DOI: 10.1111/liv.13417



WILEY Liver INTERNATIONAL

# Predictive models for recurrence risk of hepatocellular carcinoma after liver transplantation: Still an unmet need

See Article on Page 717

## 1 | INTRODUCTION

Recurrence of hepatocellular carcinoma (HCC) after liver transplantation (LT) is a frightening issue. It is considered a systemic advanced stage with poor survival rate from the time of its diagnosis, with few therapeutic treatment resources because of its metastatic nature. Initially, in the early 1980s, the survival rate was poor for patients who had undergone LT for HCC because of a high tumour recurrence rate, near 65% in most series. These results were because of a lack of clear criteria for transplant candidate's selection and tumour diagnosis at advanced stages because of the absence of routine screening in the at-risk population.

The rise of LT for HCC worldwide has been achieved after technical-surgical advances and new immunosuppressive drugs on the one hand, and to the development of selection criteria of transplant candidates (one unique tumour ≤5 cm or up to three nodules with a greater nodule diameter less than 3 cm) resulting in an excellent survival outcome (>70%) and low recurrence rate at 5 years (<15%).[1] The Milan criteria made a revolution regarding LT worldwide and are today considered the standard selection criteria. However, the selection of candidates for transplantation purely and exclusively according to number and tumour diameter is currently under focus for re-evaluation. A number of studies, including the present one by Costentin et al.[2] are worth reading focusing on a challenging issue regarding categorization of HCC recurrence and a recent tendency for "hyperselection criteria", created to balance and ensure equitable access to organ allocation policies.[3]

## 2 | PRETRANSPLANTATION PREDICTIVE MODELS: SELECTION OF CANDIDATES

The first step is to correctly determine and identify the risk factors responsible for post-LT recurrence. The selection criteria should be based on a "hyperselection" of potential candidates to LT and assessment of recurrence risk. It would be ideal to be able to design a pretransplantation predictive model by analysing longitudinal data instead of the static photograph of a single pretransplantation moment to anticipate and specify the recurrence risk in vivo.

Considering only tumour variables in terms of number and diameter in a "static" approach, both the Milan and the University of California in San Francisco (UCSF) criteria have been developed from explant analysis and then validated by imaging assessment. The UCSF criteria and the French alpha-foetoprotein (AFP) model, which includes tumour number and diameter as well as serum AFP values, are the only ones that have been validated in external cohort studies.[4-6]

The use of tumour biomarkers has made their way in the process of improving the selection of potential liver recipients, including serum AFP before transplant,[5,7] and degree of tumour differentiation evaluated with a pre-LT tumour biopsy.[8] Serum AFP, both as a continuous variable and as a dichotomous or dummy variable has been associated with HCC recurrence independently of the size and number of pretransplant nodules. What is important to highlight is that AFP correlates independently with risk factors found in the explant, such as nuclear dedifferentiation or microvascular invasion.[5,6] This is why there is a *boom* in the inclusion of AFP as a variable of *hyperselection*. The problem lies in the cutoffs arising from different cohorts, which are not yet consensual, as for example <100 ng/mL, between 101 and 1000 ng/mL or >1000 ng/mL[5,6,9]; or even cutoff points above or below 400 ng/mL or 500 ng/mL,[10] and even of 66 ng/mL.[11] Moreover, a longitudinal change of AFP values in time has been an interesting approach.[12]

Nevertheless, these slightly static variables do not take into account the changes or dynamics arising during time on the waiting list. In fact, some authors have remarked that time on the waitlist acts as a unique opportunity of "natural" selection for transplant between *progressors* vs *non progressors*.[13] This approach is quite controversial, since time on the waiting list should consider the regional-local availability of organs and the need or not of a locoregional bridging therapy before transplantation.[14] Accordingly, considering tumour dynamic changes, and progression of liver disease severity while on the waiting list, it is necessary to assess these variables longitudinally, not only as a mere photograph at the time of listing or last pretransplant assessment but also at different time-points while listed.[5,15]

These pretransplant predictive models provide a close solution but they are not perfect, as it is reflected by discordant pretransplant imaging together with the explanted liver findings that in some series was higher than 30%, as reported by Constentin et al.[2] and other authors.[6,8,9,14] It is evident that in spite of the adequate selection of candidates, re-assessment is a priority considering explanted liver data, primarily focusing on the presence of microvascular invasion and tumour dedifferentiation. While these last two variables can be assessed by a tumour biopsy prior to transplantation,[8,16] the risk of

