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Assessment of the Hong Kong Liver Cancer Staging System in Europe

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Abbreviations. HCC: Hepatocellular carcinoma, HBV: Hepatitis B virus, HCV: Hepatitis C virus, ASH: alcoholic steatohepatitis, NASH: nonalcoholic steatohepatitis, BCLC: Barcelona Clinic Liver Cancer, EASL: European Association for the Study of the Liver, AASLD: American Association for the Study of Liver Diseases, TACE: trans-arterial chemoembolization, HKLC: Hong Kong Liver Cancer, ECOG PS: Eastern Cooperative Oncology Group performance status, BIC: Bayesian Information Criterion, EORTC: European Organization for Research and Treatment of Cancer, OS: overall survival

Conflict of interest

None to declare

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Background & Aims: European and American guidelines have endorsed the Barcelona Clinic Liver Cancer (BCLC) staging system. The aim of this study was to assess the performance of the recently developed Hong Kong Liver Cancer (HKLC) classification as a staging system for hepatocellular carcinoma (HCC) in Europe.

Methods: We used a pooled set of 1693 HCC patients combining three prospective European cohorts. Discrimination ability between the nine substages and five stages of the HKLC classification system was assessed.

To evaluate the predictive power of the HKLC and BCLC staging systems on overall survival, Nagelkerke pseudo R2, Bayesian Information Criterion and Harrell's concordance index were calculated. The number of patients who would benefit from a curative therapy was assessed for both staging system.

Results: The HKLC classification in nine substages shows suboptimal discrimination between the staging groups. The classification in five stages shows better discrimination between groups. However, the BCLC classification performs better than the HKLC classification in the ability to predict OS. The HKLC treatment algorithm tags significantly more patients to curative therapy than the BCLC.

Conclusions: The BCLC staging system performs better for European patients than the HKLC staging system in predicting OS. Twice more patients are eligible for a curative therapy with the HKLC algorithm, whether this translates in survival benefit remains to be investigated.

Key points

- Three European cohorts from three different countries have been pooled to assess the Hong-Kong Liver Cancer (HKLC) staging system
- While the HKLC 9-stages classification shows suboptimal stage differentiation, the HKLC 5-stages classification shows good discrimination between groups
- The Barcelona Clinic Liver Cancer (BCLC) staging system performs better than the HKLC classification to predict the overall survival
- The HKLC treatment algorithm tags significantly more patients to curative therapies than the BCLC

INTRODUCTION

With a worldwide incidence of 782,000 new cases, hepatocellular carcinoma (HCC) is the fifth most common cancer type in men and the ninth in women, and the second most common cause of cancer-related death.[1] Most common causes for developing HCC are chronic infection with hepatitis B virus (HBV), hepatitis C virus (HCV), alcoholic steatohepatitis (ASH) and nonalcoholic steatohepatitis (NASH). HCC presents a geographical pattern, with more than 85% of all worldwide cases in East Asia, sub-Saharan Africa and Melanesia. In these regions, HBV prevalence is high and is therefore the most common cause for HCC. In Western countries (Europe and the United States), HCV infections, ASH and NASH play an important role in the development of HCC.[1]

The classical staging system based on TNM is not used for HCC. The TNM classification does not consider information regarding the liver function or the health status of the patient. Several HCC-specific staging systems have been developed.[2], [3], [4], [5], [6], [7], [8]. The Barcelona Clinic Liver Cancer (BCLC) staging system is the most accepted and has been endorsed by the European Association for the Study of the Liver (EASL) and the American Association for the Study of the Liver Diseases (AASLD). It presents the appealing feature of linking specific stages with treatment options. Originally developed for cirrhotic patients[4], the authors of this staging system suggested lately that the treatment of HCC in a non-cirrhotic liver should follow the same principles, although the efficacy and impact on outcome are less predictable.[9] Nevertheless, the BCLC system has been developed in Europe, and may be less adapted for regions where HBV is the predominant

etiology for HCC. However, it has been argued that the BCLC treatment algorithm might be too conservative. Some studies showed a better overall survival (OS) for patients who received surgical resection against those who received trans-arterial chemoembolisation (TACE) for intermediate HCC.[10], [11] In fact, the BCLC B stage (intermediate HCC) assembles a heterogeneous group of patients. Consequently, a substaging of BCLC B has been proposed [12], with alternative therapies such as radioembolisation[13],[14] or sorafenib[15] suggested for selected patients in this stage.

