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Metroticket 2.0 Model for Analysis of Competing Risks of Death Following Liver Transplantation for Hepatocellular Carcinoma

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Transplantation for Hepatocellular Carcinoma

Short title: Metroticket 2.0 model for Liver Transplantation in HCC

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Abbreviations: LT, liver transplantation; HCC, hepatocellular carcinoma; HCV, hepatitis C virus;

AFP, alpha-fetoprotein; CID, cumulative incidence of death; HBV, hepatitis B virus; MELD, model

for end-stage liver disease; IQR, interquartile range; RFS, recurrence-free survival; OS, overall

survival; mVI, microscopic vascular invasion; DBD, donation from brain-death; PVT, portal vein thrombosis.

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ABSTRACT

Background & Aims: Outcomes of liver transplantation for hepatocellular carcinoma (HCC) are determined by cancer-related and non-related events. Treatments for hepatitis C virus (HCV) infection have reduced non-cancer events among patients receiving liver transplants, so reducing HCC-related death might be an actionable endpoint. We performed a competing risk analysis to evaluate factors associated with survival of patients with HCC, and developed a prognostic model based on features of HCC patients before liver transplantation.

Methods: We performed multivariable competing risk regression analysis to identify factors associated with HCC-specific death of patients who underwent liver transplantation. The training set comprised 1018 patients who underwent liver transplantation for HCC from January 2000 through December 2013 at 3 tertiary centers in Italy. The validation set comprised 341 consecutive patients who underwent liver transplantation for HCC during the same period at the Liver Cancer Institute in Shanghai, China. We collected pre-transplant data on etiology of liver disease, number and size of tumors, patient level of alpha-fetoprotein (AFP), model for end-stage liver disease score, tumor stage, numbers and types of treatment, response to treatments, tumor grade, micro-vascular invasion, dates and causes of death. Death was defined as HCC-specific when related to HCC recurrence after transplant, disseminated extra- and/or intra-hepatic tumor relapse and worsened liver function in presence of tumor spread. The cumulative incidence of death was segregated for HCV status.

Results: In the competing-risk regression, the sum of tumor number and size and of Log_{10} level of AFP were significantly associated with HCC-specific death ($P<.001$), returning an average c-statistic

of 0.780 (95% CI, 0.763–0.798). Five-year cumulative incidence of non-HCC–related death were 8.6% in HCV-negative patients and 18.1% in HCV-positive patients. For patients with HCC to have a 70% chance of HCC-specific survival 5 years after transplantation, their level of AFP should be below 200 ng/mL and the sum of number and size of tumors (in cm) should not exceed 7; if the level of AFP was 200–400 ng/mL, the sum of the number and size of tumors should be 5 or less; if their level of AFP was 400–1000 ng/mL, the sum of the number and size of tumors should be 4 or less. In the validation set, the model identified patients who survived 5 years after liver transplantation with 0.721 accuracy (95% CI, 0.648%-0.793%). Our model, based on patients' level of AFP and HCC number and size, outperformed the Milan, UCSF, Shanghai-Fudan, Up-to-7 criteria (P<.001), and AFP French model (P=.044) to predict which patients will survive for 5 years after liver transplantation.

Conclusions: We developed a model, based on level of AFP, tumor size and tumor number, to determine risk of death from HCC-related factors after liver transplantation. This model might be used to select endpoints and refine selection criteria for liver transplantation for patients with HCC. To predict 5-years survival and risk of HCC-related death using an online calculator, please see: www.hcc-olt-metroticket.org/

Key words: liver cancer, prognosis, mortality, competing-risk analysis

INTRODUCTION

Hepatocellular carcinoma (HCC) has become a leading indication to liver transplantation (LT), even if LT for HCC remains an unfinished product searching for perfectibility.[1] The recent introduction of effective anti-hepatitis C virus (HCV) agents[2] together with the practice to down-stage tumors originally thought to be ineligible for transplantation[3] could increase the number of HCC within the transplant waiting-lists[4-7] and lead to contrasts between cancer and non-cancer indications in the current scenario of persistent organ shortage.

Cancer vs. non-cancer conditions are known to affect post-transplant outcome of individual patients, as well as liver function at the time of surgery, etiology of liver disease, co-morbidities, quality of the implanted graft and peri-operative management. All these features weight differently in determining overall survival. In fact, in case of HCC unadjusted survival, analysis may not fully discriminate among competing cancer and non-cancer events, hiding the observation of the events of interest during follow-up, particularly those cancer-specific[8] – as, for example, when death for causes other than tumor precedes the recurrence of the tumor itself.

In the last two decades, several selection criteria for HCC have been developed on pre-transplant features or explant pathology[9-12] in order to optimize overall patients survival after transplantation. Most of them include tumor parameters (size and number of tumor nodules), as well as biology surrogates such as serum alpha-fetoprotein (AFP) and response to pre-transplant neo-adjuvant therapies.

Although increasingly refined, all current criteria remain elusive when searching for HCC-specific survival. Conversely, the life expectancy achievable free of tumor as the cause of death should be obtainable, to compare cancer and non-cancer patients outcomes. Available criteria accurately predict post-transplant recurrence-free survival but advancement in the treatment of

HCC have produced significantly longer survival expectations in case of tumor recurrence: that is, HCC diagnosis after transplantation, albeit a dreaded event, often do not represent a diagnosis of imminent death. [13]

All these considerations underline the need for an appropriate analysis of competing events that occur in the natural history of LT for HCC. In competing-risk survival analysis the risks of death due to various causes can be discriminated so to produce a more reliable estimate of cancer and non-cancer related outcomes in respect to conventional survival analyses. To date, prognostication tools based on tumor parameters detectable pre-operatively and applicable to competing-risk analysis, are lacking.

In this study we sought at investigating the endpoint of cancer-specific survival in the setting of liver transplantation for HCC – namely considering as events of interest only those deaths caused by tumor recurrence. By means of competitive-risk analysis the independent oncologic determinants of cancer-specific survival were investigated with a prognostic model based on pre-transplant HCC features. This model and the related calculator may upgrade the current prognostic endpoints in this setting[14,15] and refine selection criteria for liver transplantation in patients with HCC.

METHODS

To produce a robust tool to predict post-transplant *"HCC-specific survival"* considering competing events, two parallel populations of patients were collected: a Western cohort (with HCV-prevailing chronic liver disease) for the training/internal validation set and an Eastern cohort (with HBV-prevailing background) for the external/independent validation set.

Patients

The training/internal validation set was used to develop, and to internally test, the competing-risk regression model. This cohort included all patients who underwent LT for HCC between January 2000 and December 2013 at three tertiary referral hepato-biliary and transplant Centers in Italy, prospectively collected on a common database and subsequently retrospectively analysed. The external validation set consisted of an independent consecutive cohort of patients who underwent LT for HCC during the same period at the Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai, China.

For both cohorts, only patients with documented pre-operative diagnosis of HCC, either non-invasive[16,17] or after confirmation biopsy, were included. No particular restrictions were made on whether LT was the first treatment option or a delayed procedure after neo-adjuvant therapies, including hepatic resection, according to different transplant policies, time periods and waiting-list capabilities. Incidental HCC found on the explanted liver and patients younger than 18 were excluded, as well as any kind of pre-operative portal vein thrombosis (PVT), in order to avoid misdiagnoses of non-neoplastic PVT, lack of shared protocols for PVT and any bias in evolution of diagnostic tools. In both cohorts, LTs were performed with grafts donated from brain-dead (DBD) subjects.

