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Difficulties for providing evidence in Hepatocellular Carcinoma with Child-Pugh B liver function.

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Conflict of interest statement: JE and JFB received funding from Beigene for conducting a study in Hepatocellular Carcinoma patients with Child-Pugh B liver function (the HESTIA trial, clinicaltrials.gov identifier NCT05622071). JE will be participating in an AstraZeneca study in this patients' population.

Data Availability Statement: this comment does not contain new data.

Lay Summary: In this comment, we discuss the result of a study published in this issue of Liver International, by Jeon and colleagues. This study is important because it provides data on a population of patients with liver cancer and moderately-impaired liver function, frequent in the clinics but understudied. We also discuss the difficulties about conduction clinical research in this population.

In this issue of *Liver International*, Jeon *et al* present a study regarding the treatment of Hepatocellular Carcinoma (HCC) in patients with Child-Pugh (CP) B liver function¹. Despite the high prevalence of this situation in daily practice (for example, it represented 23% of all HCC cases recorded in the BRIDGE global cohort²), this population remains understudied, and providing higher level of evidence is of paramount importance. The authors investigated the data from the Korean Central Cancer Registry from 2008 and 2016, focusing on the 2,318 patients included in the Korean Primary Liver Cancer Registry with CP B and describing their outcomes depending on the first treatment received, categorized whether it respected the BCLC algorithm. Their conclusions are that regardless of BCLC stage, transarterial chemoembolization (TACE) was the most frequently used treatment, and that for BCLC A and B stages, treatment according to recommendations was associated with the best outcomes, but that in BCLC C stages treatment with systemic therapies provided poor outcomes. To note, more than half of the CP B population was classified as BCLC C (n=1,454) in this registry.

The main strengths of the study are the use of a population-based registry, with high coverage of the Korean population, the use of the Korean Primary Liver Cancer Registry part of this registry, ensuring that data required for HCC management (such as BCLC stages, liver function...) were available (which might not be the case for non-specialized registries), and the large number of patients analyzed. The main limitations, acknowledged by the authors, are the absence of randomization, making comparisons of treatment choices uncertain (possibly influenced by unknown confounding factors), some data important for treatment decision (portal hypertension, comorbidities) were lacking. Also, there was no data on treatment tolerance or liver function worsening, which are of major importance in this population. The difference of population and management of HCC between East and West might also make the conclusions less applicable in a Western population. Finally, despite the high overall numbers, some subgroups are small (for example, n=17 for curative treatment in BCLC B), questioning the validity of some results when selection bias could not be definitively ruled out.

Apart from the conclusions of the authors, which should be balanced by the unknown selection biases and the absence of data on safety, other very important messages could be illustrated by this study. Firstly, it confirms in real-life the major prognostic impact of liver function in HCC. In the BCLC B group, median Overall Survival (OS) was 15 months for patients treated with TACE, and in the BCLC C group, median OS was only 3 months for patients treated with systemic therapy (presumably mostly sorafenib due to the study period), both considerably lower than what is expected in a CP A population. Thus, despite the exclusion of CP B of most clinical trials, there remains a huge unmet need for this population.

Secondly, the authors' conclusions tend to support an aggressive approach to treatment, comparable to those of CP A population, and even suggest to use locoregional treatment in patients with BCLC C stage and CP B liver function. However, we believe we should be more cautious about these conclusions. As discussed by the authors, the very low median OS in patients treated with systemic therapy, while comparing to the relatively higher median OS of 9 months in patients treated with TACE, might suggest a selection bias with more advanced patients treated with systemic therapy as compared to TACE. Moreover, locoregional treatment are often associated with decrease of liver function, and should then be used with caution in this population³. In this study as in others, sub-classification of CP B population either comparing B7 vs B8-9 or using ALBI grade 1-2 vs ALBI grade 3 might help to better define population at risk of toxicity, and increased benefit from the treatment^{4,5}. Furthermore, liver dysfunction might be more at risk in patients with other etiologies than Hepatitis B Virus.

Thirdly, this registry illustrates the discordance between BCLC recommendations and everyday practice. As was previously described not specifically for the CP B population, TACE remains the most frequently proposed first treatment, with very similar frequencies as resection in the BCLC A in the global BRIDGE study of practice, and higher frequency of use in China and South Korea as compared with other countries². There are two directions for interpreting these discordances between

recommendations and actual practice: the first is to emphasize the potential loss of chance of not adhering to guidelines, as illustrated by the non-application of curative treatment in BCLC A patients. Of course, appropriate management of HCC patients, including discussion within specialized multidisciplinary team meeting adhering to validated guidelines, should always be favored⁶. However, the other direction is to consider that in some aspects the BCLC algorithm might not always be applicable to everyday patients. The CP B population is a good example of this difficulty: it was at some point included beside CP A in the main BCLC algorithm, despite the lack of evidence validating any treatment in this population usually excluded from clinical trials; currently, the phrasing is “preserved liver function”, with explicit exclusion of patients with decompensation (jaundice, ascites, encephalopathy), but no further discussion within the CP B population. Interestingly, the last versions of the BCLC algorithm introduced the notion of treatment stage migration, and for example the possibility to apply TACE in BCLC A patients for which curative treatment are not feasible or failed. This makes the BCLC algorithm more applicable, for example for a CP B patient for which the surgeon judges the operating risk too high, and whose lesion is in a location of difficult access to ablation. Clearly, HCC is a strong example of the need for an individualized decision for each patient diagnosed with cancer, and the need for multidisciplinary discussion to provide an evaluation of the feasibility of every treatment modality possible.

Finally, and most importantly, we must continue to build evidence in the CP B population presenting with HCC. During the more than 10 years of availability of sorafenib as first-line treatment, we were able to complete only one randomized trial with this drug, the PRODIGE 21 trial⁵. In this phase 2 trials that randomized 160 patients, we suggested that sorafenib might be associated with clinically-relevant OS benefit only in patients with either CP B7 or ALBI grade 1-2 liver function. Other attempts to demonstrate benefit failed due to lack of accrual^{7,8}, illustrating the difficulty of randomizing such population, with some investigators reluctant to treat these patients with aggressive therapies due to their poor liver function, and others reluctant to provide best supportive care alone... However, in the context of lack of evidence and potential toxicity, it is still important to conduct prospective

studies in this population, such as was made for nivolumab⁹ and is currently planned for durvalumab-tremelimumab or tislelizumab (clinicaltrials.gov identifier NCT05622071). Innovative trial designs, such as synthetic controls or emulated trials, might help to overcome resistance to randomization in this context¹⁰.

In conclusion, the analysis of the Korean registry illustrates the high unmet need of the CP B population. This population, as every HCC patients but highlighted by to lack of adequately evidence-based recommendations, requires an individualized approach as regards to treatment decisions. Continuation of efforts of clinical research should be a priority for our community.

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