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## **Charting the Path Forward for Risk Prediction in Liver Transplant for HCC: International Validation of HALTHCC amongst 4,089 patients**

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## Abstract

Prognosticating outcomes in liver transplant (LT) for hepatocellular carcinoma (HCC) continues to challenge the field. While Milan Criteria (MC) generalized the practice of LT for HCC and improved outcomes, its predictive character has degraded with increasing candidate and oncological heterogeneity. We sought to validate and recalibrate a previously developed, preoperatively calculated, continuous risk score, the hazard associated with liver transplantation in HCC (HALTHCC) in an international cohort. From 2002-2014, 4,089 patients (both MC in and out [25.2%]) across 16 centers in North America, Europe, and Asia were included. A continuous risk score using pre-LT levels of alpha fetoprotein, model for end stage liver disease sodium score, and tumor burden score was recalibrated amongst a randomly selected cohort (n=1,021) and validated in the remainder (n=3,068). This study demonstrated significant heterogeneity by site and year, reflecting practice trends over the last decade. On explant pathology, both vascular invasion (VI) and poorly differentiated component (PDC) increased with increasing HALTHCC score. The lowest risk patients

(HALTHCC 0-5) had lower rates of VI and PDC than the highest risk patients (HALTHCC>35) (VI:7.7%[1.2-14.2] vs 70.6%[48.3-92.9] and PDC:4.6%[0.1-9.8%] vs 47.1%[22.6-71.5];  $P<0.0001$  for both). This trend was robust to MC status. This international study was used to adjust the coefficients in the HALTHCC score. Before recalibration, HALTHCC had the greatest discriminatory ability for overall survival (C-index=0.61) compared to all previously reported scores. Following recalibration, the prognostic utility increased for both recurrence (C-index=0.71) and overall survival (C-index=0.63).

**Conclusion:** This large international trial validated and refined the role for the continuous risk metric, HALTHCC, in establishing pre-LT risk amongst candidates with HCC worldwide. Prospective trials introducing HALTHCC into clinical practice are warranted.

## Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer by global incidence.<sup>1,2</sup> For most patients, liver transplantation (LT) offers the only reasonable chance at cure since it replaces the carcinogenic background liver and leaves the diseased liver capsule and vasculature undisturbed.<sup>3,4</sup> While LT is preferred, limited donor organs and poorer outcomes from cancer recurrence limited its application until the groundbreaking Milan Criteria (MC: a single-tumor $\leq$ 5cm or up to 3 tumors, all $<$ 3cm).<sup>3-5</sup> In the subsequent two decades, MC has allowed transplant centers around the world to treat HCC patients with similar, acceptable outcomes.<sup>2,6-8</sup> However, several groups have suggested that MC is too stringent.<sup>8-10</sup> With increasing penetration of down-staging loco-regional therapy (LRT), the predictive quality of MC has decreased.<sup>9,11</sup> This can be attributed to tumor morphology alone not reflecting the biology of HCC, however, it is also worth noting LRT was uncommon when MC was developed.<sup>12</sup>

Many factors have been suggested to improve patient selection. Unfortunately many models incorporated genetic parameters/serum assays not routinely collected in clinical practice<sup>6,7,13-15</sup> or pathologic factors which cannot be used for selection.<sup>8,16,17</sup> Most studies presented dichotomous criteria; the patient is in or out. Although simple and convenient,

modelling risk in binary terms discards variance, which could be associated with outcomes and results in poorer discrimination.<sup>18</sup> Such models need to be reconstructed *de novo* with population or clinical practice shifts. The hazard associated with LT for HCC (HALTHCC) model sought to remedy these strategic missteps by forming a continuous spectrum of risk upon which a patient can be judged relative to others.<sup>9</sup> Its value is calculated by common clinical variables which were determined in a single center to be relevant for post-LT survival and validated amongst the entire national experience of the United States.<sup>9</sup> It was also validated for post-LT recurrence and its longitudinal measurement was associated with dropout in a multicenter study.<sup>11</sup>

In setting potential LT candidates on a spectrum of risk, population characteristics can continuously change without the model being so stiff as to stop being useful. Further, maintaining the equation as a set of beta coefficients is a flexible framework familiar to the transplant community in the form of the model for end stage liver disease (MELD) equation and allows continual improvement in accuracy without reinvention of the concept. While HALTHCC is a valuable lens through which to observe candidate risk, its utility amongst international centers is unknown. The aim of this study was three-fold: to create a broad and heterogeneous cohort representative of world-wide LT for HCC; to test the hypothesis that HALTHCC will maintain its predictive character for post-LT outcomes in this cohort; and to test the feasibility and efficacy of recalibrating the beta coefficients for HALTHCC as has been done for MELD in the past.

## Methods

### *Patient Data and Competitor Models*

This multicenter trial was conducted using data from prospectively collected transplant records of patients undergoing LT for HCC from 2002-2014. The inclusion criteria were intentionally broad to generate a heterogeneous sample: adult recipients of LT (whole organ or partial) with a primary or secondary diagnosis of HCC. Patients were included regardless of whether they had access to preoperative LRT. Across sixteen sites and eight

countries, 4,089 patients were registered. Patient selection, management, and follow-up was determined by center practice and local/regional/national law. Data sharing was restricted to variables from common clinical practice to construct the investigated risk models. Competitor models were included based on literature review and available variables. Search terms, search strategy, and model inclusion are described in **Supplemental Appendix (SA) Table 1**. This study was approved by the Institutional Review Boards at participating institutes and data maintained at the Cleveland Clinic (IRB#17-772).

### *Study Design and Statistical Analysis*

The TRIPOD-IV framework was followed in reporting this study.<sup>19</sup> Two lines of investigation were conducted:

1. The original HALTHCC score (oHALTHCC) was examined with respect to explant pathology and then on post-LT outcomes. For pathology, focus was placed on vascular invasion (VI) and poorly differentiated component (PDC) on explant analysis since these are most strongly associated with post-LT recurrence.<sup>12,20</sup> In the same oHALTHCC analysis, post-LT outcomes were analyzed to assess discriminatory ability in the broad international cohort.
2. To test the utility of recalibration, the study population was randomized into a training set and validation set. The training set was used to find the optimal weighting of HALTHCC parameters and then this recalibrated HALTHCC score (rHALTHCC) was examined in the validation set to assess discriminatory ability of all competitor models including oHALTHCC.