Data collection, definitions and endpoints

In the training/internal validation cohort, data collection and analysis focused on different time-points during tumor and treatment history of each patient, as follows:

a) at diagnosis of HCC: etiology of liver disease, number of HCCs, maximum diameter of nodules, AFP, model for end-stage liver disease (MELD) score;

"*b)* before transplantation: total number and maximum diameter of HCCs developed prior to LT from diagnosis to transplant decision (i.e. variable n. 6 and 7 listed in table 1), number and type of loco-regional/surgical treatments (neo-adjuvant therapies) performed, response to treatments, number and maximum diameter of active HCCs at last available radiological staging preceding transplantation (i.e. variable n.10 and 11 listed in table 1), AFP, MELD score;

c) at explant pathology: number and maximum diameter of active HCCs, number and maximum diameter of necrotic nodules, poorest tumor grading according to modified Edmondson-Steiner criteria,[18] presence/absence of micro-vascular invasion;

d) during follow-up: date of death or last censoring, date of recurrence or last censoring, cause of death.

For the validation set, demographic data, etiology of liver disease, last radiological staging before transplantation and follow-up data were collected.

At whichever pre-transplant time-point, only nodules with a maximum diameter ≥1 cm counted as HCC nodules if meeting the EASL/AASLD criteria.[16,17] In particular, after neo-adjuvant treatments a tumor nodule was defined as active if showing at dynamic radiological imaging (contrast enhanced CT-scan or MRI) an enhancement in the arterial phase with venous washout even in the context of a necrotic nodule. In each nodule the maximum diameter was measured, including any concomitant necrotic areas. Response to neo-adjuvant treatments was assessed according RECIST 1.1 criteria,[19-21] also deciding to include in the definition of complete response the absence of contrast (pathological) enhancement in any of the treated nodules. Response to treatments were assessed locally but controversial cases were discussed and agreed collectively.

Death was defined as *"tumor related"* for patients with a documented HCC recurrence after transplant, in presence of a disseminated extra- and/or intra-hepatic tumor relapse,

including also those cases whose liver function worsened as the consequence of tumor spread (i.e. liver involvement >50%, development of tumor portal vein invasion, neoplastic cachexia). Any other cause of death was defined as *"non-tumor related"*. The Institutional ethical and scientific review board of the coordinating Center approved the study, registered as NCT02898415

Statistical analysis

"HCC-related death" was the primary outcome measure. When evaluated in the contest of transplantation for HCC, death may be caused either by tumor recurrence or be unrelated to pre-transplant tumor conditions (i.e. for recurrence of viral hepatitis, chronic rejection, graft malfunction, co-morbidities, de-novo tumors etc.). In order to discriminate among them, a competing-risk analysis was implemented, to define the risk of death due to HCC recurrence. Thus, the main aim of the present study was to predict – on individual basis – this specific risk of death through a competing-risk analysis. The planned deliverable was to produce a web-based calculator, after adjustment of the Up-to-7 criteria contoured plots[11] on 3 pre-transplant HCC conditions: tumor size, number of tumor nodules and AFP levels determined at the last pre-transplant visit, whatever conditions of neo-adjuvant therapy or downstaging protocol were applied. Secondary endpoint was to work out unified criteria for HCC patients candidacy and list management in a large organ procurement regions, through a simplified version of the prognostic algorithm.

Continuous data were reported as mean and standard deviation or median and interquartile range (IQR) in relationship with their parametric distribution and compared, within subgroups, with appropriate tests (ANOVA and Kruskal-Wallis). Categorical data were reported as counts and percentages and compared, when necessary, with the Fisher exact test. Survival was measured from the date of LT until death or the date of the last follow-up visit. Recurrence-free

survival (RFS) was calculated from the date of transplantation until HCC recurrence or the date of the last follow-up visit. Survival rates, observed after transplant, were obtained by plotting Kaplan-Meier curves. The last patients censoring was performed within June 30th 2016.

To overcome the exclusive reliance on explant pathology of the Metroticket model,[11] the number of tumor nodules and size of the largest tumor were replaced by parameters measured on any vital HCC at pre-transplant radiology (see previous paragraph). Similarly, microscopic vascular invasion (mVI) – an exclusive pathology variable – was replaced by the last alpha-fetoprotein value available prior to LT. Since all these variables are known to have prognostic impact after LT for HCC, no additional analyses were performed in this regards. In addition, response to bridge therapies as prognostic parameter was captured by measuring tumor features of only vital tumors. Consequently, patients with complete response after neo-adjuvant treatments were considered as carrying zero nodules with zero diameter at pre-transplant assessment. As in the Up-to-7 criteria, the sum of number and size of the largest tumor, was considered as a whole.[11] Thus, three tumoral parameters combined into two variables (Number + Diameter and AFP levels) were included in the competing-risk regression. Considering that 81 deaths occurred as a consequence of HCC recurrence in the collected population the *"ten events per variable"* rule was satisfied, implying sufficient accuracy of regression estimates.

The competing-risk analysis[22] was planned by including these two variables into a multivariable model, performed on the training/internal validation cohort, through a 10-fold cross validation approach[23]. The failure event was represented by *"HCC-related death"* whereas *"death for other than HCC"* represented the competing event and was aimed at obtaining coefficients for the prediction of the risk of death due to HCC recurrence. Subsequently, in order to obtain the prediction of *"death for other than HCC"* a second competing-risk regression was modelled considering this event as the failure event and the *"HCC-related death"* as competing event. This

second model was based on sex, age and hepatitis C status and was necessary to derive the predicted cumulative incidence of death (CID) – at mean of covariate and segregated for HCV – for mortality due to causes different from HCC recurrence.

The tumor variables used for the model were those collected at pre-LT last radiology assessment. In the training/internal validation and in the external validation cohort, the discriminatory ability of the model was assessed by the means of the modified c-statistic for competing-risk analyses proposed by Wolbers.[24] In the external validation cohort, this discriminatory ability was tested against that of the most commonly used prognostic criteria for liver transplantation in HCC patients, namely, Milan criteria,[9] AFP-French model,[25] UCSF criteria,[10] Fudan-Shangai criteria,[26] and Up-to-7 criteria.[11] Since the Wolbers's method does not provide a comparison between different c-statistic values, the Harrell's c-statistic was provided and calculated assuming *"HCC-related death"* as failure event, and by censoring *"deaths for other than HCC"*.

Statistical analyses were performed using the STATA syntax "stcompet" and "stcrreg" (StataCorp. *Stata* Statistical Software: Release 12) and the packages "survival", "risk-regression", and "pec" of R-project (R version 2.13.0; R Foundation for Statistical Computing, Vienna, Austria). A p-value <0.05 was considered statistically significant in all the analyses.

RESULTS

1. Model construction and results in the training/internal validation cohort

The training cohort consisted in a consecutive series of 1018 recipients (*Table 1*). During a median follow-up of 70.8 months (95%CI: 67.1-70.6), 111 patients experienced HCC recurrence after LT and 240 deaths were recorded, of which 81 (33.8%) were tumor-related. Kaplan-Meier estimates of overall survival were 78.0% and 67.9% at 5 and 10 years respectively and of recurrence-free survival were 87.4% and 85.7% at 5 and 10 years respectively. Cumulative incidences of *"HCC-related death"* and of *"death for other causes"* are depicted in *Figure 1*.

Response to neo-adjuvant therapies

Confirming current selection criteria, at diagnosis and at last radiological assessment most patients were within UNOS T2 stage (88% and 89.4% respectively). The majority (860 patients; 84.5%) underwent neo-adjuvant treatments and, at the last radiological assessment prior to transplant, 38.7% of patients showed complete response, 37.4% partial response/stable disease and 23.9% disease progression (*Table 1*). The median time from last radiological assessment to transplantation was 2.3 months (95%CI: 0.2-11.4). Response to neo-adjuvant therapies (*Table 2*) significantly correlated with tumor morphology and biological characteristics at any assessment (i.e. number of tumors, size, AFP, therapies applied) with $p < 0.001$ in all instances (Spearman's rho for number+size = 0.874; for Log10 AFP = 0.535; p<0.001). As can be noted, in Cohen's terms, the correlation is above the threshold of 0.5 to be considered as a large correlation. For this reason, radiological response was not included as a covariate in the competing-risk regression.

