HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

A Model for Dropout Assessment of Candidates With or Without Hepatocellular Carcinoma On a Common Liver Transplant Waiting List

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In many countries, the allocation of liver grafts is based on the Model of End-stage Liver Disease (MELD) score and the use of exception points for patients with hepatocellular carcinoma (HCC). With this strategy, HCC patients have easier access to transplantation than non-HCC ones. In addition, this system does not allow for a dynamic assessment, which would be required to picture the current use of local tumor treatment. This study was based on the Scientific Registry of Transplant Recipients and included 5,498 adult candidates of a liver transplantation for HCC and 43,528 for non-HCC diagnoses. A proportional hazard competitive risk model was used. The risk of dropout of HCC patients was independently predicted by MELD score, HCC size, HCC number, and alpha-fetoprotein. When combined in a model with age and diagnosis, these factors allowed for the extrapolation of the risk of dropout. Because this model and MELD did not share compatible scales, a correlation between both models was computed according to the predicted risk of dropout, and drop-out equivalent MELD (deMELD) points were calculated. ***Conclusion:*** **The proposed model, with the allocation of deMELD, has the potential to allow for a dynamic and combined comparison of opportunities to receive a graft for HCC and non-HCC patients on a common waiting list.** (HEPATOLOGY 2012;56:149-156)

Since the publication of the Milan selection criteria in 1996, liver transplantation has been recognized as the best treatment for selected patients with nonresectable hepatocellular carcinoma (HCC).[1] Over the years, HCC has become one of the main indications for liver transplantation as a result of the combined effects of an increasing incidence of new HCC cases (matching the incidence of hepatitis C infection) and the use of more extended selection criteria.[2-4] These factors combined exert an increasing pressure on the limited liver donor pool.

Access to transplantation for HCC and non-HCC patients is granted on the basis of different approximations of utility. In nonmalignant patients, utility is represented by transplantation benefit (i.e., survival compared to death), whereas HCC patients are selected according to a longer term utility perspective (Milan: expected 5-year survival over 70%). The Model for End-Stage Liver Disease (MELD) score allows for the selection and priority transplantation of patients with the highest short-term risk of death.[5,6] Because most HCC candidates maintain relatively good liver function, they are poorly served (and infrequently transplanted) with the use of the raw MELD score; as such, "exception" points that increase their priority ranking have been artificially allocated. Originally, U.S. patients within Milan criteria (single HCC $\leq$5 cm in diameter and $\leq$3 HCCs $\leq$3 cm) were attributed 24

Abbreviations: AFP, alpha-fetoprotein; CI, confidence interval; deMELD, dropout equivalent MELD; Diag, diagnosis; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; hemoc, hemochromatosis; HRSA, Health Resources and Services Administration; MELD, Model for End-Stage Liver Disease; MHCC, Model for HCC; MnonHCC, model for non-HCC; NASH, nonalcoholic steatohepatitis; OPTN, Organ Procurement and Transplantation Network; SD, standard deviation; SRTR, Scientific Registry of Transplant Recipients; TTV, total tumor volume; UNOS, United Network for Organ Sharing.

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Received July 4, 2011; accepted January 2, 2012.

C.T. was supported by the Swiss National Science Foundation (SCORE grant 3232230-126233). N.M.K. was supported by a Canada Institutes of Health Research/Wyeth Research Chair in Transplantation and was a Senior Scholar of the Alberta Heritage Foundation for Medical Research. The study was supported by the Artères Foundation and the Astellas Foundation Europe.

(stage 1: single HCC $\leq$2 cm) and 29 (stage 2: other patients within Milan) MELD points. With time, it appeared that these exception points overestimated the risk of HCC progression and dropout, and that HCC patients had easier access to transplantation than non-HCC ones. As a consequence, exception points have been recalculated and only 22 are currently allocated to candidates with stage 2 HCCs (and none to stage 1 patients).

This said, the likelihood of undergoing transplantation still remains substantially higher for HCC candidates than for other patients in the United States.[7] In addition, modern wait-list management of HCC patients has become extremely dynamic, with the use of aggressive local HCC treatments to maintain HCC under control or in view of downstaging.[8] As a consequence, a specific patient could be originally outside transplant criteria, subsequently become a candidate after the local treatment of an HCC, and later drop from the list because of a progression of the carcinoma. In this regard, a continuous scale assessing the risk of dropout of HCC patients would be useful. Ideally, it should allow for a similar drop-out assessment as the MELD score for the non-HCC patients, thus allowing equitable management of both HCC and non-HCC patients on a common waiting list.

