Editorial

# Incorporating alpha-fetoprotein within dimensional criteria for hepatocellular carcinoma transplantation

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Since the adoption of Milan criteria more than 20 years ago, selection criteria for liver transplantation (LT) in patients suffering from hepatocellular carcinoma (HCC) represented a debated issue. Halazun and colleagues presented at the American Surgical Association of 2018, and published on the issue of October of *Annals of Surgery*, their results from an analysis aimed at including alpha-fetoprotein (AFP) in a model developed to predict long-term results after LT for HCC (1). Of 1,450 patients included between 2001 and 2013, 16.2% were outside Milan criteria, 61.1% were hepatitis C virus (HCV) positive and more than 80% of candidates received pre-LT locoregional therapies. Their study showed that incorporating AFP levels at diagnosis, maximum AFP (Max-AFP) at any time point, and the final immediate pre-transplant AFP (Final-AFP) to tumor number and diameter can well stratify different groups of patients at different risks of HCC recurrence after LT (NYCA model).

The quality of the present study relies on the use of AFP as the surrogate of response to pre-LT therapies and this latter, in turn, can be considered a biological marker of tumor aggressiveness (and vice-versa). As outlined, more than 80% of patients underwent some kind of neo-adjuvant therapies. However, the assessment of modern mRECIST is time consuming and can be subject to disagreement between different radiologists (2). In this sense, AFP provides a more objective response criteria. This is a conceptual improvement in the development of a replicable prognostic model in the present clinical scenario.

However, to fully understand the importance of the present study in this specific field it should be briefly pointed out what is the already knowledge in regards of such predictive models. Authors underlines in their work that already developed calculators as Duvoux's French AFP score (3) and Mazzaferro's Metroticket 2.0 (4) used AFP at a single time point, even though patients usually wait many months for transplantation during which neo-adjuvant therapies are commonly administered. Effectively, the Duvoux model used AFP level at listing with a median waiting time to LT of 4.7 months (3). Nevertheless, taking into account tumor features on re-assessment, the French AFP model was still able to discriminate patients at high- and low-risk of recurrence (3). The Metroticket 2.0 used the relationship existing between radiological response to neo-adjuvant therapies, being final AFP and pre-LT tumor features as determinant of post-LT prognosis (4). Consequently, present findings did not significantly improve our knowledge. The novelty has to be searched in the fact that it was developed in a US cohort, whereas the previous two were developed in European countries but most aspects were already addressed in such previous literature (3-5). However, the present study takes the right road for future improvements which should be represented by external validation and the adoption of competing-risk analysis.

In fact, both the model of Duvoux and of Mazzaferro were externally validated (2,4), being the Metroticket 2.0 also validated in an Eastern cohort (2), providing the necessary robustness for being used in the clinical setting.

The study from Halazun lacks of such external validation, which should be planned in the future. Authors claimed that the C-statistic for NYCA was significantly superior to those of Milan and of the French AFP scores (P<0.001) but such comparison can not be considered correct, since before comparing C-statistics of different prognostic models an independent external validation group must be identified.

Second, in the present study competing-risk analysis was only marginally adopted, correctly assuming death as competing to recurrence. This could have been a quality of the present work, since 61.1% of patients were HCV+, transplanted in an era [2001–2013] burdened by untreatable and deadly HCV recurrence. Thus, early death for HCV-recurrence can mistakenly lead to the conclusion that large/multinodular HCCs +/– high AFP levels can be safety transplanted simply because the event of interest (recurrence) never occurred due to the premature death of the patient (6-8). Unfortunately, such quality was restricted to a final additional analysis whereas all the study should be more robust if Cox was abandoned in favor of competing-risk (4). To date, only Metroticket 2.0 addressed such a clinical complex requisite (4).

In conclusion, in the last decade many efforts have been made to build prognostic systems able of improving discrimination and calibration of Milan criteria. The two more recent are now adults, while the present is still young to be applied clinically, but paved the road for future improvement in the future LT criteria in US.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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