HALTHCC is a continuous score based on preoperatively accessible clinical characteristics which was previously reported.<sup>9</sup> Original HALTHCC (oHALTHCC) is calculated by:

**Equation 1: oHALTHCC** =  $(1.85 * \ln(AFP)) + (1.27 * \text{tumor burden score (TBS)}) + (0.26 * MELD - Na)$ . Overall survival (OS) was defined as the time interval from LT to either,

mortality or last follow-up (where censored). Recurrence was monitored using center specific practice and reported as location and time from LT. HCC related mortality was defined as mortality after recurrence (either intra or extra-hepatic spread). Cox proportional hazards models, ordinal logistic models, and the Kaplan-Meier (KM) method were used to assess associations with OS, recurrence, and HCC related mortality. In order to maintain statistical validity and avoid overfitting, the cohort was divided into a training and validation set for rHALTHCC. Significant differences between the original cohort and this international cohort (SA Table 2) strengthen the generalizability of any findings. Block randomization was performed in a 3:1 fashion (with each center serving as a block) to maintain similar representation of every center.<sup>21</sup> Recalibration was performed on the training cohort (n=1,021) using ordinal logistic modeling of a composite endpoint (one point for either recurrence or mortality and two points for recurrence leading to mortality) in an effort better balance the competing interests in allocation policy.<sup>22-24</sup> Throughout the modeling, attention was paid to ensure an adequate ratio of events to explanatory variables (ratios maintained >10:1) and proportional hazards assumption (assessed by Schoenfeld global test [ $P=0.08$ ]). Post-estimation concordance and discrimination was applied to the validation cohort (n=3,068) using Harrell's C-index, Akaike Information Criterion (AIC), net reclassification improvement (NRI) and integrated discrimination improvement (IDI).<sup>25</sup> Calibration between the oHALTHCC and rHALTHCC was compared by estimating predicted 1-, 3- and 5-year survival and overall recurrence rates for 10 randomly selected cohorts amongst the 3,068 patients. Categorical variables are displayed as counts and percentages whereas continuous variables were reported as medians and interquartile range (25<sup>th</sup>-75<sup>th</sup> percentiles). All testing performed was two-sided and compared against a 5% alpha using STATA 13 (STATA Corp, College Station, Texas, USA).

## Results

### Population Composition

The population distribution and characteristics are visualized in **Figure 1** and **SA Figure 1** and summarized in **SA Table 3**. Significant differences were seen in recipient underlying liver disease and MELD-Na at listing, tumor burden and AFP at listing, waiting time, proportion of candidates receiving LRT while waiting, and tumor characteristics at LT (**Figure 1A**). In addition to heterogeneity across world region, there were trends over time (**Figure 1** and **SA Figure 1**). For example, increased waiting time in North America due to shifts in allocation policy have led to increased penetration of LRT and decreased the active tumor burden at transplantation. The Asian cohort changed dramatically over the study period, government reimbursement and focus on outcomes have decreased the tumor burden of candidates undergoing LT. The European cohort was more stable over time with only minor trends towards increasing penetration of LRT and some, likely related decreases in tumor burden at transplantation.

#### *Explant Pathology*

The relationship between risk scores and pathological features is demonstrated in **Figure 2**. Amongst MC-in patients, VI and PDC on explant pathology were present in 19.2 and 11.1% of patients; MC-out status increased the incidences to 38.3 and 18.4%, respectively ( $P < 0.0001$ ). The Metroticket 2.0 paradigm has introduced three groups of candidates amongst which LT should have comparable outcomes.<sup>26</sup> There was an increase in both VI and PDC from Group 1 (AFP < 200 and Up-to-7; VI: 19.0%[95%CI:17.3-20.6] and PDT: 11.0%[95%CI:9.7-12.3]) to Groups 2 (AFP 200-400 and Up-to-5; VI: 40.7%[27.5-54.0] and PDT: 22.2%[11.0-33.4]) and 3 (AFP 400-1000 and Up-to-4; VI: 32.1%[14.5-49.8] and PDT: 14.3%[10.8-27.5]). Interestingly, patients not indicated to receive LT, here termed Group 4 (AFP > 1000 or sum of lesion size and number greater than allowed with a given AFP for Groups 1-3) had similar rates of VI (45.9%[41.4-50.3]) and PDC (21.3%[17.6-24.9])(**Figure 2A**). Another alternative to HALTHCC is the MORAL score. As indicated in **Figure 2B** there was poor corroboration between increasing MORAL score and explant pathology. HALTHCC had a clear and robust association between estimated pre-LT risk and

explant pathology, both VI and PDC increased with increasing HALTHCC score (**Figure 2C**).

The lowest risk patients (HALTHCC 0-5) had much lower rates of VI and PDC than the highest risk patients (HALTHCC>35) (VI: 7.7%[1.2-14.2] vs 70.6%[48.3-92.9] and PDC: 4.6%[0.1-9.8%] vs 47.1%[22.6-71.5];  $P<0.0001$  for both). This trend was robust to MC status indicating that HALTHCC may be a useful tool to estimate risk of poor pathologic features using only preoperatively accessible variables.

### *Modeling Post-LT Outcomes*

oHALTHCC was tested for association with post-LT outcomes (**Figure 3A-B**). This analysis showed generally promising validation of the US national experience; lower risk patients had higher survival and lower recurrence. However, in this cohort, the very low risk patients (oHALTHCC<5) and the penultimate high risk group (oHALTHCC 30-35) were overlapping with nearby risk cohorts; identifying clear areas where risk estimation could be improved. oHALTHCC's discrimination was consistent with the US national experience for recurrence (C-index: 0.69), OS (0.62), and HCC related death (0.72).

