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ORIGINAL ARTICLE

Comparison of two equivalent model for end-stage liver disease scores for hepatocellular carcinoma patients using data from the United Network for Organ Sharing liver transplant waiting list registry

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SUMMARY

Patients with hepatocellular carcinoma (HCC) have been advantaged on the liver transplant waiting list within the United States, and a 6-month delay and exception point cap have recently been implemented to address this disparity. An alternative approach to prioritization is an HCC-specific scoring model such as the MELD Equivalent ($MELD_{EQ}$) and the mixed new deMELD. Using data on adult patients added to the UNOS waitlist between 30 September 2009 and 30 June 2014, we compared projected dropout and transplant probabilities for patients with HCC under these two models. Both scores matched actual non-HCC dropout in groups with scores <22 and improved equity with non-HCC transplant probabilities overall. However, neither score matched non-HCC dropout accurately for scores of 25–40 and projected dropout increased beyond non-HCC probabilities for scores <16. The main differences between the two scores were as follows: (i) the $MELD_{EQ}$ assigns 6.85 more points *after* 6 months on the waitlist and (ii) the deMELD gives greater weight to tumor size and laboratory MELD. Post-transplant survival was lower for patients with scores in the 22–30 range compared with those with scores <16 ($P = 0.007$, $MELD_{EQ}$; $P = 0.015$, deMELD). While both scores result in better equity of waitlist outcomes compared with scheduled progression, continued development and calibration is recommended.

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Key words
equity, equivalent model for end-stage liver disease scores, hepatocellular carcinoma, transplant prioritization, waitlist dropout

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Introduction

Under Organ Procurement and Transplantation Network (OPTN) policies, many liver transplant patients are prioritized using the Model for End-Stage Liver Disease (MELD) score. In accordance with recent policies, patients with hepatocellular carcinoma (HCC) who met criteria for exception received a MELD score at listing that is equivalent to a 15% risk of 3-month mortality. Every 3 months after this, they received additional MELD points equivalent to a 10% increase in their mortality risk until they underwent transplantation or became unsuitable for transplant [1]. Under this system, despite previous modifications, patients with HCC

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continued to have an advantage for access to transplantation when compared to patients without HCC [2,3]. To help mitigate the advantage to patients with HCC, the United Network for Organ Sharing (UNOS) recently implemented two changes to the granting of exception points to patients with HCC [4,5]. First, a delay of 6 months was implemented before granting these additional points, so patients are listed at their laboratory MELD score until the second three-month extension. This was intended not only to reduce transplant rates for patients with HCC but also to screen patients with aggressive tumor biology prior to transplantation. Second, the MELD progression is restricted to a maximum of 34 points, so that patients with HCC are not candidates for regional sharing under the Share 35 policy.

Investigators have also proposed alternative MELD scores for patients with HCC [6–11] in attempt to address this disparity. These scores were intended to more accurately reflect mortality risk for patients with HCC based on HCC and patient characteristics in addition to the laboratory MELD. Several of these scores are described in a mini-review by Toso *et al.* [12]. Two of these scores, the $MELD_{EQ}$ [11] and the mixed new dropout equivalent MELD [9] (referred to as "deMELD" for this writing), were derived by determining dropout risk based on established HCC characteristics as well as laboratory MELD, and then equating this risk to that of non-HCC patients to find the corresponding MELD score. Both deMELD and $MELD_{EQ}$ scores could be used for patients with HCC comparably to the laboratory MELD for non-HCC patients as they are on the same scale. The deMELD was designed according to the probability of dropout from the waiting list, to predict the same dropout probability as a non-HCC patient with the same MELD value. The $MELD_{EQ}$ was derived similarly but equated dropout hazards.

While the current allocation scheme implementing a six-month delay prior to granting exception points should improve equity of outcomes, reverting to scheduled progression after 6 months may still advantage patients with HCC and prioritizes all patients with HCC equally regardless of tumor characteristics or laboratory MELD [5,13]. As the recent policy changes may not provide the final solution for equitable transplant for HCC and non-HCC patients, in the interim it is instructive to evaluate potential candidates for equivalent MELD scores to assess their strengths and weaknesses. Hence, the primary aims of the current study were to evaluate possible effects of prioritization with the deMELD and $MELD_{EQ}$ on waitlist dropout and transplant probabilities for patients with HCC. These outcomes were studied in both original publications [9,11], but our intent was to validate the scores with newer data from UNOS and to compare the scores with each other. We also studied how changes in HCC-related covariates affected both alternative MELD scores, and compared post-transplant survival between patients stratified by the scores.

Materials and methods

Data

Data were obtained on all patients added to the United Network for Organ Sharing (UNOS) liver transplant waitlist on or after 1 October 2009, based on OPTN data as of 30 June 2014, and who were at least 18 years old at time of initial listing. We obtained data on all patients with HCC exceptions (and no other exceptions) for the HCC group, and all patients with no exceptions for the non-HCC group. Status 1 patients (n = 1173), those listed as inactive (n = 586), and three patients with HCC missing HCC-related covariate data were also excluded.

Outcomes and covariates

The main outcomes studied included waitlist dropout and transplant for patients with HCC. We also evaluated post-transplant survival of patients stratified by ranges of the $MELD_{EQ}$ and deMELD. In addition, we examined how differences in the covariates included in the two scores affected categorization by the models. The covariates from these two models were alpha-fetoprotein (AFP) or the natural log of AFP, laboratory MELD, maximum tumor size, and number of tumors. Additionally, the $MELD_{EQ}$ calculation includes a constant which increases when waitlist time reaches 6 months.