In an effort to better characterize the risk of HCC progression beyond transplant criteria and death, Freeman et al. have designed a score based on a Cox model taking into account MELD, maximum tumor size, and alpha-fetoprotein (AFP).[9] More recently, another study, also based on the U.S. Organ Procurement and Transplant Network (OPTN) data, performed a similar assessment in a more recent dataset (March 2005-June 2008) and using a more appropriate competitive risk model.[7] MELD, AFP, tumor size, and number came out as significant predictors, but no correlation to non-HCC candidates was performed and the proposed score could not be used when HCC and non-HCC patients are on a common waiting list.

The present study is based on a more recent, larger dataset of the OPTN, uses a competitive risk model assessment, and, more important, suggests a model for comparing the opportunities of receiving a graft for both HCC and non-HCC patients on a common waiting list and, potentially, for an equitable graft allocation.

Patients and Methods

Patients. This study analyzed data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donors, wait-listed candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network (OPTN), and has been described elsewhere.[10] The Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors. The study has been reviewed and approved by the Health Research Ethics Board at the University of Geneva (Geneva, Switzerland).

The study population included all adult patients, listed for liver transplantation from January 2004 to December 2009. To build models on comparable populations of HCC and non-HCC patient regarding age, only patients $\geq$45 years were included. This strategy excluded only a marginal number of HCC candidates (4.5%). HCC patients were identified as having "hepatocellular carcinoma" or "hepatoma" at the time of listing. All other patients, including those with incidental HCCs, were included in the non-HCC group.

Outcome Definition. Dropout was defined as the removal from the waiting list as a result of poor medical condition (i.e., "too sick for transplantation"), HCC progression beyond transplant criteria, or death. According to the OPTN/United Network of Organ Sharing (UNOS) rules, transplantation can only be performed within Milan criteria and patients progressing beyond Milan should be excluded from transplantation and drop from the list (with the exception of a few more liberal regions accepting downstaged patients or selected patients beyond Milan, i.e., Region 5). The occurrence and the date of death were obtained from data reported by the transplant centers and were completed by data from the U.S. Social Security Administration and the OPTN. Of note, the model was designed according to the risk of drop-out at 3 months.

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DOI 10.1002/hep.25603

Potential conflict of interest: Nothing to report.

The data reported here have been supplied by the Arbor Research Collaborative for Health (Arbor Research) as the contractor for the Scientific Registry of Transplant Recipients (SRTR). The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy of or interpretation by the SRTR or the U.S. government. C.C. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Potential Predictors of the Risk of Dropout. Explored variables, included age at listing, primary underlying liver disease (i.e., diagnosis; Diag), MELD score at listing, date of listing, number of tumors, maximum HCC size, total tumor volume (TTV), and AFP (analyzed as LnAFP). To avoid small samples (with low statistical accuracy), patients were categorized into only five diagnosis groups (hepatitis C virus [HCV], alcohol, hepatitis B virus [HBV], nonalcoholic steatohepatitis [NASH], and hemochromatosis [hemoc]). All other diagnoses, including autoimmune and cholestatic diseases, were grouped as "other." TTV was calculated as the sum of the volume of each tumor ($(4/3)\pi r^3$) based on the maximum radius of each tumor.[4,11] Analyses were conducted with the use of continuous variables (except for strictly categorical variables).

Statistical Analysis. In the HCC population, the risks of dropout and of transplantation were assessed by a nonparametric multistate model in the whole sample and according to categories of patient characteristics.[12] Factors associated to the risk of dropout were also assessed by using a proportional hazard competitive risk model.[13] Univariate analyses were performed, and all covariates were introduced in a multivariate model. The competitive risk model was chosen because subjects are at risk of two excluding events (i.e., dropout and transplantation), and the event of interest is dropout. If both events were independent, we could have considered transplantation as a censored data (this censorship is assumed noninformative) and analyzed the data by usual methods, such as Kaplan-Meier's and Cox's regression models.[14] Though this assumption is not true in the present study (some variables, including MELD, can alter both dropout and transplantation[7]), the use of Cox's regression model for the analysis of factors associated with the risk of dropout would lead to a bias in the assessment of these factors. A competing risk analysis is therefore more appropriate, because a patient experiencing a competing risk event is censored in an informative manner.

The proportionality of hazards was checked (test on Schoenfeld's residuals and/or graphical assessment). The final multivariate model (model for HCC; MHCC) included as predictors recipient age, diagnosis, MELD, number of HCC, HCC size, and AFP level, providing a linear combination of these factors (weighted by the regression parameters) associated with the risk of dropout. The predictive performance of this model for the dropout was assessed by C index.[15] We then examined the relationship between the observed risk of dropout at 3 months and the MHCC values. For this purpose, we categorized the MHCC and assessed the proportion of dropout in each category by a nonparametric multistate model. We then modeled the risk according to the median value of MHCC in each category. After applying a logit transformation on the risk of dropout (log(p/(1-p)), the relationship was linear and a linear regression model was performed.