### *Recalibration of HALTHCC*

The ordinal logistic modeling used to recalibrate HALTHCC is detailed in **Table 2**. This confirmed the highly statistically significant nature of the original components of HALTHCC and also provided evidence that regional variation (especially Asia) was contributing to deviations from risk-outcomes relationships being observed in the US experience. Together, these estimates were used to generate **Equation 2:  $r\text{HALTHCC} = (2.31 * \ln(\text{AFP})) + (1.33 * (\text{TBS})) + (0.25 * \text{MELD} - Na) - (5.57 * \text{Asia})$** . The validation cohort was thusly estimated and then KM estimates of survival and recurrence compared to the oHALTHCC equation (**Figures 3C-D**). This analysis provided a greatly improved range of outcomes across all levels of risk. The 5-year post-LT OS ranged from 82.4% in the lowest risk group ( $r\text{HALTHCC}<5$ ,  $n=145/3,068$ ) to 32.4% in the highest risk group

(rHALTHCC>35, n=24/3,068). A similar trend was observed with 5-year post-LT recurrence which ranged from, 8.6% (rHALTHCC<5, n=145/3,068) to 70.0% (rHALTHCC>35, n=24/3,068). The robustness with which rHALTHCC stratified risk of post-LT events was much greater than all competitor scores (**SA Figure 2**).

#### *Discriminatory Ability and Accuracy of HALTHCC*

Following recalibration of HALTHCC in the training set, comparison of discrimination for post-LT mortality, recurrence, and HCC-related mortality was conducted amongst competitors. Compared to its closest competitor, rHALTHCC was a statistically superior discriminator as measured by Harrell's C (0.63 [0.61-0.65] vs Metroticket 2.0 (0.57 [0.55-0.58]);  $P<0.0001$ ), NRI (0.330 [0.261-0.391] vs Metroticket 2.0, 0.260 [0.201-0.315]), IDI (0.043 [0.031-0.057] vs Metroticket 2.0, 0.016 [0.009-0.025]), and AIC (14332 vs Metroticket 2.0, 14401), for post-LT survival (**SA Table 4**). This difference persisted for recurrence (0.71 [0.68-0.74] vs Metroticket 2.0, 0.65 [0.62-0.67];  $P\text{-value}<0.0001$ ; **SA Table 5**) and HCC-related mortality (0.74 [0.71-0.77] vs Metroticket 2.0, 0.66 [0.63-0.69];  $P\text{-value}<0.0001$ ; **SA Table 6**). Lastly, estimates of 1-, 3-, 5-year post-LT survival, and overall recurrence rates derived from o-, and, rHALTHCC were compared to observed values of these post-LT outcomes to demonstrate calibration of the estimating equations underlying their discriminatory ability (**SA Figure 3**). It is clear to observe visually how the linear regressions of the randomly selected clusters improve in their estimation of the observed values moving from A-B, C-D, etc, which confirms the model's improvement.

#### **Discussion**

In a large and heterogeneous worldwide cohort, this validation study confirmed superior discriminatory characteristics of HALTHCC for explant pathology and post-LT outcomes. Recalibration of the score improved its prognostic utility. While MC was critical to widespread success in LT for HCC, its utility has decreased over-time due to changes in clinical practice. Many models were developed to replace MC and several did possess

improved prognostic discrimination,<sup>6–8,16,20,27–29</sup> however, most fell by the wayside because of poor generalizability. Those models were developed in single institutes where the patient population and treatment strategy are homogeneous. As a result, they failed to show similar excellence in other cohorts. Consequently, other groups made their own model in their cohorts and our field has been trapped in a loop. HALTHCC was developed to defeat this loop and form the basis of a new allocation system to improve prognostic utility and fair and reasonable organ allocation between HCC and non-HCC patients. This validation study using a heterogeneous, worldwide cohort with the hypothesis: if HALTHCC is truly measuring the disease HCC, it should work in any environment. Statistical analyses showed that there were extensive differences of tumor/treatment characteristics in 4,089 worldwide patients. The original HALTHCC score's performance was consistent with past studies as a discriminator of, recurrence (C-index: 0.69), OS (0.62), and HCC related mortality (0.72). Recalibration of HALTHCC was conducted and improved statistical discrimination over oHALTHCC as measured by C-index ( $P<0.001$  for recurrence,  $P=0.051$  for survival, and  $P=0.003$  for HCC-related mortality) and also visual discrimination using Kaplan Meier and calibration curves (**Figures 3 and SA Figure 3**).

While original HALT-HCC was validated in the US national experience, it was unknown how this clinical score would perform in an entirely new population with high heterogeneity with most patients outside the US (**SA Table 2**). As shown in **Figure 1**, this study cohort consisted of populations with different treatment strategies and tumor characteristics. Although it is known that high heterogeneity decreases performance of prediction models<sup>30</sup>, the oHALTHCC score maintained a high level of discrimination, especially for recurrence. Moreover, HALTHCC showed significant association with explant pathology, such as vascular invasion and poorly differentiated component (**Figure 2**). MC demonstrated a single level increase in rates of both VI and PDC consistent with its binary nature. However, when compared against all other criteria, increased HALTHCC score was most closely and reliably related to both VI and PDC. This is without any explicit modeling of pathology done at any phase in HALTHCC's development. These results suggest this

continuous risk score is measuring tumor features underlying risk of poor outcomes not statistical static.

One might entertain the critique that a continuous score's form is too complicated and that our purpose seems more about chasing statistical excellence rather than usability. However, the transplant community is already familiar with the concept of continuous scoring, demonstrated by MELD/MELD-Na scores, those risk metrics were similarly statistically derived and optimized. Moreover, it is well known that the alternative, categorical or ordinal scoring systems discard accuracy and their cutpoints promote controversy instead of easing decision making.<sup>18</sup> After HALTHCC's development, a close competitor, the Metroticket 2.0 model was introduced. This model is derived from a statistical basis and estimates risk from a continuous formulation which is then binned into risk categories based on risk planes. While we applaud the derivation, its application to bins is overly simplistic. The benefit realized by switching from a categorical logic to a continuous risk score is significant and encourages the community to embrace statistically valid and efficient methodologies. Organ allocation is a national issue; therefore, even small improvements in predictive utility could affect and contribute to large changes in organ utilization. We believed balancing statistical accuracy with a minimally complex model would increase the number of LT for HCC without adversely affecting outcomes. In fact, there is evidence that priority allocation using HALTHCC would allow fine tuning of "acceptable outcomes" and serve as a simple metric for transplant center comparison across regions.<sup>11</sup> Further, a continuous risk score is advantageous compared to a dichotomous model since the continuous score can be recalibrated easily when necessary, as was the case with the MELD and MELD-Na scores previously.