Competing-risk regression model

In *Table 3* results from 10-fold cross validation competing-risk regression model[23] are summarized also reporting the necessary reference to solve the Fine and Gray CID. In each of the ten samples, coefficients for the sum of the number of tumor nodule and diameter of the largest nodule and for $Log_{10}AFP$ were significant (p<0.001). The average c-statistic in the training group was 0.780 (95%CI: 0.763-0.798) and in the internal validation group was 0.733 (95%CI: 0.704-0.763), providing good accuracy of the present model in the prediction of the cumulative incidence of *"HCC-related death"*. The average values of coefficients and of the baseline cumulative sub-hazard function were used to construct the final model. *Figure 2A* summarizes, in a contour plot, variations of the HCC-specific survival at 5 years (obtained by subtracting the predicted HCC 5-year risk of death from 100), related with Number+Size of the tumor and AFP. The individual case prognostication algorithm was made available at the website: *www.hcc-olt-metroticket.org*

AFP adjusted-to-HCC size criteria

The competing-risk regression on the event *"death for other causes"* returned a 5-year CID of 13.2%, ranging between 8.6% for HCV-negative patients and 18.1% for HCV-positive patients (p<0.001). Thus, to obtain the overall individual prediction of 5-year risk of death, these values, considering or not the liver disease etiology, should be summed to the 5-year HCC-specific CID.

A secondary endpoint of the study was to provide a dichotomous criteria for transplantability, that would allow a 5-year mortality < 50%. To do so, given an average 5-year CID for other causes of 13.2%, the 5-year *"HCC-related death"* CID was arbitrarily set at a threshold of 30% to allow for confidence bands. This safety threshold was fulfilled in 3 pre-transplant

incremental and distinctive tumor conditions, defining the AFP-adjusted-to-HCC size criteria (depicted in a simplified layout in *Figure 2B*):

a) HCC at pre-transplant radiology within the up-to-7 criteria, if AFP < 200ng/mL;

b) HCC at pre-transplant radiology within the up-to-5 criteria, if AFP 200 - 400 ng/mL;

c) HCC at pre-transplant radiology within the up-to-4 criteria, if AFP 400 - 1000 ng/mL;

considering as up-to-7, to-5 or to-4 the maximum allowed sum of size (in cm) and number of tumors derived in any given HCC prior to transplantation on the last radiology assessment, whether or not preceded by neo-adjuvant therapies.

Patients outcomes in both cohorts captured by overall, HCC-specific and RFS curves are reported in *Figure 3* in which patients within vs. beyond the proposed criteria adjustment are compared. It is worth of note that in the patients within vs. beyond the AFP-adjusted-to-HCC size criteria showed a 5-year overall (*Panel A*), HCC-specific (*Panel B*) and recurrence-free survival (*Panel C*) of 79.7% vs. 51.2% (p < 0.0001), 93.5% vs. 55.6% (p < 0.0001) and 89.6% vs. 46.8% (p < 0.0001) respectively.

2. Validation cohort

Characteristics of the external validation cohort are detailed in *Table 1*. With respect to the training cohort, the external validation cohort had a significantly lower median age and MELD score at transplant, was significantly most frequently affected by HBV-related chronic liver disease and AFP and tumour stage were significantly worse both at diagnosis and at the last staging before liver transplantation. Thus, the search for heterogeneity in etiology and tumor features with respect to Western patients was satisfied.

During a median follow-up of 76.7 months (95%CI: 73.3-80.2), 73 patients experienced post-transplant HCC recurrence and 95 deaths were recorded, of which 64 (67.4%) were tumor-

related. Overall survival was 74.9% and 68.6% at 5 and 10 years respectively, similar to that of the training cohort (p=0.423). Of note, RFS was 77.9% and 76.6% at 5 and 10 years respectively, significantly lower than the corresponding 89.6% and 87.4% observed in the Western training cohort (p<.0001).

In *Figure 3*, the survival curves of patients from the Eastern cohort are reported aside of those of the training set. The 5-year overall, HCC-specific and recurrence-free survivals were significantly different when comparing cases within vs. outside the proposed AFP-adjusted-to-HCC size criteria and in fact were 80.8% vs. 63.3% (p=0.001), 90.1% vs. 66.6% (p < 0.0001) and 86.4% vs. 62.0% (p < 0.0001) respectively.

In *Table 4* the Harrell's and Wolbers's c-statistics of the proposed model are tested in the validation cohort, and compared to that of commonly used transplant criteria for HCC patients. As can be noted, both the Harrell's and the Wolbers's c-statistics are the highest for the present model. In addition, the Harrell's c-statistics was significantly higher to that of the Milan criteria (p<0.001), the Shangai-Fudan criteria (p<0.001), the UCSF criteria (p<0.001), the Up-to-seven criteria (p<0.001) and the AFP French model (p=0.044).

DISCUSSION

Hepatocellular carcinoma brings a "double prognosis" depending on two main components: tumor burden and liver function. That is, cancer-specific outcome in such patients remains difficult to determine, considering the influence of non-tumoral conditions on patient performance status, eligibility to therapies, risk of de-novo tumors and ultimately survival. The introduction in recent years of effective treatments achieving control of hepatitis B and C viruses[2]

has greatly reduced the prognostic impact of underlying liver disease on HCC evolution and this has fostered a reappraisal of cancer-specific survival as an endpoint worth investigation. Competing-risk analysis is pertinent in this setting, as it allows cancer-related events of interest to emerge from unadjusted survival curves, also estimating individualized risks of cancer recurrence and cancer-related death.

In this observational study conducted on 1058 Western patients transplanted for HCC, individual prediction of cancer-specific events in comparison with the non-cancer counterparts has been taken as main endpoint (*Figure 1*). Of note, outcome prediction was conducted using pre-operative determinants of prognosis easily determinable in current practice (*Figure 2*), such as tumor morphology at conventional CT/MRI scan and the biomarker AFP, frequently associated with higher risk of pre-transplant tumor progression and poorer post-transplant survival.[25,27]

Loading those variables in a web-based calculator freely accessible at *www.hcc-olt-metroticket.org* cancer-specific outcome in any individual patient can be objectivized. This facilitates decision on transplant eligibility at various time-points during patient history and particularly after completion of neo-adjuvant tumor treatments. This represents an improvement with respect to most prognostication tools based on post-transplant tumor pathology assessment and generate an applicable score for Centers that perform various forms of neo-adjuvant treatments.

Of note, the proposed AFP-adjusted-to-HCC size criteria based on HCV-predominant Western patients were externally validated in a large sample of Eastern HBV-predominant patients (*Table 3* and *Figure 3*) and turned to be competitive with respect to the current transplant criteria for HCC (*Table 4*). In addition to the confirmed accuracy of the AFP-adjusted-to-HCC size criteria, the comparison of viral hepatitis etiologies among training and external validation sets supports

the concept of post-transplant outcome in HCC as a summation of cancer-related and non-cancer related survivals – the latter particularly linked to HCV control – each being determinable for better stratification of the post-transplant predictions.

Significant differences among training and validation cohorts in incidence of HCV infection (56.9% vs. 2.6%), tumor stage >T2 at transplant (31% vs. 12%) yielded a 10.5% increment in HCC recurrence-rate in China with respect to the Europe (77.9% vs. 87.4%, p: <.0001) but no significant impact on overall survival (74.9% vs. 78.0%, p: 0.423). This confirms that post-transplant overall survivals in Eastern and Western HCC patients can equate, irrespective of hepatitis etiology once viruses are effectively controlled and tumor stage are similar, therefore when cancer and the main non-cancer-related causes of death are equalized.

