TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Dynamic changes in MELD score not only predict survival on the waiting list but also overall survival after liver transplantation

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Keywords
liver transplantation, MELD, post-transplant survival.

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Conflicts of Interests
The authors have declared no conflict of interest.

Received: 16 December 2011
Revision requested: 17 January 2012
Accepted: 4 June 2012
Published online: 9 July 2012

doi:10.1111/j.1432-2277.2012.01519.x

Summary

The predictive value of MELD score for post-transplant survival has been under constant debate since its implementation in 2001. Aim of this study was to assess the impact of alterations in MELD score throughout waiting time (WT) on post-transplant survival. A single-centre retrospective analysis of 1125 consecutive patients listed for liver transplantation between 1997 and 2009 was performed. The impact of MELD score and dynamic changes in MELD score (DeltaMELD), as well as age, sex, year of listing and WT were evaluated on waiting list mortality and post-transplant survival. In this cohort, 539 (60%) patients were transplanted, 223 (25%) died on list and 142 (15%) were removed from the waiting list during WT. One-, three- and five-year survival after liver transplantation were 83%, 78% and 76% respectively. DeltaMELD as a continuous variable proved to be the only significant risk factor for overall survival after liver transplantation (hazard ratio (HR): 1.06, 95% confidence interval (CI) 1.02–1.1, $P = 0.013$). The highest risk of post-transplant death could be defined for patients with a DeltaMELD > 10 (HR: 4.87, 95% CI 2.09–11.35, $P < 0.0001$). In addition, DeltaMELD as well as MELD at listing showed a significant impact on waiting list mortality. DeltaMELD may provide an easy evaluation tool to identify patients on the liver transplant waiting list with a high mortality risk after transplantation in the current setting. Temporarily withholding and re-evaluating these patients might improve overall outcome after liver transplantation.

Introduction

The application of MELD score has come a long way since its initial development to predict 90-day survival in cirrhotic patients undergoing transjugular intrahepatic portosystemic shunt in 2000 [1]. Various previous studies have validated MELD score as a good predictor for mortality in patients with end-stage liver disease [2–4]. Based on these results and the finding that increased waiting time (WT) is not associated with an increased risk of mortality, MELD has been established as the primary liver allocation scheme by the United Network of Organ Sharing (UNOS) in the USA in 2002 [5–7].

In further studies, MELD score was challenged to serve not only as predictor for waiting list mortality but also as indicator for post-transplant survival. Several publications investigated MELD score as predictive factor for post-transplant survival [8–13], reporting controversial and nonconclusive data.

As a consequence, further refinements to MELD score were evaluated taking into account dynamic alterations in disease severity during WT. Controversial results were

reported for waiting list mortality [14,15]. In addition, limited information is available about the influence of MELD changes during WT on post-transplant survival [16–18]. After implementation of MELD allocation in the Eurotransplant area in 2006, discussions on the strength and weaknesses of a MELD-based allocation system have flared up [13,19–21]. In recent literature, there is an ongoing debate on the concept of prioritizing patients with the maximum benefit of available organs [21,22].

The aim of this study was to evaluate the predictive value of MELD score alterations (DeltaMELD) during WT on both waiting list mortality and post-transplant survival.

Methods

A retrospective analysis on all adult patients listed for liver transplantation between 1997 and 2009 at the Department of Transplantation, Medical University of Vienna was performed. Patients listed for retransplantation were not included in this cohort. As weighing of standard exceptions and consequently influencing prioritization of these patients on the waiting list was not topic of this study, exclusively laboratory MELD values were considered for analysis. Consequently, patients listed for acute hepatic failure and malignancy were excluded from analysis.

All data were collected prospectively in the transplant surgery database including standard demographic data, indication for liver transplantation, date of listing, date of transplantation, MELD lab values at time of listing, MELD lab values before transplantation as well as serial MELD lab values every 4 weeks during WT.

