [IQR])	65 [55–75]
Male, n (%)	2440 (77)
Etiologies of liver diseases (HBV/HCV/alcohol/mixed/cryptogenic), n (%)	1292/726/152/536/476 (41/23/5/16/15)
Performance status (0/1/2/3/4), n (%)	1806/704/336/225/111 (57/22/11/7/3)
α-fetoprotein (ng/mL, median [IQR])	46 [9–799]
Child–Turcotte–Pugh score (mean ± SD)	6.1 ± 1.6
Albumin–bilirubin grade (1/2/3), n (%)	1199/1670/313 (38/52/10)
MELD score (mean ± SD)	9.9 ± 4.2
Tumor nodularities (1/2/3/ > 3), n (%)	1973/545/262/402 (62/17/8/13)
Maximal tumor diameter (≤2/2–5/ > 5 cm), n (%)	573/1216/1393 (18/38/44)
Total tumor volume (cm^3, median [IQR])	48 [9–382]
Vascular invasion (negative/intrahepatic/extrahepatic invasion), n (%)	2376/418/388 (75/13/12)
Extrahepatic vascular invasion and/or metastasis, n (%)	579 (18)
BCLC stages (0/A/B/C/D), n (%)	265/736/503/1282/396 (8/23/16/41/12)
HKLC stages (I/IIa/IIb/IIIa/IIIb/IVa/IVb/Va/Vb), n (%)	1001/331/531/86/235/181/115/170/532 (31/10/17/3/7/6/4/5/17)
CLIP score (0/1/2/3/ > 3), n (%)	969/873/482/364/494 (31/27/15/11/16)
TIS score (0/1/2/3/ > 3), n (%)	1125/706/386/382/583 (35/22/12/12/19)
Treatment modalities (resection/ablation/TACE/systemic therapy/others)	911/604/881/337/449 (29/19/28/10/14)
Median follow-up duration (months, median [IQR])	17 [5–44]

BCLC = Barcelona Clínic Liver Cancer, CLIP = Cancer of the Liver Italian Program, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HKLC = Hong Kong Liver Cancer, IQR = interquartile range, MELD = Model for End-stage Liver Disease, SD = standard deviation, TACE = transarterial chemoembolization, TIS = Taipei Integrated Scoring System.

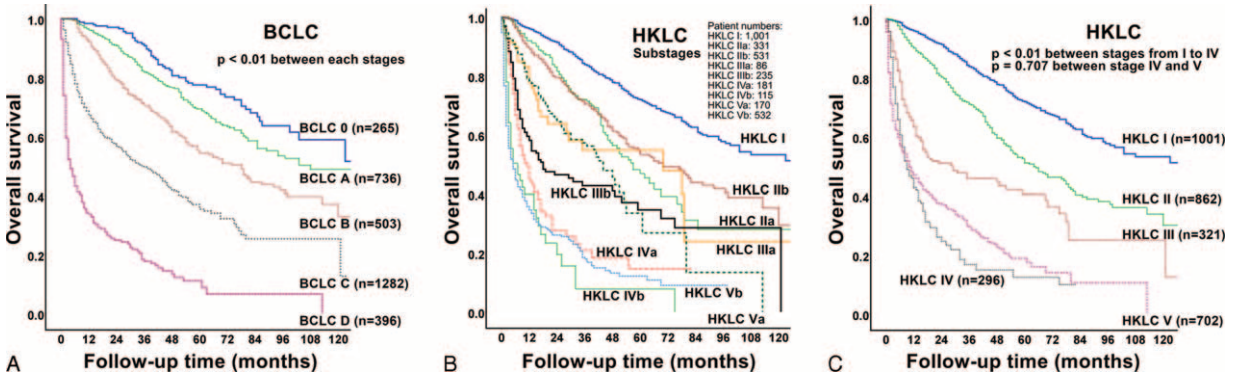

FIGURE 1. Comparison of survival distributions among different Barcelona Clínic Liver Cancer (BCLC) and Hong Kong Liver Cancer (HKLC) stages. A, There are statistically significant differences in survival across all BCLC stages from 0 to D (all $P < 0.01$). B, Distributions of survival among HKLC substages. C, Distributions of survival among HKLC main stages. There are significant survival differences across HKLC main stages from I to IV ($P < 0.01$).