Recently, the Hong Kong Liver Cancer (HKLC) reported a new staging system, which, like the BCLC, links HCC stages to treatment options.[16] Based on a large cohort of patients treated in the same centre and essentially with chronic hepatitis B as their underlying liver disease, this classification showed interesting features. It was reported to be a better predictor of survival than the BCLC system in the cohort studied. Furthermore, patients staged BCLC B and HKLC II had a survival probability of 52% at 5 years if they underwent surgical resection as first treatment, compared with a survival probability of 18.7% at 5 years if they received first-line TACE. This algorithm expands the scope of surgical resection.

Assessment of the HKLC staging system outside of Asia is essential. In this study, we applied the HKLC staging system to pooled data from three European prospective cohorts of patients with HCC. The results highlight the differences with the BCLC algorithm.

PATIENTS AND METHODS

For this study, we combined HCC cohorts that were assessed in three different European centres: the cohort from Clinica Universidad de Navarra, Spain; the cohort from Newcastle Hospitals, UK; and the cohort from University Hospital Bern, Switzerland with a total of 1693 patients. The diagnosis of HCC was established following the EASL clinical practice guidelines.[1] All patients older than 18 years were invited to participate and standardised prospective information was collected. In Pamplona, patient information was collected in line with local hospitals and ethics committee (Comité Ético de Investigación, Clínica Universitaria de Navarra, Pamplona, Spain) guidelines and approval. In Newcastle, patient information was collected as part of an audit approved by the Newcastle upon Tyne Hospitals NHS Fundation Trust and shared in an anonymised form. In Bern, patient information collection was approved by local ethics committee (Kantonale Ethikkommission Bern, Bern, Switzerland). All enrolled patients signed an informed consent. The following variables were documented: tumour status (size, number of nodules), presence of vascular invasion, existence of metastases, BCLC classification, Child-Pugh grade and its variables (albumin, bilirubin, prothrombin time, ascites and encephalopathy), Eastern Cooperative Oncology Group performance status (ECOG PS), comorbidity, etiology and treatment. The HKLC classification was applied to each patient using ECOG PS, Child-Pugh grade, presence or absence of extrahepatic metastasis, and tumour status. The latter was defined by the size of the tumour, the number of nodules, and the presence or absence of intrahepatic vascular invasion.

OS was defined as the time from the date of first diagnosis of HCC to the time of death, last follow-up evaluation or the date of data censoring. Cumulative survival rates were calculated by the Kaplan–Meier method, and survival curves were compared using the log-rank test. Cox proportional hazards regression, with each staging system as a covariate, was used to estimate Nagelkerke pseudo R2 to determine the percentage variance of the predicted OS (i.e. to assess prediction accuracy) by each model.[17] In order to compare the models, we calculated the Bayesian Information Criterion (BIC) for each model and calculated the differences between the two BIC.[18]. The Harrell's concordance index was also calculated for each model[19]. In order to compare the characteristics of the three cohorts and the hypothetical number of patients undergoing either curative or palliative therapy according both treatment algorithms, we used the Pearson chi-square test. All analyses were conducted using R version 3.1.1 [20], and a p value of less than 0.05 was considered statistically significant.