MELD scores were calculated using serum bilirubin (mg/dl), serum creatinine (mg/dl) – capped at four if on renal replacement therapy – and INR according to the formula currently in use:

$$\begin{aligned}\text{MELD} = {} & [0.957 \times \ln(\text{creatinine mg/dl}) + 0.378 \\ & \times \ln(\text{bilirubin mg/dl}) + 1.12 \times \ln(\text{INR}) + 0.643] \\ & \times 10(6).\end{aligned}$$

MELD values were truncated at the value of 40. MELDon was defined as MELD score at time of listing. MELDoff was defined as the MELD score at the time of liver transplantation or the last MELD score calculated before death on the waiting list (DOL). DeltaMELD was defined as MELDoff minus MELDon, and used as continuous variable in all calculations.

In addition, a subgroup analysis was performed considering changes in monthly MELD scores. MELD alterations during a 30-day period, regardless of the time lag to transplantation were defined as 30-day DeltaMELD (DeltaMELD30d).

Statistical analysis

Continuous data are given as the median and the interquartile range (IQR, range from the 25th to the 75th percentile) or as mean and standard deviation where applicable. Discrete data are presented as counts and percentages.

In univariate Cox regression analyses, the influence of potential risk factors were calculated. For analysing survival on the waiting list sex, age, year of listing for transplantation, DeltaMELD, MELDon and MELDoff were considered. *P*-values, Hazard ratios (HR) and corresponding 95% confidence intervals were calculated. In the same manner, the influence of sex, age, year of listing for transplantation, DeltaMELD, MELDon and MELDoff as well as DeltaMELD30d and WT were investigated for post-transplant patient survival.

A multiple model for DeltaMELD was calculated, adjusted for age, sex, WT and year of listing. A Kaplan–Meier curve was plotted and the corresponding log rank test was calculated. In addition, a logistic regression analysis was computed to analyse the impact of DeltaMELD as well as age, sex, WT and year of listing on the 1-year survival: Odds ratios, 95% confidence intervals and *P*-values are reported. *P*-values < 0.05 were considered statistically significant. All analyses were performed using the statistical computing environment R version 2.12.0 (http://cran.r-project.org/).

Results

A total of 1125 patients were listed for primary liver transplantation. Twelve patients listed for acute hepatic failure and 209 patients listed for malignancy were excluded from analysis, resulting in a final study cohort of 904 patients (Fig. 1). Standard demographic data for all patients are provided in Table 1.

Waiting list

A total of 142 (15%) listed patients were removed from the waiting list, mainly owing to clinical improvement or stabilization ($n = 99$). Detailed information on reasons for removal is shown in Fig. 1.

A total of 223 (25%) patients died during WT. Mean MELDon was 21 ± 7 and mean MELDoff was 28 ± 10. Mean DeltaMELD was 7.6 ± 9.4. Median time on list was 69 (IQR = 96) days.

In these patients, MELDon ($P < 0.0001$, HR = 1.13, 95% CI: 1.12–1.15) and DeltaMELD ($P < 0.0001$, HR = 1.09, 95% CI: 1.08–1.11) were highly significant for survival on the waiting list. Other statistically significant factors were age ($P = 0.024$, HR = 1.02: 95% CI: 1–1.03),

