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Model of Urgency for Liver Transplantation in Hepatocellular Carcinoma: A Practical Model to Prioritize Patients With Hepatocellular Carcinoma on the Liver Transplant Waitlist

Joshua S. Norman,[1] Neil Mehta,[2] W. Ray Kim,[3] Jane W. Liang,[4] Scott W. Biggins,[5] Sumeet K. Asrani,[6] Julie Heimbach,[7] Vivek Charu,[4,8] and Allison J. Kwong[3]

[1]Department of Medicine, Stanford University, Palo Alto, California; [2]Division of Gastroenterology, University of California, San Francisco, San Francisco, California; [3]Division of Gastroenterology and Hepatology, Stanford University, Palo Alto, California; [4]Quantitative Sciences Unit, Stanford University, Palo Alto, California; [5]University of Pittsburgh, Pittsburgh, Pennsylvania; [6]Baylor University Medical Center, Dallas, Texas; [7]Mayo Clinic, Rochester, Minnesota; and [8]Department of Pathology, Stanford University, Palo Alto, California

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BACKGROUND & AIMS: Currently, patients with hepatocellular carcinoma (HCC) in the United States are assigned a uniform score relative to the median Model for End-Stage Liver Disease (MELD) at transplant after a minimum 6-month waiting period. The authors developed a risk stratification model for patients with HCC using the available and objective variables at time of listing. **METHODS:** Adult liver transplant candidates with approved HCC exception in the Organ Procurement and Transplantation Network database from 2015–2022 were identified. Cox regression analysis, as well as machine learning models (random survival forest and neural network), were used to develop models predicting waitlist dropout. Predicted waitlist dropout for patients with HCC was scaled to patients without exception using MELD 3.0. **RESULTS:** There were 18,273 patients with HCC listed for liver transplant with a median MELD 3.0 of 11 (interquartile range, 8–15) and α-fetoprotein of 6 ng/mL (interquartile range, 4–17 ng/mL). Because all models performed similarly, a parsimonious Cox-based model composed of MELD 3.0, α-fetoprotein, tumor burden, and Model of Urgency for Liver Transplantation in HCC, was selected, with a C-statistic of 0.71 (95% CI, 0.69–0.74) for 6-month dropout in the validation set, outperforming previous models, including HALT-HCC (Hazard Associated with Liver Transplantation for HCC), deMELD (Dropout Equivalent MELD), and MELD-Eq (MELD Equivalent). **CONCLUSIONS:** An urgency-based priority system for patients with HCC, similar to MELD for patients with chronic liver disease, is achievable with a parsimonious model incorporating α-fetoprotein, MELD 3.0, and tumor size. This approach can be applied to the liver allocation system to prioritize patients with HCC and can inform decision making regarding urgency weights for exception cases in the upcoming continuous distribution system.

Keywords: Hepatocellular Carcinoma; HCC; Liver Transplant; Organ Allocation; Model for End-Stage Liver Disease; MELD.

Liver transplantation is the definitive therapy for early-stage hepatocellular carcinoma (HCC).[1] Since 2002, the Model for End-Stage Liver Disease (MELD) has been used as an objective measure of disease severity and priority on the liver transplant waitlist in the United States. However, patients with HCC often do not generate laboratory-derived MELD scores sufficient to compete for liver transplantation. Consequently, patients with HCC have been assigned MELD exception points to provide access to liver transplant.

Exception points for HCC have been controversial, as early iterations overprioritized patients with HCC, requiring several modifications between 2003 and 2015, when ultimately a cap on the number of exception points was implemented, as well as a 6-month minimum waiting period before exception points would be granted (cap and delay). In 2019, the establishment of the National Liver Review Board (NLRB) to address geographic variability resulted in the transition from a fixed number of exception points via an escalator/elevator system to the median MELD at transplant 3 (MMaT-3)—initially around the donor service area, then the transplantation center, and as of 2022, the donor hospital.[2] With the implementation of these policies, transplantation rates for patients with HCC and patients without HCC have equalized, and the proportion of transplants with HCC exception in the United States has decreased from 27.0% in 2012 to 15.5% in 2022.[3] Adoption of MMaT-3 has reduced the overall waitlist dropout (ie, waitlist removal for death or being too sick) for both patients with and without HCC, but has lengthened waiting times for patients listed for HCC.[4,5]

Currently, all patients with stage T2 HCC (within Milan criteria) receive uniform MMaT-3 regardless of their tumor characteristics or behavior. However, it is well-recognized that there is heterogeneity in tumor behavior and

Abbreviations used in this paper: **AFP, α-fetoprotein; HCC, hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease; MMaT-3, median Model for End-Stage Liver Disease at transplant 3; Multi-HCC, Model of Urgency for Liver Transplantation in Hepatocellular Carcinoma; NLRB, National Liver Review Board; OPTN, Organ Procurement and Transplantation Network.**

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

In the United States, patient with hepatocellular carcinoma (HCC) meeting transplant criteria currently receive uniform priority on the liver transplant waitlist, without stratification by medical urgency.

NEW FINDINGS

We developed the Model of Urgency for Liver Transplantation in HCC, a parsimonious risk stratification model incorporating Model for End-Stage Liver Disease 3.0, α-fetoprotein, and tumor burden at the time of listing, to prioritize patients with HCC on the waitlist based on their urgency for transplant.

LIMITATIONS

This model was developed using the Organ Procurement and Transplantation Network database, which includes a finite number of variables suitable for allocation.

CLINICAL RESEARCH RELEVANCE

The Model of Urgency for Liver Transplantation in HCC can improve allocation of livers for patients with HCC and overall organ utility.

BASIC RESEARCH RELEVANCE

We describe a method to scale a model for waitlist mortality to the Model for End-Stage Liver Disease 3.0, allowing for direct comparison of urgency between candidates with HCC and without HCC, which may be extrapolated to other types of exception cases.

transplant benefit for patients with HCC. A subgroup of patients with HCC with exceedingly low risk of waitlist dropout have been identified (MELD score <15, Child-Turcotte-Pugh class A, α-fetoprotein (AFP) $\leq$20 ng/mL, and a single tumor 2–3 cm at listing), making up a substantial and increasing proportion of liver transplant candidates with HCC.[6,7] Conversely, although more liver-directed and systemic therapies are becoming available for HCC, patients with more advanced liver disease may be less able to tolerate such treatments and thus may have greater urgency for transplant. Previous risk stratification scores, such as HALT-HCC (Hazard Associated with Liver Transplantation for HCC), deMELD (Dropout Equivalent MELD), MELD-Eq (MELD Equivalent), and OPOM (Optimized Prediction of Mortality) have consistently identified AFP, tumor burden, and liver dysfunction, to be common predictors of waitlist dropout.[8–13] However, these scores were developed in older cohorts and have not gained traction, due in part to their complexity. The planned implementation of a continuous distribution for liver allocation in the United States presents an opportunity to account for the differential medical urgency of patients with HCC, separate from other attributes, such as post-transplantation survival, patient access, and placement efficiency.[14]

We developed a risk stratification model for patients with HCC, using objective variables at the time of listing obtained during the modern policy era, without compromising post-transplantation survival. We also explored scaling the model to estimate the number of MELD 3.0 points required to match the waitlist dropout of patients with HCC to those without HCC (by MELD 3.0).

Materials and Methods

Data

We identified adult patients listed for liver transplant who received an initial approved HCC exception from October 8, 2015 (implementation of the 6-month waiting period) to December 31, 2022, in the Organ Procurement and Transplantation Network (OPTN) database, which captures all waitlist, transplantation, and donation events in the United States. Variables available closest to the time of first approved HCC exception, including AFP, tumor burden, and MELD 3.0, were collected. Entries without a complete set of these data within 90 days of the first approved exception (n = 646) were excluded. Tumor burden was categorized by the initial reported tumor size and number into the United Network for Organ Sharing T1 (below Milan), T2 (within Milan), or T3 (outside Milan), with T2 subcategorized into (1) solitary tumor 2–3 cm, (2) solitary tumor >3 and $\leq$5 cm, or (3) multifocal tumor. Patients with T1 disease reported at the time of the first initial exception were categorized on the basis of their original tumor size, if reported. Those remaining in the lowest-risk groups (T1 or solitary tumor 2–3 cm) at listing were combined to represent the reference group (T2 $\leq$3 cm).

