Refining Milan criteria: is the alpha-fetoprotein model ready to cross borders?

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More than two decades after the adoption of Milan criteria for selection of hepatocellular carcinoma (HCC) patients for liver transplantation (LT) in the majority of the centers worldwide, several assumptions can be made.

Firstly, it is not controversial that Milan criteria, limiting the size and number of HCC for LT, allowed excellent outcomes for these patients (1,2) with 5-year survival rates similar to those observed after LT for benign liver diseases (around 70%), whereas non-transplanted HCC patients have poor outcomes. Secondly, these criteria have been challenged many times over the years because it became obvious to physicians that they excluded selected patients with potential good results (3,4). But the disrespect of Milan criteria with unreasonable heterogeneity in clinical practice has been accused of bad outcomes, not acceptable speaking of a scarce resource (5). Thirdly, emerged the evidence that biological markers of HCC, known as predictors of recurrence, such as alpha-fetoprotein (AFP) or des-gamma-carboxy-prothrombin (DCP), should be taken into account in the selection process (3,6-9).

On these bases, the Liver Transplantation French Study Group designed and validated in 2012 a new predictive model, the AFP model, that combines AFP values at listing with criteria of tumor size and number (10), and can be reassessed during the waiting time. What was at stake was a pre-operative model able to offer LT to patients exceeding Milan criteria with good outcomes (around 16% in the study) because of favorable biological features and at the opposite to exclude patients within Milan if despite bridging treatments they kept an AFP score higher than 2.

A first concern about this model is its extern validity, since it was validated on a French cohort of 435 patients, where alcohol represented a main cause of underlying liver disease (45% of patients, *vs.* 44% for post-hepatic disease).

In the study by Notarpaolo and colleagues in this issue of the *Journal of Hepatology* (11), the authors showed that the AFP model was also valid and superior to Milan for the selection of HCC patients for LT in an Italian multicentric cohort of 574 patients, although more than 80% of patients had a post-hepatic disease. Of note, 25% of the patients did not fulfill Milan criteria at listing. They report a risk of tumor recurrence of 13.2%±1.8% and 49.8%±8.7% (P<0.001) in patients with AFP score ≤2 and >2, and 13.6%±2.0% and 27.4%±4.6% (P<0.001) in patients within or beyond Milan. Within Milan as well as beyond, the recurrence and survival differed according to AFP score ≤2 *vs.* >2. The net reclassification improvement analysis showed that the AFP model improved prediction of non-recurrence compared to Milan criteria. Of interest, the analyses in the subgroups of hepatitis B virus (HBV) and hepatitis C virus (HCV) patients showed similar results, and one can be surprised by the high incidence of 5-year recurrence in the HCV population with AFP score >2 (67.8%±3.0%). Since this last etiology is suspected of particular tumor behavior (4), the ongoing comparisons of pathological features of HCC in the HCV *vs.* non-HCV populations according to the AFP model should be of interest.

A second concern about the AFP model implementation

is the unknown burden of what it would cause. It has to be underlined this is a central reason why Milan criteria have never been replaced for now in a majority of countries: "expanded" criteria would negatively influences the non-HCC waiting list (12), taking into account that the rate of patients listed for HCC is constantly increasing. The authors evaluate at 14% the burden caused by the application of the AFP model in their study (because 80/574 patients were beyond Milan but with AFP score ≤2), but the calculation must not be that simple. First, they do not give the number of patients to exclude because they were within Milan but with an AFP score >2. Second, and most importantly, this is not an intention-to-treat study, and there is no information about the wait-list drop-out due to the AFP model. In a prospective study assessing the total tumor volume (TTV)/AFP score (TTV/AFP score), the risk of drop-out at 12 months for patients beyond Milan, but within TTV/AFP score was much higher than those of patients within Milan (around 56% *vs.* 19%) (13). Length on waiting list, as well as response to bridging therapies (7,14) interfere on the drop-out rate and the addition of a marker of tumor behavior could lead to exclude more patients. It is not so obvious that the AFP model belongs to "expanded criteria".

The main limitation to this study is due to it retrospective design, because the calculation of the AFP score had to be done from imaging reports, as well as the response to treatment after loco-regional therapy. All patients had not the same assessment of HCC [CT scan, MRI or contrast-enhanced ultrasound (US)], with no central analysis, and the evaluation of "residual viable tumor tissue" can lead to a certain heterogeneity.

It would have been of interest, since the responses to bridging therapies are evoked in the results and in the discussion as a way to limit the burden of HCC patients on waiting list, to properly separate the analysis of patients who underwent salvage transplantation, although it might have concerned only a small number of patients.

Overall, the study by Notarpaolo *et al.* complete data on the good predictive results of the AFP model, in Italia, after France (10) and Latin America (15).

Of note, the French Organization for Organ Sharing officially implemented this model in 2013, and the UK LT program discussed these criteria in the National Consensus Meeting.

As far as determining if its use would be beneficial in other countries really depend on allocation policies and practice (notably for countries where living donor LT is massive) since respect of Milan criteria and median waiting time differ as much as etiologies of underlying diseases. Direct-acting antivirals should also modify the number and patient's repartition of indications on waiting lists. But it seems that this whole dynamic in the topic deserve prospective studies to test this model in other countries.

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Footnote

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