A similar approach was applied to the non-HCC patients. The risk of dropout was modeled by age, diagnosis, and MELD. The linear combination of these factors (weighted by the regression parameters) associated with the risk of dropout was denoted MnonHCC. Finally, the logit of the probability of dropout (log(p/(1-p)) was linearly associated with the median of the MnonHCC within categories.

To establish a correspondence between the models developed for HCC and non-HCC patients, we derived a drop-out equivalent MELD (deMELD) score corresponding to a given risk of dropout in non-HCC patients. Such estimated points could be used for HCC candidates together with calculated MELD points for the non-HCC patients on a common waiting list.

Other statistical tests included the use of the Student's t and chi-square tests to compare the demographic variables between groups. Results were provided as mean $\pm$ standard deviation (SD). Standard alpha of 0.05 indicated statistical significance. Analyses were conducted using R for Windows (version 2.12.0), with the packages "etm" version 0.5-2 (empirical transition matrix)[12] for the nonparametric analyses and "mstate"[13] for the competitive risk regression models.

Results

Overall, 5,498 adult HCC and 43,528 non-HCC patients listed for a liver transplant were included in the study (Table 1). The HCC group was older (58.0 $\pm$ 6.6 versus 56.3 $\pm$ 6.5 years, on average; P = 0.001) and included more male patients (female/male ratio: 1:3.8 versus 1:1.8; P = 0.001). The incidence of HCV-induced liver disease was higher among HCC patients (P = 0.001). Calculated MELD scores, not adjusted for tumor-exception points, were lower in the HCC group (12.5 $\pm$ 6.2 versus 17.7 $\pm$ 8.3; P = 0.001). In the HCC group, most patients were within Milan criteria (94.4%), with a mean number of tumors of 1.4 $\pm$ 0.7 and a mean TTV of 20.9 $\pm$ 81.0 cm^3.[11] AFP levels showed a wide distribution, with a mean of 312.2 $\pm$ 1,753.8 ng/mL.[4,8]

Modeling Dropout in HCC Patients. Most listed HCC and non-HCC patients were either transplanted or had dropped from the list within the first year. The likelihood of transplantation was higher in patients

Table 1. Patient and Tumor Characteristics

Characteristics	HCC Patients	non-HCC Patients
Patients (number)	5,498	43,528
Mean age at listing (years ±SD)	58.0 ± 6.6	56.3 ± 6.5
Patients older than 60 years (%)	33.9	22.3
Gender (ratio)	female: 1145/ male: 4,353	female: 15,373/ male: 28,155
Cause of liver disease (%)		
HCV (±alcohol, ±HBV)	2911 (68.9)	17108 (39.3)
HBV	168 (4.0)	1093 (2.5)
Alcohol	458 (10.8)	7980 (18.3)
NASH	169 (4.0)	2916 (6.7)
Hemochromatosis	264 (6.2)	331 (0.8)
Other	258 (6.1)	14100 (32.4)
MELD score at transplantation (±SD)	12.5 ± 6.2	17.7 ± 8.3
Mean largest HCC diameter (cm±SD)	2.7 ± 1.3	NA
Mean TTV (cm^3 ±SD)	20.9 ± 81.0	NA
Mean number of HCC (±SD)	1.4 ± 0.7	NA
Mean serum AFP level (ng/mL ±SD)	312.2 ± 1753.8	NA

Abbreviation: HBV, heaptitis B virus infection; HCV, hepatitis C virus infection; MELD, Model for End-Stage Liver Disease; NA, not applicable.

with cancer (Fig. 1). In the HCC group, 46.0% (95% confidence interval [CI]: 44.6-47.3) of patients were transplanted and 5.4% (95% CI: 4.8-6.0) had dropped within 3 months of listing. In the non-HCC group, 29.3% (95% CI: 28.9-29.8) of patients were transplanted and 8.7% (95% CI: 8.4-8.9) had dropped within 3 months of listing.