The efficiency of the proposed model relies on the inclusion of AFP in the equation predicting post-transplant prognosis in HCC. With respect to other AFP-including models[25,28] the present simplified AFP-adjusted-to-HCC size criteria (*Figure 2B*) increased to three the cutoffs eliciting progressive morphology restrictions for HCCs considered for transplant (i.e. 200 ng/mL for the up-7 sum in size + number of tumor nodules; 400 ng/mL for the up-5 and 1000 ng/mL for the up-4). Such AFP cutoffs confirm previous studies showing decreases in post-transplant survival as pre-transplant level of AFP increases[25,28,29] and add flexibility to the system. In fact, rather than at listing,[25,28] the presented model calculates cancer-specific outcome on the last AFP level available prior to liver transplant (median 2.3 months): a condition that allows tumor re-assessment during the waiting phase while responses to neo-adjuvant treatment can be observed as a markers of tumor aggressiveness.[30] Although not a single AFP threshold reliably predicts poor prognosis, the inverse interaction between AFP and tumor morphology demonstrated in the presented model

may help in refine priority among HCC listed patients and select drop-outs during the waiting period when, despite treatment, cancer-specific risk may exceed the expectations[31].

Detailed assessment of pre-transplant HCC treatment on post-transplant outcome was beyond the scope of the present analysis, being treatment protocols too heterogeneous among Centres to draw solid conclusions. As expected, efficacy of neo-adjuvant treatments was significantly correlated with HCC features and AFP (*Table 2*) and that excluded radiologic response as a covariate in the competing-risk analysis. This did not impede the resulting model prediction to be well applicable to the pre-transplant condition of individual patients with different presentation of HCC (Spearman correlation >0.5). Lack of central review and adherence to the non-HCC specific response criteria are another bias of this study. However, the presented outcome data concurred in defining as active and measurable any HCC that after neo-adjuvant treatment is still showing at CT/MRI scan an enhancement in the arterial phase with venous washout, even in the context of a necrotic nodule. [20,21] Another potential limitation of the study is the variability of pre-LT imaging and techniques across the study period and among Centers. The impact of that on the presented results was not assessed, as it depends on several variables (i.e. comparative sensitivity and specificity of CT and MRI, inter-observer fluctuation in tumor assessment etc.) whose collection and analysis were beyond the scope of the study.

No aspect of liver transplant for HCC is untouched by a reliable prediction of prognosis. A refinement of post-transplant endpoints based on HCC-specific outcomes could update current recommendations for cirrhotic patients with HCC[15] and put transplant criteria in perspective. Treatment planning may also benefit of a prediction focused on cancer, considering the great improvement in management of non-cancer events, especially viral hepatitis. The presented

model, built on pre-operative tumor variables, adds individualized, calculator-assisted survival predictions at various time points of the patients' history according to the variegated effects of neo-adjuvant therapies. This could ease decisions-making at all levels of the transplant and oncology communities.

REFERENCES

1. Starzl TE, Todo S, Tzakis AG, et al. Liver transplantation: an unfinished product. Transplant Proc 1989;21:2197–2200.

2. Felmlee DJ, Coilly A, Chung RT, et al. New perspectives for preventing hepatitis C virus liver graft infection. Lancet Infect Dis 2016;16:735–745.

3. Yao FY, Mehta N, Flemming J, et al. Downstaging of hepatocellular cancer before liver transplant: long-term outcome compared to tumors within Milan criteria. Hepatology 2015;61:1968–1977.

4. Kim WR, Lake JR, Smith JM, et al. OPTN/SRTR 2013 Annual Data Report: liver. Am J Transplant 2015;15 Suppl 2:1–28.

5. NHS. UK Liver tranplant Registry data 2015. NHS. Available at: http://www.odt.nhs.uk/pdf/organ_specific_report_liver_2016.pdf [Accessed November 5, 2016].

6. Angelico M, Cillo U, Fagiuoli S, et al. Liver Match, a prospective observational cohort study on liver transplantation in Italy: study design and current practice of donor-recipient matching. Dig Liver Dis 2011;43:155–164.

7. Wang H, Jiang W, Zhou Z, et al. Liver transplantation in mainland China: the overview of CLTR 2011 annual scientific report. Hepatobiliary Surg Nutr 2013;2:188–197.

8. Noordzij M, Leffondré K, van Stralen KJ, et al. When do we need competing risks methods for survival analysis in nephrology? Nephrol. Dial. Transplant. 2013;28:2670–2677.

9. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693–699.

10. Yao FY. Liver transplantation for hepatocellular carcinoma: Expansion of the tumor size limits does not adversely impact survival. Hepatology 2001;33:1394–1403.

11. 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.

12. Raj A, McCall JL, Gane E. Validation of the "Metroticket" predictor in a cohort of patients transplanted for predominantly HBV-related hepatocellular carcinoma. J Hepatol 2011;55:1063–1068.

13. Bodzin AS, Lunsford KE, Markovic D, et al. Predicting Mortality in Patients Developing Recurrent Hepatocellular Carcinoma After Liver Transplantation: Impact of Treatment Modality and Recurrence Characteristics. Ann Surg 2016.

14. Clavien P-A, Lesurtel M, Bossuyt PMM, et al. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. Lancet Oncol 2012;13:E11–E22.

15. Llovet JM, Di Bisceglie AM, Bruix J, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. J. Natl. Cancer Inst. 2008;100:698–711.

16. European Association for the Study of the Liver EASL EASL, European Organisation For Research And Treatment Of Cancer. EASL-EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2012;56:908–943.

17. Bruix J, Sherman M, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology 2011;53:1020–1022.

18. Nzeako UC, Goodman ZD, Ishak KG. Comparison of tumor pathology with duration of survival of north american patients with hepatocellular carcinoma. Cancer 1995;76:579–588.

19. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur. J. Cancer 2009;45:228–247.

20. Lencioni RA, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin. Liver Dis. 2010;30:52–60.

21. Wald C, Russo MW, Heimbach JK, et al. New OPTN/UNOS policy for liver transplant allocation: standardization of liver imaging, diagnosis, classification, and reporting of hepatocellular carcinoma. Radiology 2013;266:376–382.

22. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. Journal of the American Statistical Association 1999;94:496–509.

23. Steyerberg E. *Clinical prediction models: a practical approach to development, validation, and updating*. New York; Springer New York 2009:209–210.

24. Wolbers M, Blanche P, Koller MT, et al. Concordance for prognostic models with competing risks. Biostatistics 2014;15:526–539.

25. Duvoux C, Roudot-Thoraval F, Decaens T, et al. Liver transplantation for hepatocellular carcinoma: a model including α-fetoprotein improves the performance of Milan criteria. Gastroenterology 2012;143:986–994.

26. Fan J, Yang G-S, Fu Z-R, et al. Liver transplantation outcomes in 1,078 hepatocellular carcinoma patients: a multi-center experience in Shanghai, China. J Cancer Res Clin Oncol 2009;135:1403–1412.

27. Llovet JM, Peña CEA, Lathia CD, et al. Plasma biomarkers as predictors of outcome in patients with advanced hepatocellular carcinoma. Clinical Cancer Research 2012;18:2290–2300.

28. Toso C, Meeberg G, Hernandez-Alejandro R, et al. Total tumor volume and alpha-fetoprotein for selection of transplant candidates with hepatocellular carcinoma: A prospective validation. Hepatology 2015;62:158–165.