HKLC compared with BCLC at 1-year ($P < 0.001$). The AUC was similar between BCLC and HKLC systems at other time points and for patients with HCV-related HCC.

Therapeutic Efficacy of BCLC and HKLC Staging Systems

The distributions of treatments the patients received according to each BCLC or HKLC stage are shown in Table 6. More patients received recommended managements according to the HKLC scheme than according to the BCLC scheme (57% vs. 47%, $P < 0.001$). The survival was similar for patients following the BCLC or HKLC treatment suggestions ($P = 0.07$, Figure 2). Patients not treated according to the BCLC scheme had better prognosis compared with patients not treated according to the HKLC scheme ($P = 0.001$)

Aside from comparing the original data, a hypothetical cohort was also created. This hypothetical analysis showed that patients receiving the suggested treatments according to the HKLC system had better overall survival compared with patients treated according to the BCLC scheme (Figure 3A, $P < 0.001$). The median overall survival for the hypothetical BCLC and HKLC cohorts was 12 and 17 months, respectively.

In patients with HBV-related HCC, the HKLC treatment scheme was associated with improved survival compared with the BCLC system (Figure 3B, $P < 0.001$). For HCV-related patients, the therapeutic efficacy between BCLC and HKLC treatment suggestions was similar (Figure 3C, $P = 0.79$).

According to BCLC and HKLC schemes, concordance on treatment suggestions occurred in BCLC-0/HKLC-I, BCLC-A/HKLC-I, BCLC-A/HKLC-IIa, BCLC-B/HKLC-III, BCLC-C/HKLC-IV, and BCLC-D/HKLC-V dual-classification cohorts. A total of 1421 (45%) patients had discordant treatment recommendations between BCLC and HKLC systems (Figure 4). Subgroup analysis showed that the distribution of BCLC/HKLC dual classifications differed between patients with HBV- and HCV-related HCC. Fewer patients in the HCV cohort (283 patients, 39%) had discordant treatment suggestions from the BCLC and HKLC staging systems compared with patients in the HBV cohort (582 patients, 45%, $P = 0.009$).

DISCUSSION

There are increasing debates regarding the optimal staging and treatment selection for HCC patients. The HKLC system

TABLE 2. Survival in Relation to BCLC or HKLC Staging Systems in All Patients

Staging Systems	Number (%)	Median Survival (Mo)	Kaplan–Meier Log-Rank *P* Value Between Adjacent Stages	
BCLC stages				
0	265 (8)	57.5		
A	736 (23)	39.0	0 vs. A	0.008
B	503 (16)	29.0	A vs. B	<0.001
C	1282 (40)	7.0	B vs. C	<0.001
D	396 (13)	2.0	C vs. D	<0.001
HKLC stages				
I	1001 (32)	43.0		
II	862 (27)	27.5	I vs. II	<0.001
III	321 (10)	9.0	II vs. III	<0.001
IV	296 (9)	4.0	III vs. IV	<0.001
V	702 (22)	2.0	IV vs. V	0.72

BCLC = Barcelona Clínic Liver Cancer, CI = confidence intervals, HKLC = Hong Kong Liver Cancer, HR = hazard ratio.