Outcomes and Predictors

Our primary goal was to stratify patients on the basis of their risk of waitlist dropout within 6 months from the time of first approved exception (time to event). Waitlist dropout was defined as removal from the waitlist for death or being too sick. Surviving patients were censored at waitlist removal for transplant or a reason other than death or being too sick to receive transplant, or after 6 months, whichever occurred first, with the end of follow-up on April 5, 2024. The primary end point at 6 months was selected to be the most clinically relevant, given the 6-month period that patients with HCC were required to wait before gaining exception points during the study timeframe. Predictors were selected for model development on the basis of previous evidence, excluding variables such as age, race, ascites, or encephalopathy, which have been considered not suitable for allocation in the United States. Ultimately, the following were considered in model development: MELD 3.0 score, components of MELD 3.0 (ie, creatinine, sodium, bilirubin, albumin, international normalized ratio, and female sex), AFP, and tumor burden.

Statistical Analysis

The data were randomly divided for model training and testing via a 70/30 train/test split. We considered several approaches to modeling right-censored time-to-event data, including Cox proportional hazards models, and the following machine learning approaches: random survival forests, gradient boosting, DeepHit,[15] and DeepSurv.[16] Raw predictors as well as transformed predictors (eg, natural logarithm-transformed) were considered, with the machine learning models simultaneously incorporating both the raw and transformed predictors. A generalized additive model form of the Cox model was used to evaluate the relationship between AFP and risk of death in a flexible shape via a smoothing spline, adjusted for

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MELD 3.0 and tumor size. We examined the extent to which the relationship between AFP and risk of death is linear and whether setting lower and upper bounds—the limits beyond which linearity of the relationship breaks down—would improve the fit.

For each model, we estimated C-statistics and integrated Brier scores. A bootstrapping method was used to obtain bias-corrected 95% CIs for each model's Harrell's C-statistic, Uno's C-statistic, and integrated Brier score. C-statistics in the test set were compared across models as well as with previously developed scores, including HALT-HCC, deMELD, and the waitlist dropout score developed by Mehta et al.[13] *P* values to compare 2 Harrell's C-statistics were computed via a nonparametric approach described in Kang et al[18]; *P* values to compare 2 Uno's C-statistics were computed via a perturbation-resampling method described in Uno et al.[17] Although the C-statistic measures the discriminatory performance of the model, the integrated Brier score captures both discrimination and calibration, and is best interpreted as an overall measure of model performance. We also plotted the observed and model-predicted waitlist survival within strata of the developed score to visualize model calibration. A sensitivity analysis was performed to analyze model performance in patients registered in the NLRB/MMaT-3 era, that is, listed after May 14, 2019.

We selected the model with the ideal combination of performance, transparency, and usability, and evaluated probabilities of waitlist dropout by risk quartile. Kaplan–Meier analysis was used to assess waitlist mortality and 5-year post-transplantation patient survival across quartiles risk derived from the chosen model, and a log-rank test was used to compare the survival distributions across the 4 groups. The post-transplantation end point was selected to represent the timeframe in which HCC recurrence, which has the largest impact on post–liver transplantation survival, was observed, balanced with the duration of available post-transplantation follow-up for this cohort.

Finally, we considered how the selected model could be integrated into liver allocation within the framework of continuous distribution, the proposed points-based system in the United States—specifically, how the selected model developed for patients with HCC exceptions can inform the number of "points to add" to represent medical urgency, that is, their additional dropout risk on top of their biologic MELD 3.0 score. Ideally, a score developed to risk-stratify patients with HCC (regardless of approach) would be comparable in some way to existing risk stratification schema for patients without HCC (eg, MELD 3.0) because patients with and without HCC "compete" for livers. We developed a statistical approach to link predictions from the chosen model to MELD 3.0, producing a "MELD 3.0–equivalent" formula for patients with HCC exceptions. This resulting formula ensures that a patient without HCC with a given MELD 3.0 score and a patient with HCC with a matching "MELD 3.0–equivalent" Model of Urgency for Liver Transplantation in HCC (Multi-HCC) score have the same predicted 90-day waitlist dropout probability. The outcome of 90-day waitlist dropout was selected to align with MELD 3.0, even though the chosen model for HCC was developed using 6-month waitlist dropout. Thus the numerical output of Multi-HCC is scaled to MELD 3.0 to visualize the equivalent 3-month waitlist dropout risk, but the relative rankings (discrimination) are still based on the more clinically relevant 6-month end point. For patients with HCC, this approach also allows us to estimate the number of "points to add" to their biologic MELD 3.0, based on the chosen model. Technical details are provided in the Supplementary Materials.

The intent of the above steps was to create a MELD-equivalent model for HCC, where waitlist dropout would be comparable between patients with the same Multi-HCC (if HCC) and MELD (if chronic liver disease) scores. However, this exercise revealed that although many candidates with HCC would gain some priority on top of their biologic MELD score, it would not be nearly as much as they receive in the current allocation system, which is calibrated to equalize transplant rates—not waitlist dropout—between patients with and without HCC. We proposed some potential strategies for implementation, where Multi-HCC can be used to risk-stratify patients with HCC instead of 1 uniform score, and the MMaT preserves transplant access.

For all analyses, adjusted *P* values of $<.05$ after Holm correction were considered significant, and all tests were 2-tailed. In descriptive analyses, variables were compared among groups using the *t* test, χ^2 test, 1-way analysis of variance, and Wilcoxon rank-sum test, as appropriate. Statistical analyses were performed using R, version 3.6.2 (R Foundation, Vienna, Austria). The code to reproduce this analysis is available at: https://github.com/vivekcharu/Multi-HCC. The study, consisting of analysis of deidentified data, was deemed exempt by the institutional review board at Stanford University.

Results

Demographic characteristics of the cohort are provided in Table 1. During the study period, there were 18,237 patients with HCC listed for a liver transplant; median age was 63 years (interquartile range, 58–66 years), MELD 3.0 score was 11 (interquartile range, 8–15), and AFP was 6 ng/mL (interquartile range, 4–17 ng/mL) at the first approved exception. Within this cohort, 52.6% had T2 $\leq$3 cm, 21.2% had solitary tumors $>$3 and $\leq$5 cm, 15.7% had multifocal HCC, and 10.6% had T3 disease; 69.6% had a reported history of locoregional therapy before the first approved exception. In terms of eventual outcome among patients with HCC, 11,018 patients (60.4%) were removed for deceased donor liver transplant; 315 (1.7%) were removed for living donor liver transplant, 957 (5.2%) were removed for death, and 2619 (14.4%) were removed for being too sick.