In this study, recalibration of HALTHCC was performed as planned at the conception of HALTHCC and this statistically significantly increased its discriminatory ability.<sup>9</sup> Following randomization of the study population into similarly composed cohorts (**Table 1**), the training set underwent ordinal logistic regression using a weighted composite endpoint. The estimation amongst the randomized cohort demonstrated statistical significance for all the

factors in oHALTHCC. **SA Table 7** outlines the composition of the validation cohort stratified by rHALTHCC score and MC status. If we were to re-allocate the livers in this study based on composite risk, we can provide priority to nearly 74.6% of MC-out candidates without post-LT outcomes suffering. Further, we can reallocate ~4-5% of MC-in recipients with higher composite risk. This approach would have the net effect of greater equity and lower post-LT recurrence rates. However, care must be taken since these estimates are all derived post-hoc in a cohort influenced by MC. A consensus meeting is necessary to finalize the form and composition of predictive models our community would like to explore prior to embarking on prospective trials. For example, we previously demonstrated the value of including MELD-Na in HALTHCC to improve prediction of overall survival, however it has relatively less impact on modeling recurrence.<sup>9,11</sup> Clearly recurrence is of prime interest in LT for HCC, however while 3-year recurrence runs 7-10%, transplant related mortality at 3-years is 15-20%<sup>26</sup>; candidate selection is about more than tumor size and number and transplantation is not benign. As a community we need to decide the most critical outcomes of interest for future prospective studies and then optimize our risk measure. A single system from presentation through locoregional therapy and into the transplant period is preferred since it would simplify a complex clinical decision tree but also improve outcomes.

Moving away from waiting time based standard exception points with individualized applications to a mathematic transformation of risk and benefit has many advantages. In Figure 4 six example patients are outlined to demonstrate three proposed models of allocation through which to explore competing concepts in allocation related to HCC. It is important to note these draft models are simply examples to discuss possible strategies in allocation, a final or “best model” will require advanced simulation studies to estimate the impact between non-HCC and HCC cohort dropout, transplant volumes, and post-LT outcomes. In the first draft model, post-LT survival is maximized (model alpha). This model prioritizes long term survival after liver transplantation alone, patients who have lowest HALTHCC score prior to organ allocation wait the least time, have the least disease burden and have the highest overall survival rates and lowest recurrence. However, one can argue

that many of these low risk patients would go for many months after LRT without disease recurrence or a new lesion, in contrast many patients who could have benefited from timely transplantation may have progressed. Second, the model prioritizing oncological risk in a fashion similar to the “sickest first” policy (model gamma). In this model, high HALTHCC patients have the highest priority since they presumably have the most to benefit from immediate and early transplantation. However, this model performs poorly in metrics of organ utilization and post-LT population recurrence rates. It could be argued that many moderate risk patients with lower priority may not have progressed had they been transplanted early whereas this model may inadvertently prioritize transplantation of patients with almost certain distant microscopic disease. Lastly the model balancing the middle group of patients, those with near mean risk best served by timely transplantation (model beta). These patients are clearly at risk of dropout but also have a reasonable chance at cure from timely transplant. In model beta, patients closest to the mean historical risk at transplant achieve the highest priority by simply transforming their mathematical distance from the mean using absolute values. Patients with very high risk at presentation may naturally dropout but may be able to get sufficient priority to access LT if they have an appropriate response to LRT as measured by HALTHCC.<sup>11</sup> Patients with very low risk may go many months or even years after LRT without disease recurrence, however, with the field effect of cirrhosis in place it is likely that another lesion will at some point crop up; in that case their HALTHCC score will increase and their priority for transplantation will increase. This balanced approach provides a compromise between sickest first and survival conscious or utility concepts. The beauty of all of these models compared to something like MC or other binary systems (including the complex criteria currently required to meet exceptional status under UNOS) is that there is no cutoff at which point patients with only marginally increased risk suffer from total ineligibility (eg one tumor sized 5.2cm vs one tumor sized 4.8cm or AFP level of 1005 vs 995). Lastly, these models can be easily adjusted in two future oriented ways:

1. They can have the constant term adjusted by UNOS region to help negotiate disparities in rates of transplantation by MELD/priority score.
2. They can have the multipliers modified to adjust the risk tolerance of the society if recurrence rates are too high or there is too much dropout.

These models serve as the most basic and first in a series of studies our group hopes to employ to estimate the impact advanced, HALTHCC based, allocation models can have on our society.

Despite its size, this large study has some limitations to consider. First, it is a retrospective study, therefore we cannot definitively infer any causality related to HALTHCC score. Also, due to time constraints we were not able to collect detailed longitudinal data on tumor size, serum tumor markers, exact times of multiple LRT, nor the response to LRT. Methodologically, assumptions need to be made to adjust for regional differences in outcomes. One can either allow the individual coefficients to vary for each region (ie estimate a new equation per region) or allow an omnibus adjustment at the end, assuming biological determinants like AFP, TBS, MELD-Na will have similar orders of influence by region. In scenario 1 above, we assume knowledge of the mechanism by which outcomes vary between different locations in the world. In reality, it could be population genetics, donor types, or other unspecified practice patterns which most significantly account for the difference in outcomes for a given HALTHCC score (unadjusted by region). In contrast, in scenario 2 we acknowledge that outcomes for similar patient characteristics may differ around the world. However, that doesn't mean they are not comparable, nor that the difference is not estimable. In fact, the difference is estimable, we just don't know the mechanism through which that difference acts. Our assumption in acting through scenario 2 is that AFP, TBS, and MELD-NA have a relatively similar contribution (at least in a similar order of magnitude) to risk to poorer outcome across location. However overall risk of a given outcome is not proportional strictly to those biological factors. Since the mechanism of risk modification is unknown we chose the method of omnibus adjustment of risk for a given location. In fact, this method is the most conservative from both a clinical reasoning