TABLE 3. Comparison of BCLC/HKLC Stages and Overall Survival Between HBV- and HCV-Related HCC

Variables	HBV-Related HCC	HCV-Related HCC	*P* Value
Staging parameters			
Patient numbers	1292 (41)	726 (23)	
All vascular invasion, n (%)	344 (27)	117 (16)	<0.001
Extrahepatic vascular invasion, n (%)	155 (12)	55 (8)	0.002
Extrahepatic vascular invasion/metastasis, n (%)	237 (18)	83 (11)	<0.001
Performance status (0/1/2–4), n (%)	802/261/229 (62/20/18)	457/135/134 (63/19/18)	0.67
Child–Turcotte–Pugh class (A/B/C), n (%)	979/247/66 (76/19/5)	552/152/22 (76/21/3)	0.07
Albumin–bilirubin grade (1/2/3), n (%)	553/620/119 (43/48/9)	233/434/59 (32/60/8)	<0.001
BCLC stages (0/A/B/C/D), %	9/23/18/40/10	12/31/13/33/11	< 0.001
HKLC stages (I/II/III/IV/V), %	33/27/11/10/19	43/26/7/5/19	<0.001
Treatment (SR/ablation/TACE/others), n (%)	449/225/311/307 (35/17/24/24)	170/183/241/132 (24/25/33/18)	<0.001
Overall survival (median, [IQR])	19 [5–49]	22 [7–49]	0.53
BCLC 0/A patients			
BCLC stage 0–A, n (%)	411 (32)	315 (43)	<0.001
Treatment (SR/ablation/TACE/others), n (%)	196/145/58/7 (48/36/14/2)	106/129/74/4 (34/41/24/1)	<0.001
Overall survival (median, [IQR])	43 [21–75]	40 [18–67]	0.01
BCLC B/C/D patients			
BCLC stage B–D, n (%)	881 (68)	411 (57)	<0.001
Treatment (SR/ablation/TACE/others), n (%)	253/80/253/300 (29/8/29/34)	64/54/167/128 (16/13/40/31)	<0.001
Overall survival (median, [IQR])	11 [3–33]	13 [3–29]	0.71
HKLC I/II patients			
HKLC stage I–II, n (%)	768 (60)	498 (69)	<0.001
Treatment (SR/ablation/TACE/others), n (%)	376/182/181/29 (49/24/23/4)	155/161/161/21 (31/32/32/5)	<0.001
Overall survival (median, [IQR])	33 [17–68]	32 [15–60]	0.05
HKLC III/IV/V patients			
HKLC stage III–V, n (%)	524 (40)	228 (31)	<0.001
Treatment (SR/ablation/TACE/others), n (%)	73/43/130/278 (14/8/25/53)	15/22/80/111 (7/9/35/49)	0.003
Overall survival (median, [IQR])	5 [2–15]	6 [2–18]	0.40

BCLC = Barcelona Clínic Liver Cancer, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HKLC = Hong Kong Liver Cancer, IQR = interquartile range, SR = surgical resection, TACE = transarterial chemoembolization.

was proposed to be a system of better prognostic accuracy as well as superior treatment allocation but is lack of external validation. Our study utilizes a large HCC cohort and provides evidence supporting that HKLC may offer better prognostic ability compared with the BCLC system. Moreover, patients treated according to the HKLC recommendations had significantly better long-term survival compared with patients treated by the BCLC scheme. In subgroup analysis, the percentages of patients in each BCLC or HKLC stage differed between patients with HBV- or HCV-related HCC. For patients with HBV-related HCC, the HKLC scheme was consistently associated with better prognostication as well as superior treatment efficacy. However, for patients with HCV-related HCC, the HKLC system has a similar discriminatory ability of mortality compared with the BCLC system. Our results confirm the superiority of HKLC systems in terms of both prognostic accuracy and treatment efficacy in general HCC population, and point out the crucial role of viral etiology in cancer staging and treatment algorithm.

TABLE 4. Prognostic Performance Evaluation of BCLC and HKLC Staging Systems

Patient Groups	Homogeneity (Wald χ^2)	Akaike Information Criterion
All patients (n = 3012)		
BCLC	920.995	5582.845
HKLC	1370.156	5334.156
Hepatitis B patients (n = 1222)		
BCLC	375.187	2218.055
HKLC	608.025	2090.452
Hepatitis C patients (n = 688)		
BCLC	174.604	1161.814
HKLC	213.825	1141.855

HKLC stage Va was excluded in the analysis. For evaluation of BCLC staging system, 5 BCLC stages (0, A, B, C, and D) were used. For HKLC staging system, the 5 main HKLC stages (I, IIa + IIb, IIIa + IIIb, IVa + IVb, and Vb) were evaluated. BCLC = Barcelona Clínic Liver Cancer, HKLC = Hong Kong Liver Cancer.