We developed several models for waitlist dropout within 6 months for patients with HCC exceptions, including conventional statistical models (Cox regression) and several machine learning models. The models incorporated various combinations of MELD 3.0, MELD 3.0 components (ie, international normalized ratio, bilirubin, creatinine, sodium, albumin, and sex), AFP, and tumor size and number. Table 2 compares the model discrimination metrics for these models as well as previously developed scores (Supplementary Table 1). The 3 best models based on discriminatory performance were the gradient boosting model (Harrell's C-statistic, 0.72; 95% CI, 0.69–0.74), random survival forest model (Harrell's C-statistic, 0.71; 95% CI, 0.68–0.73), and a Cox model incorporating MELD

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Table 1. Demographic Characteristics of Liver Transplantation Candidates With Approved Hepatocellular Carcinoma Exception: Development and Validation Cohorts

Characteristic	Development cohort (n = 12,673)	Validation cohort (n = 5564)
Age, *y*, median (IQR)	63 (58–66)	62 (58–66)
Sex, male, n (%)	9609 (76)	4276 (77)
MELD score, median (IQR)	10 (8–13)	10 (8–13)
MELD-Na score, median (IQR)	11 (8–15)	11 (8–14)
MELD 3.0 score, median (IQR)	11 (8–15)	11 (8–15)
Serum bilirubin, *mg/dL*, median (IQR)	1.2 (0.7–2.0)	1.2 (0.7–2.0)
Serum INR, median (IQR)	1.2 (1.1–1.3)	1.2 (1.1–1.3)
Serum creatinine, *mg/dL*, median (IQR)	0.86 (0.72–1.05)	0.87 (0.71–1.05)
Serum albumin, *g/dL*, median (IQR)	3.5 (3.0–3.9)	3.5 (3.0–3.9)
Serum sodium, *mmol/L*, median (IQR)	138 (136–140)	138 (136–140)
AFP, *ng/mL*, median (IQR)	6 (4–16)	6 (4–17)
AFP category, n (%)		
≤20 ng/mL	9971 (79)	4329 (78)
21–40 ng/mL	919 (7)	412 (7)
41–250 ng/mL	1320 (10)	626 (11)
250+ ng/mL	463 (4)	197 (4)
Tumor type (%)		
T2 ≤3 cm	6701 (53)	2886 (52)
T2 >3–5 cm	2684 (21)	1175 (21)
T2 multifocal	1949 (15)	907 (16)
T3 (down-staged)	1339 (11)	596 (11)
History of locoregional therapy, n (%)	8816 (70)	3875 (70)

IQR, interquartile range.

3.0, log(AFP), and tumor burden (Harrell's C-statistic, 0.71; 95% CI, 0.69–0.74). Meaningful differences between Harrell's and Uno's C-statistics were not seen. For the Cox model, AFP values >250 ng/mL were capped at 250 ng/mL, producing a linear relationship between the risk of death and log(AFP) (Supplementary Figure 1). Similarly, as in the MELD score, bilirubin, international normalized ratio, and creatinine values <1.0 were set to 1.0; serum creatinine was capped at 3.0 mg/dL; and lower and upper bounds were set at 1.5 g/dL and 3.5 g/dL for albumin, and 125 mmol/L and 137 mmol/L for sodium, respectively.

To balance model transparency, interpretation, and performance, we selected the Cox-based model, with MELD 3.0, log(AFP), and tumor burden, as the final model. The C-statistics (Harrell's and Uno's, with administrative censoring at 6 months) for the selected model were superior to MELD 3.0 alone ($P < .01$) and existing scores, including HALT-HCC, MELD-Eq, deMELD, and Mehta et al.'s[13] waitlist dropout score ($P < .01$ for all), which incorporated the Child-Pugh score, and had a similar performance to the gradient boosted and random survival forest machine learning models ($P = .53$). Table 3 shows the fitted coefficients for the final Cox model chosen, based on MELD, AFP, and tumor size, in the training cohort for waitlist dropout after 6 months. In calibration plots, predicted survival probabilities for the selected model approximated observed survival within model-based risk groups across a 6-month time period. The integrated Brier score for the model was 0.034 (95% CI, 0.031–0.037) (Figure 1). In a sensitivity analysis of patients with HCC registered in the NLRB/MMaT-3 era, model discrimination was similar, with a C-statistic of 0.71 (95% CI, 0.67–0.75).

Based on the fitted Cox model, we developed a MELD 3.0–equivalent score for patients with HCC exception points, such that a patient with HCC with a given MELD 3.0–equivalent score and a patient without HCC with a matching MELD 3.0 score will have the same risk of waitlist dropout within 90 days (Supplementary Materials and Methods, Supplementary Figure 2, and Supplementary Figure 3). The resulting equation for our proposed, MELD-matched Multi-HCC score is: 0.868 * (MELD 3.0) + 1.859 * log(AFP) + 2.123 * [T2 3–5] + 1.174 * [multifocal] + 3.472 * [T3] – 0.36, rounded to the nearest integer. The distribution of the score is presented in Figure 1*A*, with calibration over 6-month waitlist dropout among quartiles of the score in Figure 1*B*. In the Kaplan–Meier analysis, overall waitlist dropout among patients with HCC in the test cohort was 3.7% at 90 days, 8.9% at 6 months, and 21.5% at 1 year. The

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Table 2. Comparison of Model Performance for 6-Month Waitlist Dropout in the Test Set, C-Statistics With 95% Bootstrap CI

Variable	Harrell's C-statistic (95% CI)	*P* value[a]	Uno's C-statistic (95% CI)	*P* value[a]
Cox: MELD 3.0 + $\log_e$(AFP) + tumor burden (Multi-HCC)	0.71 (0.69–0.74)	Reference	0.71 (0.69–0.74)	Reference
Cox: MELD 3.0	0.66 (0.64–0.69)	<.01	0.66 (0.63–0.68)	<.01
Cox: MELD 3.0 components	0.67 (0.65–0.70)	<.01	0.67 (0.64–0.69)	<.01
Random survival forest	0.71 (0.68–0.73)	.53	0.70 (0.68–0.73)	.30
Gradient boosting model	0.72 (0.69–0.74)	.53	0.71 (0.69–0.74)	.86
DeepHit	0.64 (0.61–0.67)	<.01	0.64 (0.61–0.67)	<.01
DeepSurv	0.69 (0.67–0.72)	.03	0.69 (0.67–0.72)	.02
Mehta et al[13]	0.69 (0.67–0.72)	<.01	0.69 (0.67–0.72)	<.01
HALT-HCC	0.67 (0.65–0.70)	<.01	0.67 (0.65–0.70)	<.01
deMELD	0.62 (0.60–0.65)	<.01	0.62 (0.59–0.64)	<.01
HCC-MELD	0.62 (0.59–0.65)	<.01	0.61 (0.58–0.64)	<.01
MELD-Eq	0.65 (0.62–0.68)	<.01	0.64 (0.62–0.67)	<.01

[a]*P* values for significant difference in C-statistics between the Multi-HCC and each of the other approaches. All *P* values reported have been adjusted using the Holm correction.

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observed risk of waitlist dropout at 6 months was 20.5% for the highest risk quartile in the test cohort, compared with 3.5% for the lowest risk quartile. Liver transplant recipients in the highest risk quartile exhibited similar 5-year post-transplantation survival of 73.9%, compared with 75.9% and 77.1% in the middle risk quartiles, and 80.5% in the lowest risk quartile (log-rank $P = .02$; Figure 2).

An advantage of our statistical approach is that we can estimate the number of MELD 3.0–equivalent points to add to the laboratory-derived MELD 3.0 score of a patient with HCC to match their urgency with the non-HCC population. Figure 3 displays the median number of MELD 3.0–equivalent points to add to MELD 3.0 among patients with HCC compared with those without HCC to achieve the same risk of 90-day waitlist dropout. For example, a patient with HCC and a calculated laboratory MELD 3.0 of 6 would need, on average, 4 more MELD points to match the 90-day dropout risk of a similar patient with chronic liver disease and a MELD 3.0 of 10. Beyond a laboratory MELD 3.0 of 20, patients with HCC did not have substantially larger predicted dropout risk beyond their calculated laboratory MELD. Supplementary Figure 4 illustrates the fraction of patients with HCC classified into each of 4 Multi-HCC risk quartiles for a given MELD 3.0 score.

Table 3. Cox Proportional Hazards Analysis for 6-Month Waitlist Dropout in the Development Cohort for the Selected Model

Variable	Univariable HR (95% CI)	Multivariable HR (95% CI)
MELD 3.0 (per unit increase)	1.14 (1.13–1.16)	1.15 (1.14–1.16)
$\log_e$(AFP)	1.35 (1.30–1.41)	1.34 (1.29–1.40)
Tumor burden		
T2 ≤3 cm	1.00	1.00
T2 >3–5 cm	1.31 (1.10–1.57)	1.21 (1.01–1.44)
T2 multifocal	1.38 (1.18–1.61)	1.40 (1.20–1.64)
T3 (down-staged)	1.51 (1.24–1.83)	1.74 (1.43–2.11)

HR, hazard ratio.