Dropout was defined as removal from the waiting list due to death, determined medically unsuitable, or too sick for transplant. Transplant was defined as having received transplant for any reason. Those who remained on the waiting list or were removed due to improvement were considered censored.

Statistical methods

All data analysis and statistical calculations were performed using SAS (version 9.4, Cary, NC, USA) and R (version 3.1.1). The $MELD_{EQ}$ and deMELD were calculated for each observation of patients with HCC in the dataset using the following equations:

$$\begin{aligned}\text{MELD}_{\text{EQ}} = \max(&\text{laboratory MELD}, 1.143 * \text{MELD} \\ &+ 1.324 * \ln(\text{AFP}) + 1.438 \\ &* \text{Number of Tumors} + 1.194 \\ &* \text{Max Tumor Size (cm)} + c(t)),\end{aligned}$$

where $c(t) = -13.70$ for $t < 6$ months and $c(t) = -6.85$ for $t \geq 6$ months

$$\begin{aligned}\text{deMELD} = \max(&\text{laboratory MELD}, -37.8 + 1.9 \\ &* \text{MELD} + 5.9 \text{ if Number of Tumors} \geq 2 \\ &+ 21.2 \text{ if Max Tumor Size} > 1 \text{ cm} \\ &+ 5.9 \text{ if AFP} > 400)\end{aligned}$$

Alpha-fetoprotein values (assumed to be recorded as ng/ml here and throughout this paper) were floored at 1 for the purpose of calculating ln (AFP). The MELD_{EQ} and deMELD scores were then categorized into ranges of <12, 12–15, 16–18, 19–21, 22–24, 25–30, 31–35, and 36–40. These categories were used as the transient states in nonparametric multistate models for dropout and transplant probabilities, using the R package *msSurv* [14]. A diagram of the multistate model is included in Figure S1. In the multistate model, patients can transition between the transient states at any time, but cannot transition out of the absorbing or terminal states. The model accounts for transitioning between these states prior to transplant or dropout, as well as transitioning to the absorbing states of transplant or dropout. A separate multistate model was constructed for each score range (deMELD or MELD_{EQ} for HCC, laboratory MELD for non-HCC), taking time zero to be the time a given score range was first entered. This method was used as projections from a current MELD_{EQ} or deMELD score range may be of greater interest than projections from listing. Then, actual dropout and transplant probabilities were obtained from these models.

Projected HCC dropout and transplant probabilities were based on our previously described procedure [11]. Briefly, the HCC and non-HCC multistate models described above were used to obtain projections as follows. The transplant hazard rates from the *non-HCC* models were substituted into the HCC models for analogous score ranges (e.g., the transplant rate for MELD scores of 12–15 was substituted for the transplant rate of MELD_{EQ}/deMELD scores of 12–15). This was done to mimic a situation whereby patients with HCC with a given score would be transplanted at *the same rate* as a non-HCC patient with the same score. These new transition hazards were then used to project transplant and dropout probabilities for patients with HCC using the Aalen–Johansen estimator [14,15].

Matching of projected HCC transplant and dropout probabilities under each scheme to non-HCC probabilities was assessed graphically. Matching of projected dropout was also assessed numerically for each stratum by calculating the absolute value of the difference between non-HCC probabilities and projected HCC dropout probabilities. Similarly, we calculated the relative difference as a proportion of non-HCC probabilities. To obtain an overall estimate of projected comparability to non-HCC probabilities, we averaged these absolute and relative differences over all times through 1 year and across all risk (score) strata (the averages were weighted proportionally by the number at risk in each strata at each time). Smaller values indicate better equality between HCC and non-HCC dropout probabilities.

Differences in how the two alternative scores classified patients were explored by comparing covariate values for observations where the score categories agreed versus those where they did not. The concordance index was used to compare overall predictive accuracy for waitlist dropout [16]. Lastly, we compared post-transplant survival between the risk groups for both scores using Kaplan–Meier curves, the log-rank test, and Cox proportional hazard models.

Results

After all exclusions, 7928 patients with HCC exceptions and 34 868 patients with standard MELD scores, listed during the time frame between 1 October 2009 and 30 June 2014, remained for analysis. Table 1 shows the distributions of the two scores at initial listing and last follow-up. The overall C-indices for HCC waitlist dropout were 0.586 (95% CI: 0.562, 0.61) for exception MELD scores, 0.653 (95% CI: 0.624, 0.682) for laboratory MELD, 0.678 (95% CI: 0.649, 0.707) for MELD_{EQ}, and 0.664 (95% CI: 0.635, 0.693) for deMELD. In comparison, the C-index for non-HCC waitlist dropout was 0.832 (95% CI: 0.822, 0.842) for MELD.

Figure 1 compares actual HCC dropout and transplant probabilities obtained from our multistate models stratified by the MELD_{EQ} and deMELD for lower-risk categories (scores ≤21, solid lines). The dashed lines on the figure give corresponding non-HCC levels. Both scores effectively stratify HCC patient risk for these lower levels, although the deMELD appears to have slightly closer matching to non-HCC levels. The HCC risk strata for actual transplant probabilities completely overlap, in accordance with the scheduled progression in effect during this time. To contrast what might occur if the scores were implemented, Fig. 2 gives projected

Table 1. Frequency distributions of the model for end-stage liver disease equivalent ($MELD_{EQ}$) and dropout equivalent model for end-stage liver disease (deMELD) scores for patients with hepatocellular carcinoma (HCC) at first listing and at last follow-up on the waitlist.