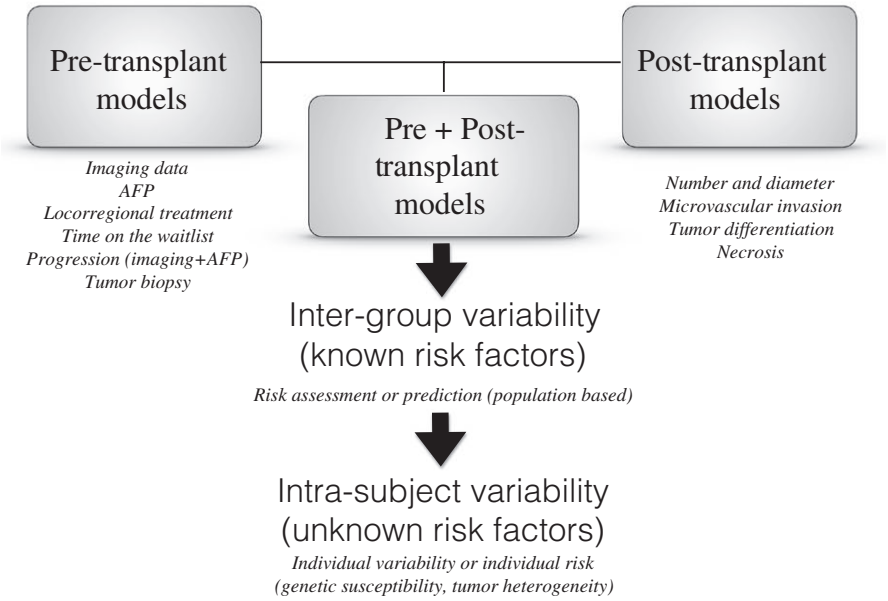


**FIGURE 1** Population based models are close to predict, though not perfect, individual's risk for HCC recurrence

tumour seeding and biopsy complications generate a safety limit. Additionally, performing a tumour biopsy is sometimes not technically viable and the absence of a microvascular invasion in a tumour biopsy does not completely exclude it. Besides, in spite of an adequate concordance or kappa agreement (intra-observer agreement) in the assessment of nuclear grade differentiation between pre and post-liver transplant evaluation,[16] the degree of concordance between different observers (inter-observer agreement) has been reported as low[17] or not evaluated.[8] Therefore, the risk of HCC recurrence after LT should be re-assessed with the explant findings.

## 3 | MODELLING THE RISK OF RECURRENCE WITH PRE AND POST-LIVER TRANSPLANTATION VARIABLES: CATEGORIZATION

According to Costentin et al.,[2] it is important to highlight the following: (i) Causes of imaging-explanted liver discordance that might be either the consequence of tumour progression during waiting list ("false" discordance) or a "real" discordance in terms of a low imaging accuracy, (ii) Which baseline of comparison is taken into account; according to imaging assessment at time of inclusion on the waitlist or with the last pretransplant imaging evaluation (information bias), (iii) The effects of locoregional therapy while on the waiting list, and (iv) Ultimately, the need of recategorizing recurrence risk after explanted liver analysis.

But then, what is the utility of recategorizing HCC recurrence risk? Firstly, risk categorization considering predictive models as a starting point should be considering that multivariate logistic or Cox regression models consider average population rather than individual risk (Figure 1). In order to calculate individual or interindividual risk, the individual variability should be considered, which, these multivariate models do not examine.[18] Therefore, there is a transplantation need to create predictive models that include pre and post-LT variables, including dynamic tumour changes and other biomarkers.

The comparison of the four predictive models based on variables from the explant made by Constentin et al.[2] showed that the Up-to seven criteria[19] and Decaens et al.[16] model presented the best discrimination power or AUROC of 0.79 and 0.74, respectively. Even when microvascular invasion was not considered in the Up-to seven criteria, as originally proposed by Mazzaferro et al. However, these models only discriminate two populations of HCC recurrence, low (<10%) and high risk (>40%). This categorization considering only two populations at risk is not useful, or at least has little application. For instance, tumour recurrence risk divided into low (<10%) and high (>40%) generates a big grey area among 10%-40% of medium-risk subjects, which does not clearly define clinical algorithms or recommendations to follow and not easily transferrable to the individual patient.

More recently, a predictive scoring model has been created including pre and post-transplant variables, the RETREAT score.[9] Despite adequate discrimination power (AUROC 0.82 CI 0.77; 0.86), as in other models, this score broadens the risk categorization framework not distinguishing intermediate subgroups. In the selection framework of dichotomous cutoffs over a ROC curve, it will depend on the chosen cutoff criteria used, either more sensitive or more specific.

Summing up, these models can always be improved and they should be first internally validated and then evaluated with external validation cohorts. There is a need for improvement in these predictive models, at population and individual levels, aiming to categorize them in no less than three groups of risk of recurrence, low <10%, intermediate 11%-20% and high >20%. This would mean an improvement in the process of selection of candidates, a more equitable distribution of organs considering the donor offer, and apart from these, the possibility to stratify risk for the development of future adjuvant therapies.[20] After all, it is important to consider that these regression models inform an average population risk rather than individual ones. It is therefore vital to improve the creation of these models including

further biomarkers and reduce the difficulties in their application or the actual transference to an individual patient.