RESULTS

A total of 1575 eligible adult HCC patients were included (Spanish cohort, n=738; UK cohort, n=631 and Swiss cohort n=206). The clinical and tumour burden characteristics of these patients are shown in Table 1. The median (range) age at presentation was 65 (18–92) years, and the majority (82.5%) of patients were male. Etiology of HCC was ASH for 483 patients (30.7%), HCV for 450 patients (28.6%), NASH for 209 patients (13.3%), HBV for 161 patients (10.2%) and hemochromatosis for 63 patients (4.0%). Seventy-five percent of the patients had a cirrhotic liver, among them, 58% of the cirrhotic

patients were Child-Pugh A, 29.5% Child-Pugh B and 12.5% Child-Pugh C. Forty-five percent of patients had a solitary lesion, 27.1% had 2–3 lesions and 29.9% >3 lesions. The size of the biggest nodule was ≤2 cm in 12.4% of patients, >2 to ≤5 cm in 43.8% and >5 cm in 43.8%. Treatment details according to BCLC and HKLC stages are detailed in Supplementary Tables 1 and 2 and the median overall survival according to BCLC stages and treatment options are detailed in Supplementary Table 3.

Performance as a staging system

When applied to our patients, the 9-stages HKLC staging system estimated Kaplan–Meier OS curves were not clearly distinct from each other (Figure 1), although an overall Log-Rank $p < 0.001$. Pairwise Log-rank tests between stages provided the following results (Supplementary Table 4): stage I (differing in ECOG PS 0 vs 1 or Child-Pugh A vs B) was not significantly different (p=0.212) from stage IIa; stage IIIa (differing in Child-Pugh B vs A and tumor status) was not significantly different (p=0.085) from stage IVa; stage IIIa (differing in ECOG PS 0-1 vs 2-4 or Child-Pugh B vs C or tumor status) was not significantly different (p=0.567) from stage Va; stage IIIb (differing in tumor status and presence of metastasis) was not significantly different (p=0.906) from stage IVa; stage IIIb (differing in ECOG PS 0-1 vs 2-4 or Child-Pugh A/B vs C or tumor status) was not significantly different (p=0.129) from stage Va; stage IVa (differing in Child-Pugh A vs B) was not significantly different (p=0.053) from stage IVb; stage IVa (differing in ECOG PS 0-1 vs 2-4 or Child-Pugh A vs C or tumor status) was not significantly different (p=0.241) from stage Va. Stage Va particularly lacks of distinction from other HKC substages. This stage concerns patients with advanced tumor

who were largely transplanted (24.2%) and therefore expected to have a good survival. Excluding these patients improves a little bit the stage distinction but not completely (remains statistically indistinct from stages IVa and IVb).

HKLC with only five stages demonstrated a better separation of the survival curves (Figure 2). Although some curves are not clearly separated anymore after 7 years, the overall log-rank test confirmed the significant survival differences between stages ($p < 0.001$). The BCLC classification (A, B, C, D) also provided a good overall stratification (Figure 3), whereby the log-rank test between all stages was highly significant ($p < 0.001$). In order to compare the two models (BCLC A, B, C, D versus HKLC I, II, III, IV, V), we performed Cox proportional hazards regression with each staging system as a covariate (Loglikelihood for BCLC -6903.9, for HKLC -6941.5). Based on these results, we estimated the Nagelkerke pseudo R2 which was 0.354 for BCLC and 0.308 for HKLC. The BIC was 13814.77 for BCLC and 13889.98 for HKLC. The difference between the two BIC was 75.21, which gives strong evidence that the BCLC is a better model to predict the survival than the HKLC system[18]. Finally, we calculated Harrell's C-index with 0.739 for BCLC and 0.728 for HKLC. This result also gives an indication that the BCLC classification provides a better fit of the survival than the HKLC system.

If the patients of our cohort were mainly treated following the BCLC treatment algorithm, it could lead in a potential bias of this result. Therefore, we assessed the number of patients that were treated accordingly to their respective stage for both treatment algorithms. 537 (34.1%) patients were treated according the BCLC treatment algorithm and 603 (38.3%) patients were treated according to the HKLC treatment algorithm (see Supplementary

Tables 2 & 3 for further details). Therefore, treatments received by the patients of the cohort cannot be considered as a potential bias that would give an advantage to the BCLC staging system. In order to definitively avoid any bias due to given treatments we also tested the two staging systems on patients who only got best supportive care. Based on Cox proportional hazards regression we obtained for BCLC a Likelihood of -2380.3 and -2386.6 for HKLC. Based on this, Nagelkerke pseudo R2 was 0.367 for BCLC and 0.349 for HKLC. BIC was 4766.71 for BCLC and 4779.34 for HKLC, difference was 12.63, which again gives strong evidence that the BCLC is a better model to predict the survival than the HKLC system. Finally, Harrell's C index was 0.699 for BCLC and 0.692 for HKLC, which once more speaks for the BCLC model.