In light of these findings and the goal to preserve transplant access and maintain similar waiting times and transplant outcomes as the current system, we considered potential allocation schemes that would incorporate the Multi-HCC model for risk stratification, but also preserve transplant access and other elements of the current liver allocation system for HCC, including the 6-month waiting period. In practice, Multi-HCC could be distributed as a continuous score around MMaT-3, or used to categorize patients into several bins between MMaT-1 and MMaT-5, with the intent to maintain similar waitlist outcomes, transplant rates, and wait times as MMaT-3 does as an aggregate (Figure 4).[19] Interval increases in the risk category may be considered in case of transition to higher risk, or after 3–6 months of waiting time, to preserve access for candidates with tumor that has been appropriately treated.

Discussion

Here we proposed the Multi-HCC as a new risk stratification score for HCC derived in the modern policy era. Our model has comparable or superior performance to

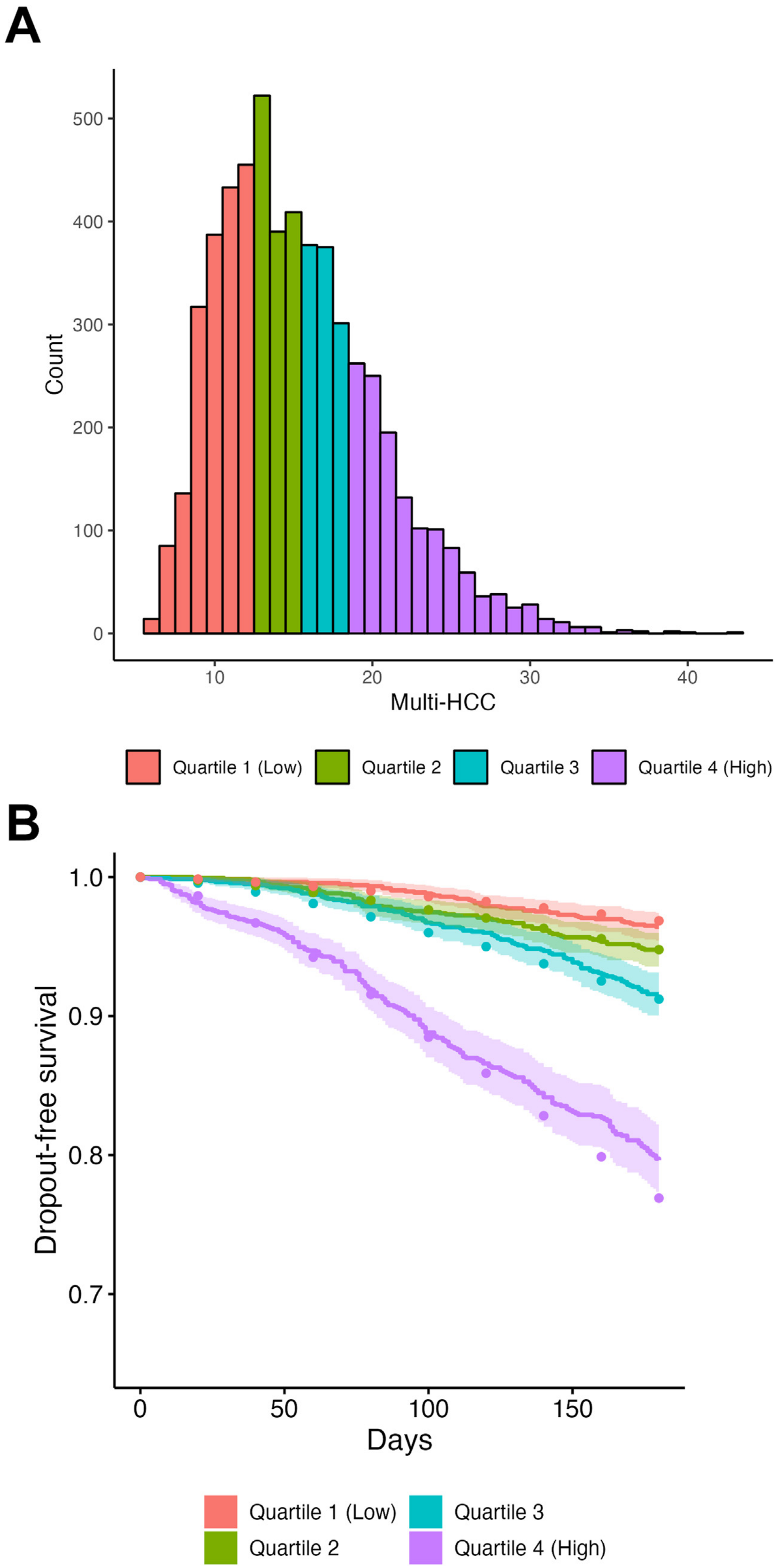

Figure 1. (*A*) Distribution of the risk score, shaded by quartile of predicted risk. (*B*) Kaplan–Meier curves for time to waitlist dropout in the validation set, by quartile of predicted risk. *Solid lines* represent observed survival curves within each quartile, with the *shaded area* represents 95% CI. The *solid circles* are the model-based predictions at 10 evenly spaced intervals. For a well-calibrated model, the points should follow the empirical curves closely and fall within the 95% CI.

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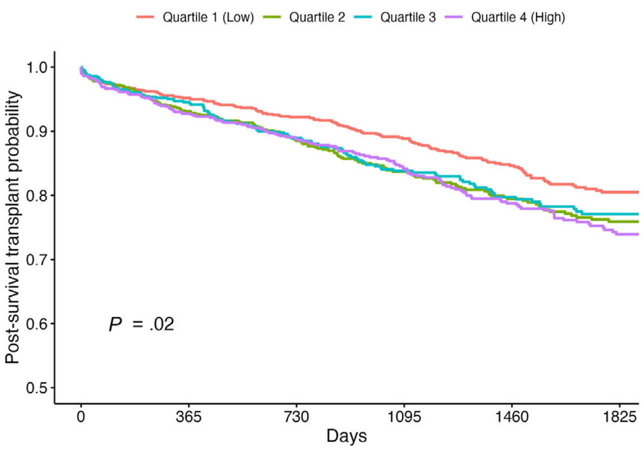

Figure 2. Post-transplantation survival over 5 years of follow-up in the validation set, stratified by Multi-HCC risk quartile. Quartile 4 represents the highest risk group; quartile 1 represents the lowest risk group.

previously proposed models with a C-statistic of 0.71 over 6 months, the time point that patients with HCC currently gain priority for transplant via exception points. This score maintained performance when restricted to the NLRB/MMaT-3 era, when wait times for patients with HCC were longer, with a C-statistic of 0.71. This parsimonious score is straightforward to calculate; similar to the MELD score; and includes tumor size and number, AFP, and MELD 3.0, while excluding variables not appropriate for allocation, such as age or race, and subjective measures, such as hepatic encephalopathy or ascites. In our study, machine learning techniques, including the random survival forest and neural network–based models, did not result in superior performance, indicating that machine learning approaches using the currently available variables collected by the OPTN are unlikely to improve the prediction, and that our model does not overlook major latent or nonlinear interactions. By scaling the Multi-HCC score to MELD 3.0, risk predictions for patients with and without HCC can be interpreted on the same scale, that is, a patient with HCC and a Multi-HCC score of 18 would have the same risk of waitlist dropout over 90 days without transplant as a patient with end-stage liver disease and a MELD 3.0 of 18. This statistical approach can inform decision making regarding urgency weights for not only HCC, but also other exception cases in the upcoming continuous distribution system.

