

A method for establishing allocation equity among patients with and without hepatocellular carcinoma on a common liver transplant waiting list

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Background & Aims: The current organ allocation system for liver transplantation (LT) creates an imbalance between patients with and without hepatocellular carcinoma (HCC). We describe a model designed to re-establish allocation equity among patient groups using transplant benefit as the common endpoint.

Methods: We enrolled consecutive adult patients entering the waiting list (WL group, n = 2697) and undergoing LT (LT group, n = 1702) during the period 2004–2009 in the North Italy Transplant program area. Independent multivariable regressions (WL and LT models) were created for patients without HCC and for those with stage T2 HCC. Monte Carlo simulation was used to create distributions of transplant benefit, and covariates such as Model for End-stage Liver Disease (MELD) and alpha-fetoprotein (AFP) were combined in regression equations. These equations were then calibrated to create an “MELD equivalent” which matches HCC patients to non-HCC patients having the same numerical MELD score.

Results: Median 5 year transplant benefit was 15.12 months (8.75–25.35) for the non-HCC patients, and 28.18 months (15.11–36.38) for the T2-HCC patients ($p < 0.001$). Independent

predictors of transplant benefit were MELD score (estimate = 0.89, $p < 0.001$) among non-HCC patients, and MELD (estimate = 1.14, $p < 0.001$) and logAFP (estimate = –0.46, $p < 0.001$) among HCC patients. The equation “HCC-MELD” = $1.27 * \text{MELD} - 0.51 * \log \text{AFP} + 4.59$ calculates a numerical score for HCC patients, whereby their transplant benefit is equal to that of non-HCC patients with the same numerical value for MELD.

Conclusions: We describe a method for calibrating HCC and non-HCC patients according to survival benefit, and propose that this method has the potential, if externally validated, to restore equity to the organ allocation system.

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Introduction

Liver transplantation (LT) is the best curative treatment for patients with end-stage liver disease, but is limited by organ supply [1,2]. Priority assessment for allocation of organs among patients waiting for LT is currently based on the principle of urgency [3]. In order to operationalize this principle, most centers worldwide use the Model for End-stage Liver Disease (MELD) score. Composed of serum bilirubin, creatinine, and international normalized ratio (INR), this score is a strong predictor of 3-month mortality from liver disease [4,5].

One problem is that patients with hepatocellular carcinoma (HCC) represent a growing group, whose urgency is not represented by the MELD score because they often have preserved liver function. For this reason, artificial MELD scores have been

Keywords: Liver transplantation; Surgical oncology; Hepatocellular carcinoma; Cirrhosis; Clinical decision making.

Received 21 June 2013; received in revised form 13 September 2013; accepted 2 October 2013; available online 23 October 2013

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Abbreviations: LT, Liver Transplantation; HCC, hepatocellular carcinoma; WL, waiting list; MELD, model for end-stage liver disease; AFP, alpha-fetoprotein; INR, international normalized ratio; NITp, North Italy Transplant program; IQR, interquartile range; CR, competing risk; HCV, hepatitis C virus; HBV, hepatitis B virus; HR, hazard ratio; CI, confidence interval.



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introduced for HCC patients to increase their priority rankings [5]. For example, in the U.S., HCC patients receive an artificial score that increases automatically every 6 months. Therefore it is not surprising that the likelihood of undergoing transplantation is substantially higher for HCC candidates than for other patients [7]. The use of LT for HCC patients is increasing in the U.S.A. [1], and in Italy HCC has become the main indication for LT [2], thus putting patients with non-malignant liver disease at an unfair disadvantage.

More precise and accurate models have been proposed to describe the drop-out risk of HCC patients [5–7]. Washburn *et al.* showed that AFP and MELD score were the most important dropout predictors in HCC patients, when competing risk analysis was applied [7], while the impact of nodule size and number was negligible. Toso *et al.* was the first author to propose a common priority scale for HCC and non-HCC patients in a common waiting list, based on the dropout equivalent of MELD score [6].

However, equity in priority assessment using 3-month dropout risk as an endpoint has two main problems: (a) two different biological events are equated (i.e., drop-out in HCC is due mainly to tumour progression while drop-out in non HCC patients is mainly due to death); (b) an allocation system unbalanced towards urgency risks compromises utility [3,8]. Indeed, as Cucchetti and co-workers have shown [9], the higher the priority score for HCC patients the lower the post transplant outcome.

Transplant benefit is an innovative endpoint proposed for both patients with and without HCC, having the potential to create an ideal balance between urgency based and utility based endpoints [3,10,11].