	HCC $MELD_{EQ}$		deMELD	
Score ranges	Initial listing	Last follow-up	Initial listing	Last follow-up
6–11	4759 (60.0)	4081 (51.5)	4861 (61.3)	4580 (57.8)
12–15	2075 (26.2)	2021 (25.5)	1803 (22.7)	1814 (22.9)
16–18	692 (8.7)	933 (11.8)	676 (8.5)	766 (9.7)
19–21	267 (3.4)	469 (5.9)	250 (3.2)	279 (3.5)
22–24	103 (1.3)	226 (2.9)	160 (2.0)	222 (2.8)
25–30	29 (0.4)	155 (2.0)	134 (1.7)	173 (2.2)
31–35	1 (0.01)	32 (0.4)	31 (0.4)	56 (0.7)
36–40	2 (0.03)	11 (0.1)	13 (0.2)	38 (0.5)

Numbers in each cell are the count and percentage of patients out of 7928 total patients with HCC.

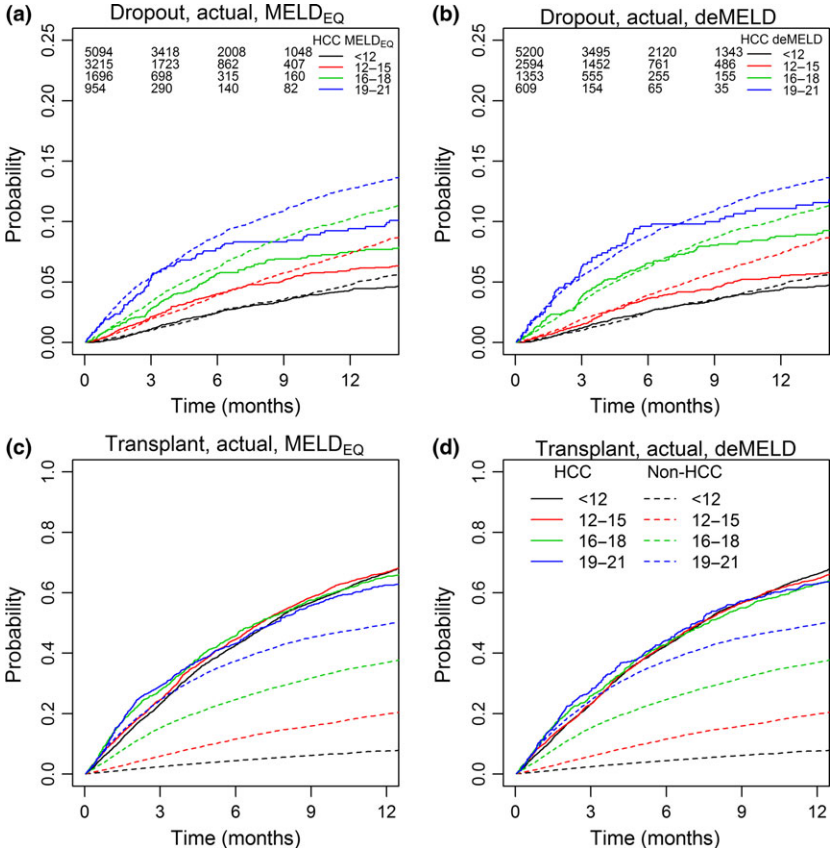

Figure 1 Actual time to dropout/transplant for patients with hepatocellular carcinoma (HCC) with model for end-stage liver disease equivalent ($MELD_{EQ}$) and dropout equivalent model for end-stage liver disease (deMELD) scores <22. Time is from entry into the corresponding $MELD_{EQ}$ (left panels a and c) or deMELD (right panels b and d) range for patients with HCC and the MELD range for non-HCC patients. Solid lines indicate probability of transplant (bottom panels c and d) and dropout (top panels a and b) for patients with HCC, whereas dashed lines indicate corresponding actual probabilities for non-HCC patients. All probabilities were obtained from corresponding multistate models in each case. The number at risk for patients with HCC at 0, 3, 6, and 9 months is given in panels (a and b).

HCC dropout and transplant for the same risk categories, obtained using our multistate models and the described projection method. In both cases, projected HCC transplant probabilities are slightly lower than non-HCC probabilities, while projected HCC dropout is slightly higher than non-HCC levels. Again, the deMELD appears slightly better at matching non-HCC strata on projected dropout and transplant probabilities.

Figures 3 and 4 give corresponding actual (Fig. 3) and projected (Fig. 4) HCC dropout and transplant probabilities for higher risk scores (≥22). The deMELD shows slightly better separation of risk strata on actual dropout (Fig. 3), although neither score does well at matching non-HCC strata. For projected probabilities, the deMELD does better at matching non-HCC strata on transplant probabilities, but poorly on projected

