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**Manuscript entitled:** BCLC Outperforms HKLC Staging of Hepatocellular Carcinoma in Multiethnic Asians – Real-World Perspective

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#### **REVIEWER’S COMMENTS TO AUTHORS**

“Arguments for the opportunity of this research paper: ----The topic is one of great interest today. I would insist more about the fact that the criteria raised in the HKLC system remain to be further adjusted and verified. The BCLC system, although widely used was created based on several small Western cohorts of patients with predominant alcoholic liver disease and hepatitis C related HCC. The system which links stage stratification with corresponding therapeutic recommendations was criticized for being too restrictive, having in mind for example, that liver resection is recommended only to the patients with early stage tumors, or the fact that patients with cancer- related symptoms should be classified as advanced HCC. More, recent papers argue that this system is indeed able to provide accurate outcome prediction and treatment recommendations for HCC patients with hepatitis B virus as the predominant etiology. The HKLC staging system recently proposed has been show to achieve better prognostic ability and to identify subsets of patients for more aggressive treatment (intermediate and advanced stage patients) in Eastern population, with hepatitis B as main etiology. The improved stratification of the patients with intermediate-to-advanced stage using the triad of tumor size, number of nodules and tumor thrombus seems to offer to this patients with multiple tumors the possibility to achieve a better outcome if they receive hepatic resection following HKLC criteria. It worth mentioning that this is still a controversial point, if we keep in mind regarding the patients with multiple tumors the problem of cancer genetic heterogeneity. “Cancer genetic

heterogeneity is an ignored factor that leads to inconsistent surgical outcomes in patients with multiple tumors. There are differences between patients and between tumor nodules in the same patient, and even within a single tumor nodule [14]. For example, previous studies using whole-genome sequencing examining each nodule in one patient with multiple tumors identified different driver mutations in each nodule [15, 16]. The intratumoral heterogeneity might reflect the existence of distinct pools of cancer stem-like cells that exhibit different tumorigenicities and independent genomic evolution [17]. Therefore, if multifocal HCC develops as a consequence of intrahepatic metastases of the same primary cancer, such patients should belong to an advanced stage, which would lead to poor surgical outcomes. However, if multiple tumors arise either synchronously or metachronously as primary tumors (multicentric occurrence), such patients might still be classified as early stage, and surgical removal could achieve satisfactory results. These uncertainties made prognostication after surgery very difficult for individual patients and reasonably explained the results that no significant association was found between tumor number and postoperative survival in patients with multiple tumors” Another controversial part of this new staging system is that it allows patients with adequate tumor status to be transplanted, independent of PS, fact that demands validation from more transplant centers. ---The limitations of the study are well and completely described. --- This is a single center data and a retrospective study but the population included is large, well characterized and appropriately chosen. 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. ---Hepatitis B was the predominant etiology and HKLC was consistently associated with better prognostication for HBV related HCC. But, more and more papers suggest that clinical heterogeneity among HBV and HCV- related HCC implies that HCC of different etiologies may deserve distinct staging and treatment algorithms. ---In most of the series, outcomes are based on HKLC re-staging, but on BCLC management. In this study”

### **Answer to Reviewer**

We thank the reviewer for the time and effort in critiquing our manuscript. The detailed and insightful comments are very helpful. The revised manuscript is attached, and we thank the reviewer once again for acknowledging our work.