The aim of this study is to describe a model with the potential to establish priority assessment equity between HCC and non-HCC patients using the transplant benefit as the main endpoint.

Patients and methods

The overall design of this study involved analysing survival of waiting list and post-transplant populations, and then creating a Markov model to calculate survival benefit.

Study population

The study population included all adult patients with chronic end-stage liver disease, listed for liver transplantation from January 2004 to December 2009 in the North Italy Transplant program (NITp) area including 9 LT centres in northern Italy. NITp central office records in a common database prospectively collected data from each centre at different time points (at the moment of waiting list inscription, during pre-LT follow-up visits, at the moment of LT and during post-LT visits).

According to NITp policy, organs are assigned in a sequential fashion to each transplant centre, and each centre selects a suitable recipient from its own waiting list (WL). Some patients judged at high risk of drop-out from the WL may receive extra priority at a regional level (whole NITp area), that causes them to be offered organs out of the normal sequence. Similarly, a regional priority bonus is given to increase the possibility to perform *in situ* split liver transplantation for adult and paediatric patients [12]. Only patients listed for emergency re-LT or with a preoperative diagnosis of acute liver failure take national priority as Status 1 patients. When a centre receives an organ from the regional or national level, it has to “pay back” with the following local organ.

Despite having a centre based allocation system, since 2004 the MELD score has become the main priority and allocation tool for cirrhotic patients in the NITp area. Most NITp centres used UNOS arbitrary MELD score for stage 2 HCC patients. There were only 2 exceptions: (a) the National Tumours Institute of Milan, which had only HCC patients in its WL; and (b) the University Hospital of Padua, which had created for each blood group a NON MELD list, including HCC patients and

other exceptions with a MELD <20. HCC patients were stratified in Padua according to a specific score based on response to therapy [13]. In general, all NITp centers adopted a prioritization policy for HCC, which did not take into account their biochemical MELD score. The NITp protocol for inclusion of HCC patients in the WL was strictly based on Milan criteria in almost all centers.

Patients with T1 and T3 HCC were excluded from the present analysis for several reasons:

- (1) The aim of this study was to re-establish equity between non-HCC patients and those HCC patients actually receiving an excess of arbitrary priority. The last are represented only by T2 HCC patients in the majority of LT centers worldwide.
- (2) The proportion of T1 and T3 HCC patients in the NITp WL during the study period was negligible (<10%) and thus their introduction not only could give misleading results on the impact of T stage on transplant benefit, but also may confound the impact of T2 stage on benefit itself.
- (3) We already demonstrated [11] that the impact of number and size of nodules on transplant benefit is negligible.

Moreover, due to the particular priority policy to recipients of partial graft from *in situ* splitting, these patients were excluded from this study.

Statistical analysis

Descriptive statistics

Qualitative data were described by frequency and percentage. Quantitative data were described by median (interquartile range (IQR)). In the comparison between different subgroups, quantitative variables were compared using Student's *t* or Wilcoxon Rank Sums tests, as appropriate. Categorical variables were compared using χ^2 or Fisher's exact tests, as appropriate. Time on the waiting list, length of follow-up and survival are expressed as medians (IQR). Overall survival was calculated from the baseline visit until death from any cause or latest follow-up. Dropout was defined as removal from the waiting list due to disease progression or patient death before LT.

Inferential statistics

The analytic strategy is summarized as follows. First, survival was modelled in the pre- and post-transplant populations. Next, monthly death probabilities from these models were used to simulate a randomized trial, in which two similar but independent populations were considered, one immediately undergoing LT, the other given the best non-transplant standard of care while on WL. This was done in order to calculate survival benefit, which can be thought of as the additional time gained from transplantation. Monte Carlo simulation was used to calculate the impact of individual variables (e.g., AFP) on survival benefit. Finally, the output of the simulation was used to combine these variables into a numerical score for each HCC patient that describes his or her survival benefit. This score was calibrated to the MELD score, and is called “HCC-MELD.” For example, a HCC patient with a HCC-MELD score of 16 would have the same survival benefit from transplantation as a patient with non-malignant liver disease who has a laboratory MELD score of 16. Each step is described in further detail below.

Survival modelling

We considered two study populations, that of patients with T2-HCC and that of non-HCC patients. As in Schaubel's study [3], for each study population we created two independent survival models for patients in the waiting list (WL group) and for those undergoing LT (LT group). In the first model, the baseline visit was considered the day of inclusion in the WL; in the second model, the day of LT. In the WL survival analysis, survival was calculated from the day of listing until death before LT, transplantation, or latest follow-up (which continued after dropping out up until latest follow-up or death). In the post LT survival analysis, survival was calculated from the day of LT until death after LT, or latest follow-up. Follow-up data were collected up until September 30, 2012, when our initial data analysis was performed.

