Title page

Title: MELD Score Measured Day 10 after Orthotopic Liver Transplantation Predicts Death and Re-transplantation within the First Year

Running headline: Prediction of Outcome after Liver Transplantation

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Abstracts and key words

Abstract

Objective The impact of early allograft dysfunction on the outcome after liver transplantation has yet to be established. We explored the independent predictive value of the Model for End-Stage Liver Disease (MELD) score measured in the post-transplant period on the risk of mortality or re-transplantation. **Material and methods** Retrospective cohort study on adults undergoing orthotopic deceased donor liver transplantation from 2004 to 2014. The MELD score was determined prior to transplantation and daily until 21 days after. The risk of mortality or re-transplantation within the first year was assessed according to quartiles of MELD using unadjusted and adjusted stepwise Cox regression analysis. **Results** We included 374 consecutive liver transplant recipients of whom 60 patients died or were re-transplanted. The pre-transplant MELD score was comparable between patients with good and poor outcome, but from day 1 the MELD score significantly diversified and was higher in the poor outcome group (MELD score quartile 4 versus quartile 1-3 at day 10: HR 5.1, 95% CI: 2.8-9.0). This association remained after adjustment for non-identical blood type, autoimmune liver disease, and hepatocellular carcinoma (adjusted HR 5.3, 95% CI: 2.9-9.5 for MELD scores at day 10). The post-transplant MELD score was not associated with pre-transplant MELD score or the Eurotransplant donor risk index. **Conclusion** Early determination of the MELD score as an indicator of early allograft dysfunction after liver transplantation was a strong independent predictor of mortality or re-transplantation and was not influenced by the quality of the donor, or preoperative recipient risk factors.

Key words:

Liver Transplantation

Postoperative Complications

Mortality

Graft survival

Bilirubin

International Normalized Ratio

Creatinine

Alanine Transaminase

Retrospective Studies

Abbreviations

CI, confidence interval

HR, hazard ratio

INR, international normalized ratio

MELD, Model for End-Stage Liver Disease

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Introduction

Liver transplantation is the best treatment for end-stage liver disease as well as a variety of other liver diseases. The outcome after liver transplantation has improved over time, but in recent years the improvement has stagnated to a graft failure rate of approximately 13% at 1-year and 29% at 5-years (1). An adverse outcome within the first year after liver transplantation is primarily caused by allograft related complications and infections (2). Adverse outcome predicted by early allograft dysfunction has yet to be fully established, identification of prognostic markers would facilitate a more rational risk stratification management.

The Model for End-stage Liver Disease (MELD) score reflects the severity of liver disease and was developed to predict 3-month mortality in patients undergoing trans-jugular intrahepatic portal systemic shunt procedure (3). The MELD score is used as a tool to prioritize patients who await a liver transplantation due to its superiority to other more subjective scoring systems such as the Child-Pugh score and UNOS status (4-6). The pre-transplant MELD score predicts death on the waiting list, but poorly predicts outcome after liver transplantation (6-11). In contrast, the MELD score measured early after liver transplantation, has been found to be a reasonable predictor of 3-month mortality and maybe superior to other prognostic scores, although it remains unknown whether the prognostic value of the MELD score persists if the association is adjusted for known risk-factors of a poor outcome (12-18).

The aim of the study was to investigate the independent predictive ability of the MELD score measured in the early period after liver transplantation on the risk of mortality and re-transplantation within the first year.

Methods

In a retrospective study we included 374 consecutive adult patients who underwent orthotopic liver transplantation in Denmark from brain-dead donors between 1st of January 2004 and 18th September 2014 at Rigshospitalet, Copenhagen University Hospital. The hospital performs between 45 and 55 liver transplants annually and covers the entire Danish population of 5.5 million.

The endpoint, all-cause death or re-transplantation, within the first year was ascertained using the Danish national social security number system on 10th of November 2015 and hence is complete. The underlying cause of death or re-transplantation was established by medical chart review using a coding system developed for transplant recipients (TxCode, unpublished) and reviewed by a senior liver transplant consultant.

All available biochemical tests done as parts of routine care were electronically recorded in a database. The analyses focused on results immediately prior to transplantation and from day 1 to day 21 after transplantation. If biochemical tests were measured more than once a day the median value was used. The MELD score was calculated using the formula: 3.78 ln(serum bilirubin mg/dl) + 11.2 ln(INR) + 9.57 ln(creatinine mg/dl) + 6.43. Creatinine levels were converted to 4 mg/dl, the day after initiation and to three days after the last use of renal or liver replacement therapy if the procedure was done more than once.

Early allograft dysfunction was defined as total bilirubin of ≥171 micromoles/L or INR ≥1.6 at day 7 after liver transplantation, or if plasma alanine aminotransferase > 2000 IU/L within the first 7 days after transplantation (16).

All underlying causes of liver diseases leading to the transplantation were determined, thus patients may have more than one diagnosis. Status on whether the recipient was hospitalized just prior to transplantation was available from 1st of January 2007. Acute rejection was diagnosed according to

Banff criteria and results were extracted from a liver biopsy database established 1st of January 2007 (19). Surgery time, from incision to last suture, was extracted from an electronic surgery booking system from 1st of January 2008.

Donor characteristics were quantified by the EuroTransplant-Donor risk index (20). Gamma-glutamyltransferase was not measured routinely in donors and was left out of the formula. Cold ischemia was defined as the time from infusion of cold storage solution to reperfusion of the allograft. Allocations were defined as: local if recipient lived within the capital region, regional if within other parts of our country, and extraregional if outside Denmark.

The study was approved by the Danish data protection agency and the institutional Ethics Committee (H-4-2013-173) and informed consent was waived.