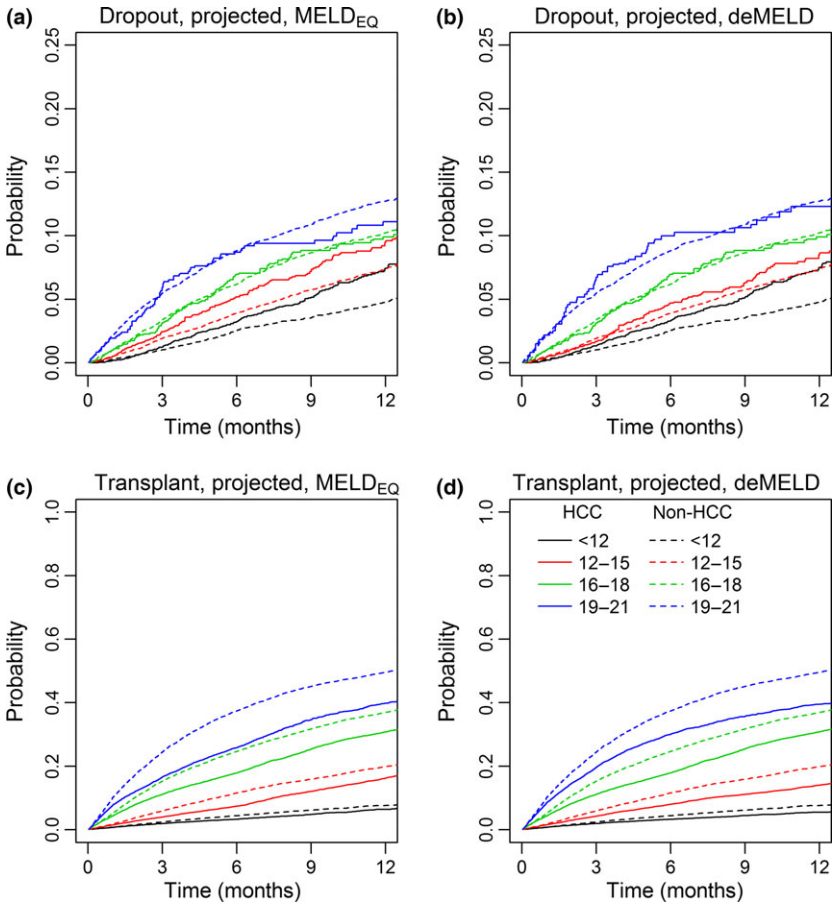

Figure 2 Projected time to dropout/transplant for patients with hepatocellular carcinoma (HCC) with model for end-stage liver disease equivalent ($MELD_{EQ}$) and dropout equivalent model for end-stage liver disease (deMELD) scores <22. Time is from entry into the corresponding $MELD_{EQ}$ (left panels a and c) or deMELD (right panels b and d) range for patients with HCC and the MELD range for non-HCC patients. Solid lines indicate projected probabilities of transplant (bottom panels c and d) and dropout (top panels a and b) for patients with HCC, whereas dashed lines indicate corresponding actual probabilities for non-HCC patients. These results were obtained from the multistate models after employing the described projection procedure.

dropout where all the risk strata are clumped together (Fig. 4). The $MELD_{EQ}$ has considerably fewer patients classified in the highest risk strata (≥31) compared with the deMELD.

Table 2 displays absolute and relative differences by stratum and overall average difference between non-HCC dropout and projected HCC dropout under each equivalent MELD score. Matching to non-HCC dropout probabilities is similar between the deMELD and the $MELD_{EQ}$ for equivalent scores <12, 16–18, and 31–35. Matching is better for deMELD scores of 12–15 (relative difference of 18.4% vs. 29.8% for $MELD_{EQ}$). Matching is better for $MELD_{EQ}$ scores of 22–24 (12.0% vs. 38.9% for deMELD), 25–30 (37.4% vs. 50.4% for deMELD), and 35–40 (35.9% vs. 75.8% for deMELD). The weighted overall difference is very similar between the two scores.

Effect of covariates on $MELD_{EQ}$ and deMELD

To investigate the level of agreement/disagreement between the two scores, we constructed a cross-tabulation of how each observation on the waiting list was categorized by them (Table 3). Risk groups with $MELD_{EQ}$ and deMELD scores <19 had the most agreement between the two scores: The majority of observations placed in these categories by one score were also placed there by the other score. To delve further, we summarized the contributions from each of the variables in the scores (e.g., AFP, tumor size, number of tumors, laboratory MELD, and waitlist time) for observations that were placed in the same category by both scores (purple shaded cells in Table 3) and select cells where the observations were categorized differently (orange shaded cells in Table 3). These results are presented in Table S1 (for cells where both scores agree) and Table S2 (for cells where the scores disagree). Our assessment of these tables indicated that the variables having the most profound effect on differences between the deMELD and $MELD_{EQ}$ included waitlist time (the $MELD_{EQ}$ assigns 6.85 more points when waitlist time is at least 6 months), tumor size (tumor size >1 cm adds 21.2 points to the deMELD score, compared with 1.194 points for each centimeter increase for the MELDEQ), and laboratory MELD (the deMELD assigns 1.9 points for every 1 point increase in laboratory MELD compared with 1.143 points for the $MELD_{EQ}$). The $MELD_{EQ}$ gave more points for higher AFP levels (7.93