29. Pommergaard H-C, Burcharth J, Rosenberg J, et al. Serologic and molecular biomarkers for recurrence of hepatocellular carcinoma after liver transplantation: A systematic review and meta-analysis. Transplant Rev 2016;30:171–177.

30. Vibert E, Azoulay D, Hoti E, et al. Progression of alphafetoprotein before liver transplantation for hepatocellular carcinoma in cirrhotic patients: a critical factor. Am J Transplant 2010;10:129–137.

31. Mazzaferro V. Squaring the circle of selection and allocation in liver transplantation for HCC: An adaptive approach. Hepatology 2016;63:1707–1717.

TABLE LEGEND

Table 1. Clinical characteristics of the study populations who underwent liver transplantation with a pre-transplant diagnosis of HCC on chronic liver disease

Table 2. Patients and HCC characteristics related to the last available radiological assessment (median: 2.3 months) before liver transplantation.

Table 3. Ten-fold cross-validation multivariable competing-risk regression on *"death due to HCC recurrence"* in the training/internal validation cohort.

Table 4. Accuracy of AFP-adjusted-to-HCC size criteria compared with current criteria for liver transplantation in HCC in the external validation cohort.

FIGURES LEGEND

Figure 1: **Cumulative incidence function of** *"HCC-related death"* **and of** *"death for other than HCC"* **in 1018 liver transplant recipients.**

HCC cancer–specific mortality was lower than noncancer-specific mortality during the entire post-transplant period.

Figure 2: **HCC-specific survival at 5 years after liver transplantation, according to variations in Number of nodules + Diameter of the largest nodule and Alpha-fetoprotein** (*panel A*) **with the derived AFP-adjusted-to-HCC-size criteria** (*panel B*)**.**

A. HCC-specific survival estimates (contour plot) can be determined on the last available HCC features along the patients' follow-up, namely before/after neo-adjuvant treatments, while on the transplant waiting list. Individual prognostication is accessible for any given patient at: www.hcc-olt-metroticket.org . To obtain the individual prediction of overall survival, an additional 8.6% (for HCV-negative patients) or 18.1% (for HCV-positive patients) should be subtracted from the individual HCC-specific survival. The contour plot is derived from the average estimates from the training cohort of Table 3.

B. Dichotomous (in/out) criteria of transplantability identify 3 incremental combinations in HCC morphology parameters (largest vital tumor size + number of vital tumor nodules) and biology (AFP), determined at pre-transplant radiology staging before/after neoadjuvant tumor treatments. The *AFP-adjusted-to-HCC size criteria* (green areas) assume a 5-year HCC-related death and overall mortality of 30% and <50% respectively. The criteria applied to the studied population allowed 79.7% overall survival at 5-year (see figure 3).

Figure 3: **Long-term outcome of liver transplantation for HCC applying the AFP-adjusted-to-HCC-size criteria.**

Kaplan–Meier estimates of overall survival (*Panel A*), tumor-specific survival (*Panel B*) and recurrence-free survival (*Panel C*), according to the AFP-adjusted-to-HCC-size criteria (AFP-UTS) in the training and validation sets. In all instances, survival was significantly different when comparing patients within (green) vs. outside (red) the *AFP-adjusted-to-HCC size criteria*. No significant difference in survival was observed among Western and Eastern cohorts, providing

adhesion to the proposed criteria. The hazard-ratio values decreased in the validation cohort with respect to the training set due to the slight reduction in accuracy in the cohort not used to develop the score, while the c-statistics remained >0.5 in both cohort and within/outside criteria.

Table 1. Clinical characteristics of the study populations who underwent liver transplantation with

a pre-transplant diagnosis of HCC on chronic liver disease

Variables	Training set (Western n: 1018)	Validation set (Eastern n: 341)	P
Age (years)			<0.0001
Mean (SD)	55.9 (7.0)	51.9 (9.2)	
Median (IQR)	56.6 (51.1 – 61.1)	52.3 (45.9 – 58.0)	
Gender			0.854
Male	884 (86.8%)	295 (86.5%)	
Female	134 (13.2%)	46 (13.5%)	
Cause of cirrhosis*			<0.0001
Hepatitis C	579 (56.9%)	9 (2.6%)	
Hepatitis B	327 (32.1%)	328 (96.2%)	
Alcohol	202 (19.8%)	-	
Other	71 (6.9%)	2 (0.6%)	
UNOS T stage at diagnosis (n=975[#]/196[§])			<0.0001
T1	280 (28.7%)	38 (19.4%)	
T2	578 (59.3%)	96 (49.0%)	
T3-T4a	117 (12.0%)	62 (31.6%)	
Starting AFP (ng/mL) (n=942[#]/196[§])			<0.0001
Mean Log_{10} (SD)	1.12 (0.68)	1.8 (1.0)	
Median (IQR)	9.2 (4.7 – 28.5)	49.8 (9.7 - 346.7)	
Total number of tumors developed prior to LT (n=937[#])	NA		
Single nodule	467 (49.8%)		
2-3 nodules	366 (39.1%)		
3-5 nodules	80 (8.5%)		
More than 5	24 (2.7%)		
Largest tumor developed prior to LT (cm) (n=937[#])	NA		
Mean (SD)	2.6 (1.4)		
Median (IQR)	2.5 (1.7 – 3.0)		
Neo-adjuvant therapies prior to LT*			
TACE / TAE	579 (56.9%)	120 (35.2%)	
Ablation / Ethanol injection	456 (44.8%)	28 (8.2%)	
Hepatic Resection	95 (9.3%)	85 (24.9%)	
TARE / EBR	12 (1.2%)	14 (4.1%)	
Radiological response at last assessment prior to LT (n=918[#])	NA		
Complete response	355 (38.7%)		
Partial response / stable disease	343 (37.4%)		
Disease progression	220 (23.9%)		
Number of vital tumors at pre-LT radiology (n=953[#]/341[§])			<0.0001
None	355 (37.3%)	0	
Single nodule	325 (34.1%)	211 (61.9%)	
2-3 nodules	230 (24.1%)	86 (25.2%)	
More than 3 nodules	43 (4.5%)	44 (12.9%)	
Largest vital tumor at pre LT radiology (cm) (n=581[#]/341[§]) **			<0.0001
Mean (SD)	2.5 (1.4)	3.8 (2.6)	
Median (IQR)	2.0 (1.5 – 3.0)	3.0 (2.0 – 4.7)	
UNOS – T stage at transplant (n=937[#]/341[§])			<0.0001
T0	355 (37.9%)	0 (0%)	
T1	163 (17.4%)	62 (18.2%)	
T2	320 (34.1%)	150 (44.0%)	
T3-T4a	99 (10.6%)	129 (37.8%)	
			<0.0001

Variables	Training set (Western n: 1018)	Validation set (Eastern n: 341)	P
Last AFP prior to LT *(ng/mL) (n=956[#]/341[§])*			
Median (IQR)	8.3 (4 – 22)	32.9 (6.6 – 232.9)	
Mean Log_{10} (SD)	1.04 (0.64)	1.7 (1.0)	
<100 ng/mL	870 (91.0%)	228 (66.9%)	
100 – 400 ng/mL	64 (6.7%)	45 (13.2%)	
>400 ng/mL	22 (2.3%)	73 (21.4%)	
MELD score at LT *(n=951[#]/341[§])*			<0.0001
Mean (SD)	12.9 (5.7)	10.9 (4.6)	
Median (IQR)	11 (9 – 15)	10 (8 – 13)	
Transplant period			<0.0001
2000 – 2005	339 (33.3%)	42 (12.3%)	
2006 – 2010	378 (37.1%)	180 (52.8%)	
2011 – 2013	301 (29.6%)	119 (34.9%)	
Overall Survival			0.423
3-yr	83.3%	78.1%	
5-yr	78.0%	74.9%	
Recurrence-free Survival			<0.0001
3-yr	89.6%	81.0%	
5-yr	87.4%	77.9%	
HCC-specific Survival			<0.0001
3-yr	93.4%	84.4%	
5-yr	91.6%	82.0%	

\# Number of evaluable patients in the training set.

