Response to "Influence on the other patients in the waiting list when expanding the Milan criteria" and "Can Milan criteria be expanded effectively for liver transplantation in patients with HCC?"

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We thank Dr. Sugawara Y and Dr. Kim R for their insightful comments on our recent study (1). Organ allocation and selection of eligible candidates have always been a dilemma in liver transplantation for hepatocellular carcinoma (HCC). Milan criteria successfully defined a subset of patients with acceptable outcomes. However, several groups have presented excellent outcomes when extending Milan criteria. And strict adherence to Milan criteria denies access to a possible curative liver transplant in around 1/3 of potential recipients (2). To approach an optimized patient selection criteria, our group proposed Hangzhou criteria, which use a strategy combining tumor biological behavior and morphology (3). About Hangzhou criteria, both the two commentaries provide interesting but incisive insights, which are noteworthy.

Dr. Sugawara points out that "*any kind of expansion in size or number of the tumor includes the potential to worsen the post-transplant survival in patients with HCC*", which he described as "metroticket paradigm" (4). This is always a major concern when designing a study attempting to extend the standard inclusion criteria. In our study, we further proposed the stratification system based on Hangzhou criteria. The results showed that Hangzhou A (AFP <100 ng/mL) had excellent outcomes, which were close to those fulfilling Milan criteria, but much better than Hangzhou B. And to minimize "metroticket paradigm", we also suggest performing post-transplant chemotherapy for Hangzhou B.

China Liver Transplant Registry (CLTR) is the 3rd largest liver transplantation database all across the world. However, data quality was relatively poor during the early years, and we regret having to exclude those cases with incomplete information. On the other hand, CLTR is currently being well administrated to make sure that data as well as its analysis is reliable. Both the participating centers and CLTR routinely review the data to ensure its high quality. All the procedures are monitored in real time by the supervising department.

Dr. Sugawara also noted the morality on waiting list, because extended criteria increase the scarcity of available donor livers. Candidate selection between benign and malignant liver diseases has always been difficult, and the principle drifts in different countries. As the developing medical treatments will be able to cure many liver diseases such as hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, the role of liver transplant for HCC is evolving dramatically. China has the heaviest HCC burden all around world, accounting for 55% of all newly diagnosed HCC (5). Extended criteria shed light on this dilemma, and offered the massive HCC population a chance of curative transplantation. Based on the China Organ Transplant Response System (COTRS), which was launched by Ministry of Health of China (6), Hangzhou stratification system will hopefully help China achieve the balance between morality and extended inclusion criteria in organ allocation.

In Dr. Aucejo's commentary, they talked about the

feasibility of pre-transplant biopsy (7). Increasing evidences have demonstrated that tumor biological features play a key role in the prognosis prediction and even therapy guidance (8). Biopsy has been accepted as a routine and safe examination before transplantation or hepatectomy. Our center annually performs over 1,000 cases of liver/liver tumor biopsies. An ongoing study of our group evaluated the outcomes of biopsy in an HCC cohort. We've already found that biopsy is reliable and its risk can be minimized if performed by experienced radiologist carefully.

Another major issue raised in the commentary is specific biomarkers for post-transplant outcomes. Modern medicine aims at developing individualized therapy based on tumor biological behaviors. However, a universal set of criteria to conform to is still necessary. Therefore, Hangzhou criteria is valuable, as it increases eligible candidate number substantially, and still achieves acceptable post-transplant outcomes.

In conclusion, the strategy for liver transplant recipient selection for in HCC patients is evolving to be more precise and individualized, and should be able to minimize the risk of worsen outcomes caused by extended criteria. A reasonable organ allocation system should be established to achieve the balance between morality and extended inclusion criteria.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest.

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