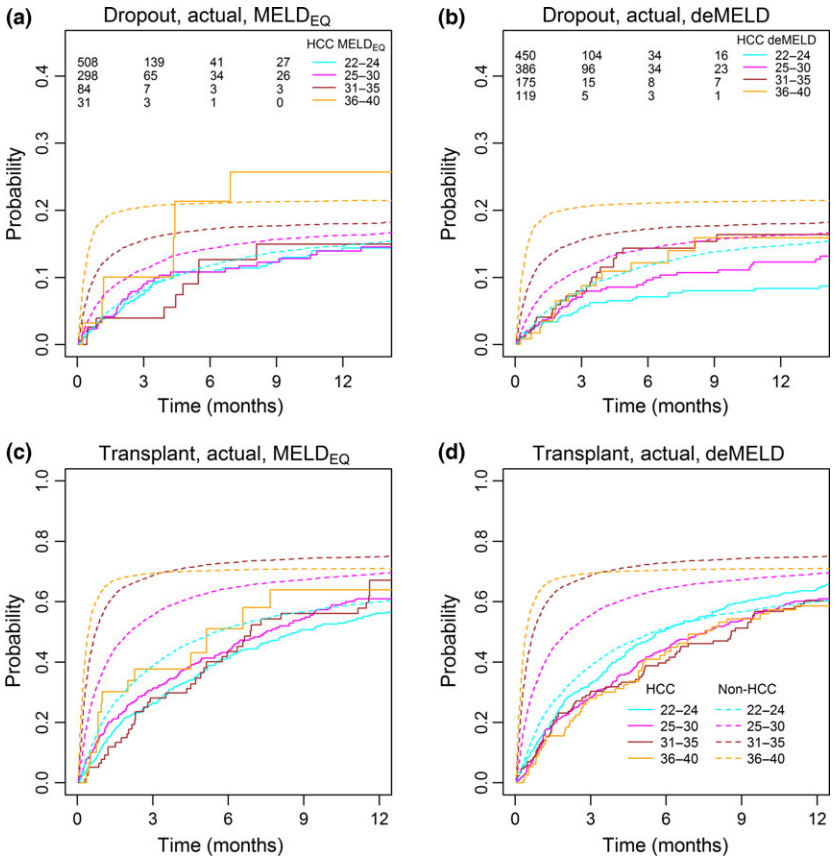

Figure 3 Actual time to dropout/transplant for patients with hepatocellular carcinoma (HCC) with model for end-stage liver disease equivalent (MELD$_{EQ}$) and dropout equivalent model for end-stage liver disease (deMELD) scores ≥22. Time is from entry into the corresponding MELD$_{EQ}$ (left panels a and c) or deMELD (right panels b and d) range for patients with HCC and the MELD range for non-HCC patients. Solid lines indicate probability of transplant (bottom panels c and d) and dropout (top panels a and b) for patients with HCC, whereas dashed lines indicate corresponding actual probabilities for non-HCC patients. All probabilities were obtained from corresponding multistate models in each case. The number at risk for patients with HCC at 0, 3, 6, and 9 months is given in panels (a and b).

points for an AFP of 400 ng/ml compared with 5.9 points for the deMELD), but only 3.2% of observations had AFP >400 ng/ml. Number of tumors was not a significant differentiator between the two scores, as ~80% of observations in the dataset had only one tumor (in which case the MELD$_{EQ}$ gave 1.438 points for number of tumors while the deMELD gave 0 points).

To illustrate the similarities and differences between the two scores, we plotted both as a function of laboratory MELD, waitlist time (listing vs. 6 months), AFP (10 vs. 500 ng/ml), and tumor size (1 vs. 3 cm) (Figure S2). The number of tumors was fixed at one. For small tumors (1 cm or less) at listing, the two scores largely agree with each other and are equivalent to the laboratory MELD (bottom row, left two panels in Figure S2). This is true even for AFP as high as 500 ng/ml (bottom row, 2nd panel from left in Figure S2). However, for tumor sizes of 3 cm at listing, the deMELD exceeds the laboratory MELD and MELD$_{EQ}$ starting around a laboratory MELD of 20 for AFP of 10 ng/ml (3rd panel from left in Figure S2) or laboratory MELD of 15 for AFP of 500 ng/ml (far right panel in Figure S2). The situation is somewhat reversed starting at 6 months postlisting. In this case, the MELD$_{EQ}$ exceeds the deMELD for smaller tumors (≤1 cm) for both lower AFP levels (10 ng/ml, top left panel in Figure S2) and by an even greater margin for higher AFP levels (500 ng/ml, 2nd panel from left in top row of Figure S2). For larger tumor sizes (3 cm) at 6 months postlisting, the MELD$_{EQ}$ is higher than the deMELD for lower laboratory MELD scores (roughly ≤25), but the situation is reversed after that point (top row, right two panels in Figure S2).

In summary, waitlist time, maximum tumor size, and laboratory MELD score had the greatest effect on the differences between the two scores.

Post-transplant survival

Post-transplant survival was compared for alternative MELD scores in ranges 6–15, 16–21, 22–30, and 31–40; see Figure 5. A significant difference was seen between the lowest risk group and the 22–30 group under both scores (Table 4). In neither case was the survival for the highest risk group significantly different from the baseline group, although the number of subjects was low. The highest risk group for deMELD did, however, have a sharp decrease in survival during the first 1½ months. Survival for subjects with scores in the 16–21 range was also not significantly different from the baseline group.

