Editorial

The optimal threshold for α-fetoprotein and vitamin K absence or antagonist-II is still an open issue

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Liver transplantation is an important therapy for early-stage hepatocellular carcinoma (HCC). Although patients within the Milan criteria that refer to tumor size ≤5 cm, tumor number ≤3 and no macrovascular invasion has excellent survival outcome, tumor recurrence is a major limitation of long-term survival in liver transplant patients (1,2). Currently, many centers have performed liver transplantation extended criteria beyond the Milan criteria (3). Several studies have been done to investigate the outcomes of patients who exceed the Milan criteria and to enable more patients to benefit from liver transplantation. And some prognostic models have been proposed that expand the Milan criteria including University of California, San Francisco criteria (UCSF) and Koyoto criteria, etc. (4,5). Under this circumstance, it is essential to identify the accurate prognostic factors that beyond the Milan criteria and could bring survival benefit for patients.

Conventional models were based on tumor parameters in terms of tumor size, numbers and vascular invasion. Recently, inclusion of biologic tumor markers such as alpha fetoprotein (AFP), protein induced by vitamin K antagonist II (PIVKA II), and positive positron emission tomography (PET) in addition to parameters of tumor morphology have been proposed and might be the key to establish the best criteria for living donor liver transplantation (LDLT) for HCC. These biologic tumor markers may be additional useful variables to optimize the current Milan criteria. In the study by Kim *et al*. in this issue of the *Hepatobiliary Surg Nutr* (6), the authors investigated the effect of preoperative level of AFP and PIVKA II on the prognosis of HCC patients after LDLT and the results showed that tumor size >5 cm, AFP >150 nag/mol and PIVKA-II >100 maul/mol were significant risk factors for recurrence.

AFP assessment is a simple and reproducible method as a biomarker for prognosis of HCC patients after surgery, locoregional and systemic therapy. Its importance has been highlighted in lots of studies and has been included into the Cancer of the Liver Italian Program (CLIP) staging system (7,8). PIVKA II is another serum marker used for both surveillance of at-risk patients and early-stage HCC diagnosis (9-12). It was reported that PIVKA-II was related to microvascular invasion and histological tumor grade (3-5,7-9). Interestingly, compared with AFP, it was suggested that PIVKA-II may be more efficient than AFP for the diagnosis of early HCC and is a predictive biomarker for microvascular invasion (10). In patients with locally advanced HCC, Park *et al*. found that the use of a combination of AFP and PIVKA-II, appears useful in predicting treatment outcomes through the subdivision of prognostic groups (11). However, it remains controversial about the threshold of AFP and PIVKA-II value. Different studies obtained the various cut-off points for AFP and PIVKA-II, respectively. In the recent study by Park *et al*., the sensitivity of AFP and PIVKA-II was 59.2% and 88.8% for patients developing recurrent HCC after LDLT, respectively. When the two markers were combined, the sensitivity

increased to 92.5% with the cut-off value 20 ng/mL for AFP and 40 ng/mL for PIVKA-II (12). In addition, Takada *et al*. defined new Kyoto criteria and suggested that maximal tumor size >5 cm, tumor number ≥11, AFP >400 ng/mL, and PIVKA-II >400 mAU/mL represented significant predictors of higher recurrence and shorter survival (13). The lack of consensus on cutoff points resulted in heterogeneity in clinical practice and become a barrier for adding pre-operative AFP and PIVKA-II into unified prognostic models of LDLT.

The main limitation to this study is that the threshold of AFP and PIVKA-II value has not been validated in internal and external cohort. In addition, because LDLT has significant disadvantages including risk to the liver donor and perioperative mortality, most patients had undergone history of non-transplant treatments for down-staging and received LDLT as a rescue therapy (4). Some studies even suggested that not preoperative staging (in or out of Milan criteria) but the characteristics of patients of tumor response to transarterial chemoembolization (TACE) is critical for selecting patients to receive LDLT treatment (14). In this study, 60% of patients had pre-transplant treatments including TACE, radiofrequency ablation and percutaneous ethanol injection. It would be interesting and important to compare the transplant outcomes between pretreated and non-pretreated groups and include the previous therapy into multivariate analysis.

In conclusion, critical evaluation of the patients' baseline characteristics is needed in clinical decision-making process for LDLT. AFP and PIVKA-II play an important role in the prognostic model. More prospective studies are needed to investigate and validate the threshold to get a consensus for the cutoff points in prognostic model.

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