§ Number of evaluable patients in the validation set.

* A single patient could have more than one causes of cirrhosis and can be submitted to more than one bridge therapy; consequently, the sum of different causes of cirrhosis is not necessarily 100%. Sorafenib was occasionally given in association with neo-adjuvant loco-regional therapies.

** Includes only patients with vital tumors, thus, diameters of non-vital tumors were excluded from the calculation.

Abbreviations: SD = Standard deviation; IQR = Interquartile range (25th – 75th percentiles); NA = not available; UNOS = United Network for Organ Sharing; LT = liver transplantation; AFP = alpha-fetoprotein; TACE = trans-arterial chemo-embolization (includes drug-eluting beads); TAE = trans-arterial embolization; TARE = trans-arterial radio-embolization; EBR = external beam radiation; MELD = Model for End-Stage Liver Disease

Table 2. Patients and HCC characteristics related to the last available radiological assessment (median: 2.3 months) before liver transplantation.

Variables	Complete Response (no. of patients)	Partial Response and Stable Disease (no. of pts.)	Disease (HCC) Progression (no. of pts.)	p
UNOS – T stage				
T1 – T2 *(800)*	39.9% *(319)*	34.6% *(277)*	25.5% *(204)*	0.001
T3 - T4a *(107)*	24.3% *(26)*	60.7% *(65)*	15.0% *(16)*	
Starting AFP (ng/mL)				
Median (IQR)	8 (5 – 27) *(329)*	9 (4 – 24) *(317)*	11 (5 – 39) *(207)*	0.058
Mean Log_{10} (SD)	1.10 (0.70) *(329)*	1.10 (0.68) *(317)*	1.20 (0.64) *(207)*	0.201
Total number of tumors developed prior to LT				
Median (IQR)	1 (1 – 2) *(355)*	2 (1 – 3) *(343)*	3 (2.0 – 3.5) *(220)*	0.001
Largest tumor developed prior to LT (cm)				
Median (IQR)	2.0 (1.5 – 3.0) *(355)*	2.4 (1.7 – 3.2) *(343)*	2.7 (2.0 – 3.5) *(220)*	0.001
Neo-adjuvant therapies adopted prior to LT				
Hepatic Resection or ablation *(482)*	51.5% *(248)*	26.6% *(128)*	22.0% *(106)*	0.001
Other *(436)*	24.5% *(107)*	49.3% *(215)*	26.1% *(114)*	
Number of vital tumors at pre-LT radiology				
Median (IQR)	0 *(355)*	1 (1 – 2) *(343)*	2 (1 – 3) *(220)*	0.001
Largest vital tumor at pre-LT radiology (cm)				
Median (IQR)	0 *(355)*	2.0 (1.4 – 2.9) *(343)*	2.5 (2.0 – 3.3) *(220)*	0.001
Number + Size*				
Median (IQR)	0 *(355)*	3.4 (2.5 – 4.5) *(343)*	4.8 (4.0 – 6.0) *(220)*	0.001
Last AFP prior to LT (ng/mL)				
Median (IQR)	7.0 (3.5 – 20.0) *(339)*	8.2 (4.0 – 20.1) *(322)*	11.0 (5.0 – 34.0) *(207)*	0.001
Mean Log_{10} (SD)	0.95 (0.61) *(339)*	1.03 (0.63) *(322)*	1.19 (0.68) *(207)*	0.001
MELD score at LT				
Median (IQR)	10 (8 – 14) *(322)*	12 (9 – 17) *(320)*	12 (9 – 16) *(209)*	0.001

For each reported variable, the number in italic between brackets gives the number of patients in which a pre-LT radiological re-assessment on that variable was available. Tumor response/progression was assessed according to RECIST 1.1[19] criteria [including in the definition of complete response the absence of contrast (pathological) enhancement in any of the treated nodules]. Abbreviations: SD = Standard deviation; IQR = Interquartile range (25th – 75th percentiles); LT = liver transplantation; AFP = alpha-fetoprotein; MELD = Model for End-Stage Liver Disease. *Number+Size = number of tumor nodules summed to the size (in cm) of the largest nodule. T stage = tumor stage according to UNOS classification (United Network for Organ Sharing).

Table 3. Ten-fold cross-validation multivariable competing-risk regression on *"death due to HCC recurrence"* in the training/internal validation cohort.

	Sample										Mean (95%CI)
	1	2	3	4	5	6	7	8	9	10	
Sample size of the training cohort (no.)	790	786	795	790	791	793	790	791	787	789	
Coefficients											
$\quad$Log$_{10}$AFP (ng/mL)	0.8392	0.7278	0.8679	0.8595	0.8842	0.8124	0.7721	0.7999	0.8141	0.7912	0.817 (0.787 – 0.846)
$\quad$Number + diameter of vital tumors	0.2288	0.2654	0.1933	0.2420	0.2267	0.2156	0.2434	0.2195	0.2006	0.2327	0.227 (0.214 – 0.240)
Baseline cumulative sub-hazard function											
$\quad$1-year	0.0028	0.0029	0.0027	0.0026	0.0025	0.0027	0.0028	0.0027	0.0022	0.0028	0.003 (0.002 – 0.004)
$\quad$3-year	0.0110	0.0102	0.0115	0.0094	0.0105	0.0123	0.0110	0.0119	0.0111	0.0118	0.011 (0.010 – 0.012)
$\quad$5-year	0.0141	0.0132	0.0143	0.0121	0.0133	0.0156	0.0137	0.0146	0.0145	0.0143	0.014 (0.013 – 0.015)
c-statistic	0.763	0.774	0.768	0.774	0.759	0.783	0.767	0.755	0.846	0.814	0.780 (0.763 – 0.798)
Sample size of the testing cohort (no.)	88	92	83	88	87	85	88	87	91	89	
c-statistic*	0.740	0.657	0.754	0.657	0.784	0.757	0.702	0.793	0.754	0.754	0.733 (0.704 – 0.763)

Average values were used for the contour plot by solving the Fine and Gray formula[22].
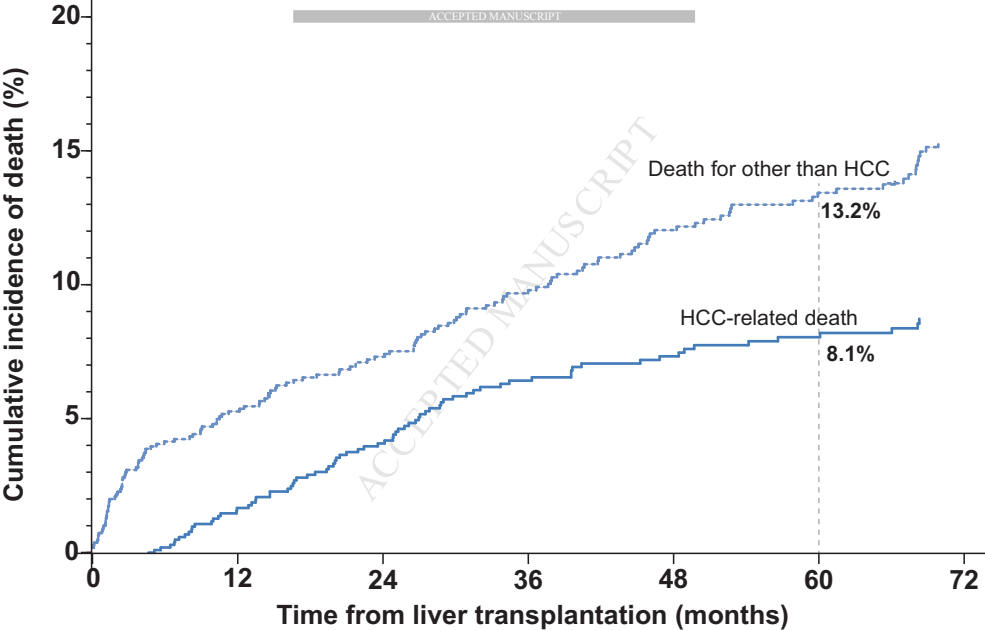
The cumulative incidence function of *"death for other than HCC"* was modelled on age (coefficient = -0.007 per year), sex (coefficient = -0.4958; male = 1; female = 0) and hepatitis C status (coefficient = 0.7925; positive = 1; negative = 0). The 5-year baseline cumulative sub-hazard function was 0.1419. The 5-year mortality, at the mean of covariates sex, age and hepatitis C status was 13.2%, ranging between 8.6% for HCV-negative patients and 18.1% for HCV-positive patients.