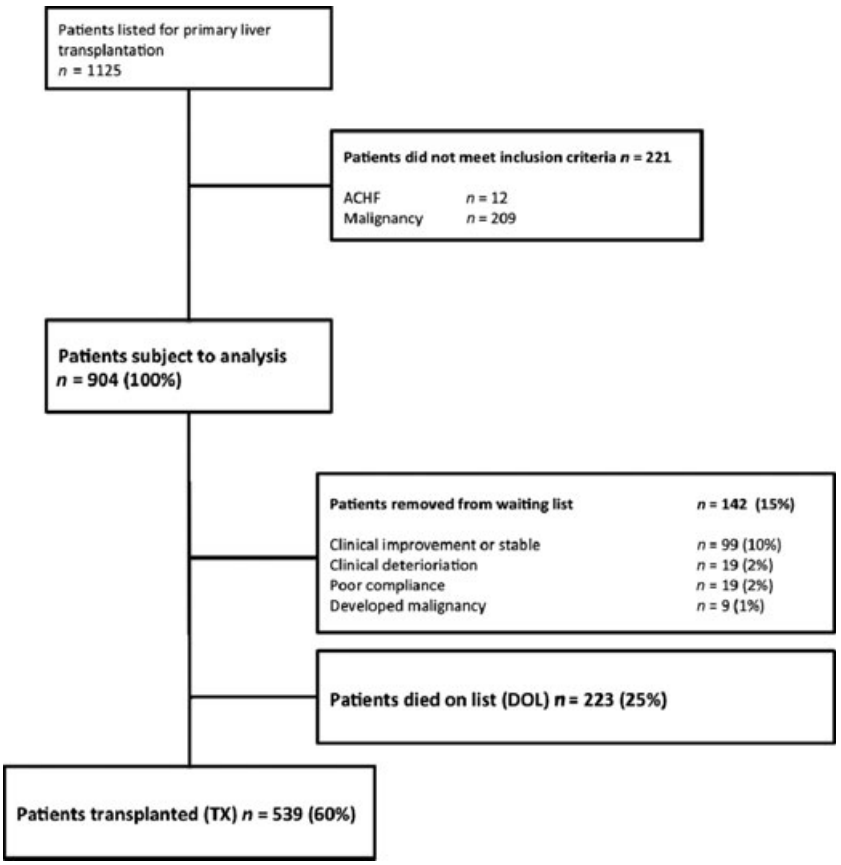

Figure 1 Patient selection flowchart.

sex ($P = 0.018$, HR = 1.37: 95% CI: 1.06–1.78) and year of listing ($P = 0.001$, HR = 0.94: 95% CI: 0.9–0.97).

Survival after liver transplantation

Finally, 539 (60%) of 904 patients were transplanted. The median time on the waiting list (WT) was 112 days (IQR = 175) for patients who received a graft; mean MELDon was 17.5 ± 5, and mean MELDoff was 18.2 ± 6.1. Mean DeltaMELD was 0.7 ± 4.3. Median follow-up after transplantation was 3.6 years (1392 days, IQR = 2327), 108 patients died during follow-up. One-, three- and five-year survival were 83%, 78% and 76% respectively. Causes of death were infection in 36 (33.3%), cardiovascular in 13 (12.1%), respiratory in 8 (7.4%), liver failure in 7 (6.5%), PTLD in 6 (5.6%), gastro intestinal in 5 (4.6%), rejection (acute/chronic) in 4 (3.7%), renal failure in 4 (3.7%), primary nonfunction in 2 (1.8%), other reasons in 8 (7.4%) and unknown reasons in 15 (13.9%) respectively.

In the univariate analysis, DeltaMELD and age were significant for 1-year survival, whereas the only significant risk factor for overall patient survival was DeltaMELD (HR: 1.06, 95% CI: 1.02–1.1, $P = 0.013$). In this cohort,

Table 1. Patient baseline data according to groups.

	LISTED *N* = 904	TX *N* = 539	DOL *N* = 223
Age median (IQR)	54	53 (12)	55 (11)
Sex			
Male *N* (%)	602 (67)	371 (69)	142 (63)
Female *N* (%)	302 (33)	168 (31)	81 (37)
Indication for oLT			
Alcoholic Cirrhosis *N* (%)	424 (47)	241 (45)	111 (50)
Hepatitis C Cirrhosis *N* (%)	194 (21)	122 (23)	42 (19)
Biliary Cirrhosis *N* (%) (Primary, secondary, sclerosing cholangitis)	67 (8)	49 (9)	13 (6)
Cryptogenic Cirrhosis *N* (%)	63 (7)	33 (6)	20 (9)
Hepatitis B Cirrhosis *N* (%)	44 (5)	27 (5)	12 (5)
Autoimmune Cirrhosis *N* (%)	31 (3)	14 (2)	9 (4)
Metabolic disease *N* (%)	10 (1)	7 (1)	3 (1)
Other *N* (%)	71 (8)	46 (9)	13 (6)
MELDon mean (±SD)	18 (±6.2)	17 (±0.2)	21 (±0.5)
MELDoff mean (±SD)	20 (±9.1)	18 (±0.3)	28 (±0.7)
WT median (IQR)	106 (168)	112 (175)	69 (96)

TX, patients transplanted; DOL, died on list; IQR, inner quartile range; oLT, orthotopic liver transplantation; *N*, number; MELDon, MELD score at placement on transplant list; MELDoff, MELD score at time of transplantation or death; WT, waiting time.