Multivariable analyses were based on the conventional Cox proportional hazards regression (non-competing risk) for the LT model. For the WL model we used the competing risk (CR) method of Fine and Gray [14]. The CR methods allows for all patients to be placed into a category; transplanted, died or still waiting. In the Cox analysis, patients are censored for any event other than death.

In both models, a multivariable analysis was performed to evaluate the prognostic power of MELD score adjusted for the following covariates: age, sex, hepatitis C virus (HCV) cirrhosis, and hepatitis B virus (HBV) cirrhosis. For HCC patients we also tested the prognostic performance of AFP, while in the LT model we considered donor age also as a covariate. There was no missing data for these variables, and no other variables were available.

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The correlations between MELD and survival derived from the WL and post-LT multivariable models were expressed as hazard ratio (HR) and 95% confidence interval (CI).

WL and post-LT regressions were used to calculate monthly death probabilities (mdp) according to MELD according the formula [15]:

$$\text{mdp} = -\text{LN}(S(t))/t, \text{ where } t \text{ is expressed in months.}$$

Model assessment was done graphically with cumulative sums of martingale residuals.

Survival benefit calculation

A simple multi-state Markov prediction model was then developed to estimate the survival benefit of LT in the two study populations (T2-HCC and non-HCC patients). Markov models are particularly useful when a decision problem involves a risk that is ongoing over time [16], for example the risk of mortality. The Markov model assumes that the patient is always in one finite number of states of health referred to as Markov states. The time horizon of the analysis is divided into equal increments of time, referred to as Markov cycles. During each cycle, the patient may make a transition from one state to another. In this study, we used an extremely simple (two health states) Markov decision tree and a cycle length of 1 month, whereas the time horizon was 60 months.

For each population (HCC and non-HCC), we constructed the model by simulating the ideal clinical scenario for a randomized trial, in which two similar but independent populations were considered, one immediately undergoing LT, the other given the best non-transplant standard of care while on WL.

The Markov model converted monthly death probabilities (derived from CR and Cox analyses) in life expectancy values. The survival benefit of LT (gain in life expectancy) at 60 months was calculated by subtracting the no-LT life expectancy predictions from the post-LT life expectancy predictions.

We preferred to use a Markov model with the respect to other experiences based on direct calculation of area under the survival curve [3] to obtain transplant benefit estimations for two main reasons: (a) Markov model and Monte Carlo simulation [17] allow consideration of covariate hazard ratios together with their 95% confidence intervals. In this view, they better account for model uncertainty than traditional calculations; (b) as in the Toso's study [6], multi-state models calculate a pre-established number of endpoint outcomes for each study population (i.e., transplant benefit estimations) that can be easily equated in order to find a common prognostic scale, which was the main aim of this study.

One-way sensitivity analysis was used to graphically describe the transplant benefit in months at different MELD values in the two populations of T2-HCC and non-HCC patients.

An exploratory Markov simulation showed an overestimation of 5 year WL life expectancy. As in the Schaubel study [3], 5 year life expectancy in the WL of patients with high MELD score (>30) resulted higher than 1 year. This result clearly was in contrast with the severity of their liver disease and was probably due to the inability of statistical expedients (i.e., competing risk analysis or inverse probability of censoring weighting) to resolve completely the selection bias intrinsic to the MELD-based high priority given to these patients for LT. For this reason, we further calibrated MELD related HRs in the WL models of both HCC and non-HCC patients in order to give more weight to the HRs of increasing MELD points. This HR weighting was based on recent evidences measuring the MELD impact on 3-months WL death [18]. Adjusted HRs were finally applied to the baseline survival function according MELD score calculated in the whole WL study population using the CR method.

Calculating HCC-MELD

Since the aim of the study was to develop a prediction model for calibrating survival benefit of HCC patients to non-HCC patients, a Monte Carlo simulation [17] was used to understand the impact of MELD and other covariates on the model results and to estimate the level of uncertainty that can be placed in analysing such results.

The uncertainty of life expectancy estimations was estimated assuming a triangular distribution for MELD hazard ratios (with their relative confidence intervals), a normal distribution for logAFP, and uniform distributions for MELD score (range 6–40) in both T2-HCC and non-HCC patients. Using the Monte Carlo simulation we obtained a list of 1000 outcomes (life expectancy in months) for each population based on covariate distributions.

