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ORIGINAL ARTICLE

Model for end-stage liver disease-sodium and survival benefit in liver transplantation

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Summary

There are currently no studies calculating the survival benefit of liver transplantation (LT) according to model for end-stage liver disease-sodium (MELD-Na) and based on the competing risk (CR) method. We enrolled consecutive adult patients with chronic end-stage liver disease entering the waiting list (WL) for primary LT (WL group = 337) and undergoing LT (LT group = 220) in the period 2006–2009. Two independent multivariable regressions (WL and LT models) were created to measure the prognostic power of MELD-Na with respect to MELD. For the WL model, both Cox and CR multivariable analyses were performed. Estimates were finally included in a Markov model to calculate 3-year survival benefit. WL Cox model: MELD-Na ($P < 0.0001$) and MELD ($P < 0.0001$) significantly predicted survival. WL CR model: MELD-Na ($P = 0.0045$) and MELD ($P = 0.0109$) significantly predicted survival. LT Cox model: MELD-Na ($P = 0.7608$) and MELD score ($P = 0.9413$) had not correlation with survival. Benefit model: MELD and MELD-Na had an overlapping significant impact on 3-year survival benefit; CR method determined a significant decrease in 3-year life expectancy (LE) estimations. MELD-Na and MELD scores similarly predicted 3-year LT survival benefit, but the gain in LE is significantly lower when a CR method is adopted.

Introduction

The liver allocation system in the USA for adult patients with cirrhosis has adopted the model for end-stage liver disease (MELD), a 3-month mortality risk endpoint, to stratify patients in the waiting list (WL) for liver transplantation (LT) [1]. MELD score is an objective, continuous scale that has proven an effective tool for prioritizing cirrhotic patients, reducing their drop-out risk before LT. More recently [2], a population-wide study showed that both the MELD score and the serum sodium (Na) concentration are important predictors of short-term survival among candidates for LT and that the effect of the serum Na concentration was greater in patients with a low MELD score. Thus, a predictive model combining these two variables, the MELD-Na model, has been proposed to improve the assignment of priority in patients waiting for LT. MELD-Na adjustment, however, is focused on 3-month mortality and it has never been evaluated on a mid-long-term perspective.

An urgency-based system, such as that strictly using MELD or MELD-Na, assigns donor organs to patients who are most likely to die while on the WL, but this approach may be to the detriment of utility (i.e. post-LT survival) because patients at the greatest risk of death while on the WL may also be patients with the highest post-LT mortality risk [3,4].

An innovative allocation endpoint, the LT survival benefit [4] has been developed in recent years to create an ideal

balance between urgency and utility endpoints. The transplant benefit is calculated by subtracting the area under the survival curve without LT from the area under the survival curve after LT, and coincides with the gain in life expectancy (LE). A recent study, based on a large cohort of patients in the USA [4], has clearly shown that the total life-years lived by the WL population are maximized when the primary endpoint of deceased donor allocation is the LT survival benefit. The same authors showed in different studies that the MELD score is strongly correlated with the LT survival benefit [4–6] while there are no studies on the correlation between MELD-Na and LT survival benefit. Moreover, previous studies on transplant benefit did not account for the competing risks (CR) faced by waiting patients (i.e. transplant, continued waiting, or death). As Cox estimation may overestimate death rates (in particular, at later time points) by censoring for transplantation rather than including them in a CR assessment [7], a reexamination of transplant using a CR analysis for the WL survival model could potentially refine survival benefit predictions.

The aim of this study was to evaluate the prognostic ability of MELD-Na score in predicting both WL survival and transplant benefit with respect to conventional MELD score on a mid-long-term perspective using both Cox and CR methods in a cohort of Italian patients waiting for LT.

Patients and methods

This is a retrospective study including all consecutive adult patients undergoing to first cadaveric LT for chronic liver disease at Padua University Hospital in the period 2006–2009.