In the current US liver allocation system, MELD exception points are awarded to patients with HCC, who often lack liver synthetic dysfunction to generate a laboratory MELD score sufficient to compete for transplant with patients without HCC. MELD was developed to estimate the risk of waitlist dropout with 90 days, which serves as a surrogate for mortality and, therefore, medical urgency.[14] The OPTN Final Rule mandates that organs are allocated, to the extent possible, through objective and measurable medical criteria, ordered from the most to least medically urgent.[15] In a patient without HCC, “sicker” relates to an increased risk of death in the order of months due to liver dysfunction. In contrast, for patients with HCC, dropout means they have missed their window for a curative therapy. A 90-day prediction for MELD is optimal, as patients with decompensated cirrhosis in need of transplant may have a rapidly progressive disease course, and their MELD score will increase as their mortality risk increases. In contrast, a patient with HCC at risk for dropout may not necessarily demonstrate worsening biomarkers and is more likely to be removed from the list due to disease spread than death. Once their disease is beyond transplantable criteria, for example, extrahepatic spread, they lose their window for transplant but may still be a candidate for additional liver-directed or systemic therapy. Unlike patients with decompensated cirrhosis, the velocity of disease progression and urgency for transplant for patients with HCC may not be accurately represented or measured on the order of weeks or a few months, and a longer time horizon, that is, at 6 or 12 months, may be needed to properly assess the risk of waitlist dropout.[4] Thus, the Multi-HCC score was developed based on a primary end point of 6-month waitlist dropout and developed on a cohort relatively unaffected by informative censoring from transplantation during the 6-month waiting period, reflecting as much as possible the natural history of the disease—before changes in recent years enabling earlier transplantation, including machine perfusion and policy revisions (from July 2022) to allow recurrent disease after previous treatment (resection or locoregional therapy) to bypass the waiting period. In this latter context, Multi-HCC would help to more accurately prioritize those candidates eligible for MELD exception points up front.[20]

Although it would be useful to predict mortality on the same scale for patients with and without HCC (ie, MELD interdigitation), our analysis highlights the challenges of using this approach alone. With a median laboratory MELD score of 11 among patients with HCC, we find that adding priority based on shorter-term waitlist dropout risk would add only a handful of points on average, resulting in noncompetitive MELD scores for transplant and likely a substantial drop in the number and proportion of patients undergoing transplantation for HCC. In the United Kingdom, similar attempts to rank patients with and without HCC on the same scale via the Transplant Benefit Score led to erroneous and counterintuitive predictions, where the presence of HCC actually decreased the expected survival benefit of liver transplantation and disadvantaged patients with HCC—emphasizing the importance of clinical intuition and extensive testing of a model before adoption.[21]

In the US allocation system, MMaT-3 was selected by the United Network for Organ Sharing to provide equity in access by equalizing transplant rates for patients with and without HCC—while not affecting waitlist mortality or post–liver transplantation survival mortality—to maintain the status quo[2] and to ensure that patients with HCC were transplanted at a similar rate as in prior eras. MMaT-1 resulted in fewer patients without HCC being transplanted, although MMaT-5 led to fewer patients with HCC being transplanted. If we accept that MMaT-3 is the appropriate average transplant priority for patients with HCC, then the concept of matching waitlist dropout for patients with and

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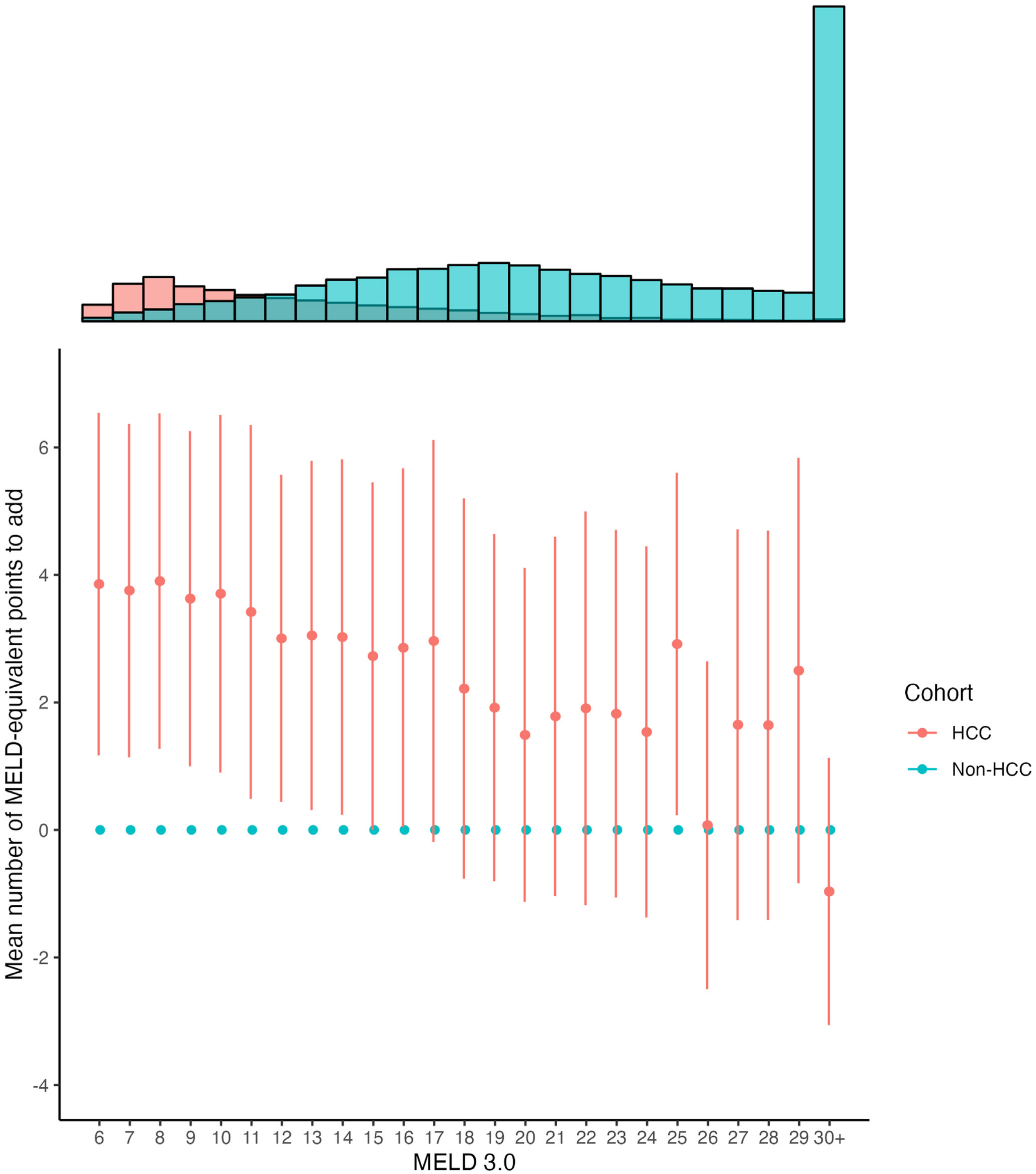

Figure 3. *Plot* demonstrating the estimated median number of points to add to MELD 3.0 among patients with HCC compared with those without HCC to achieve the same risk of 90-day waitlist dropout. *Error bars* indicate the interquartile range. The distribution of biologic MELD 3.0 scores at the time of listing are provided for patients with HCC (*red*) and without HCC (*blue*) at the *top panel*.

without HCC is misguided, as waitlist dropout behaves differently in these cohorts and does not lead to empiric derivation of a priority nearly equivalent to MMaT-3. Considering the heterogeneity in HCC waitlist dropout, and to honor the Final Rule and the "sickest first" principle, we propose that Multi-HCC be used to represent medical urgency and MMaT to be the geographical benchmark for transplant access, as illustrated in Figure 4.