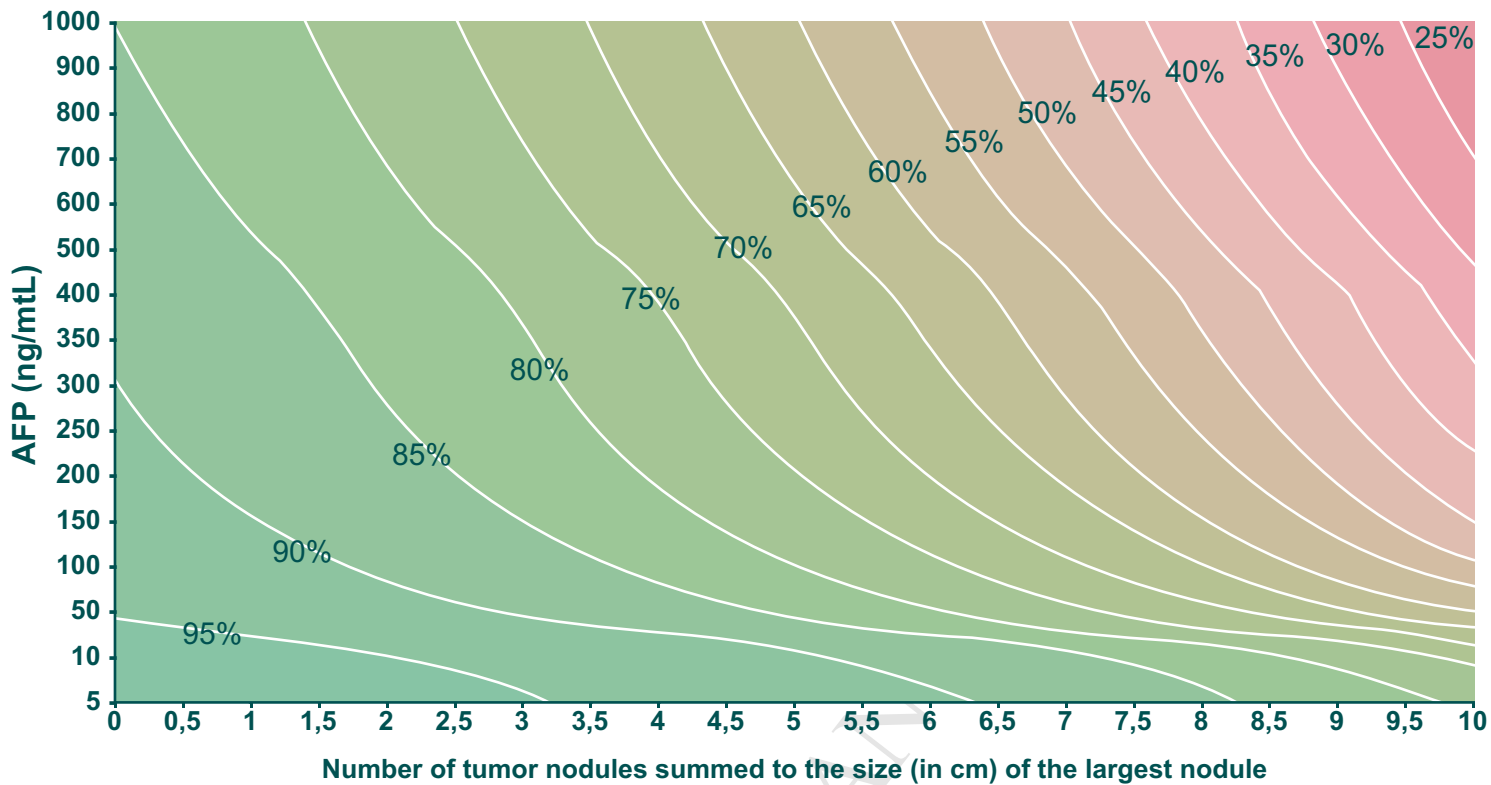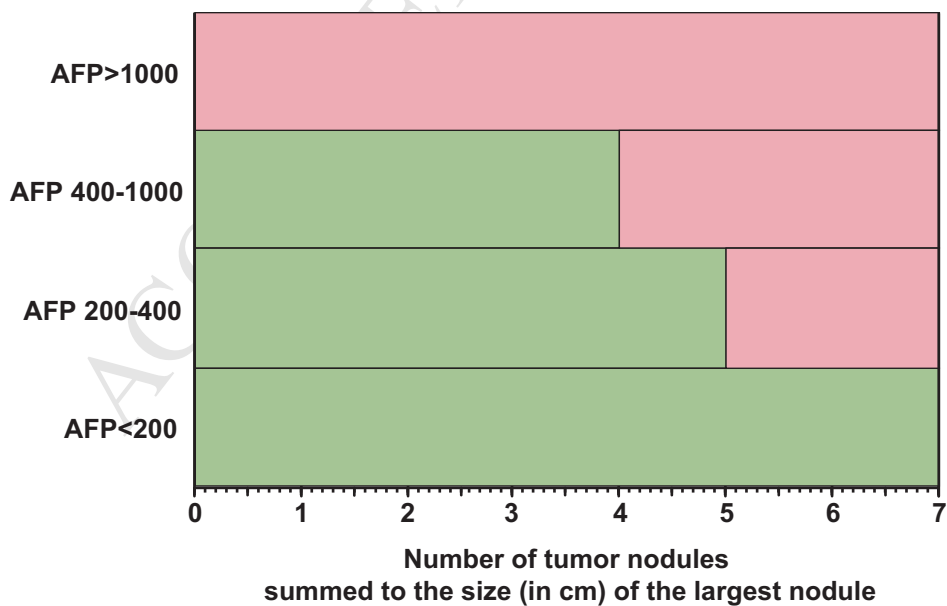*c-statistic was calculated using Wolbers's c- statistic for competing-risk models

Table 4. Accuracy of AFP-adjusted-to-HCC size criteria compared with current criteria for liver transplantation in HCC tested in the external validation cohort.