We first assessed the HCC group (Table 2). In univariate analysis, the risk of dropout was significantly increased according to MELD score, number of HCCs, and AFP (Fig. 2). Of note, TTV and the size of the largest HCC were not associated to dropout. All variables (regardless of significance) were used in the multivariate analysis, and MELD score, HCC number, HCC size, and AFP remained significant in predicting dropout in the HCC group. The assumption of proportional hazard was respected for all variables (test on Schoenfeld's residuals was not significant for all variables and the global *P* value was 0.38). The prognostic assessment provided a C-index of 0.72 (95% CI: 0.69-0.79). From the multivariate analysis, the following MHCC associated with the risk of dropout in the HCC group was created:

$$\begin{aligned}\text{MHCC} = {} & 0.24545 \times \text{Age}/10 + 0.1704 \times \text{MELD} \\ & + 0.1730 \times \text{Tumor Size} \\ & + 0.13455 \times \log(\text{AFP}) \\ & + 0 \text{ if Diag} = \text{HCC} \\ & + 0.11966 \text{ if Diag} = \text{HBV} \\ & + 0.22216 \text{ if Diag} = \text{Alcohol} \\ & + 0.24714 \text{ if Diag} = \text{NASH} \\ & + 0.01097 \text{ if Diag} = \text{Hemoc} \\ & + 0.08875 \text{ if Diag} = \text{Other} \\ & + 0.61967 \text{ if Nb Tumors} \geq 2\end{aligned}$$

Categorizing the MHCC equation, the risk of dropout was spread between 0.9% (for an MHCC of approximately 3.5) and 17.0% (for an MHCC of approximately 6.6) at 3 months after listing (Fig. 3A). By performing a linear regression to model the risk of dropout estimated by the multistate model as a function of the MHCC, we established the following relationship:

$$\begin{aligned}\text{Logit(risk of dropout)} = {} & -8.41291 + 1.05498 \\ & \times \text{MHCC}\end{aligned}$$

The R^2 value of the regression was 0.99.

Modeling Dropout in Non-HCC Patients. In the non-HCC group, age and MELD were significant independent predictors of dropout (Table 2; Fig. 4). The assumption of proportional hazard was respected according the test on Schoenfeld's residuals for all variables, except MELD and "other" diagnosis. Graphical explorations (e.g., Martingale's residual plot, scaled Schoenfeld's plot, and drop-out risk curves) showed that the proportionality was not strongly violated for both MELD and "other" diagnosis, and they were kept in the model. The statistical significance of the test on Schoenfeld's residuals for MELD and "other" diagnosis

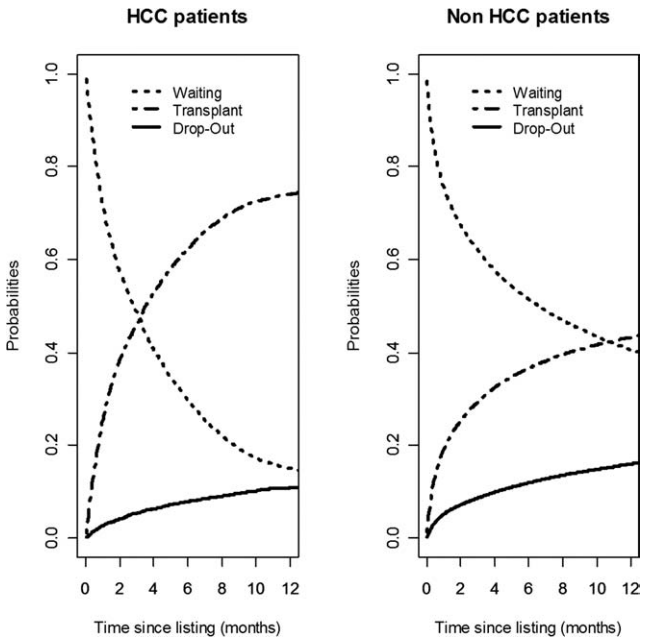

Fig. 1. Time-dependent probability of dropout and of transplantation in the HCC and non-HCC groups.

Table 2. Univariate and Multivariate Competitive Risk Assessment of Dropout and Transplantation in HCC and non-HCC Patients