In this way, using a standard least square regression model, we obtained a regression defining the 5 year LT benefit of non-HCC patients based on MELD score, and another regression defining the survival benefit of T2-HCC patients based on MELD score and AFP.

By equating the LT survival benefit of the two populations, we generated a simple regression model to calculate a transplant benefit based MELD score (HCC-MELD) in T2-HCC patients derived from biochemical MELD score and from AFP.

Statistical significance was set at $p < 0.05$. All statistical calculations were performed using SAS (version 9.2, Cary, NC, U.S.A.) or R for Windows (Version 2.5.1). The Markov simulation model was performed using TreAge Pro v2008 (TreAge Software, Williamstown, MA, U.S.A.).

Results

Patient characteristics

In the study period 2697 patients were included in the WL for LT and a large proportion of them 925 (34%) had T2-HCC at the moment of listing.

Median time in the WL of the whole population was 4.7 months (IQR, 1.7–12.9). Three-hundred-six patients (11%) died waiting for LT, 161 (6%) were excluded due to progression of liver disease and died after a median time of 3 months after exclusion, 1734 underwent LT (64%) and formed the post-LT group of this study, 496 (19%) are still waiting LT or were removed from the WL due to liver disease improvement.

The two populations of patients with and without HCC were significantly different in terms of age, sex, cirrhosis aetiology, MELD score, time on the WL, drop-out events due to patient death and donor age (Table 1).

Median time in the waiting list of patients with different blood groups was: 5.4 months (2.1–14.6) for blood group O, 4.63 (1.6–12.7) for group A, 3.7 (1.6–10.0) for group B, 3.1 (1.0–10.6) for group AB. There was clearly a significant difference ($p < 0.001$) between common blood groups (O–A) and rare blood groups (B–AB) in terms of median waiting time (4.9 vs. 3.5 months). Interestingly, when we considered separately the two populations of patients with and without HCC, the significant impact of blood group on waiting time was maintained only in non-HCC patients (5.7 vs. 3.4 months) while it disappeared in HCC ones (4.0 vs. 3.7 months).

The overall rate of dropout from the waiting list was 14% in the HCC group; 79 HCC patients (9%) dropped out due to tumour progression and 49 (5%) for patient death. Dropout due to HCC progression was in all cases characterized by macroscopic vascular invasion or extra-hepatic metastases development. In the non-HCC population, the overall drop-out rate was 19%; 26% for patients with MELD score ≥ 22 and 16% for those with MELD < 22 (Fig. 1).

Multivariate CR and Cox analyses

Covariates of T2-HCC and non-HCC populations described in Table 1 were introduced in CR and Cox multivariable models.

In the WL CR model, MELD significantly predicted survival in both T2-HCC (HR = 1.08, 95% CI = 1.05–1.11) and non-HCC (HR = 1.04, 95% CI = 1.03–1.10) patients.

Also in the post-LT Cox model, MELD significantly predicted patient survival in both T2-HCC (HR = 1.04, 95% CI = 1.01–1.08) and non-HCC (HR = 1.04, 95% CI = 1.02–1.06) patients.

AFP, evaluated as LogAFP, reached a marginal statistical significance in predicting death of T2-HCC patients in the WL (HR = 1.31, 95% CI = 0.99–1.75), while it obtained a more significant impact on post-LT survival (HR = 1.29, 95% CI = 1.49–1.72).

Hazard ratios derived from CR and Cox analyses were used to calculate WL and 5 year post-transplant survival rates according to MELD score and LogAFP (Fig. 2). The impact of MELD score on WL survival was higher on T2-HCC than in non-HCC patients,

Table 1. Patient characteristics of non-HCC and HCC populations both in the WL and in the post-LT groups.

Variable	WL group		Post-LT group	
	Non-HCC (n = 1773)	T2-HCC (n = 925)	Non-HCC (n = 992)	T2-HCC (n = 742)
Age (yr), median (IQR)	54 (46-59)	58 (52-61)	53 (45-59)	56 (50-61)
Female sex, n (%)	521 (29)	132 (14)	308 (31)	96 (13)
B-AB blood groups	291 (16)	158 (17)	167 (17)	133 (18)
HCV positive, n (%)	689 (39)	526 (57)	410 (41)	337 (45)
HBV positive, n (%)	273 (15)	251 (27)	204 (21)	227 (31)
MELD score, median (IQR)	16 (13-21)	11 (9-14)	17 (13-25)	11 (9-14)
AFP (ng/ml), median (IQR)	-	9 (5-30)	-	10 (5-31)
Time on the WL (mo), median (IQR)	5.3 (1.6-16.3)	3.9 (1.9-9.3)	-	-
Dropout from the WL due to death, n (%)	257 (15)	49 (5)	-	-
Donor age (yr), median (IQR)	-	-	54 (38-66)	58 (44-69)

HCC, hepatocellular carcinoma; IQR, interquartile range; HCV, hepatitis C virus; HBV, hepatitis B virus; MELD, model for end stage liver disease; AFP, alpha-fetoprotein; WL, waiting list.