## CONFLICTS OF INTEREST

The authors of this manuscript have no conflicts of interest to disclose as described by the *Liver International Journal.*

## FUNDING INFORMATION

Federico Piñero and Marcelo Silva received a Clinical Research Grant from the National Institute of Cancer (INC), Argentina.

Federico Piñero[1]
Flair J. Carrihlo[2]
Marcelo O. Silva[1]

[1]*Liver Transplant and Hepatology Unit, Faculty of Biomedical Science, Hospital Universitario Austral, Austral University, Pilar, Argentina*
[2]*Gastroenterology and Hepatology, Hospital da Clinicas, University of Sao Paulo School of Medicine, State University of Sao Paulo, Sao Paulo, Brazil*

## REFERENCES

1. Mazzaferro V, Bhoori S, Sposito C, et al. Milan criteria in liver transplantation for hepatocellular carcinoma: an evidence-based analysis of 15 years of experience. *Liver Transpl*. 2011;17:S44-S57.
2. Costentin C, Amaddeo G, Decaens T, et al. Prediction of hepatocellular carcinoma recurrence after liver transplantation: comparison of 4 explant-based prognostic models. *Liver Int*. 2017;37:717–726.
3. Goldberg D, French B, Abt P, et al. Increasing disparity in waitlist mortality rates with increased model for end-stage liver disease scores for candidates with hepatocellular carcinoma versus candidates without hepatocellular carcinoma. *Liver Transpl*. 2012;18:434-443.
4. Yao FY. Liver transplantation for hepatocellular carcinoma: beyond the Milan criteria. *Am J Transplant*. 2008;8:1982-1989.
5. Duvoux C, Thoraval FR, Decaens T, et al. Liver transplantation for hepatocellular carcinoma: a model including α-fetoprotein improves the performance of Milan criteria. *Gastroenterology*. 2012;143:986.e3-994.e3
6. Piñero F, Tisi Baña M, de Ataide EC, et al. Liver transplantation for hepatocellular carcinoma: evaluation of the AFP model in a multicenter cohort from Latin America. *Liver Int*. 2016;36:1657-1667.
7. Toso C, Trotter J, Wei A, et al. Total tumor volume predicts risk of recurrence following liver transplantation in patients with hepatocellular carcinoma. *Liver Transpl*. 2008;14:1107-1115.
8. Sapisochin G, Goldaracena N, Laurence JM, et al. The extended Toronto criteria for liver transplantation in patients with hepatocellular carcinoma: a prospective validation study. *Hepatology*. 2016;64:2077-2088.
9. Mehta N, Heimbach J, Harnois DM, et al. Validation of a risk estimation of tumor recurrence after transplant (RETREAT) score for hepatocellular carcinoma recurrence after liver transplant. *JAMA Oncol*. 2017;3:493–500.
10. Toso C, Asthana S, Bigam DL, et al. Reassessing selection criteria prior to liver transplantation for hepatocellular carcinoma utilizing the scientific registry of transplant recipients database. *Hepatology*. 2008;49:832-838.
11. Berry K, Ioannou GN. Serum alpha-fetoprotein level independently predicts posttransplant survival in patients with hepatocellular carcinoma. *Liver Transpl*. 2013;19:634-645.
12. Dumitra TC, Dumitra S, Metrakos PP, et al. Pretransplantation α-fetoprotein slope and Milan criteria. *Transplantation*. 2013;95:228-233.
13. Samoylova ML, Dodge JL, Yao FY, et al. Time to transplantation as a predictor of hepatocellular carcinoma recurrence after liver transplantation. *Liver Transpl*. 2014;20:937-944.
14. Otto G, Schuchmann M, Hoppe-Lotichius M, et al. How to decide about liver transplantation in patients with hepatocellular carcinoma: size and number of lesions or response to TACE? *J Hepatol*. 2013;59:279-284.
15. Parikh ND, Waljee AK, Singal AG. Downstaging hepatocellular carcinoma: a systematic review and pooled analysis. *Liver Transpl*. 2015;21:1142-1152.
16. Decaens T, Roudot-Thoraval F, Badran H, et al. Impact of tumour differentiation to select patients before liver transplantation for hepatocellular carcinoma. *Liver Int*. 2011;31:792-801.
17. Parfitt JR, Marotta P, AlGhamdi M, et al. Recurrent hepatocellular carcinoma after transplantation: use of a pathological score on explanted livers to predict recurrence. *Liver Transpl*. 2007;13:543-551.
18. Singh SK, Kaplan B, Joseph Kim S. Multivariable regression models in clinical transplant research. *Transplantation*. 2015;99:2451-2457.
19. Mazzaferro V, Llovet JM, Miceli R, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. *Lancet Oncol*. 2009;10:35-43.
20. Geissler EK, Schnitzbauer AA, Zülke C, et al. Sirolimus use in liver transplant recipients with hepatocellular carcinoma: a randomized, multicenter, open-label phase 3 trial. *Transplantation*. 2016;100:116-125.