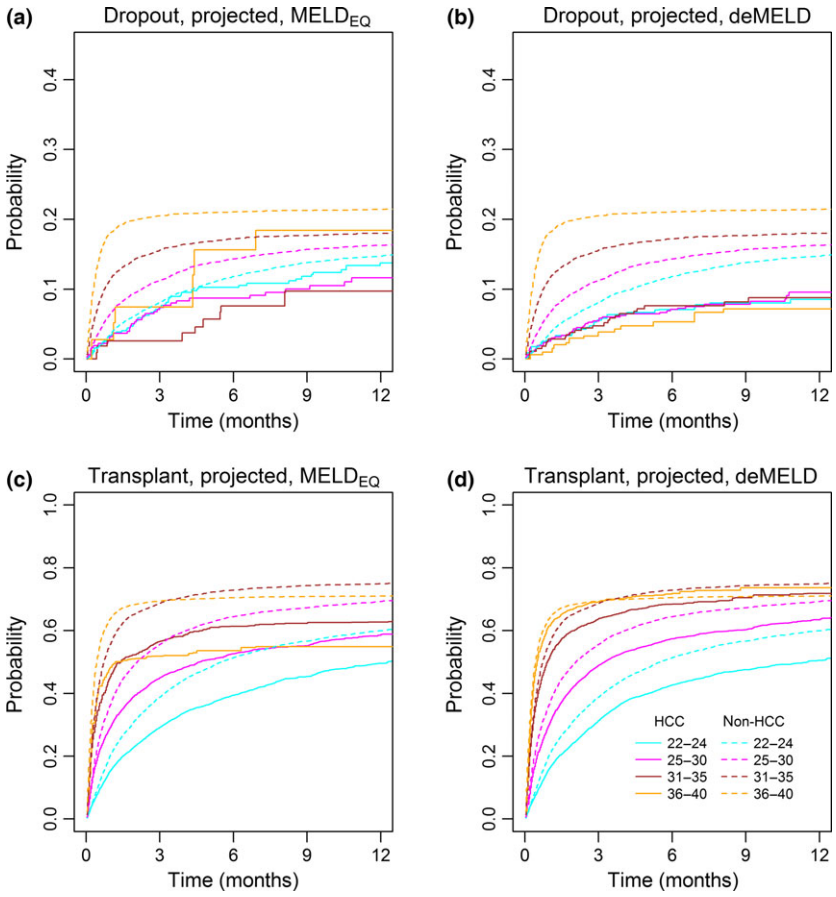

Figure 4 Projected time to dropout/transplant for patients with hepatocellular carcinoma (HCC) with model for end-stage liver disease equivalent ($MELD_{EQ}$) and dropout equivalent model for end-stage liver disease (deMELD) scores ≥22. Time is from entry into the corresponding $MELD_{EQ}$ (left panels a and c) or deMELD (right panels b and d) range for patients with HCC and the MELD range for non-HCC patients. Solid lines indicate projected probabilities of transplant (bottom panels c and d) and dropout (top panels a and b) for patients with HCC, whereas dashed lines indicate corresponding actual probabilities for non-HCC patients. These results were obtained from the multistate models after employing the described projection procedure.

Table 2. Average absolute and relative differences between non-hepatocellular carcinoma (HCC) and projected HCC dropout probabilities under model for end-stage liver disease equivalent ($MELD_{EQ}$) or dropout equivalent model for end-stage liver disease (deMELD) by range of each equivalent model for end-stage liver disease (MELD) score.

Equivalent MELD score Range	$MELD_{EQ}$ Difference from non-HCC		deMELD Difference from non-HCC	
	Absolute	Relative (%)	Absolute	Relative (%)
<12	0.01002	39.7	0.01049	41.4
12–15	0.01152	29.8	0.00647	18.4
16–18	0.00236	6.9	0.00239	6.9
19–21	0.00745	9.5	0.00564	9.4
22–24	0.01178	12.0	0.04148	38.9
25–30	0.04693	37.4	0.06388	50.4
31–35	0.09742	63.4	0.09372	60.6
35–40	0.06820	35.9	0.15135	75.8
Overall	0.01030	32.0	0.01034	32.6

Smaller values indicate closer matching between the equivalent MELD range and the target non-HCC MELD range. The overall differences weighted by number at risk in each stratum and averaged over all times through 365 days are shown in the bottom row.

In both cases, the proportional hazard assumption was met ($P = 0.129$, $MELD_{EQ}$; $P = 0.296$, deMELD) [17]. Because post-transplant survival was lower for the 22–30 group for both the deMELD and $MELD_{EQ}$, we compared post-transplant survival between those transplanted within 6 months versus those transplanted after

Table 3. Cross-tabulation of equivalent model for end-stage liver disease (MELD) score assignments by model for end-stage liver disease equivalent ($MELD_{EQ}$) and dropout equivalent model for end-stage liver disease (deMELD).

$MELD_{EQ}$ category	deMELD category								Row Totals
	<12	12–15	16–18	19–21	22–24	25–30	31–35	36–40	
<12	27 189 99.9% 89.9%	24	2	0	0	0	0	0	27 215 50.7%
12–15	2552	10 640 76% 82.7%	789	13	1	0	0	0	13 995 26.1%
16–18	409	1608	3269 54.3% 64%	342	390 6.5% 31.8%	2	0	0	6020 11.2%
19–21	57	543	747 23.6% 14.6%	1168 36.9% 60.8%	337	310	0	0	3162 5.9%
22–24	12	55	261	297	383 22.3% 31.2%	530 30.9% 39.1%	176	0	1714 3.2%
25–30	12	0	42	102	116	480 39.7% 35.4%	285 23.6% 52.1%	171 14.2% 41.6%	1208 2.3%
31–35	0	0	0	0	1	31	80 30.9% 14.6%	147 56.8% 35.8%	259 0.5%
36–40	0	0	0	0	0	2	6	93 92.1% 22.6%	101 0.2%
Column Totals	30 231 56.3%	12 870 24%	5110 9.5%	1922 3.6%	1228 2.3%	1355 2.5%	547 1%	411 0.8%	53 674

The numbers in each cell are the number of HCC observations categorized by the deMELD score in the column heading and the $MELD_{EQ}$ score in the row heading followed by the row percent and column percent. The row and column totals shown include the percent of total observations. Each individual patient can have multiple observations representing different follow-up times on the waiting list. The cells where scoring systems agree are shaded purple, while those selected for comparison where scores do not agree are shaded orange.