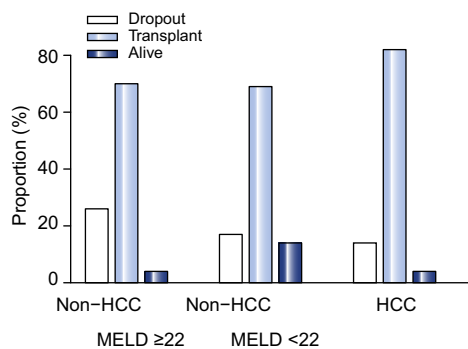


Fig. 1. Proportions of transplantations and dropouts in the study population. Histograms represent the proportion of dropouts, transplants, and patients still awaiting LT in T2-HCC and non-HCC subgroups in the NITp area.

while it was similar on post-LT survival (Fig. 2A). The impact of AFP on WL and post-LT survival was similar as shown by the quite parallel course of the two lines in Fig. 2B.

Multi-state Markov model and Monte-Carlo simulation

We used Monte Carlo simulation to estimate more precisely the effect of AFP and MELD score on 5 year transplant benefit, in a fashion that accounts for confidence intervals of these predictors. We obtained as result 1000 outcomes for T2-HCC patients and 1000 for non-HCC ones.

Median 5 year transplant benefit was 15.12 months (8.75–25.35) for the non-HCC patients, and 28.18 months (15.11–36.38) for the T2-HCC patients ($p < 0.001$).

In Fig. 3A, we represented 5 year benefit values according to quartiles of MELD score among HCC and non-HCC patients: the graph clearly showed that the 5 year transplant benefit for the T2-HCC patients in each MELD quartile was significantly higher than that of non-HCC ones. In Fig. 3B, the 5 year benefit values according to three classes of AFP values was depicted: box-plots showed that the effect of AFP on transplant benefit was minimal,

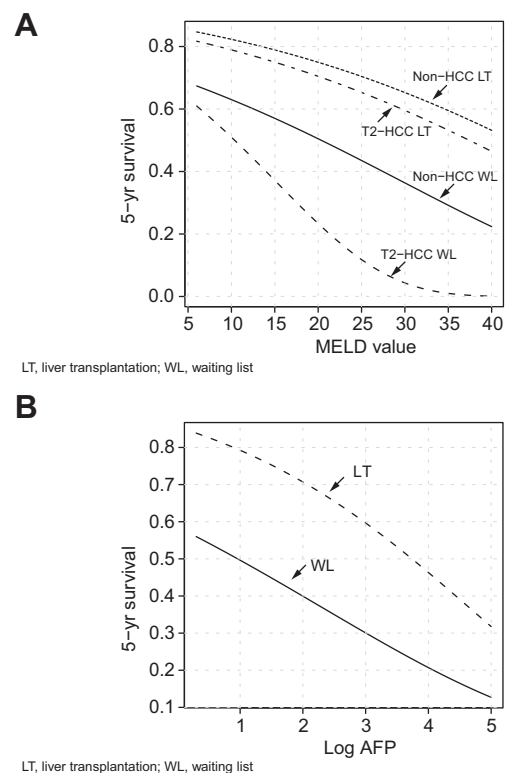


Fig. 2. Impact of MELD score and AFP on WL and post-LT survival. Continuous and dashed lines describe 5 year survival point estimates with and without LT according MELD score (A) and AFP (B). LT, liver transplantation; WL, waiting list.

but that AFP had globally a negative effect on transplant benefit, especially for values higher than 1000 ng/ml.

Using a least square regression model applied to the results of Monte Carlo simulation, we obtained the following regressions for the two study populations:

$$\begin{aligned} \text{5 year LT benefit non-HCC (months)} \\ = 0.89 * \text{MELD} - 3.59 \quad (\text{Rsquare} = 0.97) \end{aligned}$$