Using Kaplan–Meier survival analyses, we showed that both the BCLC and HKLC systems are capable of stratifying patients into distinctive prognostic groups. In parametric survival analyses, the HKLC staging system was associated with a higher homogeneity and a lower AIC level. When the staging systems were compared by the AUC method, the HKLC system was also found to have higher discriminatory ability for mortality at 1- and 3-year intervals. Consistent with the original HKLC reports, our results supported that the HKLC system was associated with a better prognostic accuracy compared with the BCLC system.

TABLE 5. Discriminatory Ability for Death at 1, 3, and 5 Yr of BCLC and HKLC Staging Systems

	1-Yr Mortality			3-Yr Mortality			5-Yr Mortality		
	AUC	95% CI	*P* Value	AUC	95% CI	*P* Value	AUC	95% CI	*P* Value
All patients (n = 3012)									
BCLC	0.840	0.824–0.857	0.001	0.809	0.790–0.828	0.03	0.817	0.797–0.837	0.54
HKLC	0.867	0.845–0.885		0.822	0.803–0.840		0.813	0.794–0.833	
Hepatitis B patients (n = 1222)									
BCLC	0.843	0.816–0.869	<0.001	0.815	0.786–0.844	0.14	0.819	0.788–0.845	0.70
HKLC	0.880	0.853–0.908		0.828	0.799–0.858		0.816	0.785–0.846	
Hepatitis C patients (n = 688)									
BCLC	0.834	0.790–0.878	0.21	0.784	0.740–0.827	0.15	0.787	0.742–0.832	0.17
HKLC	0.818	0.768–0.869		0.764	0.718–0.809		0.766	0.723–0.809	

Patients with HKLC stage Va and patients who were censored prior to 1-, 3-, and 5-yr were excluded. For evaluation of BCLC staging system, 5 BCLC stages (0, A, B, C, and D) were used. For HKLC staging system, the 5 main HKLC stages (I, IIa + IIb, IIIa + IIIb, IVa + IVb, and Vb) were evaluated. AUC = area under receiver operator characteristic curve, BCLC = Barcelona Clínic Liver Cancer, CI = confidence interval, HKLC = Hong Kong Liver Cancer.

Like many staging systems, the BCLC system was constructed by retrospective cohort studies and is anchored on tumoral factors, liver functional reserve, and performance status. Several reasons may explain why the HKLC system has a superior prognostic accuracy compared with the BCLC system. First, evidence revealed that patients with only mild tumor-related symptoms had better prognosis than patients with debilitating symptoms and could benefit from aggressive therapies.[27] However, in the BCLC system, but not in the HKLC system, patients with mild symptoms would be classified as at least advanced HCC. Second, patients with HCC invading main portal trunk and patients with tumor involving smaller vascular branches had apparently different prognosis.[28] The HKLC system utilizes this difference while the BCLC system does not. Third, the HKLC system defines tumor burden by composites of tumor size, number of nodules, and intrahepatic vascular invasion. The incorporation of more information may result in better predictive abilities. Finally, with sophisticated statistical analyses, time-dependent relative points of each factor were used in constructing the prognostic scheme of the HKLC system. The resultant HKLC staging system, as validated in our cohort, is therefore a classification scheme of superior prognostic accuracy compared with the BCLC staging system.