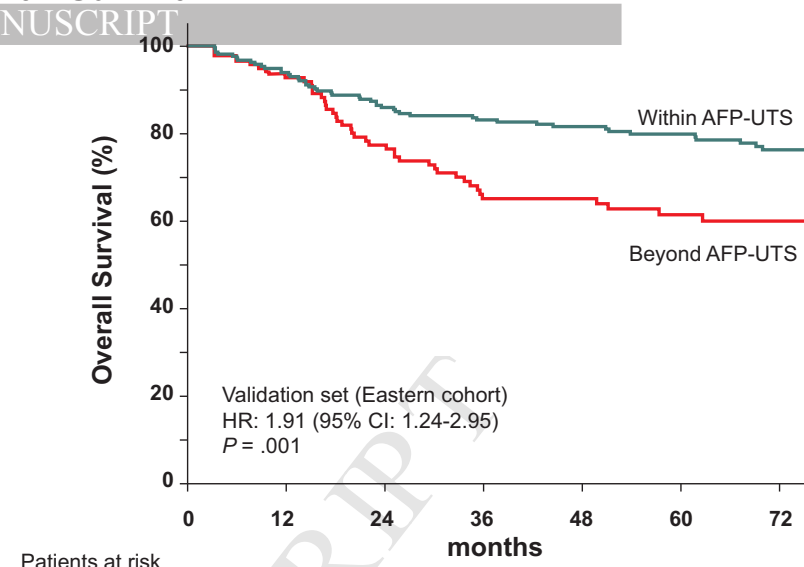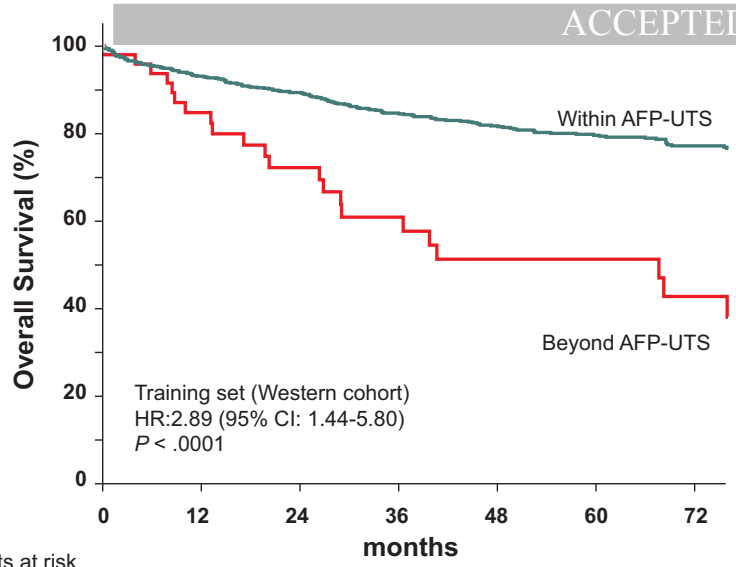| Transplant criteria	Harrell's c-index (95%CI)	P (Harrell)	Wolbers c-index (95%CI)
Current model	0.721 (0.648-0.793)	-	0.698 (0.640-0.756)
AFP French model[24]	0.672 (0.613-0.731)	0.044	0.639 (0.575-0.703)
UCSF[11]	0.621 (0.566-0.676)	0.001	0.582 (0.513-0.651)
Up-to-seven[10]	0.620 (0.569-0.671)	0.001	0.585 (0.517-0.653)
Milan[9]	0.602 (0.541-0.663)	0.001	0.558 (0.487-0.629)
Shangai-Fudan[25]	0.600 (0.551-0.649)	0.001	0.569 (0.499-0.639)

Accuracy is calculated according to HCC-specific survival (Harrell) and competing-risk survival (Wolbers). p-values refer to comparison of Harrell's c-statistics between the present model and the other clinical risk-scores

A

B

A - Overall Survival
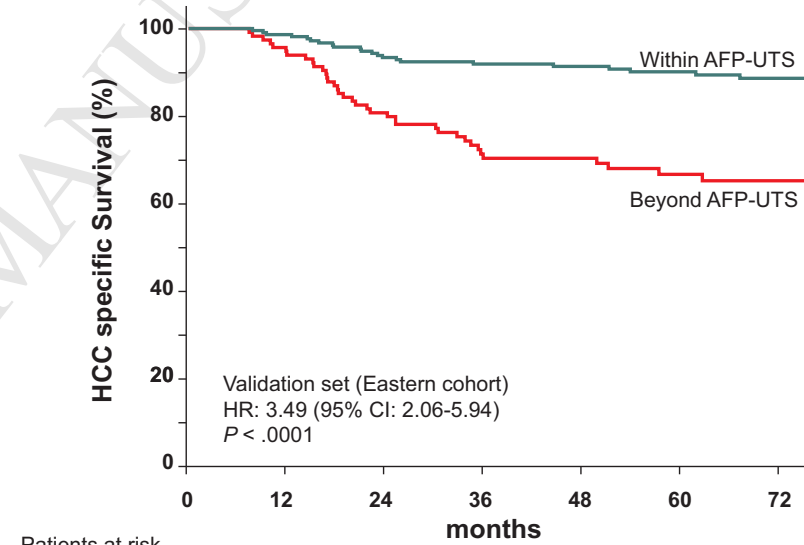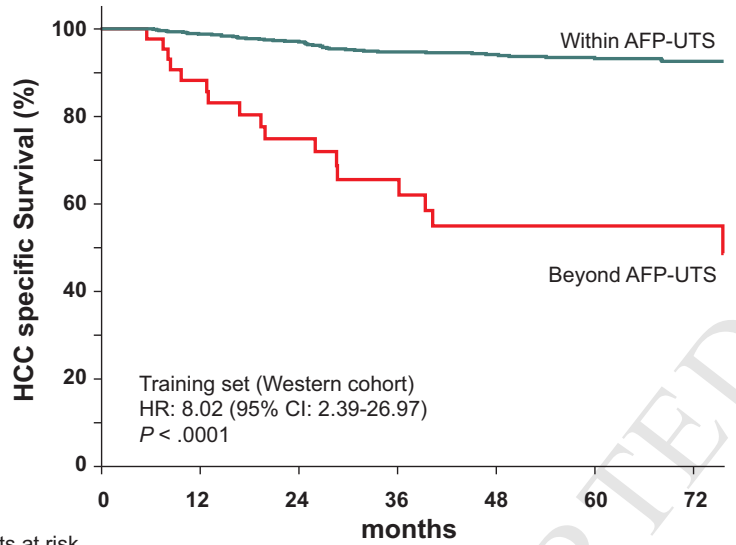
Training set (Western cohort)
HR:2.89 (95% CI: 1.44-5.80)
P < .0001

Validation set (Eastern cohort)
HR: 1.91 (95% CI: 1.24-2.95)
P = .001

Patients at risk							
Within AFP-UTS	830	717	632	525	444	368	279
Beyond AFP-UTS	48	35	27	19	16	13	10

Patients at risk							
Within AFP-UTS	225	212	194	181	161	132	103
Beyond AFP-UTS	116	109	91	71	62	48	37

B - HCC specific Survival

Training set (Western cohort)
HR: 8.02 (95% CI: 2.39-26.97)
P < .0001

Validation set (Eastern cohort)
HR: 3.49 (95% CI: 2.06-5.94)
P < .0001

Patients at risk							
Within AFP-UTS	830	701	602	509	429	358	275
Beyond AFP-UTS	48	29	21	14	14	12	9

Patients at risk							
Within AFP-UTS	225	201	187	176	154	127	100
Beyond AFP-UTS	116	85	74	64	54	43	33

C - Recurrence free Survival

Training set (Western cohort)
HR: 6.68 (95% CI: 2.35-19.02)
P < .0001

Validation set (Eastern cohort)
HR: 3.27 (95% CI: 1.99-5.38)
P < .0001

Patients at risk							
Within AFP-UTS	830	717	632	525	444	368	279
Beyond AFP-UTS	48	35	27	19	16	13	10

Patients at risk							
Within AFP-UTS	225	212	194	181	161	132	103
Beyond AFP-UTS	116	109	91	71	62	48	37