

## **Response to reviewer:**

### COMMENTS TO AUTHORS

-The aim of this study is to compare the performances of several HCC staging systems including the BCLC nomogram in the prediction of survival of a large French HCC cohort. A total of 1102 HCC patients retrospectively recruited from 5 hospitals in different areas. The objective of this study is clear and the statistical studies were well done. The conclusion is logical and adequate. The results will provide information about survival prediction of HCC patients, although there is no innovative or novel conceptual breakthrough about HCC treatment or diagnosis provided.

We thank the reviewer for this comment. The objectives of our study were: 1) to assess the performances of the BCLC nomogram in an external western cohort including HCC related to HCV infection and alcohol, at different stages (mostly advanced HCC), treated in different ways; 2) to compare them with other recognized prognostic scores and classifications; and finally, to discuss its relevance in current practice. HCC classifications especially the BCLC system have displaced scores[1-3]; this system has become the reference classification in Western countries and in clinical trials, through a simple stratification and a useful therapeutic algorithm. Improving the prognostic value of the BCLC using a nomogram (which assigns to each of the variables a coefficient) is an interesting concept, especially since the methodology used by Hsu et al[4] is robust, including a large HCC cohort at different stages with various therapeutic modalities. The predictive value for survival of the nomogram is confirmed within this European external cohort, although its prognostic value decreases after application of the changes in the BCLC system, namely the transfer of large and single tumors from the intermediate stage [5]to the early stage[6]. The nomogram is reliable for prognostic information, but it distinguishes sixteen subgroups in our cohort. We propose a simplified stratification into five different prognostic groups so that it can be used for HCC management.

We believe that the scores could be useful in HCC management, as they are complementary tools to the classifications[7-10], if they are reliable but also easy to use. As mentioned in the discussion pages 15 and 16, we are dealing with this concept of a complementarity between HCC classifications and score. The usefulness of HCC scores remains a controversial issue; except liver transplantation[11], there is no currently consensus concerning their relevance, or the scores to use. A prospective study should be conducted. Various scores have been proposed in recent years in addition to the BCLC system in order to refine the prognosis and / or guide HCC management[12, 13], as each stage of the BCLC comprises a broad spectrum of tumors with limited therapeutic options, notably for stages B and C.

-Roles of treatment selection, for example, surgery versus RFA, RFA with versus RFA with or without TACE, sorafenib treatment versus other palliative treatments in BCLC C, in the outcomes are not included in the analysis or discussed:

We thank the reviewer for his useful comments and we add in the patients and method section the criteria that leads us to choose the treatment (pages 10, 11). Patients who underwent surgery versus radiofrequency ablation were as expected younger with less cirrhosis and larger tumor size, as demonstrated in the following table 1. As mentioned in the manuscript (pages 9, 10), “in ours centers, candidates for resection are carefully selected to diminish the risk of post-hepatectomy liver failure (PHLF)”. Preoperative independent variables for mortality in HCC patients with cirrhosis treated by surgery include portal hypertension and bilirubin level[14]. We explain our routine protocols for the assessment of functional hepatic reserve (FHR) and determination of hepatectomy extent. As you can see in the following table 1, a minority of HCC patients with Child – Pugh B cirrhosis has been treated by surgical resection in this study (2%).

Patients who underwent both radiofrequency and TACE versus radiofrequency ablation alone had larger tumor size as demonstrated in the following table 2 and

more nodules (RFA+TACE: 1 nodule: 20%, 2 nodules: 55% and 3 nodules: 25% of patients vs. RFA alone: 1 nodule: 55% and 2 nodules: 45% of patients).

Patients with advanced HCC had received Sorafenib since 2008; fifty six patients of them had received other treatments including tamoxifen or pravastatine (41% of these patients), or chemotherapy with doxorubicin (36%), and others drugs in clinical trials (23%) before 2008.

<b>Surgery vs. RFA</b>	<b>Surgery (n=205)</b>	<b>RFA±TACE (n=54)</b>	<b>P</b>
Cirrhosis - N (%)	156 (76%)	52 (96%)	<.0001 (X <sup>2</sup> )
Child-Pugh B - N (%)	5 (2%)	7 (13%)	0.001 (X <sup>2</sup> )
Tumor Size			
<i>Mean±Sd mm</i>	60.4±40.5	31.1±10.5	<.0001 (Wilcoxon)
<i>Median (Q1-Q3) mm</i>	50 [31-70]	30 [25-35]	
Age			
<i>Mean±Sd years</i>	63.9±10.9	70.6±11.4	0.0003 (Wilcoxon)
<i>Median (Q1-Q3) years</i>	65 [57-72]	72 [63-79]	

**Table 1:** liver function, tumor size and patient age according to HCC treatment modalities (surgery vs. RFA).

<b>RFA+TACE vs. RF</b>	<b>RFA+TACE (n=19)</b>	<b>RFA (n=35)</b>	<b>P</b>
Tumor Size			
<i>Mean±Sd mm</i>	37.1±15.3	28.7±10.6	0.0567 (Wilcoxon)
<i>Median (Q1-Q3) mm</i>	35 [28-45]	25 [20-33]	0.0257 (Brown-Mood)

**Table 2:** tumor size according to RFA with or without TACE

Minor comments: Table 1. CLIP score and Table 2. NIACE score should be deleted. There is no need to provide a known scoring system without any additional information or modification.

According to the reviewer, we have delete table 1 and 2.

Table 4 does not demonstrate clearly. I will suggest providing the original nomogram with insertion or indication of your data. Also, the reference of the original paper describing BCLC nomogram should be provided as a note or footage to the table title.

According to the reviewer we added table 4 with the nomogram and realize the figure 4 and we added in the figure title the reference of the original paper from Hsu et al (ref.). page 17.

Table 5. A note to address the difference between BLCL nomogram and Nomogram according to BCLC last version is required.

According to the reviewer we added a footnote on the table (which became table 2) with the BCLC modifications.

Figures 1-3 are those known HCC staging systems and should be deleted. Figure 3 can be combined with Table 4 to clear demonstrate the results on the nomogram.

According to the reviewer we have made the request.

Figures 6-8 can be integrated as a single multipanel figure, which will be more clearly for the readers. Figures 5 and 9 are both KM survival curves stratified by BCLC staging and BCLC nomogram with 5 subgroups and can be demonstrated as a single two-panel figure.

According to the reviewer we have made the modification and figure 3 is the combination of OS histograms according to HKLC system, CLIP and NIACE scores. Moreover figure 2 is the combination of KM survival curves according to BCLC staging (A) and BCLC nomogram with 5 subgroups (B).

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