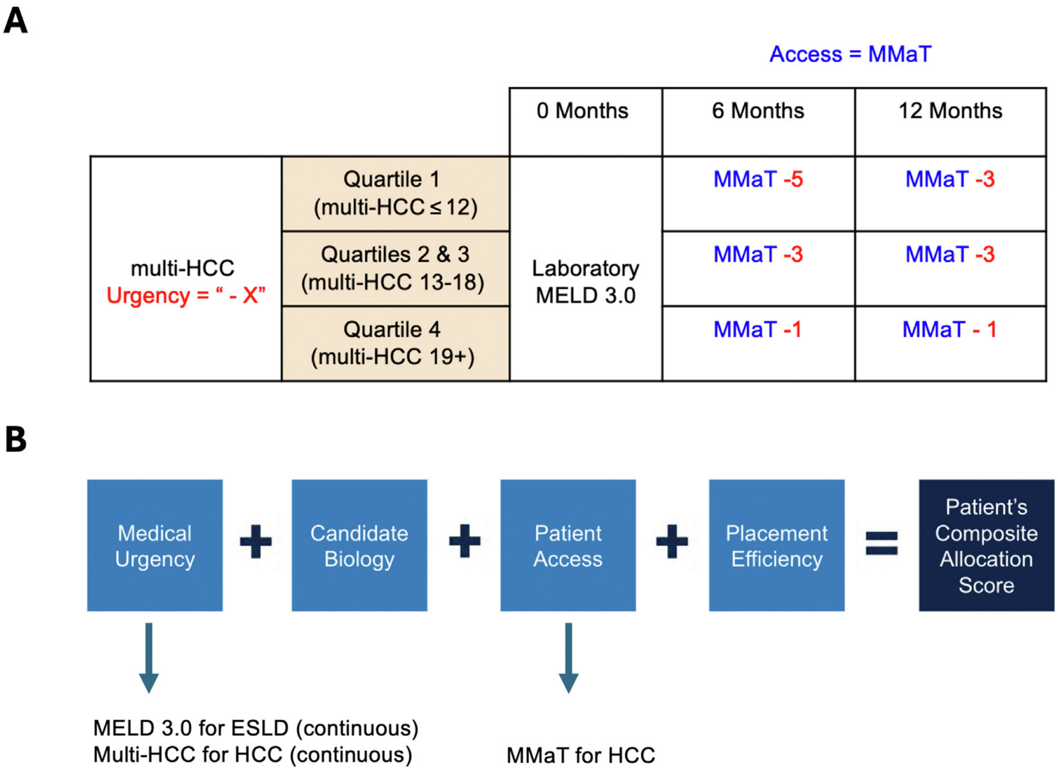

Figure 4. (*A*) Potential allocation scheme incorporating Multi-HCC, with the 6-month waiting period and additional priority for waiting time. Consistent with current policy, patients initially receive priority based on the calculated laboratory MELD 3.0; after the 6-month waiting period, they are eligible for HCC MELD exception points. (*B*) Potential allocation scheme using Multi-HCC within the continuous distribution framework. ESLD, end-stage liver disease.

The aim for a patient with HCC is to be transplanted in the "Goldilocks" window period of having sufficient tumor burden to benefit from liver transplantation, but before extrahepatic spread or excessively high risk of post–liver transplantation recurrence. Greater medical urgency for HCC would reflect the patients most likely to fall out of this window. However, patients at higher risk of dropout may have higher-risk tumors and, therefore, higher post-transplantation HCC recurrence risk. Our data demonstrate that post–liver transplantation survival outcomes remain acceptable, that is, ≥70% at 5 years, even among the higher-risk quartiles, suggesting that with the current limits for tumor size, number, and AFP, post-transplantation survival may not necessarily be compromised by prioritizing more urgent cases. In some cases, more timely transplantation for these patients with higher initial AFP or greater tumor burden may even reduce the risk of post–liver transplantation survival recurrence, when liver transplantation can be performed before disease advancement or spread. Although the 6-month waiting period was implemented to equalize the transplant rate between patients with HCC and those without, this strategy also serves to select out those patients with aggressive tumor biology who are likely to have unacceptable post-transplantation survival. These patients are appropriately removed from the liver transplant waitlist, and so we favor that a waiting period of 3–6 months be maintained to elicit tumor biology. In addition, guardrails to maintain acceptable post-transplantation survival exist, including downstaging criteria and limits on AFP—and clinicians would still have the discretion to not offer transplantation for individual high-risk cases.

Although much attention has been paid to the highest-risk tumors and upper limits of liver transplantation for HCC, identification of patients at lowest risk for waitlist dropout is equally important, as these patients have low urgency and may even have a negative survival benefit from transplant.[6,7] In the modern era, there are more available medical (ie, locoregional and systemic) therapies for HCC, potentially improving outcomes for these patients without the need for transplantation and sparing them the surgical risks of transplantation and long-term risks of immunosuppression. Deprioritizing patients with objectively low dropout risk may not only improve their individual outcome, but also redirect and allocate organs toward those patients in greater need.

Our model prioritizes simplicity and interpretability. Although the model could theoretically be improved with the inclusion of age, race, ascites, and hepatic encephalopathy, these variables have not been considered to be suitable for use in allocation, either due to bias or subjectivity. Additional biomarkers that can improve the prediction of waitlist dropout, such as AFP bound to Lens culinaris agglutinin and des-gamma-carboxy prothrombin, are not currently systematically recorded by the OPTN.[22] Dynamic modeling of AFP and tumor size could also, in theory, improve the model's performance; however, it remains undetermined whether the system would give higher or lower priority to those with rising AFP or lack of response to liver-directed therapy. In addition, incorporation of dynamic variables to account for tumor growth or response during the waiting period could influence behaviors and create disincentives to provide bridging therapy, and appropriate safeguards would need to be in place.

Although the C-statistic of 0.71 is relatively modest compared with the excellent performance of MELD 3.0 (in part limited by the fact that many patients with HCC do not produce AFP), it is still an improvement on the status quo, which does not discriminate between high-risk and low-risk cases, that is, essentially a C-statistic of 0.50. There are limitations to using the OPTN database, including data fidelity and accuracy, with data entry for both initial and extension exception requests often being manually entered. In addition, this model was developed within the population of patients meeting the relatively restrictive selection criteria for HCC exception. If in the future the qualifications for HCC exception change, such as expansion beyond Milan or downstaging criteria, the model may be updated.

The OPTN is currently in the process of transitioning the liver allocation system to a continuous distribution model that will include discrete points for medical urgency, patient access, and efficiency, among other factors.[14] We proposed the current model as a practical solution to represent medical urgency for patients with HCC on the liver transplant waitlist in the United States, as MELD 3.0 does for patients with chronic liver disease. With relatively low short-term mortality risk for patients with HCC, when considered on the same urgency scale at MELD 3.0, additional correction may be needed to maintain access to transplantation, for example, via patient access points, to maintain a transplant rate equivalent to patients with chronic liver disease, and this could continue to be based on the median MELD at transplant in order to maintain geographic equity.

In summary, an urgency-based priority system for patients with HCC, similar to MELD for patients with chronic liver disease, is achievable with Multi-HCC, a parsimonious model incorporating AFP, MELD 3.0, and tumor size. This model can be applied to the national liver allocation scheme to represent medical urgency for patients with HCC and improve organ utility for the liver allocation system.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2024.11.015.

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Correspondence
Address correspondence to: Allison J. Kwong, MD, Division of Gastroenterology and Hepatology, Stanford University, 430 Broadway Street, Floor 3, Redwood City, California 94063-3132. e-mail: ajk@stanford.edu; or Vivek Charu, MD, PhD, Quantitative Sciences Unit, Stanford University, 300 Pasteur Drive, Edwards R248B, Palo Alto, California 94304. e-mail: vcharu@stanford.edu.