According to Italian policy, donated organs are assigned to a given liver transplant unit based on geographical criteria, and each liver unit selects a suitable recipient from its own WL. Only patients listed for emergency re-LT or with a preoperative diagnosis of acute liver failure take national priority as Status 1 patients.

As previously reported [8], since 2006 our center has introduced the MELD score as main priority and allocation tool for cirrhotic patients. However, we decided to not assign arbitrary MELD scores to patients with hepatocellular carcinoma (HCC) and other exceptions; thus, we created for each blood group a NON MELD list, including HCC patients and other exceptions with a MELD < 20. As previously reported, HCC patients were stratified according to a specific score based on response to therapy [9]. When an organ was offered to our center, two patients (the first patient in the MELD list and the first in the NON MELD list with a compatible size-match) were selected and the final allocation decision was taken case-by-case only after surgical and often histological evaluation of the liver graft [8].

Statistical analysis

Qualitative data were described by frequency and percentage. Quantitative data were described by median [interquartile range (IQR)].

In the comparison of different subgroups, quantitative variables were compared using Student's t or Wilcoxon Rank Sums tests, as appropriate. Categorical variables were compared using chi-square or Fisher's exact tests, as appropriate. Time on the WL, 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 WL as a result of disease progression or patient death before LT.

As in the Schaubel's study [3], we created two independent survival models for patients in the WL (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 March 31, 2011, when our initial data analysis was performed.

Multivariable analyses were based on the conventional Cox proportional hazards regression (noncompeting risk) for the LT model. For the WL model, we used both Cox regression and the competing risk (CR) method of Fine and Gray [10]. The CR method 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 or MELD-Na scores adjusted for the following covariates: age, sex, hepatitis C virus cirrhosis, and presence of HCC. In the LT model, we also considered covariate as the donor risk index to take into account, also the relevant prognostic impact of donor factors, and ischemia time on post-LT outcome. The correlations between MELD and MELD-Na 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 equations were used to calculate monthly death probabilities according to MELD and MELD-Na.

Model assessment was carried out graphically with cumulative sums of martingale residuals. A simple Markov prediction model (Technical Appendix) was then developed to estimate the 3-year survival benefit of LT in our

cohort of patients. 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 nontransplant standard of care during WL.

Using a time horizon of 36 months, the Markov model converted monthly death probabilities in 3-year LE values. Three-year survival benefit of LT (gain in LE) was calculated by subtracting the no-LT LE predictions from the post-LT LE predictions. One-way sensitivity analyses were used to graphically describe the 3-year survival benefit in months at different MELD and MELD-Na values. Statistical significance was set at $P < .05$. All statistical calculations were performed using SAS 9.2 (SAS Software, Cary, NC, USA) or R for Windows (Version 2.5.1). The Markov simulation model was performed using TreAge Pro v2008 (TreAge Software, Williamstown, MA, USA).

Results

In the study period, 337 patients were included in our WL for LT (Table 1, WL group). The majority of them (61%) had viral cirrhosis. As direct consequence of our priority policy, the only significant differences between the WL and the post-LT groups were the median MELD score in patients without HCC and the percentage of HCC patients; both these values, in fact, were significantly higher at LT than at listing (Table 1).

Median time in the WL was 9 months (IQR, 3–21). Sixty-one patients (18%) died waiting for LT, 9 (3%) were excluded because of tumor progression and died after a median time of 3 months after exclusion, 220 underwent LT and formed the post-LT group of this study.

Tumor progression was judged of sufficient clinical relevance as to make dropout from the WL unavoidable when HCC developed macroscopic vascular invasion or extrahepatic metastases.

In the WL Cox model (Table 2), MELD-Na significantly predicted survival (HR = 1.1162; 95% CI = 1.0704–1.1643; $P < 0.0001$) similarly to MELD score (HR = 1.1073; 95% CI = 1.0596–1.1558, $P < 0.0001$);

In the WL CR model (Table 2), MELD-Na predicted survival (HR = 1.0590; 95% CI = 1.0180–1.0912; $P = 0.0045$) slightly better than MELD score (HR = 1.0540; 95% CI = .0120–1.0868), $P = 0.0109$).