Performance as a treatment algorithm

Both classification systems suggest one or more treatment for each stage. Based on our cohort, we looked at the number of patients who would benefit from a curative therapy if the suggested treatment allocation of each classification system was strictly applied. If the HKLC treatment algorithm would be strictly applied, almost one third of the whole cohort (exactly 500 more patients) would be treated with a curative therapy instead of being tagged to a palliative therapy when following the BCLC treatment ($p < 0.001$). Curative therapies are usually associated with a better overall survival than palliative therapy. Therefore, this result suggests that following the HKLC treatment algorithm instead of the BCLC may lead in an increased overall

survival for patient with HCC. However, this assumption needs to be assessed.

DISCUSSION

By applying the HKLC classification system to a large set of European patients combining three cohorts from centres in three different countries, we found that the Kaplan–Meier curves of the nine different substages did not satisfactorily distinguish survival, although this was markedly improved when using five stages. Despite highly significant survival differences between the HKLC five stages, the overall performance of the BCLC staging system was better for predicting survival. However, using the HKLC treatment algorithm would offer curative treatments to a larger number of patients than the BCLC does.

We pooled three cohorts from centres in three different countries. Public health systems differ in these, and therefore clinical characteristics were different over the three cohorts. This allowed us to build a pooled cohort representative of the European diversity and has a good repartition of the collective of patients among the different categories (e.g. early and advanced stages) which is mandatory to assess a staging system which covers all stages of the disease. The ideal staging system would be one that accurately predicts the survival for all patients, as well as to support the selection of the treatment offering the best survival opportunity across all stages of disease. The HKLC staging system classifies patients in five stages and nine substages. Some substages display similar survival curves and could be merged without loss of information in our European cohort. The simplified

HKLC system classified patients in five stages with different survivals and could be used to predict prognosis. However, the five-stage HKLC staging system was not more accurate than the BCLC staging system. The 5-stage HKLC staging system explains 30.8% of the variance, which measures the ability of a staging system to predict accurately OS, whereas the BCLC staging, explains 35.4% of the variance. This result indicates that in Europe, where the HCC etiologies are more diverse than in Asia, the HKLC staging system does not perform better than the BCLC system as a prognostic tool. This finding is confirmed by the Bayesian Information Criterion (BIC) – and the difference between these – and the Harrell's C index. We showed that this result was not biased by the treatment received by the patients, and that the result was the same if only patients who received best supportive care were taken into account. Adhoute et al. used a French cohort of 665 patients to compare the HKLC and the BCLC staging systems[21]. They found no difference between the two staging system in the ability to predict the OS. Our pooled cohort from three different countries probably represents better the European heterogeneity of diagnosed HCC and is therefore more suitable to assess the HKLC staging system in Europe.

The HKLC provides a treatment algorithm, as does the BCLC classification system. In our European cohort, if the HKLC treatment algorithm was strictly applied, almost one third of our cohort (n=500), who would be tagged to a palliative therapy following the BCLC algorithm, would be tagged to a curative one. To really benefit the patients, this curative treatment indication for more advanced tumour should be linked with a better overall survival. Therefore, there is a need to assess those differences in treatment allocation. For this

purpose, one provocative finding made by Yau et al. was that patients with intermediate stage HCC had a better survival if treated with surgery rather than TACE [16]. The EASL-EORTC and AASLD guidelines, which adopted the BCLC staging system, recommend resection for single asymptomatic HCC in patients with preserved liver function and normal portal pressure and bilirubin, and TACE for patients in BCLC B stage [1], [22]. TACE is a palliative approach with the goal of controlling tumour growth locally, where surgical resection is a curative approach with the goal of eradicating HCC. Better OS for patients with intermediate HCC undergoing surgical resection has already been published [23], [24]. It was also reported that hepatic resection can be performed in patients with major vascular invasion [25] and in patients with large or multinodular HCC [26]. Some authors suggest that surgical resection benefits BCLC B patients, but should be performed under strict intraoperative ultrasound guidance [27]. Taken together, these results imply that a subpopulation of patients with intermediate HCC do better with surgical resection than with TACE, as suggested by the HKLC treatment algorithm.