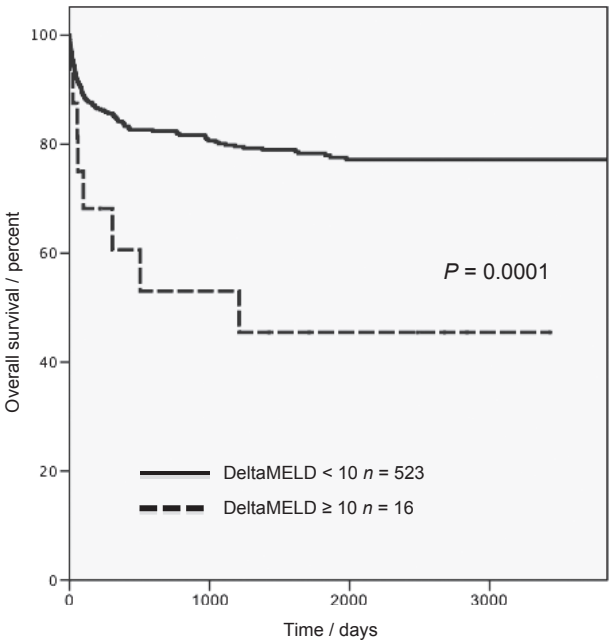

Figure 2 Kaplan–Meier Survival estimated in transplanted patients according to DeltaMELD.

patients with DeltaMELD greater than 10 (DeltaMELD > 10) showed the highest risk for post-transplant mortality (HR: 4.87, 95% CI: 2.09–11.35, $P = 0.0001$). For this cut-off DeltaMELD > 10, a sensitivity of 0.074 and specificity of 0.981 is reported (Fig. 2). Causes of death in this cohort were sepsis in six patients (80%), gastrointestinal bleeding in one patient (10%) and cerebral haemorrhage in one patient (10%).

In addition, there was a trend towards shorter overall survival with higher age ($P = 0.056$). MELD score at listing (MELDon), MELD score at transplantation (MELDoff), year of listing and time on waiting list did not show a significant impact on post-transplant survival (Table 2).

Table 2. Cox regression analysis on overall patient survival after oLT.

Variable	Hazard ratio	Lower CI	Upper CI	*P*-value
Age	1.021	0.999	1.043	0.056
Sex	1.007	0.671	1.512	0.972
DeltaMELD	1.058	1.017	1.100	0.005
DeltaMELD ≥ 10	4.870	2.090	11.347	0.000
MELDon	0.988	0.953	1.025	0.523
MELDoff	1.025	0.995	1.056	0.105
TPL	0.957	0.904	1.013	0.129
WT	1.000	0.999	1.001	0.953

DeltaMELD, continuous score calculated as MELDoff minus MELDon; DeltaMELD ≥ 10, patients with DeltaMELD larger than 10; MELD, Model of end-stage liver disease; MELDon, MELD score at time of listing; MELDoff, MELD score at time of transplantation; TPL, year of placement on the waiting list; WT, waiting time.

Further, multivariate regression analysis of post-transplant survival was performed and DeltaMELD was identified as the only independent risk factor for 1-year ($\beta = 0.074$, $P = 0.005$) and 5-year ($\beta = 0.064$, $P = 0.008$) survival.

Subgroup analysis

Thirty-day intervals

In 174 (19.2%) patients of this cohort, MELD alterations were calculated for 30 days intervals (DeltaMELD30d) during WT. DeltaMELD30d did not show a significant impact on post-transplant survival (HR: 0.98, CI: 0.82–1.17, $P = 0.83$).

Disease aetiology

In patients transplanted for alcoholic cirrhosis ($N = 241$), the predictive value of DeltaMELD was higher when compared with the overall cohort (HR: 1.1 vs. 1.06, $P < 0.00001$). This effect was not seen in patients transplanted for hepatitis C-induced cirrhosis ($n = 122$). (HR: 1.038, $P = 0.36$).

Discussion

This is the first study considering changes of MELD score throughout WT (DeltaMELD) as continuous variable. DeltaMELD was identified as independent predictor for post-transplant survival. The highest risk for post-transplant mortality was seen in patients with a MELD score increase of more than 10 points during WT (DeltaMELD > 10). Furthermore, we identified the MELD score at the time of listing (MELDon) and DeltaMELD as predictors for waiting list mortality.