In the post-LT model, neither MELD-Na (HR = 1.0082; 95% CI = 0.9550–1.0603; $P = 0.7608$) nor MELD score (HR = 0.9980; 95% CI = 0.9446–1.0493; $P = 0.9413$) was correlated with post-LT survival.

Three-year overall post-LT patient survival was 78%. According to the DEALE method [11] (Technical Appendix), this value corresponded to a monthly death probability of 0.0069, while the Markov model calculated a 3-year LE of 31.9 months. We preferred to use this value of LE as a constant in the transplant benefit Markov model because of the absence of a significant correlation between MELD and MELD-Na and post-LT survival.

Figure 1 shows a strict relationship between MELD and MELD-Na scores and LT transplant benefit at 3 years. This effect was similar for MELD and MELD-Na, as WL survival curves largely overlapped both with Cox and CR analyses (Fig. 1a and b).

The threshold values to define LT futile were 12 for MELD score and 14 for MELD-Na with Cox analysis while they were 6 and 9, respectively, with CR (Fig. 2).

Table 1. Patient characteristics.

Variable	Waiting list group (n = 337)	Post-transplant group (n = 220)
Age, years		
Median (IQR)	57 (51–62)	55 (49–61)
Female sex, *n* (%)	82 (24%)	50 (23%)
Main etiology, *n* (%)		
Hepatitis C	160 (47%)	115 (52%)
Hepatitis B	47 (14%)	30 (14%)
Alcohol	83 (25%)	36 (16%)
Cholestatic	18 (5%)	16 (7%)
Other	29 (9%)	23 (11%)
Presence of HCC, *n* (%)*	122 (36%)	99 (45%)
MELD score		
Median (IQR)	16 (13–21)	17 (12–22)
MELD score in patients without HCC*		
Median (IQR)	17 (14–22)	20 (16–24)
MELD-Na score		
Median (IQR)	18 (14–24)	17 (12–23)
MELD-Na score in patients without HCC		
Median (IQR)	20 (16–24)	20 (15–25)
Split transplantation, *n* (%)	–	26 (12%)
Donor Risk Index		
Median (IQR)	–	1.71 (1.45–2.96)

IQR, interquartile range; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; Na, sodium.
*P-value <0.05 in the comparison between groups.

Table 2. Hazard ratio (95% confidence interval) and p values for impact of MELD and MELD-Na scores on waiting list survival.

	Cox HR (95% CI); P-value	CR HR (95% CI); P-value
MELD	1.1073 (1.0596–1.1558); <0.0001	1.0540 (1.0120–1.0868); 0.0109
MELD-Na	1.1162 (1.0704–1.1643); <0.0001	1.0590 (1.0180–1.0912); 0.0045

HR, hazard ratio; CI, confidence interval; CR competing risk; MELD, model for end-stage liver disease; Na, sodium.