The HKLC staging system shows a more aggressive treatment algorithm than the BCLC staging system. This could probably be explained by HBV being the main etiology of HCC in Asia. As a matter of fact, it has been shown that cirrhotic patients with an early HBV-associated HCC are good candidates for surgical resection and have the same OS than non-cirrhotic patients[28].

In interpreting the results of our study, a number of limitations should be taken into consideration. The data were prospectively collected, but retrospectively analyzed, which can lead to several biases.

In conclusion, the BCLC staging system offers a more accurate survival prediction than the HKLC staging system in Europe, where the etiologies for HCC are more diverse than in Asia. Although the HKLC staging system offers suboptimal performances for the survival prediction in our European cohort, following its treatment algorithm offers curative therapy to a larger number of HCC patients than the BCLC algorithm does.

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TABLES

	Pamplona		Newcastle		Bern		Total		P Value
	N	%	N	%	N	%	N	%	
Sex									.042
Male	609	82.5	509	80.7	182	88.3	1300	82.5	
Female	129	17.5	122	19.3	24	11.7	275	17.5	
BCLC									.000
A	181	24.5	89	14.1	88	42.7	358	22.7	
B	276	37.4	95	15.1	71	34.5	442	28.1	
C	214	29.0	284	45.0	36	17.5	534	33.9	
D	67	9.1	163	25.8	11	5.3	241	15.3	
HKLC									.000
I	165	22.4	103	16.3	32	15.5	300	19.0	
II	207	28.0	145	23.0	110	53.4	462	29.3	
III	209	28.3	76	12.0	24	11.7	309	19.6	
IV	61	8.3	39	6.2	5	2.4	105	6.7	
V	96	13.0	268	42.5	35	17.0	397	25.3	
Etiology									
ASH	215	29.1	178	28.2	90	43.7	483	30.7	.000
HBV	90	12.2	29	4.6	42	20.4	161	10.2	.000
HCV	323	43.8	65	10.3	62	30.1	450	28.6	.000
NASH	4	0.5	136	21.6	69	33.5	209	13.3	.000
Hemochromatosis	16	2.2	34	5.4	13	6.3	63	4.0	.000
Cirrhosis	565	76.6	456	72.3	167	81.1	1188	75.4	.024
Child Pugh[1]									.000
A	333	59.0	240	52.9	114	68.3	687	58.0	
B	177	31.4	126	27.8	47	28.1	350	29.5	
C	54	9.6	88	19.4	6	3.6	148	12.5	
Tumor size									.000
≤2	70	10.2	70	11.1	49	24.1	189	12.4	
>2 to ≤5	319	46.6	265	42.0	81	39.9	665	43.8	
>5	296	43.2	296	46.9	73	36.0	665	43.8	
No. of nodules									.000
Single	267	39.5	329	52.1	83	40.7	679	44.9	
Oligonodular (2-3)	201	29.7	139	22.0	70	34.3	410	27.1	
Multinodular (>3)	208	30.8	163	25.8	51	25.0	422	27.9	

Table 1: Clinical and tumour burden information for patients in the 3 cohorts.

BCLC: Barcelona Clinic Liver Cancer, HKLC: Hong-Kong Liver Cancer, ASH: Alcoholic steatohepatitis, HBV: Hepatitis B virus, HCV: Hepatitis C virus, NASH: non-alcoholic steatohepatitis.