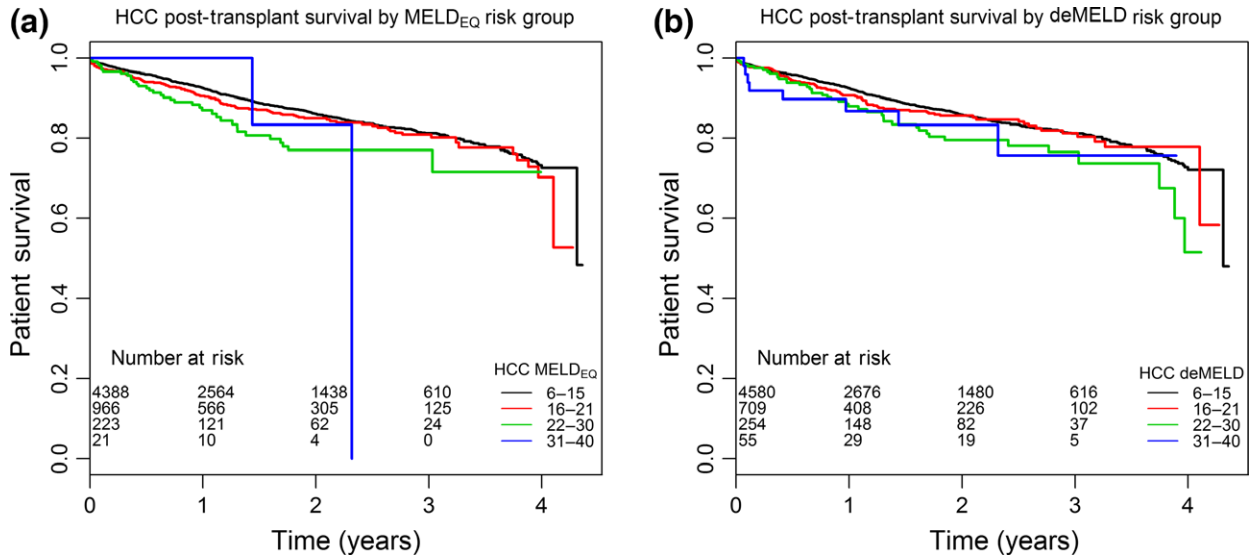

Figure 5 Post-transplant survival for patients with hepatocellular carcinoma (HCC) stratified by model for end-stage liver disease equivalent ($MELD_{EQ}$, panel a) and dropout equivalent model for end-stage liver disease (deMELD, panel b) ranges. Kaplan–Meier survival curves for patients with HCC with the indicated alternative MELD score ranges at last follow-up prior to transplant. The number at risk in each stratum is shown for 0, 1, 2, and 3 years at the bottom of each panel.

Table 4. Hazard ratios for post-transplant survival from Cox proportional hazard models.

Group	HR	95% CI	*P*-value
$MELD_{EQ}$			
<16	Reference	Reference	Reference
16–21	1.141	0.937, 1.389	0.189
22–30	1.588	1.132, 2.228	0.007
31–40	1.175	0.293, 4.712	0.820
deMELD			
<16	Reference	Reference	Reference
16–21	1.052	0.839, 1.320	0.661
22–30	1.477	1.078, 2.022	0.015
31–40	1.386	0.690, 2.787	0.359

6 months for these groups. While survival was slightly lower for the earlier transplanted groups during the first 1½ years post-transplant, the difference was not statistically significant ($P = 0.891$ $MELD_{EQ}$, $P = 0.759$ deMELD, see Figure S3). Similar results were found for comparison of post-transplant survival between those with equivalent MELD scores 22–40 transplanted before versus after 6 months ($P = 0.639$ $MELD_{EQ}$, $P = 0.464$ deMELD).

Discussion

Previous research has demonstrated that scheduled progression of exception points is not an equitable method of prioritizing liver transplants between HCC and non-HCC patients. In our recent study [13], we evaluated projected transplant and dropout probabilities between the six-month delay and the $MELD_{EQ}$. While the six-month delay was certainly an improvement over the previous scheduled progression and slightly favorable on projected outcomes compared with the $MELD_{EQ}$, it still treated all patients with HCC as having equal prioritization and favored patients with HCC overall after 6 months. In this study, the $MELD_{EQ}$ and deMELD models both show improvement over scheduled progression of exception points, with better stratification of dropout and transplant probabilities. Overall numerical comparisons of the two scores slightly favored the $MELD_{EQ}$ for dropout prediction (C-index of 0.678 compared to 0.664), although the result was not statistically significant. While these both show improvement over exception scores (C-index of 0.568), they still fall short when

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compared to the laboratory MELD for non-HCC dropout prediction (C-index of 0.832). Both scores match actual dropout probabilities comparably to non-HCC laboratory MELD for alternative MELD scores <22, while neither score matches actual dropout accurately for the higher-risk groups. Differences in *projected* HCC dropout and non-HCC dropout were similar overall between the $MELD_{EQ}$ and the deMELD. However, the projected dropout tended to be closer to non-HCC dropout under the deMELD for equivalent scores <22 and closer under the $MELD_{EQ}$ for equivalent scores ≥22.

A potential problem for both scores is that dropout is projected to increase beyond non-HCC levels for groups with equivalent scores <16. However, the average difference over 1 year between projected HCC dropout and actual dropout of analogous non-HCC groups is around 0.01 – near zero in the first few months since entering a given risk strata but increasing over time. In contrast to the <16 groups, dropout is projected to decrease for higher-risk groups (scores ≥22), especially under the deMELD. This is because actual transplant *and* dropout probabilities for the higher-risk groups are largely lower than those for corresponding non-HCC risk groups, so transplanting them at a higher rate to match non-HCC rates would be expected to decrease their dropout further. Matching between HCC and non-HCC projected transplant and dropout for scores ≥22 is poorer here compared to the original $MELD_{EQ}$ study [11].

