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## Usefulness of the HKLC vs. the BCLC staging system in a European HCC cohort

### To the Editor:

The Barcelona Clinic Liver Cancer (BCLC) staging system [1] is widely used because it is externally validated and endorsed by EASL, EORTC, and AASLD [2]. In a recent issue of *Gastroenterology*, Yau *et al.* [3] presented the Hong Kong Liver Cancer (HKLC) staging system, developed from their cohort of 3856 patients with HCC, predominantly related to hepatitis B virus. Both classifications have a prognostic part and give proposal for treatment decision. In their article Yau *et al.* have shown that the HKLC staging system was better than the BCLC system in distinguishing between patients' prognosis and in identifying subsets of patients for more aggressive treatments. But they concluded saying that validations from other populations will be welcome.

From January 2005 to June 2013, 665 HCC patients were treated in two French centres. At the time of analysis 460 had died. The median age was 67.5 years; 97% of patients had liver cirrhosis. The underlying liver disease was predominantly due to HCV infection (36%), alcohol abuse (36%) or NASH (16%). 53% received TACE (first or second line), curative procedures (resection, transplantation, percutaneous ablation) were given to 23%, sorafenib (first or second line) was given to 36% and 15% received only best supportive care, following our therapeutic guidelines based on the BCLC algorithm. The median overall survival (mOS) of our population was 18.2 months. From this data base, the HKLC stage was retrospectively determined. Comparison between the BCLC and the HKLC staging systems in their discriminatory ability to predict survival was done, using the area under the receiver operating curve (AUC-ROC), the Somers' *D* [4] and the Gamma measures at 1, 3, and 5 years.

mOS was significantly related to the HKLC and BCLC stages (Table 1). If there are clear differences between all stages following the BCLC, in the HKLC staging system, outcome of stages IIa and IIb, IIIb and IVa and finally IVb and Vb are similar in our series as in the Yau *et al.* series. When we compared the performance of these two staging systems, using those 3 tests, after exclusion of HKLC-Va patients following Yau *et al.*, we did not observed any difference between the HKLC and the BCLC staging systems in their ability to predict survival. The area under the ROC curve estimated at 1 year, 3 years and 5 years were 0.71, 0.64, and 0.55 for the HKLC system, respectively; and 0.72, 0.65, and 0.57 for the BCLC system, respectively (*p* values not significant at the 3 time points). The Somers' *D* measures estimated at 1 year, 3 years, and 5 years were 0.42, 0.28, and 0.11 for the HKLC system, respectively; and 0.44, 0.29, and 0.13 for the BCLC system, respectively (*p* values not significant at the 3 time points). The Gamma measures estimated at 1 year, 3 years, and 5 years were 0.82, 0.76, and 0.82 for the HKLC system, respectively; and 0.83, 0.76, and 0.89 for the BCLC system, respectively (*p* values not significant at the 3 time points).

The mOS of our population (18.2 month) was slightly better than in the series by Yau *et al.* (12.65 month); mOS was better in the early stages (I, IIa, IIb) in the Hong-Kong series than in our series, while in more advanced stages (from IIIa), the mOS of the French population seemed better. It is impossible to know if these differences are real and if they are related to treatment guidance different for the two systems or to the natural history of this disease with different aetiological factors. This is a limitation of the study. Treatment according to stage differs according to BCLC and HKLC; hence, outcomes are based on HKLC re-staging but BCLC management.

Stage I and some stage IIb patients in the HKLC staging system correspond to stages 0 and A in the BCLC system and curative options are proposed in both systems for these patients; stage IIa and most stage IIb patients are classified as intermediate stage (stage B) in the BCLC. The differences in prognosis between the Hong-Kong population and our patients corresponding to stages IIa and IIb can be related to a more aggressive treatment (curative option vs. chemoembolization), in a more younger Asian population (58 vs. 67.5 years), following the HKLC algorithm. But we have to keep in mind that in some selected BCLC B patients, chemoembolization can give impressive results with a mOS of 48 months [5] in a recent series. Moreover, in such "early stages", the prognosis can be more related to the severity of liver fibrosis (post-operative outcome, recurrence risk) than to the tumour or its treatment. We can hypothesize that the incidence of HCC arising on non-cirrhotic liver is higher in Asia, which can explain the better mOS in case of curative treatment in Asia, while the high frequency of cirrhosis in European patients precludes the use of resection in most.