standpoint but also statistically since we introduce far fewer additional assumptions, tests and thus reduce opportunity for bias. Further a sensitivity analysis was performed demonstrating that the coefficients for AFP, TBS, and MELD-Na were similar between the Western and Eastern Cohorts (**SA Tables 8 and 9**). Estimating the baseline hazard function between each region separately demonstrated that proportionality was not violated but that the baseline hazard is simply lower in Asia, thus our estimates of the impact of AFP, TBS and MELD-Na are valid (**SA Figures 4A-B**). Next we calculated model utility on the Western dataset alone only which only marginally decreased the utility estimates by Harrell's C (**SA Table 10**). Additionally, calibration of HALTHCC derived overall survival and recurrence predictions compared to observations were not systematically biased by region whereas its nearest competitor model Metroticket 2.0 consistently overestimated the Asian cohorts risk (**SA Figures 4C-D**) Finally, since we did not have a complete data set of all previously reported serum markers and all the individual patients' longitudinal courses we were unable to draw comparisons on utility to several recent scoring systems including the delta-HALTHCC and TRAIN scores.<sup>7,11</sup>

In conclusion this large international trial validated and refined the role for the continuous risk metric, HALTHCC. Its utility was confirmed amongst 4,089 patients undergoing LT for HCC, composing a heterogeneous data set, which strengthens generalizability. While MC has served the transplant community well for two-decades it is time for providers in this field to have our practice "bridged" until whole exome studies provide truly personalized guidance to HCC management. We proposed various models to inform allocation algorithms based on HALTHCC. Prospective trials introducing HALTHCC into observational frameworks to remove the bias laid out by two decades of practice under MC are warranted.

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# Tables:

| Table 1: Population Characteristics |                              |                                |         |
|-------------------------------------|------------------------------|--------------------------------|---------|
|                                     | Training Cohort<br>(n=1,021) | Validation Cohort<br>(n=3,068) | P-value |
| Transplant Year                     | 2008 [2005, 2012]            | 2008 [2005, 2012]              | 0.920   |
| World Region                        |                              |                                | 0.740   |
| North America                       | 460 (45.1)                   | 1391 (45.3)                    |         |
| Europe                              | 468 (45.8)                   | 1399 (45.6)                    |         |
| Asia                                | 93 (9.1)                     | 278 (9.1)                      |         |
| Sex, male                           | 689 (67.5)                   | 2133 (69.5)                    | 0.222   |
| Age, years                          | 58 [52, 63]                  | 58 [52, 63]                    | 0.360   |
| Underlying Liver Disease*           |                              |                                | 0.667   |
| HCV cirrhosis                       | 560 (54.8)                   | 1683 (54.9)                    |         |
| HBV cirrhosis                       | 192 (18.8)                   | 501 (16.3)                     |         |
| Laennec's cirrhosis                 | 203 (19.9)                   | 623 (20.3)                     |         |
| NASH cirrhosis                      | 50 (4.9)                     | 189 (6.2)                      |         |
| Other                               | 77 (7.5)                     | 248 (8.1)                      |         |
| Listing Characteristics             |                              |                                |         |
| Laboratory MELD-Na, points          | 12.0 [9.0, 16.0]             | 12.0 [9.0, 16.0]               | 0.884   |
| Tumor Number                        | 1.0 [1.0, 3.0]               | 1.0 [1.0, 3.0]                 | 0.655   |
| Tumor Size, cm                      | 2.6 [1.9, 3.6]               | 2.5 [1.8, 3.6]                 | 0.477   |
| TBS, points                         | 3.4 [2.5, 4.8]               | 3.4 [2.4, 4.6]                 | 0.445   |
| AFP, IU/mL                          | 10.0 [5.0, 37.9]             | 10.0 [4.7, 39.3]               | 0.553   |
| Patients meeting MC                 | 746 (73.1)                   | 2173 (71.0)                    | 0.786   |
| HALTHCC, points                     | 12.6 [10.0, 15.8]            | 12.6 [10.3, 15.9]              | 0.468   |
| Waiting time, days                  | 157 [60, 318]                | 149 [60, 315]                  | 0.557   |
| Pre-LT Characteristics              |                              |                                |         |
| Laboratory MELD-Na, points          | 13.0 [9.0, 18.0]             | 13.0 [9.0, 17.6]               | 0.914   |
| Tumor Number                        | 1.0 [1.0, 2.0]               | 1.0 [1.0, 3.0]                 | 0.218   |
| Tumor Size, cm                      | 2.1 [1.1, 3.0]               | 2.1 [1.0, 3.0]                 | 0.536   |
| TBS, points                         | 3.06 [1.4, 4.2]              | 3.05 [1.8, 4.2]                | 0.562   |
| AFP, IU/mL                          | 10.0 [4.5, 35.0]             | 9.8 [4.2, 37.4]                | 0.448   |
| NLR                                 | 2.7 [1.7, 4.3]               | 2.7 [1.7, 4.4]                 | 0.249   |
| Patients meeting MC                 | 752 (73.7)                   | 2308 (75.2)                    | 0.303   |
| HALTHCC, points                     | 12.0 [9.0, 15.6]             | 12.2 [9.4, 15.6]               | 0.170   |
| Follow-up time, days                | 1369 [529, 2700]             | 1445 [606, 2753]               | 0.378   |

**Note:** Continuous variables: median [interquartile range]. \*May not sum to unity due to overlapping etiologies.

**Abbreviations:** AFP: preoperative alpha-fetoprotein, HALTHCC: Hazard Associated with Liver Transplantation for Hepatocellular Carcinoma, HBV: hepatitis B virus, HCC: hepatocellular carcinoma, HCV: hepatitis C virus, MC: Milan Criteria, MELD-Na: Model of End Stage Liver Disease Sodium, NASH: non-alcoholic steatohepatitis, NLR: neutrophil-lymphocyte ratio, SRTR: Scientific Registry of Transplant Recipients, TBS: Tumor Burden Score.