While MELD score has been implemented for urgency-based organ allocation and validated to prioritize patients with high risk of waiting list mortality [3,11,23], it cannot predict post-transplant survival [10,11,13,24,25]. Therefore, in recent literature, the demand for refinements of the MELD alone concept was postulated, to allocate organs to patients with the greatest benefit from transplantation [19–22].

The evaluation of MELD score changes on waiting list mortality and post-transplant survival has been assessed before [14–18]. Bambha *et al.* [15] evaluated the impact of changes in MELD score on waiting list mortality. DeltaMELD was defined only by the two latest serially available MELD measurements prior to transplantation or death. Whereas WT had no impact on waiting list mortality, DeltaMELD was predictive for death on the waiting list only within 4 days prior to the event. Most interestingly, the more often the score was assessed, the higher was the risk for death on the waiting list. In contrast to

these previously published data, DeltaMELD over WT was a significant predictor for waiting list mortality in our cohort. The reason for these conflicting results concerning DeltaMELD might be caused by different time intervals and different data frequency for calculations. To overcome these issues, we standardized data collection and calculated DeltaMELD from two defined time-points – at time of listing and at the day of transplantation. Furthermore, in previous studies, calculations were performed on cohorts that were not actually listed, allocated and transplanted according to MELD, and therefore might be subject to a selection bias [14,15].

Northup *et al.* performed an UNOS data set analysis evaluating changes in MELD 30 days prior to transplantation. No predictive value for short-term survival after liver transplantation was found [16]. In concordance with Northup *et al.,* a subgroup analysis of our data set revealed no impact on post-transplant survival for changes in MELD 30 days prior to transplantation.

In addition, MELD increase within any 30-day interval during WT had no predictive value on post-transplant survival. It seems that temporary deterioration of disease condition during WT has no influence on post-transplant survival, as long patients recover after these events and stabilize on their base level (listing MELD).

In the current study, changes in MELD score depict the course of disease during the whole WT. Patients who continuously deteriorate during WT by more than 10 points have significantly decreased post-transplant survival rates compared with patients with almost stable courses of disease during WT, independent of their absolute MELD score at time of transplantation (MELD off).

Furthermore, even patients who intermittently deteriorated, but improved clinically during WT showed similar post-transplant outcomes compared with patients with stable courses of disease throughout their WT.

A previous study before MELD score allocation detected DeltaMELD in combination with at least two extended donor criteria as significant risk combination for primary graft dysfunction [18].

There have been numerous attempts to improve prediction of post-transplant survival in patients listed for liver transplantation based on recipient and donor factors [26–28]. These scoring systems rely on a variety of variables and might not be applicable for fast clinical decision-making.

We raise the question, if based on an intention-to-treat approach, temporarily holding patients of the group at highest risk (DeltaMELD > 10) would result in better overall survival after transplantation as the subsequent 'stable' patient will benefit from the available graft. It has to be considered that nearly 40% of patients in the DeltaMELD > 10 group died of infectious complications within 1 year after liver transplantation, compared to 14% in the overall cohort.

Nevertheless, we are aware that these retrospective findings have limitations. The cut-off value of DeltaMELD > 10, even though highly significant, is reflecting only 3% of the patients of this study cohort and might be underpowered. However, we could demonstrate that any point of increase in MELD has a negative effect on post-transplant survival. Another aspect is the relatively high waiting list mortality of nearly 25%. This finding might be biased, as all patients listed for malignancy, were excluded from analysis. Including patients listed for HCC, the overall waiting list mortality decreased below 20%.

In conclusion, our study suggests that DeltaMELD has predictive impact on survival after liver transplantation and might serve as an easily applicable tool for temporarily withholding deteriorating patients and thus allocating available organs to recipients with a higher chance for post-transplant survival.

Authorship

GPG: wrote the paper, collected data. GRS: designed the study, reviewed the manuscript. SZ: performed all statistical analyses. BK and HH: collected data. TS: interpreted data, reviewed the manuscript. RS and FM: reviewed the manuscript. GAB: supervised the study.

Funding

The authors have declared no funding.

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