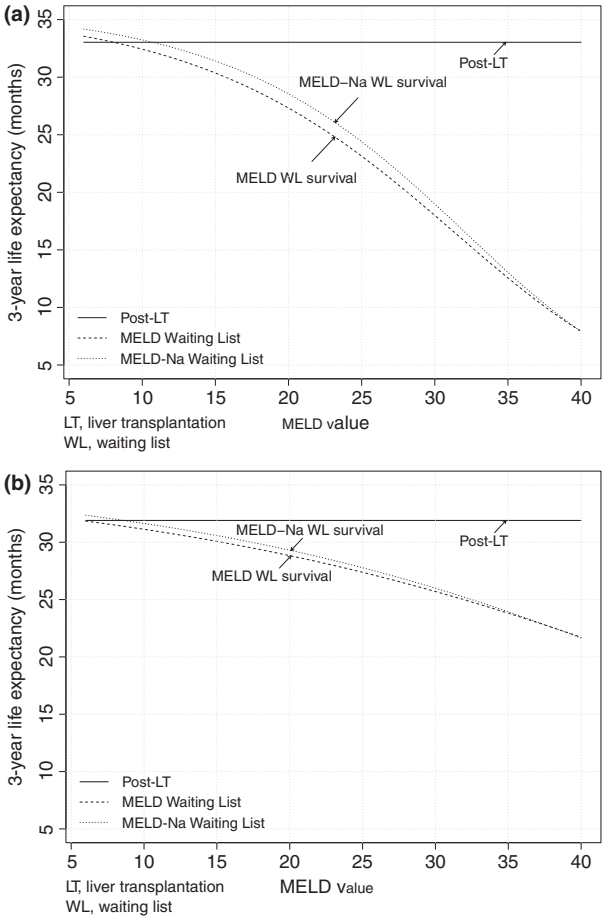

Figure 1 Post-liver transplantation and waiting list life expectancy according to MELD and MELD-Na calculated using Cox (a) and competing risk (b) multivariable analyses.

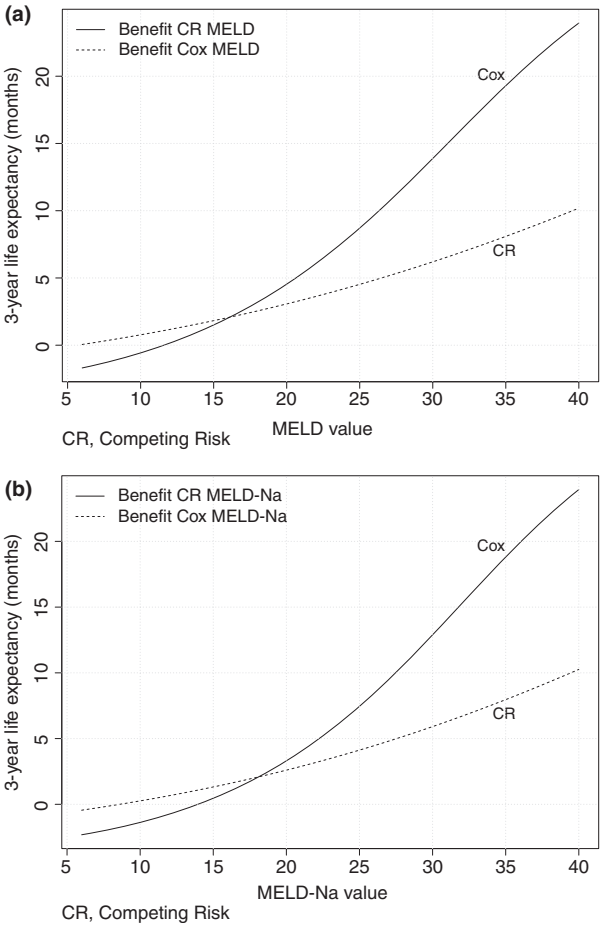

Figure 2 Gain in 3-year life expectancy (transplant benefit) according to MELD (a) and MELD-Na (b).

Median 3-year benefit (IQR) according to MELD score was 6.91 months (1.02–16.07) with Cox analysis and 3.92 (1.60–6.92) with CR analysis ($P < 0.0001$), whereas according to MELD-Na, it was 5.64 (0.02–15,26) with Cox and 3.48 (1.09–6.79) with CR ($P < 0.0001$).

Discussion

To the best of our knowledge, this is the first study analyzing the prognostic performance of the MELD-Na tool also in the mid-long term.

The first result of our analysis is a close relationship between MELD-Na and patient survival during the WL. Although median WL time of our patients was only 9 months, 25% of them remained in the WL more than 22 months making our model able to accurately estimate WL survival at 2 and 3 years. As for the short term [2], our WL Cox model results suggest that also in the mid-long term, MELD-Na has the potential to prognostically refine conventional MELD score.

MELD-Na was comparable between both the WL and LT groups of patients, while MELD was significantly different (Table 1). This discrepancy is probably because of the fact that MELD score was used as priority criterion (thus candidates with higher MELD score were selected for LT) while MELD-Na was not used to select patients.