| <b>Table 2:</b> Ordinal Logistic Model for Recalibrating HALTHCC using Training Set                                                                                                                                                                |             |                |           |                     |                  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|----------------|-----------|---------------------|------------------|
|                                                                                                                                                                                                                                                    | Coefficient | Standard error | Wald test | Odds Ratio (95% CI) | <i>P</i> -value* |
| MELD-NA, per point                                                                                                                                                                                                                                 | 0.0247      | 0.0088         | 2.82      | 1.025 (1.008-1.043) | 0.005            |
| TBS, pre point                                                                                                                                                                                                                                     | 0.1332      | 0.0233         | 5.71      | 1.143 (1.091-1.196) | <0.0001          |
| AFP, per ln(IU/mL)                                                                                                                                                                                                                                 | 0.2308      | 0.0357         | 6.46      | 1.260 (1.175-1.351) | <0.0001          |
| World Region                                                                                                                                                                                                                                       |             |                |           |                     |                  |
| North America                                                                                                                                                                                                                                      | -Base case- | -              | -         | -                   | -                |
| Europe                                                                                                                                                                                                                                             | 0.1817      | 0.141          | 1.29      | 1.199 (0.910-1.581) | 0.198            |
| Asia                                                                                                                                                                                                                                               | -0.5571     | 0.261          | -2.13     | 0.573 (0.343-0.955) | 0.033            |
| *Based on likelihood est adjusted for the other factors in the final model.                                                                                                                                                                        |             |                |           |                     |                  |
| <b>Abbreviations:</b> AFP: preoperative alpha-fetoprotein (natural log transformed), HALTHCC: Hazard Associated with Liver Transplantation for Hepatocellular Carcinoma, MELD-Na: Model of End Stage Liver Disease Sodium, TBS: Tumor burden score |             |                |           |                     |                  |

## Figure Legends

### Figure 1: Trends in Worldwide Liver Transplantation for Hepatocellular Carcinoma

A) Cartoon map of the world overlaid with the characteristics of liver transplantation (LT) for hepatocellular carcinoma (HCC) in each of the three major regions in this study. B) Proportion of LT recipients undergoing locoregional therapy prior to LT by year of LT and center region. C) MELD-Na measured just prior to LT by year of LT and center region. D) Number of viable lesions on radiographic evaluation at time of candidate listing, by year of LT and center region. E) Number of viable lesions on radiographic evaluation at last pre-LT evaluation, by year of LT and center region. F) Largest viable lesion size on radiographic evaluation at time of candidate listing, by year of LT and center region. G) Largest viable lesion size on radiographic evaluation at last pre-LT evaluation, by year of LT and center region. **NOTE:** Panel A – Boxed descriptive statistics are median [interquartile range]. Panels B-G – Bars represent means with 95% confidence intervals.

**Figure 2: Utility of Pre-Operatively Assessable Risk Metrics as Measured by Explant Pathological Features**

A) Demonstrates probability of finding vascular invasion or poor tumor differentiation of explant pathology for Milan Criteria (in vs out) and Metroticket 2.0 groupings (indicated LT patients [Groups 1-3] vs not indicated [Group 4]). B) Explant pathology rates for vascular invasion and poor tumor differentiation grading by MORAL score. C) Explant pathology rates of vascular invasion and poor tumor differentiation grading by HALTHCC score.

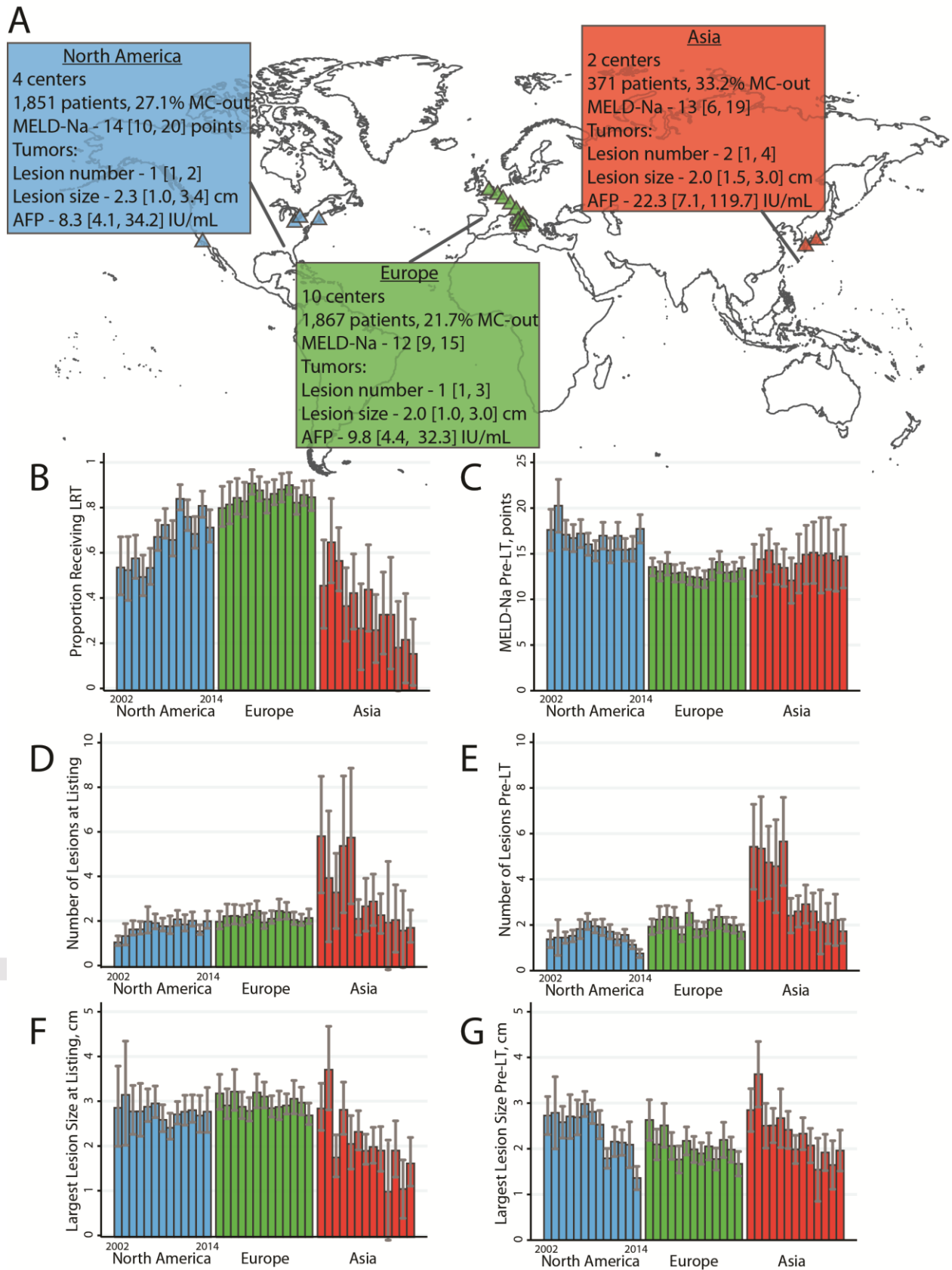
**Abbreviations:** G: group, HALTHCC: Hazard associated with liver transplantation for hepatocellular carcinoma, MC: Milan criteria, MORAL: Model of recurrence after liver transplantation, MT2.0: Metroticket version 2.0. **NOTE:** Bars demonstrate means with 95% confidence intervals for estimates.