		Univariate Analysis				Multivariate Analysis			
		Risk of Dropout		Risk of Transplantation		Risk of Dropout		Risk of Ttransplantation	
Variables in HCC Patients*		HR ["95% CI"]	*P* Value	HR ["95% CI"]	*P* Value	HR ["95% CI"]	*P* Value	HR ["95% CI"]	*P* Value
Age Diagnosis	per 10 years	1.14 [0.96;1.35]	0.14	0.93 [0.87;0.98]	0.01	1.28 [0.95;1.73]	0.11	0.90 [0.82;0.97]	0.010
	HCV	Ref		Ref		Ref		Ref	
	HBV	0.90 [0.46; 1.76]	0.76	0.84 [0.65; 1.07]	0.15	0.89 [0.28; 2.83]	0.84	0.89 [0.68; 1.16]	0.39
	Alcohol	1.15 [0.78; 1.70]	0.48	0.92 [0.79; 1.07]	0.26	1.25 [0.71; 2.18]	0.44	0.92 [0.77; 1.10]	0.36
	NASH	0.97 [0.49; 1.89]	0.92	1.10 [0.88; 1.37]	0.39	1.28 [0.50; 3.28]	0.61	1.27 [0.99;1.63]	0.06
	Hemoch	0.83 [0.48; 1.43]	0.49	0.61 [0.49; 0.76]	<0.001	1.01 [0.41; 2.51]	0.98	0.63 [0.49; 0.81]	<0.001
	Other	1.12 [0.67; 1.86]	0.68	1.06 [0.88; 1.27]	0.55	1.09 [0.53; 2.25]	0.81	0.94 [0.75; 1.18]	0.58
MELD	per unit	1.17 [1.16; 1.19]	<0.001	1.05 [1.05; 1.06]	<0.001	1.19 [1.15; 1.22]	<0.001	1.01 [0.99; 1.02]	0.35
Number of HCCs									
	1	Ref		Ref		Ref		Ref	
	≥2	1.68 [1.08; 2.35]	0.002	0.98 [0.90; 1.21]	0.73	1.86 [1.24; 2.78]	0.003	1.12 [1.00; 1.26]	0.040
Tumor size		1.04 [0.92; 1.18]	0.53	1.09 [1.05; 1.12]	<0.001	1.19 [1.01; 1.39]	0.03	1.12 [1.07; 1.16]	<0.001
Total Tumor Volume	0-25	Ref						.	
	25-50	0.93 [0.57; 1.54]	0.78	1.15 [1.01; 1.30]	0.03				
	50+	1.09 [0.62; 1.94]	0.76	1.06 [0.91; 1.24]	0.47				
Alpha fetoprotein (log)	per log	1.09 [1.01; 1.19]	0.04	1.03 [1.00; 1.05]	0.02	1.14 [1.04; 1.26]	0.005	1.03 [1.00; 1.06]	0.03
Variables in non-HCC patients		HR ["95% CI"]	*p*	HR ["95% CI"]	*p*	HR ["95% CI"]	*p*	HR ["95% CI"]	*p*
Age Diagnosis	per 10 years	1.16 [1.10; 1.21]	<0.001	1.02 [0.99; 1.05]	0.15	1.26 [1.20; 1.33]	<0.001	1.06 [1.03; 1.09]	<0.001
	HCV	Ref		Ref		Ref		Ref	
	HBV	1.59 [1.31; 1.92]	<0.001	1.73 [1.56; 1.91]	<0.001	0.96 [0.80; 1.17]	0.71	1.23 [1.11; 1.36]	<0.001
	Alcohol	1.18 [1.08; 1.30]	0.41	1.28 [1.22; 1.34]	0.003	0.89 [0.81; 0.98]	0.02	1.05 [1.00; 1.10]	0.06
	NASH	1.05 [0.92; 1.21]	0.94	1.13 [1.05; 1.22]	0.03	0.95 [0.82; 1.09]	0.46	1.08 [1.01; 1.17]	0.04
	Hemoc.	1.09 [0.74; 1.60]	0.53	1.41 [1.17; 1.70]	<0.001	0.93 [0.63; 1.37]	0.72	1.28 [1.06; 1.54]	0.01
	Other	1.35 [1.26 ;1.46]	<0.001	1.32 [1.27; 1.38]	<0.001	0.94 [0.87; 1.02]	0.12	1.08 [1.03; 1.13]	<0.001
MELD	per unit	1.17 [1.17; 1.17]	<0.001	1.12 [1.12; 1.13]	<0.001	1.17 [1.17; 1.18]	<0.001	1.12 [1.12; 1.13]	<0.001

Results are shown using continous or categorical variables according to the best results (priority is given of continous variables).
*Schoenfeld: all *P* value>0.05, and the global *P* value is 0.38.
Abbreviation: HR, hazard ratio.

was likely, at least in part, caused by the large sample size. The prognostic assessment provided a C-index of 0.55 (95% CI: 0.54-0.66). Age and MELD were combined together with diagnosis in a model for non-HCC (MnonHCC), which was predicting dropout:

$$\begin{aligned}\text{MnonHCC} = {} & 0.2349 \times \text{Age}/10 + 0.1588 \times \text{MELD} \\ & + 0 \text{ if Diag} = \text{HCV} \\ & - 0.0364 \text{ if Diag} = \text{HBV} \\ & - 0.1139 \text{ if Diag} = \text{Alcohol} \\ & - 0.0532 \text{ if Diag} = \text{NASH} \\ & - 0.0718 \text{ if Diag} = \text{Hemoc} \\ & - 0.0619 \text{ if Diag} = \text{Other}\end{aligned}$$

By performing a linear regression to model the risk of dropout estimated by the multistate model as a function of the MnonHCC, we established the following relationship:

$$\begin{aligned}\text{Logit (risk of dropout)} = {} & -5.61803 + 0.69838 \\ & \times \text{MnonHCC}\end{aligned}$$

The R^2 value of the regression was 0.98.