As second point (Figs 1 and 2), in our experience, MELD-Na was proved to be a good predictor of 3-year survival benefit.

However, when pre- and post-LT predictions were combined in the transplant benefit model (Figs 1 and 2), MELD-Na seemed to slightly underestimate the 3-year gain in LE with respect to MELD score. In particular, the threshold value to define LT futile or beneficial was 12 for MELD score and 14 for MELD-Na.

In the original New England Journal of Medicine report [2], the authors stated that their results (the MELD-Na equation) might also be depicted as the additional allocation points a patient would receive for a given MELD score and serum NA concentration. This particular concept of

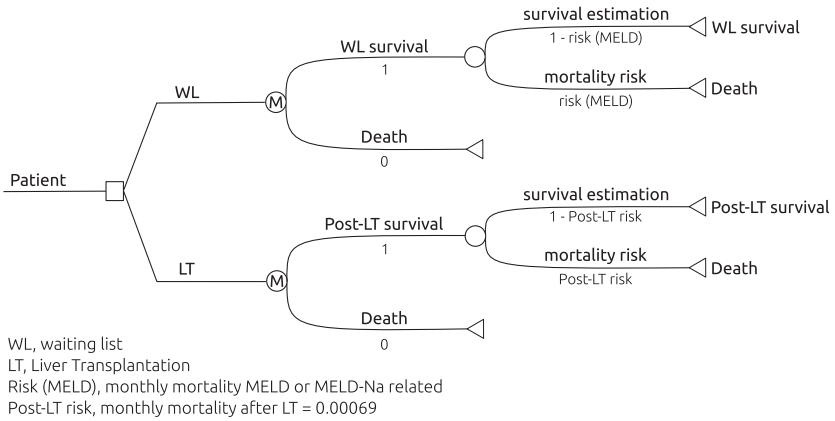

Figure 3 Exemplification of the Markov probability tree used in this study.

MELD adjustment, however, was calculated using as endpoint 3-month WL mortality. The results of our study, on the contrary, showed that MELD-Na adjustment is probably excessive when the endpoint became the 3-year transplant benefit. This means that if we strictly follow an urgency principle to allocate organs, probably we can obtain some advantages in introducing MELD-Na adjustment in our system (to improve our short-term WL survival predictions). On the contrary, if we decide to implement our allocation system according a mid-term transplant benefit principle, we probably don't need to introduce MELD-Na.

As third important point, this is the first study using the CR method to calculate the survival benefit of LT. Standard survival analysis requires that random censoring be noninformative. In the WL scenario, conversely, censoring because of LT is a typical example of informative censoring, because organs are usually assigned to patients at higher risk of dropout from the WL.

A survival analysis of WL patients taking into account that informative censoring was performed by Schaubel *et al.* [4] when he developed his transplant benefit model. However, Schaubel used the 'inverse probability of censoring weight method' [12] instead of CR method.

We decided to use the competing risk analysis for three main reasons:

1. In our opinion, considering LT as an event that happens in the CR is, probably, the simplest and most effective way to resolve the bias caused by informative censoring.

2. CR analysis has already been used in previous studies thus far to identify variables predicting the risk of dropout [7]. Dropout, however, may be as a result of both patient death while waiting LT or hepatic disease progression beyond listing criteria. This second cause of dropout is particularly important for patients with HCC who form a large proportion of our LT candidates. Survival analysis of patients waiting LT, therefore, may be significantly different from dropout analysis.

3. The 'inverse probability of censoring weight method' is commonly used only when a large sample size is available [12].

As in previous experiences [7], the CR method mitigated the prognostic effect of significant variables with respect to Cox analysis. In particular, the impact of MELD and MELD-Na on survival benefit was significantly lower when CR analysis was used (Fig. 1). Interestingly, the CR study decreased the threshold values for futile LT to six for MELD and nine for MELD-Na. The effect of CR, however, was also more relevant for higher MELD scores (Fig. 2).