CrediT Authorship Contributions
Joshua S. Norman, MD (Conceptualization: Equal; Data curation: Equal; Formal analysis: Equal; Funding acquisition: Equal; Investigation: Equal; Methodology: Equal; Writing – original draft: Lead; Writing – review & editing: Equal)
Neil Mehta, MD (Conceptualization: Equal; Formal analysis: Supporting; Writing – original draft: Equal)
W. Ray Kim, MD, MBA, FAASLD (Conceptualization: Supporting; Formal analysis: Supporting; Methodology: Supporting; Writing – original draft: Supporting)
Jane W. Liang, Ph.D. (Conceptualization: Supporting; Data curation: Equal; Formal analysis: Lead; Investigation: Equal; Methodology: Equal; Software: Equal; Writing – original draft: Supporting; Writing – review & editing: Supporting)
Scott W. Biggins, MD, MAS (Conceptualization: Supporting; Formal analysis: Supporting; Methodology: Supporting; Writing – original draft: Supporting)
Sumeet K. Asrani, MD, MSc (Conceptualization: Supporting; Formal analysis: Supporting; Methodology: Supporting; Writing – original draft: Supporting)
Julie Heimbach, MD (Conceptualization: Supporting; Formal analysis: Supporting; Methodology: Supporting; Writing – original draft: Supporting)
Vivek Charu, MD, Ph.D. (Conceptualization: Supporting; Data curation: Supporting; Formal analysis: Equal; Investigation: Equal; Methodology: Lead; Writing – original draft: Supporting; Writing – review & editing: Supporting)
Allison J. Kwong, MD, MS (Conceptualization: Lead; Data curation: Lead; Formal analysis: Equal; Funding acquisition: Lead; Investigation: Lead; Methodology: Lead; Project administration: Lead; Supervision: Lead; Writing – original draft: Equal; Writing – review & editing: Equal)

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Data Availability
The data that support the findings of this study are available from the Organ Procurement and Transplantation Network. Restrictions apply to the availability of these data, which were used under license for this study and are not publicly available.

Supplementary Materials and Methods

The overarching goal of this analysis was to risk-stratify patients with HCC using a point system that aligns with MELD 3.0, such that 2 patients with the same number of points will have the same estimated risk of 90-day waitlist dropout, regardless of the presence or absence of HCC. This is not a straightforward task because the baseline risk of waitlist dropout over 90 days is substantially different among patients with and without HCC. We devised a statistical approach to achieve this goal.

First, for the cohort of patients with HCC, we fit a Cox proportional hazards model, in which the primary outcome was time to waitlist dropout with administrative censoring at 6 months. This model is of the form:

$$h(t|X) = \lambda_0(t) exp\{\beta_1 * MELD3.0 + \beta_2 * log(AFP) + \beta_3 * tumor.burden\}$$

Based on the fitted model, we developed a risk score using the fitted linear predictor from the model above.

$$s(X) = b_1 * MELD3.0 + b_2 * log(AFP) + b_3 * tumor.burden$$

where, $b_1 \ldots b_3$ are estimates of $\beta_1 \ldots \beta_3$.

The risk score, $s(X)$, ranks patients with HCC based on their risk of waitlist dropout over a 6-month time period. In order to integrate this risk score within the continuous distribution for liver allocation in the United States, patients with HCC need to be "put on the same scale" as patients without HCC. To do so, we developed an integrated Cox proportional hazards model, using data from patients with and without HCC; this model allows us to "re-scale" the proposed risk score, $s(X)$, to numerically match the MELD 3.0 score, such that patients with HCC and without HCC with the same score will have identical 90-day waitlist dropout predictions. To achieve this goal, we fit the following model, where the outcome is the time to waitlist dropout with administrative censoring at 90 days (as in the original MELD 3.0):

$$h(t|X) = \lambda_0(t) exp\{[(1 - \text{HCC}) * \alpha_1 MELD3] + [(HCC) * [\alpha_2 + \alpha_3 s(X)]]\}$$

Notice in the above, patients without HCC have a baseline hazard of $\lambda_0(t)$, and patients with HCC have a baseline hazard of $\lambda_0(t) exp(\alpha_3\ )$. An assumption of our approach is that the baseline hazards between the HCC and non-HCC groups are proportional (Supplementary Figure 3). Also notice that by construction, $s(X)$ will still rank patients with HCC based on their risk of waitlist dropout over 6 months. This model can be simplified as follows:

$$h(t|X) = \lambda_0(t) exp\{[(1 - \text{HCC}) * \alpha_1 MELD3] + [(HCC) * [\alpha_2 + \alpha_3 s(X)]]\}$$

$$h(t|X) = \lambda_0(t) exp\{[(1 - \text{HCC}) * \alpha_1 MELD3]\} * \exp\{[(HCC) * [\alpha_2 + \alpha_3 s(X)]]\}$$

$$h(t|X) = \lambda_0(t) exp\{[(1 - \text{HCC}) * \alpha_1 MELD3]\} * \exp\left\{\left[(HCC * \alpha_1) * \left[\frac{\alpha_2 + \alpha_3 s(X)}{\alpha_1}\right]\right]\right\}$$

Notice that for patients without HCC, $h(t|X) = \lambda_0(t) exp\{\alpha_1 MELD3]\}$ and for patients with HCC, $h(t|X) = \lambda_0(t) \exp\left\{\left[(\alpha_1) * \left[\frac{\alpha_2 + \alpha_3 s(X)}{\alpha_1}\right]\right]\right\}$. This implies that the hazards in the 2 groups will be equivalent when MELD3 $= \left[\frac{\alpha_2 + \alpha_3 s(X)}{\alpha_1}\right]$. Thus, we can scale $s(X)$ by $\alpha_1, \alpha_2, \alpha_3$ to obtain a MELD 3 equivalent score for patients with HCC (Multi-HCC) that satisfies the criterion that the instantaneous hazard at time t for patients without HCC with a particular MELD3 is equivalent to the instantaneous hazard at time t for patients with HCC with the equivalent Multi-HCC score. Further algebraic manipulation yields (and assuming a_1, a_2, a_3 are estimators for $\alpha_1, \alpha_2, \alpha_3$:

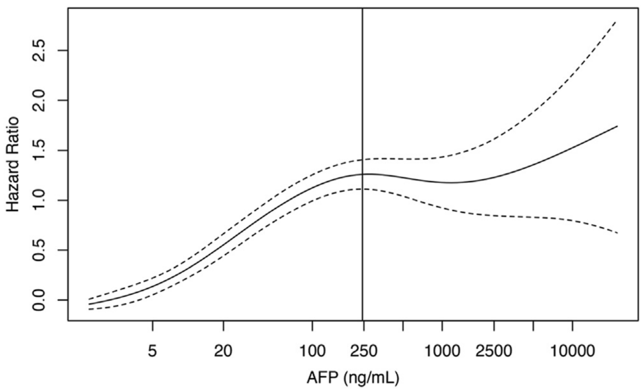
$$MultiHCC = \frac{a_2 + a_3 s(X)}{a_1}$$

$$MultiHCC = a_2/a_1 + a_3/a_1 s(X)$$

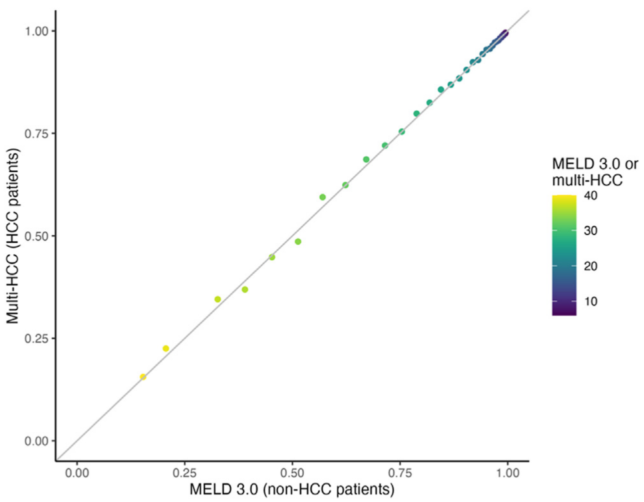
$$MultiHCC = a_2\ /\ a_1 + a_3\ /\ a_1\{b_1 MELD3.0 + b_2\ log(AFP) + b_3 tumor.burden\}$$

$$MultiHCC = a_2/a_1 + b_1 a_3/a_1 MELD3.0 + b_2 a_3/a_1\ log(AFP) + b_3 a_3/a_1 tumor.burden$$