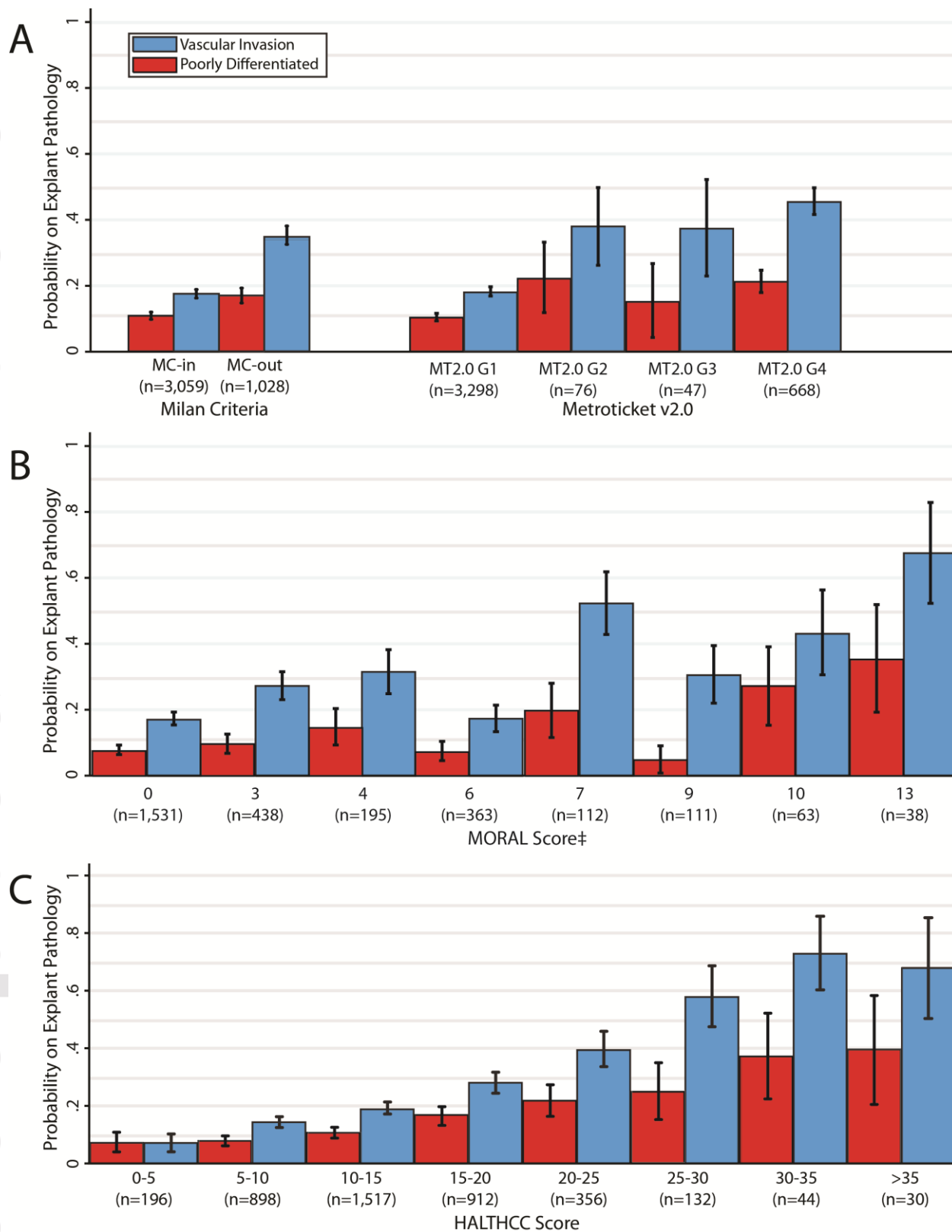
**Figure 3: HALTHCC Score is Associated with Overall Survival and Recurrence and Improved after Recalibration**

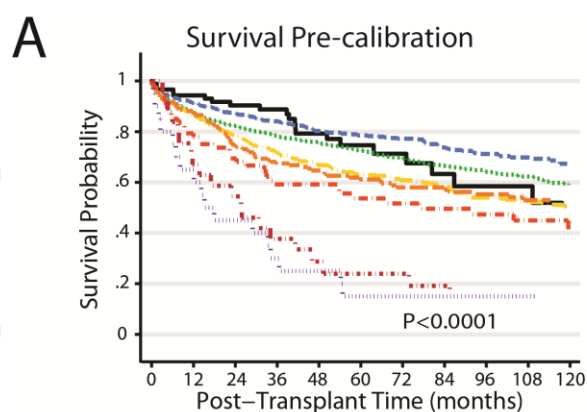
A) Kaplan-Meier (KM) survival estimates for overall survival by hazard associated with liver transplantation for HCC (HALTHCC) score by to any model recalibration. B) KM estimates for recurrence by HALTHCC score prior to any model recalibration. C) KM survival estimates for overall survival following HALTHCC recalibration using the training cohort. D) KM estimates for recurrence following HALTHCC recalibration using the training cohort. **NOTE:** Only validation cohort patients are included in the analysis of Panels A-D, the training cohort for recalibration was excluded to avoid overfitting.