One notable difference between the two scores is that the deMELD identifies more patients in higher-risk (≥22) categories at listing. The main reasons for this are as follows: (i) the $MELD_{EQ}$ assigns 6.85 more points *after* 6 months on the list and (ii) the deMELD gives much greater weight to tumor size (21.2 points for tumors >1 cm vs. 1.194 points for each cm for the $MELD_{EQ}$). The deMELD also uses discrete cutoff points for most of the HCC covariates while the MELDEQ uses continuous values. Thus, the deMELD may be more "stable" compared with the MELDEQ for higher-risk groups, in that a change in score requires a larger change in the covariates than it would for the MELDEQ.

Projected transplant under the deMELD matches non-HCC probabilities well for these higher-risk groups. However, a potential concern with prioritizing higher-risk HCC patients is earlier transplantation of patients with more aggressive tumors who may have poorer outcomes post-transplant. We did find that post-transplant survival is significantly lower for the 22–30 equivalent MELD score group compared with the lowest risk group for both scores, but no significant differences were found between the other risk groups. Adjustment of both scores may be warranted to avoid transplanting those at high risk for recurrence, a concern that was also mentioned in the original publication of the deMELD. Those authors suggested consideration of a 3- to 6-month waiting time to avoid transplanting those patients with HCC at high risk for post-transplant recurrence [9]. However, our analysis of patients in the higher-risk groups (equivalent MELD scores of 22–40) did not reveal a statistically significant difference in survival between patients transplanted within 6 months vs. after 6 months.

One limitation of our study is that we do not consider total risks/benefits between dropout, transplant, and post-transplant survival. Other investigators have discussed this [5,12,18–20], and overall utility (combined dropout/post-transplant survival) is included in the model by Vitale *et al.* [10]. Comparing that approach with those studied here is of interest, however the evaluation criteria for comparing the Vitale *et al.* score with the $MELD_{EQ}$/deMELD are difficult to determine given the differences in objectives between the studies. The covariates included in these models have also been studied as prognostic indicators for post-transplant outcomes, particularly AFP [19–22]. In particular, the Vitale *et al.* model actually deprioritizes transplantation of patients with HCC with elevated AFP levels. While we do not think it necessary to penalize patients with low to moderate AFP values, AFP above a threshold level (e.g., 500 or 1000 ng/ml) might be considered an exclusion criteria for transplant [13,23]. Another limitation of the current study is that while setting time zero as the first time a patient enters a given risk category may be of greater clinical interest, it does not allow for projections for non-HCC patients under the proposed scoring schemes [13]. However, comparison to actual non-HCC outcomes is useful for assessing how well the equivalent scores would improve equity between non-HCC and HCC transplant and dropout rates.

A strong point of this study is that although several models incorporating HCC characteristics for transplant prioritization have been proposed, no previous studies to our knowledge have compared projected outcomes between two proposed HCC-specific models. While our results do not provide a clear-cut answer to which of these scores better prioritizes patients with HCC, they do highlight strengths and weaknesses of each which can provide direction for ongoing work on an HCC prioritization score.

In summary, the $MELD_{EQ}$ and deMELD would both improve equity in transplant access between HCC and non-HCC patients compared with scheduled progression. However, noted limitations with both scores (projected dropout probabilities that exceed non-HCC probabilities for those with alternative MELD scores <16, dropout prediction that falls short of the MELD score for non-HCC patients) dampen enthusiasm for adoption into clinical practice at this point. Compounding the situation is the fact that projected long-term transplant probabilities for patients with HCC are substantially lowered under an equivalent MELD score compared with current rates [13], and calculation of life expectancy for patients with HCC is challenging given their high transplant prioritization under the current system [24,25]. However, we do envision several ways to extend and alternatively apply these scores which can be explored in the near future. First, the use of transplant-related survival benefit as a metric to develop an equivalent score would balance the need between prioritizing patients with both high urgency (high waitlist mortality) and moderate to high post-transplant survival [20]. This has previously been done in a study concerning Italian patients [10], but has not been explored with liver waitlist patients in the United States. A difficulty here is in the aforementioned challenge of determining waitlist life expectancy for patients with HCC. Second, more flexible modeling approaches can be used to capture nonlinear effects of covariates, for example, to incorporate an effect of AFP which might increase transplant priority for increasing AFP at the lower end but decrease priority for scores above a certain threshold (e.g., AFP >500 ng/ml or 1000 ng/ml). Third, in lieu of using the scores directly for transplant prioritization of patients with HCC, they can be used to identify patients with HCC at low risk of waitlist dropout (e.g., equivalent MELD scores ≤15) or at high risk of post-transplant mortality (e.g., AFP >1000 ng/ml). In fact, policies of this nature are already under discussion and review by the members of the Organ Procurement and Transplantation Network [23,26,27]. While the six-month delay, exception point cap, and other modifications to the HCC exceptions for liver candidates in the United States continue to be explored and adopted, further development of alternative MELD scores is worthwhile to continue the move away from waiting list time as the sole determinant of liver transplant prioritization among patients with HCC.

Authorship

SKA: conducted the data analysis, presented the results and drafted the manuscript. GNB: formulated the initial hypothesis, designed the study, supervised the research and helped draft the manuscript. MRM, KW and DJL: assessed the results and gave critical feedback on the research and design of the study. All authors: read and approved the final draft of the manuscript.

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Conflict of interest

None of the authors have any conflict of interests to declare.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Summary of scores and effect of covariates for categories where the $MELD_{EQ}$ and deMELD agree.

Table S2. Summary of scores and effect of covariates for categories where the $MELD_{EQ}$ and deMELD disagree.

Figure S1. Schematic diagram of multistate model.

Figure S2. Comparison of equivalent MELD scores.

Figure S3. Post-transplant survival for patients with $MELD_{EQ}$ or deMELD 22-30, transplanted within 6 months of listing vs. after 6 months.

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