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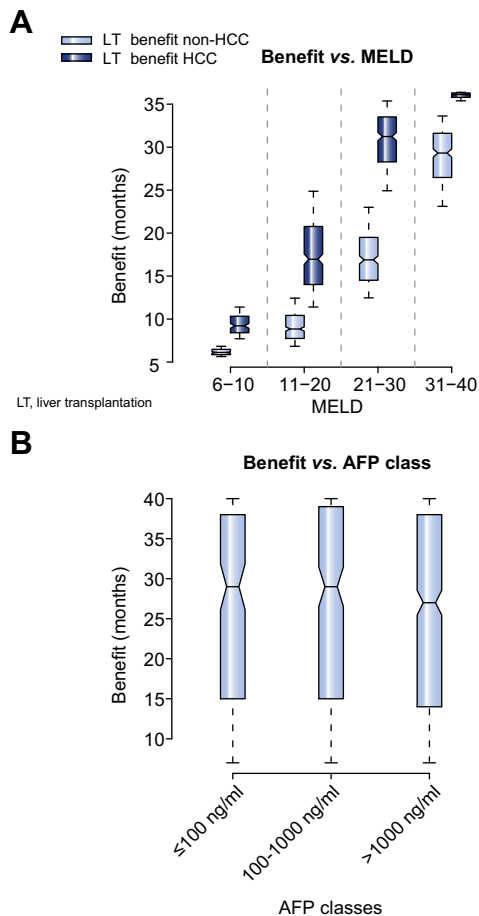


Fig. 3. Impact of MELD score and AFP on 5 year transplant benefit (months). Description of 5 year transplant benefit in months based on MELD quartiles (A) and AFP classes (B). LT, liver transplantation.

5 year LT benefit T2-HCC (months)

$$= 1.14 \cdot \text{MELD} - 0.46 \cdot \log \text{AFP} + 0.52 \quad (\text{Rsquare} = 0.94)$$

These regressions showed that independent predictors of transplant benefit were MELD score (estimate = 0.89, $p < 0.001$) among non-HCC patients, and MELD (estimate = 1.14, $p < 0.001$) and logAFP (estimate = -0.46 , $p < 0.001$) among HCC patients. Comparison of estimates in the T2-HCC population underlined first that the effect of MELD score on transplant benefit was positive while that of AFP was negative, second that the magnitude of MELD effect on benefit was much stronger than that of AFP.

We finally equated these two regressions to obtain a unique equation producing a numerical score for HCC patients ("HCC-MELD"), which matches them by survival benefit to non-HCC patients having the same numerical value for MELD score:

$$\text{HCC-MELD} = 1.27 \cdot \text{MELD} - 0.51 \cdot \log \text{AFP} + 4.59$$

Capping MELD values at 40, we obtained the same range of values (6–40) for patients with and without HCC.

The obtained HCC-MELD is a sort of "MELD equivalent" score for HCC that assigns each patient a score that equates their expected survival benefit to that of non-HCC patients in a certain MELD subgroup. So the HCC-MELD becomes a way to give

additional points to HCC patients, but these points are not arbitrary but based on transplant benefit calculation.

As expected, the effect of MELD score and AFP on HCC-MELD reflected that of the same variables on 5 year transplant benefit. MELD had a strong positive effect on HCC-MELD score (Table 2), whereas the effect of AFP was low and globally negative: the higher the AFP value the lower the calculated HCC-MELD (Table 2) of a patient with a particular value of biochemical MELD.

Finally, due to concern that the HCC-MELD would prioritize patients with very poor post-transplant survival, we performed a simple two-way sensitivity analysis to find MELD and logAFP threshold values, above which post-LT survival became lower than 50% at 5 year (Fig. 4).

We found a linear relationship between these two variables:

$$\log \text{AFP} = 4.793098 - 0.0976751 \cdot \text{MELD}$$

This simple utility MELD (uMELD) equation expresses the maximum MELD value that a hypothetical recipient should have given a specific value of AFP in order to avoid an unacceptable post-LT outcome (<50% at 5 year) and vice versa (Table 2).

In Table 3 we represented some clinical scenarios providing examples of what types of T2-HCC patients would have what survival benefit.

Discussion

Aristotle defined justice as "treating equal cases equally, and unequal cases unequally". One of the fundamental challenges of organ allocation science is maintaining equity among the heterogeneous groups of patients on the waiting list. In the specific organ allocation context, equity means treating all patients according to a common endpoint. In this perspective, the principle of equity is hierarchically more important than all others, whether we decide to favour urgency, utility or benefit as endpoints for our allocation system.