#### **Figure 4: Example Patients to Demonstrate Utility of HALTHCC Based Allocation**

Six example patients illustrate the ease and utility of longitudinal assessment with HALTHCC of HCC patients undergoing evaluation for LT. The proposed models vary in emphasis from purely post-operative survival to a sickest first and finally balanced approach. Further a simple adjustment for regional competitiveness or to balance risk of dropout can be conducted through modification of the constant terms.

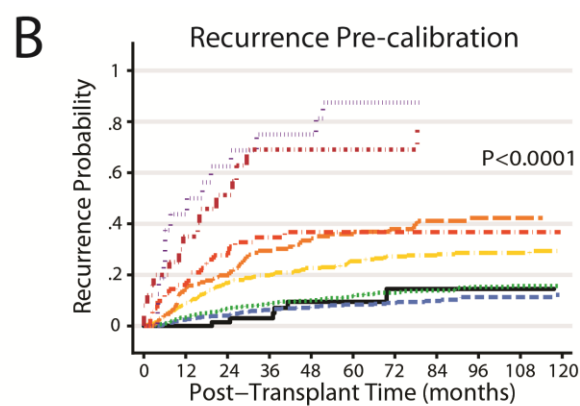
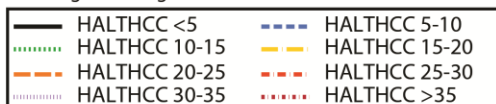






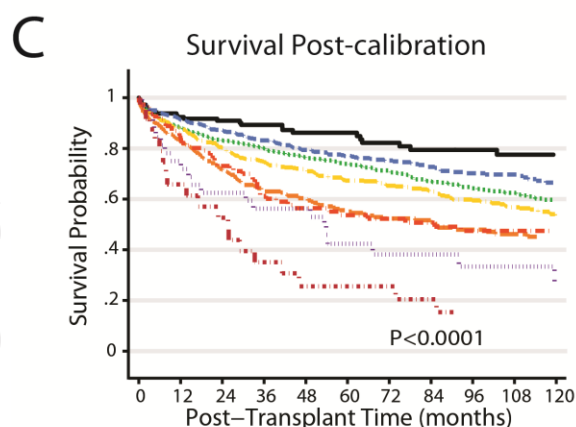
Number at risk by HALTHCC Score:

|       |      |     |     |     |     |     |
|-------|------|-----|-----|-----|-----|-----|
| <5    | 89   | 63  | 40  | 20  | 11  | 3   |
| 5-10  | 845  | 616 | 404 | 282 | 171 | 97  |
| 10-15 | 1255 | 892 | 655 | 467 | 305 | 178 |
| 15-20 | 573  | 395 | 280 | 204 | 133 | 85  |
| 20-25 | 189  | 125 | 93  | 70  | 56  | 43  |
| 25-30 | 75   | 49  | 34  | 26  | 21  | 12  |
| 30-35 | 20   | 9   | 5   | 2   | 1   | 0   |
| >35   | 25   | 13  | 6   | 5   | 3   | 3   |



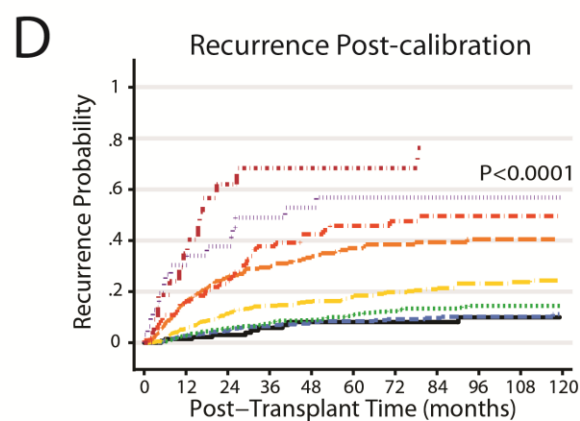
Number at risk by HALTHCC Score:

|       |      |     |     |     |     |     |
|-------|------|-----|-----|-----|-----|-----|
| <5    | 89   | 62  | 38  | 17  | 11  | 3   |
| 5-10  | 845  | 591 | 380 | 261 | 160 | 90  |
| 10-15 | 1254 | 848 | 606 | 429 | 282 | 172 |
| 15-20 | 573  | 350 | 257 | 187 | 122 | 76  |
| 20-25 | 189  | 113 | 80  | 59  | 47  | 37  |
| 25-30 | 75   | 43  | 28  | 23  | 20  | 11  |
| 30-35 | 20   | 6   | 4   | 1   | 0   | 0   |
| >35   | 25   | 9   | 4   | 4   | 3   | 3   |



Number at risk by HALTHCC Score:

|       |      |     |     |     |     |     |
|-------|------|-----|-----|-----|-----|-----|
| <5    | 145  | 115 | 78  | 62  | 46  | 33  |
| 5-10  | 681  | 510 | 332 | 232 | 147 | 87  |
| 10-15 | 1117 | 788 | 585 | 396 | 244 | 128 |
| 15-20 | 671  | 459 | 324 | 248 | 168 | 106 |
| 20-25 | 291  | 187 | 133 | 89  | 58  | 40  |
| 25-30 | 110  | 71  | 43  | 35  | 29  | 21  |
| 30-35 | 32   | 20  | 17  | 9   | 7   | 4   |
| >35   | 24   | 12  | 5   | 5   | 2   | 2   |



Number at risk by HALTHCC Score:

|       |      |     |     |     |     |     |
|-------|------|-----|-----|-----|-----|-----|
| <5    | 145  | 113 | 74  | 59  | 45  | 33  |
| 5-10  | 681  | 488 | 312 | 218 | 139 | 84  |
| 10-15 | 1117 | 751 | 541 | 361 | 225 | 119 |
| 15-20 | 670  | 424 | 302 | 228 | 154 | 98  |
| 20-25 | 291  | 157 | 117 | 76  | 49  | 33  |
| 25-30 | 110  | 65  | 35  | 28  | 25  | 19  |
| 30-35 | 32   | 17  | 12  | 7   | 6   | 4   |
| >35   | 24   | 7   | 4   | 4   | 2   | 2   |