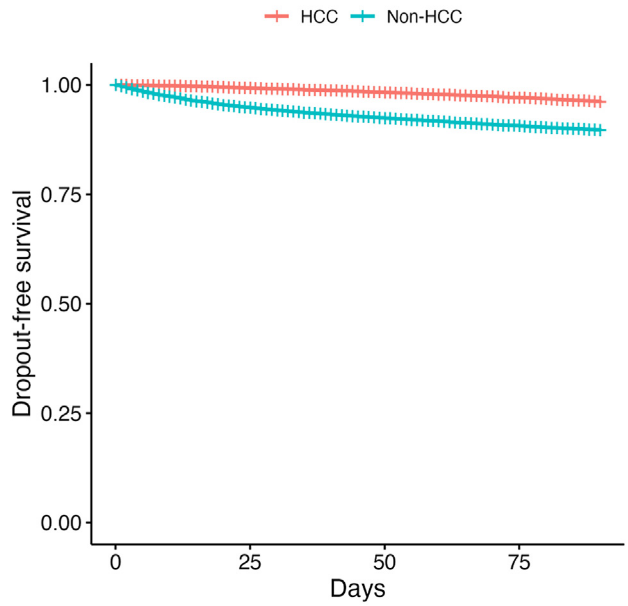
Multi-HCC produces a score that is on the same scale as MELD 3.0. By construction, a patient without HCC and a particular MELD 3.0 score, and a patient with HCC and a particular Multi-HCC score will have identical hazard functions, and identical 90-day waitlist dropout mortality predictions. Furthermore, patients with HCC are ranked according to their 6-month waitlist dropout, again by construction. This parameterization also allows us to estimate the number of points difference between MELD 3.0 and Multi-HCC for a given patient, or the number of "MELD 3.0–equivalent" points to add to MELD 3.0 to achieve the same risk of waitlist dropout.



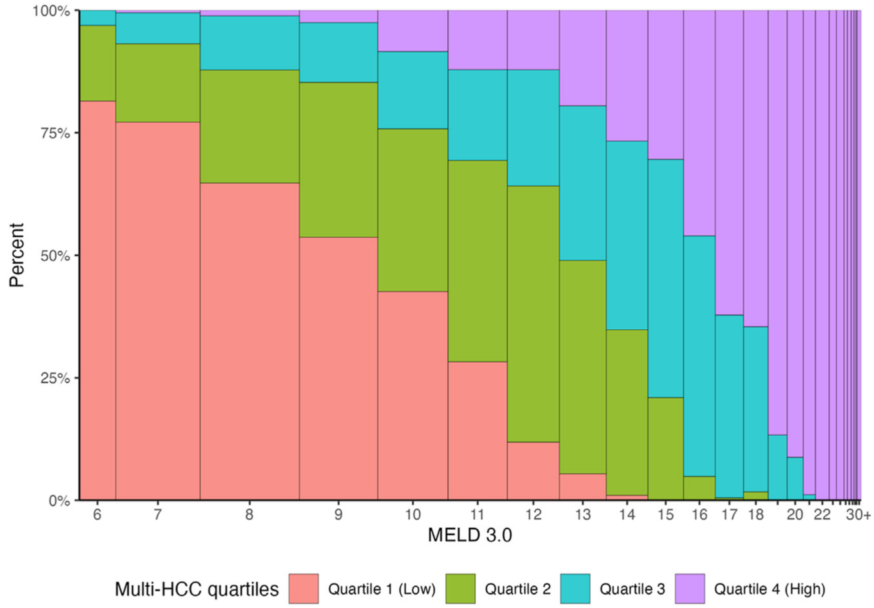
Supplementary Figure 1. Multivariable smoothing spline relating AFP with relative risk of death within 90 days.



Supplementary Figure 2. Comparison of 90-day waitlist dropout prediction for patients with HCC based on Multi-HCC (y-axis) and patients without HCC based on MELD 3.0 (x-axis). By construction, patients with identical MELD 3.0 and Multi-HCC scores have identical 90-day waitlist dropout predictions (slight differences along the diagonal due to rounding).



Supplementary Figure 3. Kaplan–Meier curves for the HCC and non-HCC cohorts, until 90 days, used to assess the proportional hazards assumption.



Supplementary Figure 4. *Barplot* demonstrating the distribution of Multi-HCC risk quartile by MELD 3.0, among patients with HCC. For each MELD 3.0 score, the fraction of patients with HCC within each of 4 risk quartiles of Multi-HCC are presented; the width of the *bars* is proportional to the number of patients with HCC with each MELD 3.0 score.

Supplementary Table 1. Formulas Used to Calculate Previously Existing Risk Stratification Scores for Waitlist Dropout

Model	Variables included	Predicted time point after listing for LT	Equation	Reported C-statistic
deMELD[8]	Age, MELD, tumor size, tumor number, AFP, etiology of liver disease	3-mo waitlist dropout	deMELD $=$ –25 $+$ (0.1 $\times$ age) $+$ (1.6 $\times$ MELD) $+$ (1.6 $\times$ tumor size) $+$ (1.3 – log (AFP)) $+$6 if tumor number $>$2 $+$0 if diagnosis $=$ hepatitis C –1 if diagnosis $=$ hepatitis B $+$3 if diagnosis $=$ alcohol $+$3 if diagnosis $=$ nonalcoholic steatohepatitis $+$1 if diagnosis $=$ other	0.72 (3 mo)
MELD-Eq[11]	MELD, AFP, tumor number, tumor size, waitlist time	12-mo waitlist dropout	MELD-Eq $=$ max(laboratory MELD, MELD-Eq$_{calculated}$) MELD-Eq$_{calculated}$ $=$ (1.143 $\times$ MELD) $+$ (1.324 $\times$ log(AFP)) $+$ (1.438 $\times$ no. of tumors) $+$ (1.194 $\times$ maximum tumor size) $+$ c(t) where c(t) is waitlist time and is –2/0.146 for c(t) $<$6 mo and –1/0.146 for c(t) $\geq$ 6 mo	0.74 (12 mo)
HALT-HCC[12,21,22]	MELD-Na, tumor number, tumor size, AFP	3-, 6-, and 12-mo waitlist dropout	HALT-HCC $=$ (1.27 TBS) $+$ (1.85 ln(AFP) $+$ (0.26 MELD-Na)) $TBS* = \sqrt{(Tumor\ \ Number)^2 + (Tumor\ Size)^2}$	0.69 (3 mo) 0.68 at 6 mo 0.66 at 12 mo
Mehta et al[13]	MELD-Na, Child-Pugh score, AFP, tumor burden	3-mo and 12-mo waitlist dropout	Mehta Model $=$ (MELD-Na $-$ 10) $+$ 3*(Child-Pugh Score-5) $+$ AFP points $+$ tumor points AFP points: $<$20 ng/mL: 0 points 21–40 ng/mL: 5 points 41–500 ng/mL: 9 points 501–1000 ng/mL: 20 points 1000 ng/mL: 23 points Tumor points: 1 lesion, 2–3 cm: 0 points 2-3 lesions: 5 points 1 lesion, 3.1–5 cm: 6 points	0.78 (3 mo) 0.74 (12 mo)
OPOM[10]	Age, MELD, sodium, bilirubin, creatinine, INR, albumin, albumin at prior visit, change in MELD, INR, tumor size, AFP, years on waitlist	3-mo waitlist dropout	http://www.opom.online/	0.86 (3 mo, combined prediction for patients with and without HCC)

INR, international normalized ratio; LT, liver transplantation.