In the majority of U.S.A. and European LT centres, patients with a T2-HCC receive an arbitrary MELD score initially set at 22 points independently of their liver function [4–7]. This means that the current system gives the same priority to a T2-HCC patient with a very low MELD score (<10) and a non-HCC patient with a biochemical MELD score of 22, but at the same time gives the same priority to a patients with MELD >22 and HCC with respect to a non-HCC patient with the same MELD. Moreover, there is no difference of indication and prioritization for LT between a low-MELD HCC patient and a high-MELD HCC patient. This highlights two kinds of inequities due to arbitrary MELD score: one between HCC and non HCC population, and the other among HCC patients, between those with T2-HCC with low vs. high MELD scores. Thus, there is the urgent ethical and clinical need to improve equity in allocation between HCC and non-HCC patients, as well as within the HCC population.

Recent proposals have tried to resolve the unbalance in the access to transplantation between HCC and non-HCC patients and within the HCC population using complex equations based on 3-month drop-out risk as common endpoint. However, this modality (i.e., to equate the drop-out risk of different patients) carries the risk of prioritizing HCC patients with higher biological aggressiveness in terms of nodule size and AFP levels, and consequently dramatically increasing the risk of post-LT tumour recurrence or death [9]. Moreover, using tumour features to

Table 2. Different potential combinations of MELD score and AFP values using “MELD-HCC” and uMELD formulas.

MELD	AFP (ng/ml)*	Log AFP	MELD-HCC	
			min	max
6	12,864	4.11	10	13
7	12,864	4.11	11	14
8	10,273	4.01	13	16
9	8204	3.91	14	17
10	6552	3.82	15	18
11	5232	3.72	17	20
12	4178	3.62	18	21
13	3337	3.52	19	22
14	2665	3.43	21	23
15	2128	3.33	22	25
16	1699	3.23	23	26
17	1357	3.13	25	27
18	1084	3.03	26	28
19	866	2.94	27	30
20	691	2.84	29	31
21	552	2.74	30	32
22	441	2.64	31	34
23	352	2.55	33	35
24	281	2.45	34	36
25	225	2.35	35	37
26	179	2.25	36	39
27	143	2.16	38	40
28	114	2.06	39	40
29	91	1.96	40	40
30	73	1.86	40	40
31	58	1.77	40	40
32	47	1.67	40	40
33	37	1.57	40	40
34	30	1.47	40	40
35	24	1.37	40	40
36	19	1.28	40	40
37	15	1.18	40	40
38	12	1.08	40	40
39	10	0.98	40	40
40	8	0.89	40	40

*Maximum AFP value above which 5 year post-LT survival becomes lower than 50% according uMELD formula.

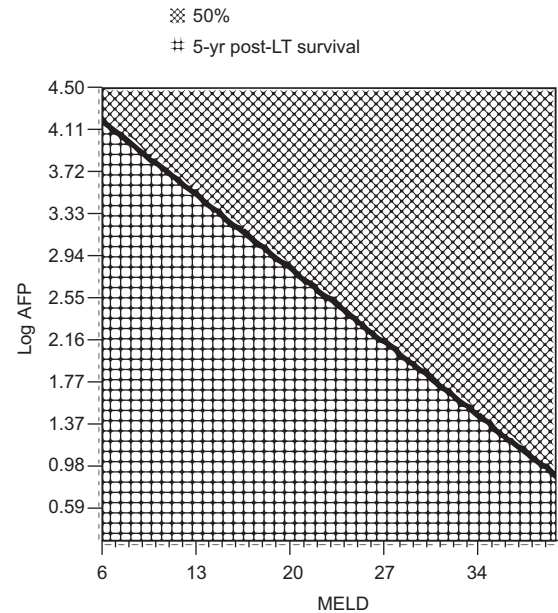
MELD-HCC min: MELD-HCC obtained using maximum acceptable AFP value obtained from the uMELD formula.

MELD-HCC max: MELD-HCC obtained assuming minimum AFP value (AFP = 1.3 ng/ml).

MELD, model for end stage liver disease; AFP, alpha-fetoprotein; MELD-HCC, benefit based score for T2-HCC; uMELD, utility based MELD.

discriminate the priority within the HCC population may be controversial. Recent data [1,10,11] has showed that if we observe the allocation issue from a transplant benefit point of view, the availability of effective therapies and liver function become the key decisional factors for HCC patients before LT, regardless of the nodule number and size criterion.

Therefore, our study hypothesis was that, in patients with HCC, liver function as described by MELD score and tumor aggressiveness measured by AFP level could be used to create a

**Fig. 4. Two-way sensitivity analysis.** This graph shows MELD and Log AFP threshold values, above which post-LT survival of T2-HCC patients became lower than 50% at 5 years.

continuous score that is calibrated by survival benefit to MELD score among non-HCC patients.