A more important feature of the HKLC system is its ability to identify patients who are suitable for more aggressive treatments. The improvements in procedural techniques, patient

TABLE 6. First Treatment Modality for Hepatocellular Carcinoma Stratified by BCLC or HKLC Stages

Staging System	Resection	Ablation	TACE	Transplantation	Systemic	Supportive Care	Subtotal	Receiving Recommended Treatments (%)
BCLC Stages								
0	101	134	28	1	0	1	265	89%
A	311	255	157	0	1	12	736	77%
B	208	37	227	1	12	18	503	45%
C	277	144	413	4	250	194	1282	20%
D	14	34	56	6	60	226	396	57%
							3182	47%
HKLC Stages								
I	432	357	194	1	2	15	1001	79%
IIa	87	121	104	2	4	13	331	63%
IIb	245	25	225	0	18	18	531	46%
IIIa	22	8	30	1	7	18	86	35%
IIIb	51	0	113	1	42	28	235	48%
IVa	21	6	45	0	75	34	181	41%
IVb	3	5	13	1	57	36	115	80%
Va	19	69	41	5	2	34	170	3%
Vb	31	13	116	1	116	255	532	48%
							3182	57%

BCLC = Barcelona Clínic Liver Cancer, HKLC = Hong Kong Liver Cancer, TACE = transarterial chemoembolization.

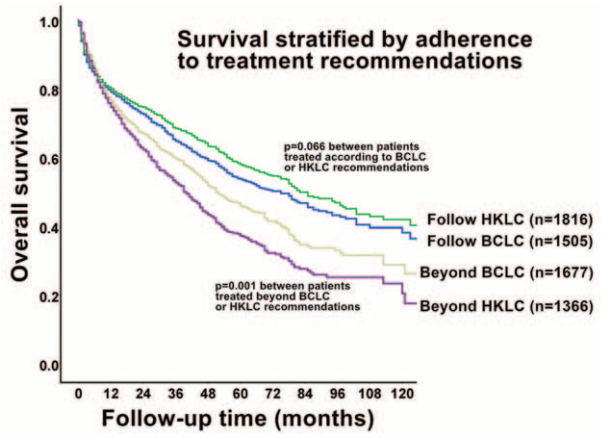

FIGURE 2. Kaplan–Meier survival curves stratified by adherence to the Barcelona Clínic Liver Cancer (BCLC) or the Hong Kong Liver Cancer (HKLC) staging systems. Patients treated according to BCLC or HKLC suggestions had similar survival ($P = 0.07$). Patients not treated according to BCLC suggestions had better survival compared with patients not treated according to HKLC suggestions ($P = 0.001$).

selection, and safety profiles in the past decade allow more patients to receive resection, ablation, or TACE.[20,29,30] The introduction of targeted therapy with sorafenib also helped to improve survival for patients with advanced disease. Designed more than 15 years ago, the BCLC system does not incorporate these changes.[31] It is apparent that patients with BCLC intermediate or advanced stage HCC could be classified as HKLC stage I or stage II, in which resection, ablation, or liver transplantation is suggested.[32] The great discrepancies in treatment suggestions are illustrated in our cohort, where nearly half (45%) of the patients had different treatment suggestions from the BCLC and HKLC systems.

It is unlikely to compare the therapeutic efficacy and survival for patients treated according to BCLC or HKLC recommendations in a prospective, randomized-controlled trial. In this retrospective analysis, we first compared the survival of patients who are treated according to BCLC or HKLC recommendations. The survival was similar between patients treated according to the BCLC or HKLC scheme. However, more patients are treated according to the HKLC system than the BCLC system. These findings suggest that the HKLC system more closely resembles real-world experiences of HCC management in Taiwan. The findings are also indirect evidences supporting superiority of HKLC treatment recommendations. We further performed analysis in a hypothetical cohort by random sampling as proposed by Yau et al in the original HKLC report.[9] In our study, patients in the hypothetical cohort treated according to HKLC recommendations had significantly better survival compared with patients treated according to the BCLC scheme. With 5 months prolongation of median survival, we confirm that the HKLC treatment recommendations are superior to the BCLC system in terms of long-term survival in a Taiwan cohort.