From this perspective, the impact of different survival modeling on survival more than the comparison itself between MELD and MELD-NA is the main result of this study. The CR method is the main reason of the low threshold values of MELD and MELD-Na. Another potential explanation is that survival benefit of LT increases as time horizon increases. In other experiences, in fact, MELD values defining 'futile' LT decreased from 15 [5] to 10 [4] when time horizon was prolonged.

These calculated threshold values are probably too low for a clinical use because an exceedingly large proportion of cirrhotic patients, according to this definition, would be eligible for LT. Because of the scarcity of donors, the crux is not to determine above which threshold is transplant benefit positive, but should be to establish the minimal value of benefit acceptable by the transplant community to consider LT beneficial and thus indicated. Based on our previous studies on transplant benefit [13], probably a benefit threshold of 10 months should be used to define a 'futile LT'.

Our study has several limitations. First of all, it is based on a relatively small number of patients from a single Institution. This aspect risks to overestimate the impact of MELD and MELD-Na on survival benefit. As well shown by Schaubel [4], in fact, the impact of different MELD classes on survival benefit is extremely variable and for this reason, other covariates are necessary to improve a clinically useful benefit

score. We are trying to organize a multicenter Italian study on transplant benefit to overcome these concerns.

Secondly, it considered only a limited number of variables in the Cox model to adjust MELD and MELD-Na predictions. While the first is an intrinsic and unchangeable point, the choice to limit the covariates of our models was deliberate. In fact, the aim of this study was not to create a new prognostic score, but to focus the attention on the comparison between MELD and MELD-Na studied in terms of mid-long-term prognostic performance. Thus, we decided to not consider some recipient and donor variables, and similarly we preferred to not consider bilirubin, creatinin, INR, and natremia separately. Moreover, in previous studies [14,15] when the survival benefit analysis was focused on specific variables, the number of covariates added in the final models was limited.

In conclusion, this study shows that MELD-Na score is a good predictor of WL survival and 3-year transplant benefit. However, its prognostic performance on this mid-long-term perspective seems to not justify the implementation of conventional MELD score in assigning priority of patients waiting for LT.

Authorship

AV: designed the study, performed the study, analyzed data, and wrote the paper. AB: performed the study and collected data. MG: collected data. FD: collected data. RRM: analyzed data and wrote the paper. ACF: analyzed data. GZ: performed the study, and collected data. DN: performed the study, and collected data. PB: performed the study, and collected data. PA: performed the study, and collected data. UC: designed the study, performed the study, and analyzed data.

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Appendix

Technical Appendix.

DEALE method

One method for estimating life expectancy (LE) is the declining exponential approximation of LE (DEALE). This is a simple arithmetical approximation of LE available to all physicians that can incorporate survival and health status from diverse sources [11].

The basilar assumption of this method is a logarithmic relationship between survival and LE/mortality rates. In

this article, we used the DEALE formula to convert a single-point survival (3-year survival) into monthly mortality rates. The average monthly mortality rate can be thus calculated using the equation:

$$\mu = -1/t * \ln(S)$$

In which S corresponds to 3-year survival probability (e.g. in our study, 3-year survival probability was 0.78), t corresponds to the number of months and μ is the monthly probability rates. In our specific case:monthly probability rate after LT was – ln (0.78)/36 = 0.0069. Taking an hypothetical average mortality rate μ, LE is as follows:

$$LE = 1/\mu$$

Markov prediction model

The above mentioned DEALE method is a simple method to estimate LE. Life expectancies may also be obtained using a Markov prediction model. 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 (Fig. 3), a time horizon of 36 months and a cycle length of 1 month. The post-transplant monthly mortality rate was assumed as a constant, whereas the WL monthly mortality rate was MELD or MELD-Na dependent on the basis of the results of Cox and CR analyses. The Markov model was thus used to perform a one-way sensitivity analysis linking MELD and MELD-Na values to the survival benefit value (Figs 1 and 2).