A limit of transplant benefit studies using WL population as control group is that median waiting list time, especially for HCC patients, is relatively short to consider 3 or 5 year survival endpoints. This bias is only partially resolved using statistical expedients such as competing risk analysis [14]. The ideal control group for a transplant benefit study should be a cirrhotic population of potentially candidates to LT excluded only for a blinded randomization, but this kind of study is obviously extremely difficult to organize for ethical reasons. The median waiting time of our population was short (Table 1) but it was comparable to that of a recent French multicenter study [19], and to that of UNOS population [6].

The first result of this study is that we have confirmed, on a large and multi-centre basis, that the MELD score is a significant predictor of transplant benefit among patients with HCC. The second fundamental result is that at each level of MELD score, survival benefit of LT was significantly higher in T2-HCC than in non-HCC patients (Fig. 3A). A third interesting result is that we explored for the first time the impact of AFP on transplant benefit. As clearly visible in Figs. 2B and 3B, although AFP had a significant impact on both WL and post-LT survival, its impact on transplant benefit was small due to the similar HRs in this two survival contexts. Globally, AFP had a low negative impact on transplant benefit (Fig. 3B). On the contrary, MELD score having a much higher impact on WL than post-LT survival, was a strong predictor of transplant benefit (Figs. 2A and 3A). This peculiarity of transplant benefit has been underlined also by other authors [3] and may explain also why other tumor covariates such as nodule size and number had a limited impact on transplant benefit [11]. Although further studies evaluating the impact of tumor variables on transplant benefit are necessary, the present analysis

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Table 3. Examples of emblematic clinical scenarios showing the potential impact of “HCC-MELD” in clinical practice.

Patients	T2-HCC	MELD	AFP	MELD-HCC	5-yr transplant benefit (mo)	Clinical indication
#1	Yes	8	126	14	9	Low priority
#2	No	22	-	-	16	Mean priority
#3	Yes	14	6	22	16	Mean priority
#4	Yes	26	126	37	29	Urgent transplant
#5	No	26	-	-	20	High priority
#6	Yes	22	830	30	24	WL-exclusion*

*Due to high AFP value and MELD score this patient has a 5 year post-LT survival lower than 50% according to uMELD formula and thus should be excluded from the WL. MELD, model for end stage liver disease; AFP, alpha-fetoprotein; MELD-HCC, benefit based score for T2-HCC; uMELD, utility based MELD.

suggests that a priority scale based on transplant benefit for HCC patients should account mainly for liver function parameters.

Concerning AFP values, it has to be underlined that median AFP values were particularly low in our population (Table 1). However, they were similar to that reported in other studies not excluding T3 patients. In a recent French multicenter study [19], for example, the median AFP value was 8 although the authors did not exclude T3 patients. Similarly, in a recent publication based on the UNOS database the median AFP value of WL patients was lower than 20 [20].

Finally, we describe a unique method for equating priority between HCC and non-HCC patients according to the common endpoint of survival benefit. The “HCC-MELD” is a continuous score of survival benefit according to liver function and AFP level, and is calibrated to the survival benefit of non-HCC patients by MELD. For example, if a HCC patient has a HCC-MELD score of 20, he or she will receive the same benefit from transplantation as a non-HCC patient with a biological MELD score of 20. So, the HCC-MELD is a way to give additional points to HCC patients, but these points are not arbitrary but based on transplant benefit calculation (Table 2).

The main suggestion of present analysis is that a priority scale based on transplant benefit for HCC patients should account mainly for liver function parameters more than for tumor characteristics.

This result, however, doesn't mean that tumor features should not be considered in the LT context. In fact, if we establish that a minimal post-LT survival threshold (utility) should be maintained (i.e., 50% at 5 year), this means that specific covariates thresholds should not be overcome.

If this concept to protect transplant utility is accepted, then it is plausible that a patient with a potential high benefit from LT and thus a high MELD-HCC score, for example patient n° 6 in Table 3, could be considered not suitable for LT and thus excluded from the WL because his expected 5 year post-LT survival was lower than 50% (due to high AFP values associated to high MELD score values).

In conclusion, the survival benefit of liver transplantation is not uniform among patients with HCC, but depends heavily upon their underlying liver function. We describe a method for calibrating HCC and non-HCC patients according to survival benefit. Although the HCC-MELD needs external validation and further refinements, we propose that ultimately this method has the potential to restore equity to the organ allocation system.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Authors' contribution

AV, TMDF, PB, LDC, LB, MC, SF, GR, EA, UB, MV, MD, UC: Collected the data. AV, UC: Designed the study. AV, ACF, RRM, UC: Analysed the data. AV, MLV, RRM: Wrote the paper.

I, AV, certify that to have had full access to all of the data in this study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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