Staging systems and treatment recommendations for HCC greatly differ around the globe.[33–35] Despite the tumor etiologies being diverse according to geographical areas, the underlying viral etiologies have never been incorporated into any staging system.[36] Interestingly, compared with HCV-related HCC, the survival rates were better for HBV-related HCC after resection or liver transplantation.[37] Patients without evidence of HBV or HCV infection had lower risks of tumor recurrence compared with patients infected with hepatotropic viruses.[14] Patients with cryptogenic HCC were usually diagnosed at later stages, but the survival was similar compared with viral or alcoholic HCC patients.[38] Even in the same clinical stage, HBV-related HCC had better outcomes compared with HCV-related HCC.[13] We analyzed our patients according to viral etiologies to examine whether the global divergences in HCC management may stem from etiological factors. In this study, despite that more HCV-related HCC were at earlier stages and the criteria for resection did not consider viral factors, more HBV-related HCC patients received surgical resection as the primary treatment. In earlier stages of HCC, the HBV cohort

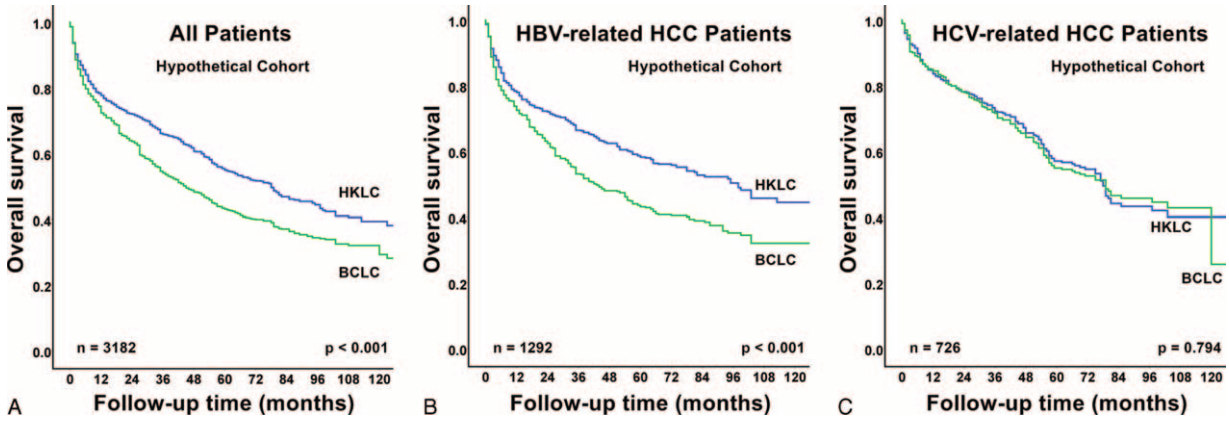

FIGURE 3. Hypothetical Kaplan–Meier survival curves of the Barcelona Clínic Liver Cancer (BCLC) and Hong Kong Liver Cancer (HKLC) staging systems in all patients and in patients with hepatitis B virus (HBV) and hepatitis C virus (HCV)-related hepatocellular carcinoma (HCC). The survival data of patients not treated according to stage recommendations were replaced by random sampling from patients of the same BCLC/HKLC dual classification receiving the recommended treatments. A, Patients treated according to the HKLC recommendations had significantly better overall survival compared with patients treated under BCLC recommendations ($P < 0.001$). The median survival was 17 and 12 mo for the hypothetical HKLC and BCLC groups, respectively. B, For HBV-related HCC, the overall survival was better if patients were treated according to HKLC recommendations instead of BCLC recommendations ($P < 0.001$). C, The overall survival was similar for HCV-related HCC patients treated by the suggested treatments from HKLC or BCLC systems ($P = 0.79$).