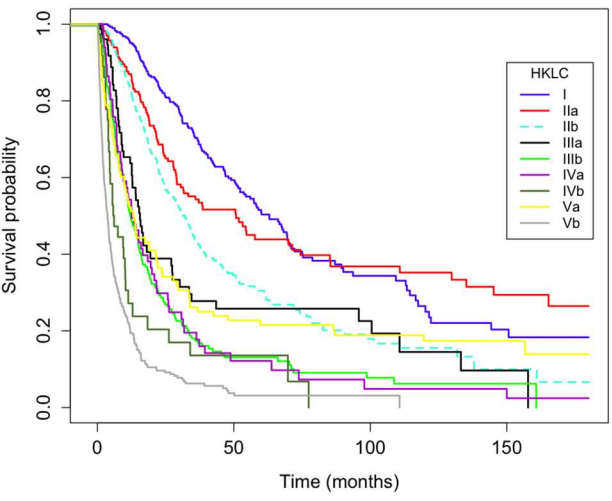
[1]Child-Pugh is given for cirrhotic patients only.

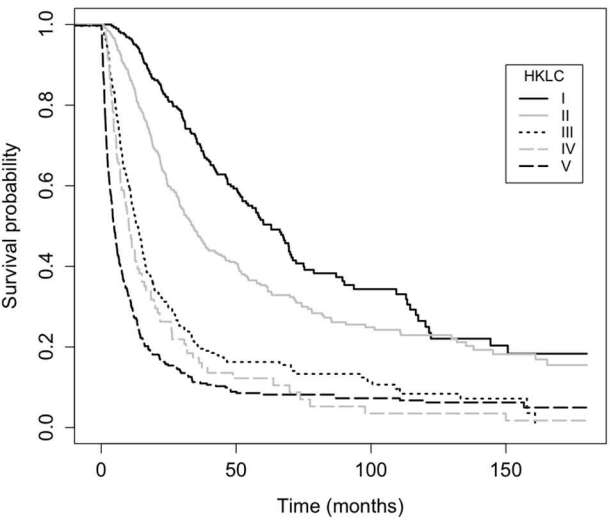
FIGURE LEGENDS

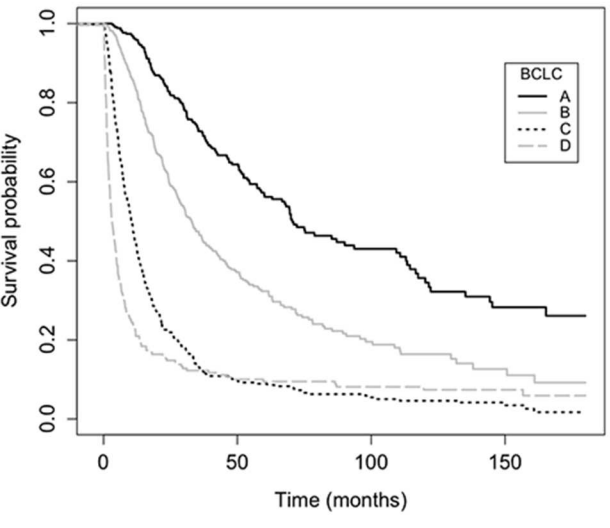
Figure 1: Kaplan–Meier estimated overall survival curves of the Hong Kong Liver Cancer (HKLC) staging system (nine stages)

Figure 2: Kaplan–Meier estimated overall survival curves of the Hong Kong Liver Cancer (HKLC) staging system (five stages)

Figure 3: Kaplan–Meier estimated overall survival curves of the Barcelona Clinic Liver Cancer (BCLC) staging system (four stages).


HKLC
I
IIa
IIb
IIIa
IIIb
IVa
IVb
Va
Vb
Survival probability
0.0
0.2
0.4
0.6
0.8
1.0
0
50
100
150
Time (months)


HKLC
I
II
III
IV
V
Survival probability
0.0
0.2
0.4
0.6
0.8
1.0
0
50
100
150
Time (months)


BCLC
A
B
C
D
Survival probability
0.0
0.2
0.4
0.6
0.8
1.0
0
50
100
150
Time (months)