Our results are better in more advanced stages, particularly IIIa, IIIb, and IVa. The major difference in treatment options between these two systems for these patients is the possibility in the HKLC scheme to propose chemoembolization in patients with intrahepatic venous invasion. In our experience, following the BCLC algorithm only stage IIIa – IIIb patients without intrahepatic venous invasion have received chemoembolization, others were treated with sorafenib. This can explain why our results are better in stage IIIa and IIIb, as it might be related to a better selection of patients, which is why systemic treatments give better results in our series.

To sum up, in a European population of HCC patients, the newly developed HKLC staging system does not seem to allow a better predictive value of outcome than the BCLC staging system. Differences in survival between these two series can be related not only to the aetiology (and stage) of the liver disease but also to their management and a more aggressive treatment cannot, from our experience, be proposed to most European patients.

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**Table 1. Survival outcomes following the HKLC and BCLC staging systems in a population of European hepatocellular carcinoma patients.**

Score	Median OS (95% CI)	p value (Log-rank)	Survival probability	
			Years	Survival probability % ± Sd
<b>HKLC stage</b>				
I (n = 135)	54.8 (39.6-80.4)	<0.0001	5	0.495 ± 0.057
Ila (n = 40)	24.3 (18.7-49.6)		5	0.255 ± 0.098
Ilb (n = 155)	26.4 (22.7-32.4)		5	0.142 ± 0.038
IIla (n = 40)	14.6 (11.2-17.2)		3	0.041 ± 0.040
IIlb (n = 172)	9.6 (8.2-11.7)		3	0.068 ± 0.023
IVa (n = 44)	9.3 (6.1-13.5)		1	0.361 ± 0.073
IVb (n = 19)	4.0 (2.4-5.1)		1	0
Va (n = 9)	8.1 (4.1-10.2)		5	0
Vb (n = 51)	3.0 (2.0-4.1)		1	0.030 ± 0.029
<b>BCLC stage</b>				
A (n = 177)	45.7 (37.5-68.0)	<0.0001	5	0.449 ± 0.049
B (n = 207)	21.3 (18.3-25.2)		3	0.264 ± 0.036
C (n = 236)	8.3 (7.1-10.1)		2	0.124 ± 0.250
D (n = 45)	2.7 (2.0-4.1)		1	0.056 ± 0.038

Survival probability estimate was reported at t = 5 years for stages I, Ila, Ilb, and Va; t = 3 years for stages III and IIIb; and t = 1 year for stages IVa, IVb, and Vb. CI, confidence interval.

**Conflict of interest**

X. Adhoute is a board member of Bayer; G. Penaranda has received grants from Bayer; J.L. Raoul is a board member of Bayer, BMS, Daichi; J.P. Bronowicki is a board member of Merck-Schering Plough, Janssen, Roche, BMS, Boehringer-Ingelheim, Gilead, Novartis, GSK, Bayer and a speaker for Merck-Schering Plough, Janssen, Roche, BMS, Boehringer-Ingelheim, Gilead, Novartis, GSK, and Bayer.

**Authors' contributions**

XA and JPB collected the data; GP performed the statistical analyses; XA, JPB, JLR, and GP analysed the data; XA, JLR, and GP wrote the manuscript.

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## Transient increase in urine protein excretion during treatment with terlipressin and albumin for type-1 hepatorenal syndrome

To the Editor:

We recently had a patient admitted to our unit with cirrhosis and type-1 hepatorenal syndrome (HRS) who developed marked proteinuria during treatment with terlipressin and albumin. This led us to investigate whether pharmacological treatment of type-1

HRS could be associated with an increase in urine protein excretion. The effects of terlipressin and albumin on kidney function in patients with type-1 HRS have been investigated extensively [1,2], but to our knowledge there is no information on the potential effects of treatment on urine protein. We evaluated a series of