Correspondence Between Risk Scores. The previously described models pictured the risk of dropout accurately for HCC and non-HCC patients, but the scales were not compatible, thus not allowing a management on a common waiting list. As a final step, the link between MHCC and MnonHCC was performed according to the risk of dropout predicted by the linear regressions outlined above. The aim was to allocate deMELD points based on HCC characteristics, express similar risks of dropout between HCC and non-HCC patients, and allow for the management of both groups on a common waiting list. The previously described equations predicting the Logit(risk of dropout) were equated, defining identical risks of dropout in both groups. The equation obtained by combining MHCC and MnonHCC was as follows:

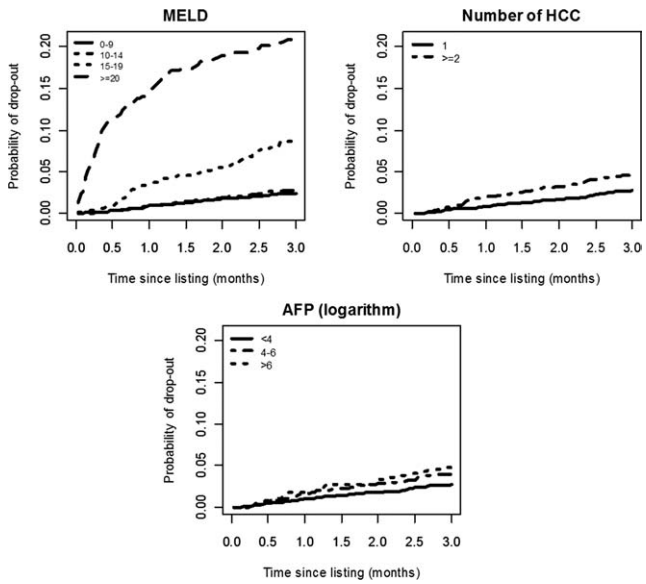

Fig. 2. Time-dependent probability of dropout in the HCC group according to MELD, number of HCCs, and AFP.

$$-5.61803 + 0.69838 \times \text{MnonHCC} = -8.41291 + 1.05498 \times \text{MHCC}$$
$$\text{or MnonHCC} = -4.0019 + 1.5106 \times \text{MHCC}$$

After expressing MHCC and MnonHCC as a function of the patient characteristics described earlier, the deMELD equation was obtained:

$$\begin{aligned}\text{deMELD} = {} & -25 + 0.1 \times \text{Age} + 1.6 \times \text{MELD} \\ & + 1.6 \times \text{Tumor Size} + 1.3 \times \text{LogAFP} \\ & + 6.0 \text{ if Nb Tumors} \geq 2 \\ & + 0 \text{ if Diag} = \text{HCV} \\ & - 1 \text{ if Diag} = \text{HBC} \\ & + 3 \text{ if Diag} = \text{Alcohol} \\ & + 3 \text{ if Diag} = \text{NASH} \\ & + 1 \text{ if Diag} = \text{Hemoc} \\ & + 1 \text{ if Diag} = \text{Other}\end{aligned}$$

To illustrate how the proposed model can be used, deMELD points were calculated for various potential HCC liver transplant candidates (Table 3). A 70-year-old patient with two 3-cm HCC lesions, an AFP of 400 ng/mL, and a calculated MELD of 15 should be allocated 23.6 points (deMELD), and this specific patient would currently be poorly served with the standard allocation of 22 points to T2 patients in the United States. Conversely, the same patient with only one HCC and an AFP of 5 ng/mL should be allocated only 12.1 points (deMELD) and is currently unfairly advantaged using current exception MELD points (22 points for T2). Overall, the deMELDs were low both in stage 1 and 2 candidates (Fig. 5). As a result, most HCC patients were allocated too many exception points, including 95.2% of T2 HCC patients (2,795 of 2,937) with deMELD <22.

Discussion

The proposed model attributes drop-out risk scores to HCC (deMELD) and non-HCC (MELD) patients that correspond to identical risks of dropout from the list. These scores should allow the comparison of the opportunities to receive a graft allocation more coherent with commonly accepted equality and utility criteria.