All HCC patients	HKLC I	HKLC IIa	HKLC IIb	HKLC III	HKLC IV	HKLC V
BCLC 0/A	916 (28.8%)	85 (2.7%)				
BCLC B	85 (2.7%)	7 (0.2%)	343 (10.8%)	68 (2.2%)		
BCLC C		239 (7.5%)	188 (5.9%)	253 (8.0%)	296 (9.3%)	306 (9.6%)
BCLC D						396 (12.3%)

HBV-related HCC	HKLC I	HKLC IIa	HKLC IIb	HKLC III	HKLC IV	HKLC V
BCLC 0/A	*380 (29.3%)	31 (2.4%)				
BCLC B	46 (3.6%)	1 (0.1%)	*161 (12.5%)	32 (2.5%)		
BCLC C		*68 (5.3%)	81 (6.3%)	112 (8.7%)	*133 (10.3%)	113 (8.7%)
BCLC D						134 (10.3%)

HCV-related HCC	HKLC I	HKLC IIa	HKLC IIb	HKLC III	HKLC IV	HKLC V
BCLC 0/A	*285 (39.2%)	30 (4.1%)				
BCLC B	23 (3.2%)	4 (0.6%)	*53 (7.3%)	15 (2.1%)		
BCLC C		*69 (9.5%)	34 (4.7%)	39 (5.4%)	*35 (4.8%)	61 (8.4%)
BCLC D						78 (10.7%)

Shaded cells indicate agreement on suggested treatments between HKLC and BCLC staging systems.
White cells indicate disagreement on treatment suggestions between HKLC and BCLC staging systems.
Asterisks (*) represent statistical significant differences in percentages between HBV and HCV cohort ($p<0.05$).

FIGURE 4. Numbers of patients in cross-classification table by the Barcelona Clínic Liver Cancer (BCLC) and Hong Kong Liver Cancer (HKLC) staging systems in hepatitis B virus (HBV) and hepatitis C virus (HCV)-related hepatocellular carcinoma (HCC). In total, 45% of patients had disagreement in treatment recommendations between HKLC and BCLC staging systems. More patients (45%) in the HBV cohort had disagreement in treatment recommendations between HKLC and BCLC staging systems than in the HCV cohort (39%, $P = 0.009$).

had better long-term survival compared with the HCV cohort. Finally, the distributions of BCLC and HKLC stages differed in HBV and HCV subsets, and more patients in the HBV cohort had discordance in treatment suggestions between the HKLC and BCLC schemes. The composite results of these complex, interwoven factors are that the HKLC treatment suggestions were associated with better clinical outcomes only in HBV-related HCC patients but not in the HCV-related hypothetical HCC cohort.

Recently, intense debates emerged among HCC specialists from the Eastern and Western countries on the optimal staging and management of HCC.[33,34] A brief report from France where hepatitis C and alcoholism accounted for two-thirds of their HCC patients showed that the HKLC system was not associated with better prognostic and therapeutic abilities compared with the BCLC system.[10] Although our results help explain that the discrepancies were partly due to etiological factors, it is still interesting to know whether if the tumor and the diseased liver behave or respond to treatment differently between HBV and HCV patients.[32] As an integral part of both BCLC and HKLC systems, the Child–Turcotte–Pugh classification may not be sensitive enough, especially when the liver function is still well preserved.[39] The ongoing inflammation with chronic HCV infection may also affect the oncogenesis and prognosis of HCC patients.[40] Altogether, the clinical heterogeneities among HBV- and HCV-related HCC and the resultant differential performance of the HKLC system imply that HCC of different etiologies may deserve distinct staging and treatment algorithms.

This study has some limitations. First, nonviral etiologies for HCC such as nonalcoholic steatohepatitis are rapidly increasing worldwide. Further studies are needed to evaluate the impact of these etiologies on staging and management of HCC. Second, liver transplantation remains an integral part in the management for HCC but could not be assessed adequately in this study due to scarcity of donors in Taiwan. Finally, HCC is a diverse disease with great heterogeneity in its etiology, presentation, and clinical practice around the world. Our data require validations by different study groups from other geographical areas.

In conclusion, our results validate the prognostic ability and treatment recommendations of the newly proposed HKLC staging system. Moreover, the HKLC system is superior to the BCLC system in terms of both outcome prediction and treatment allocation in patients with HBV-related HCC but not in HCV-related HCC. Due to intrinsic heterogeneity among HCC patients of various etiologies, staging strategy and treatment algorithm tailored to specific tumor etiologies are needed.

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