Commentary: A preoperative model for predicting microvascular invasion and assisting in prognostic stratification in liver transplantation for HCC regarding empirical criteria

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Liver transplantation (LT) has become the most effective treatment for end-stage liver diseases. Approximate 40% of LTs are performed for hepatocellular carcinoma (HCC) in China, while close to 20% of LTs were performed for liver cancer according to the European Liver Transplant Registry's 2020 data. Although LT achieves better prognosis than liver resection in HCC patients, tumor recurrence is still the main barrier for long-term survival. Candidate selection systems such as Milan, UCSF and Hangzhou criteria have been developed to not only avoid donor organ wasting but also reduce tumor recurrence after LT by analyzing the clinical risk factors for tumor recurrence. Tumor microvascular invasion (MVI), which must be properly determined by postoperatively surgical specimens, generally represents a high risk for tumor recurrence and associated poor prognosis after LT [1]. Knowing whether MVI exists before LT will be of great help to discriminate different clinical outcomes, provide prompt treatment for high-risk patients and even guide the donor organ allocation.

Previous studies have demonstrated that MVI could be predicted by preoperative noninvasive tests including blood biochemistry and imaging [2–6]. For instance, Lee et al. [7] found that the independent risk factors for MVI were alpha-fetoprotein (AFP), protein induced by vitamin K absence-II and magnetic resonance imaging (arterial peritumoral enhancement and hepatobiliary peritumoral hyperintensity). Using the above parameters, they established a predictive model, showing sensitivity of 65.2%, specificity of 97.5% and accuracy of 69.2% in the diagnosis of MVI. Chong et al. [8] developed a radiomics-based nomogram with area under curve (AUC) of 0.920 for the preoperative prediction of MVI using random forest analysis in solitary HCC patients with tumor size $\leq$ 5 cm.

I read with great interest the article by Zhang et al. [9]. The authors investigated noninvasive clinical parameters to predict the occurrence of MVI in a relatively large cohort of 455 HCC patients, who finally received LT. In this study, histologic MVI was identified in 44.8%

(204/455) cases by careful explant histopathologic examination, which was consistent with previous studies [10,11]. In the multivariate logistic analysis, they were able to select four independent risk factors that were associated with MVI, including AFP level, tumor size, peritumoral star node and tumor margin. It was not surprised that all four tumor features that were reported to be closely related to MVI separately in previous reports [2,12]. Of note, during the study, the authors identified a semiautomatic volumetric interest (VOI) system in the mixed-model images, allowing automatic calculation of the entire lesion volume with a dichotomic classification algorithm in 3-dimension and accurate evaluation of peritumoral star node and tumor margin. Also, this 3-dimension visualization technique could well present the radiomics signature of HCC and even the tumor heterogeneities [13,14]. Accordingly, they constructed a predictive model, which showed excellent diagnostic values in both training and test cohorts (AUC > 0.8). For instance, if a patient had AFP level of $\geq$ 355 ng/ml, tumor size of $\geq$ 7.5 cm and the presence of peritumoral star node and non-smooth tumor margin in computed tomography (CT) imaging, the possibility of MVI was 76.9%.

In addition, to the best of my knowledge, this is a pioneering study exploring the possible presence of MVI among LT candidate selection criteria with MVI by combining both serum AFP levels and three radiomics parameters. Previous studies have revealed that the presence of MVI significantly reduced patient tumor-free and overall survival [15,16]. In this study, Zhang et al. demonstrated that MVI could well discriminate different clinical outcomes within the Milan criteria (MC$^-$) as well as beyond the MC (MC$^+$). They integrated noninvasive MVI parameters with the MC and suggested that LT should be simply avoided or performed with great caution i.e. applying skillful surgical techniques and giving advanced anti-cancer strategies in patients with MC$^-$MVI$^+$. In contrast, LT might be recommended in those with MC$^+$MVI$^-$. The results bring us one step forward to consider improving the current

candidate selection criteria by adding cancer biology and pathology parameters, i.e. omics such as genomics, proteomics, metabolomics and radiomics.

Declaration of Competing Interest

None.

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Author contributions

None.

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