With the current allocation of exception MELD points to HCC liver transplant candidates, all patients with T2 HCCs have similar chances of undergoing transplantation. To illustrate, a patient with a 5-cm HCC and 2,000 ng/mL of AFP has the same priority as a patient with a 2.5-cm lesion and normal AFP, although they have very different risks of dropout.[8] In addition, the allocation of exception points does not take into account the current management of HCC patients on the waiting list with intensive locoregional treatments, because candidates remain with similar MELD points whether or not they had a successful ablation. The proposed model appears therefore as a useful tool for a more accurate assessment of the risk of dropout and indirectly of the need for transplantation in HCC patients, and for a more equitable allocation of organs between HCC and non-HCC patients. Continuous, it can best capture fine differences between patients and HCC changes over time.

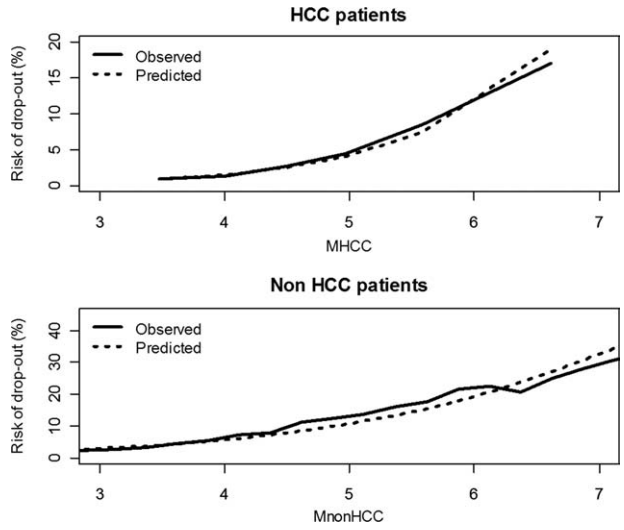

Fig. 3. Risk of dropout according to (A) MHCC in the HCC group and (B) MnonHCC in the non-HCC group.

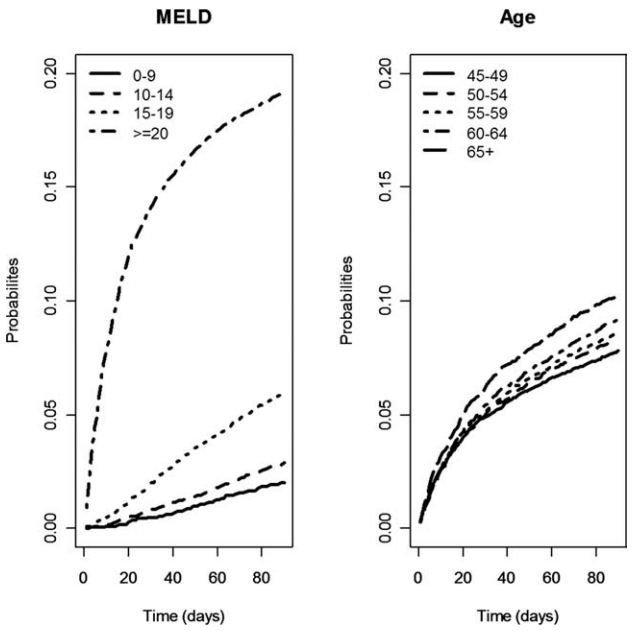

Fig. 4. Time-dependent probability of dropout in the non-HCC group according to MELD and recipient age.

With the current allocation of MELD exception points, most U.S. HCC candidates are privileged, compared to non-HCC candidates, regarding the access to liver graft (Fig. 5). To illustrate, 95.2% of stage 2 HCC candidates (one HCC between 2 and 5 cm in diameter or two or three HCCs each up to 3 cm) are currently allocated too many exception MELD points, because their deMELD is <22.

The proposed model computes the risk of dropout according to patient age, MELD score, diagnosis, HCC number, HCC size, and AFP. Of note, recipient age was retained in the model, although this is leading to higher deMELDs, easier access to transplantation to older candidates, and potential ethical concerns. Though the authors had differing opinions about this choice, the inclusion of age allowed for a more accurate model. In addition, all candidates fulfilling local listing criteria (with a defined age limit) should have a fair chance of undergoing transplantation, and the proposed strategy offers access to transplantation to the largest number of candidates.

Local wait-list HCC treatment was not taken into account because of a high risk of bias in this retrospective analysis: Patients can only be treated if they remain long enough on the waiting list, and patients dying or dropping early will have no time for a local HCC treatment. As a result, local HCC treatment is skewed toward patients at low risk of dropout. This said, post-treatment HCC size and AFP changes are captured by the proposed model, because the deMELD is continuously reassessed on the waiting list (we propose an assessment after each local HCC treatment or at least every 3 months).

It may be argued that a graft allocation based on the risk of HCC progression and dropout may impair post-transplant outcomes, because it diverts organs to patients with a poorer oncological prognosis.[16] We acknowledge that some currently delisted higher risk patients would now reach transplantation thanks to their deMELD and potentially recur thereafter. This issue would require a prospective assessment along with an external validation of the model and the deMELD. If needed, the risk of post-transplant recurrence could potentially be maintained as low with a minimum 3-month wait before

Table 3. Exemples of eMELD Points According to HCC Characteristics

Age	HCC Nb	HCC Size (cm)	AFP (ng/mL)	MELD	Score MHCC	Dropout at 3 Months %	deMELD
50	1	3	5	15	4.52	2.5	10.4
60	1	3	5	15	4.76	3.3	11.2
70	1	3	5	15	5.01	4.2	12.1
50	1	5	5	15	4.87	3.6	13.7
60	1	5	5	15	5.11	4.6	14.5
70	1	5	5	15	5.36	5.9	15.4
50	1	5	400	15	5.45	6.5	19.3
60	1	5	400	15	5.71	8.3	20.1
70	1	5	400	15	5.96	10.6	21.0
50	2	3	400	15	5.73	8.5	21.9
60	2	3	400	15	5.93	10.8	22.7
70	2	3	400	15	6.22	13.6	23.6

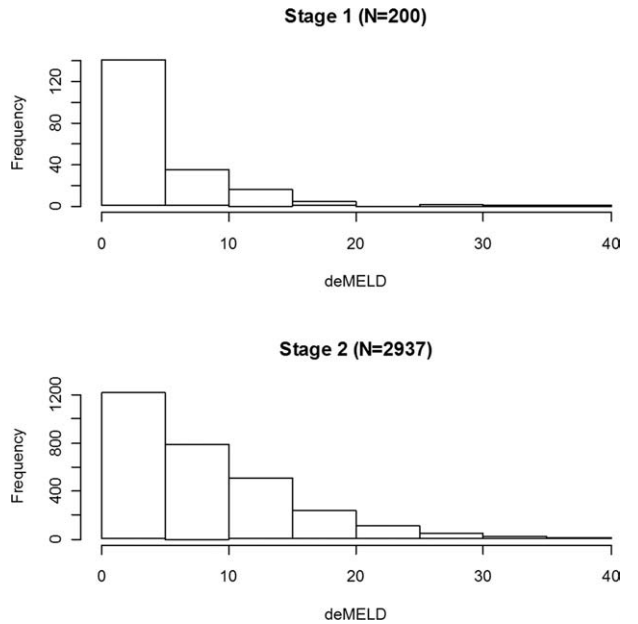

Fig. 5. Distribution of deMELDs in stage 1 and 2 HCC candidates registered in the SRTR from January 2004 to December 2009.

transplantation, similar to the one proposed after downstaging and during the 2009 National Conference on Liver Allocation in Patients with Hepatocellular Carcinoma in the United States.[17,18] Patients at high risk of early post-transplant recurrence would thus be excluded from transplantation, and only candidates with slower, less aggressive "good biology" tumors would be selected. Such a practice may be further adapted according to additional factors altering transplantation outcome, including the quality of the liver graft, the recipient disease etiology, and a number of tumor characteristic variables not included in the model, such as vascular invasion and HCC differentiation.

The significant weight of AFP in the model introduces the paradox of a system predicting dropout according to a utility endpoint (i.e., Milan criteria) while giving priority to patients with biologically unfavorable tumors. This paradox may be especially relevant considering the average high AFP of the studied population (337 ± 1,928 ng/mL) and should promote the introduction of an AFP cutoff (some have proposed a cutoff of 400 ng/mL), along with morphological variables for candidate selection.[4,8]

The predictive performance of the multivariate model for the dropout is acceptable (C = 0.72), but indicates that some factors could be missing to further explain the risk of dropout. The proposed equation for the deMELD is called to be improved by the detection of new factors associated to the risk of dropout. Moreover, it is necessary to update regularly the equation: If the risk of dropout is modified (e.g., by an evolution of the number of donors, by the use of the deMELD, or by the use of treatments improving the survival in HCC patients), the proposed model may also be modified. As a further note, the equation for deMELD calculation was established in a specific population (mainly including patients within Milan) and its application on another population may not be appropriate, thus requiring external validation.

Overall, the proposed model based on the SRTR data allow a better comparison of the opportunities of HCC and non-HCC patients to receive a graft on a common waiting list and, possibly, for a fairer allocation of liver grafts. External validation and potential adaptation to a population with larger HCC sizes are warranted.

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