Statistical analyses

All statistical analyses were done on survival data. Continuous data were reported as median and interquartile range. The kinetics of the MELD score were described prior to transplantation and from day 1 to 21 after transplantation for recipients that remained alive at each of these dates. We tested the impact of MELD score quartile 4 versus quartile 1-3 on mortality or re-transplantation by performing a Cox regression and log-rank test. Kaplan-Meier cumulative survival without re-transplantation was analyzed by stratifying the MELD score in quartiles. Patients entered the statistical analyzes prior to the day the MELD score were calculated.

Univariate Cox regressions were done to establish which background variables were associated with an increased risk of mortality or re-transplantation. All univariate significant variables were entered in a manual stepwise Cox regression, and by each step removing the covariate with the highest P-value

above 0.1. Hospitalization was entered as a dummy variable due to many missing observations. After establishing the final multivariate model we entered following variables separately: acute rejection within day 8-12, operation time, and early allograft dysfunction.

Patients with missing data were excluded from the respective statistical analyses. The P-value was considered significant if ≤ 0.05.

Statistical analyses were consistent when checked using last observation carried forward.

All statistical analyses were done using Stata 13.1 SE (StataCorp LP, College Station, Texas)

Results

A total of 374 recipients were transplanted during the study period, of whom 46 (12%) died and 14 (4%) were re-transplanted within the first year after the transplantation. The median time from transplantation to death or re-transplantation was 83 days (interquartile range: 25-178 days). Follow-up was complete for all recipients.

General characteristics at time of transplantation are described in table 1, overall and after stratification depending on whether the recipients remained alive without a need for transplantation (entitled "good outcome group") as opposed to died or were re-transplanted (entitled "poor outcome group") over the 12 months since transplantation. Poor outcome was independent of the transplant year (hazard ratio 1.0, 95% confidence interval: 0.9-1.1).

Kinetics of the MELD score after transplantation according to clinical outcome

The MELD score was determined daily from the day before the transplantation, and until 21 days after the transplantation, provided that routine biochemical tests were available. In figure 1, the daily levels

are depicted after stratifying the cohort in to the two main outcome groups. Whereas the MELD score was comparable between these groups prior to the transplantation and increased in both groups on day 1 after transplantation, the score thereafter diversified, and was consistently higher throughout the remaining period for those recipients belonging to the poor outcome group.

The prognostic performance of the post-transplant MELD score

The most optimal time of the MELD score to discriminate recipients in the good and poor outcome groups were determined (Figure 2). For this purpose, the patients were divided in quartiles depending on their MELD score on that day. Those in the highest quartile were compared with those in the three lower quartiles. The hazard ratio (HR) for those in the highest MELD score quartile compared with those in the lower three quartiles gradually increased until day 10 (cut-off ≥16.7; unadjusted HR 5.1, 95% confidence interval (CI): 2.8-9.0) with 353 recipients (11 had already died or were re-transplanted and for 10 others no biochemistry results were available; this finding was consistent if last known MELD score for the 10 recipients without day 10 value was carried forward to day 10). On day 10, the risk of poor outcome was markedly higher for recipients with a MELD score in the highest compared to each of the three lower quartiles (figure 3). One year after transplantation the cumulative survival without re-transplantation for recipients with a MELD score in the highest quartile was 68% (95% CI: 57-77%) compared to 92% (95% Cl: 88-95%) for the remaining recipients (log rank: <0.0001).
We determined the levels of the MELD score prior to day 10 according to quartiles of the MELD score at day 10 (Figure 4). The separation between the levels of the score was evident until day 10.

The independent predictive ability of the MELD score on day 10 post-transplant

The following potential confounders determined at or before day 10 post-transplant were found to be associated with a subsequent poor clinical outcome after day 10 in univariate analyses: non-identical blood type, hospitalization prior to transplantation, pre-transplant MELD score, Eurotransplant donor risk index, and underlying autoimmune liver disease, hepatitis C, fulminant hepatic failure, and hepatocellular carcinoma. After a stepwise selection process, the following 4 variables predicted a poor clinical outcome with a P-value less than 0.1 (Table 2): MELD score at day 10 post-transplant, non-identical blood-type, and underlying autoimmune liver disease or hepatocellular carcinoma. The adjusted hazard ratio (highest quartile versus rest of cohort) for the MELD score at day 10 post-transplant was 5.3 (95% CI: 2.9-9.5).

Of note, neither pre-transplant MELD score (unadjusted HR 1.2, 95% CI: 1.1-1.4) nor the Eurotransplant donor risk index (unadjusted HR 1.1, 95% CI: 1.0-1.2) remained significantly associated with clinical outcome in the multivariate analysis: adjusted hazard ratio 1.1 (95% CI: 0.9-1.3) per 5 increase in MELD score and 1.0 (0.9-1.1) per 0.1 increase in Eurotransplant donor risk index). ~~Of note, neither pre-transplant MELD score nor the Eurotransplant donor risk index independently predicted the clinical outcome (adjusted hazard ratio 1.1 (95% CI: 0.9-1.3) per 5 increase in MELD score and 1.0 (0.9-1.1) per 0.1 increase in Eurotransplant donor risk index).~~ Also, neither acute rejection observed before or immediately after day 10 post-transplant (adjusted HR 1.2, 95% CI: 0.4-3.7) nor operation time (HR 1.0 per one hour longer, 95% CI: 0.8-1.2) were independent prognostic indicators.

Comparing MELD score to the early allograft dysfunction definition

Early allograft dysfunction was diagnosed in 71 recipients (20%). For those with early allograft dysfunction the 1-year cumulative survival without re-transplantation was 70% (95% CI: 58-80%)

compared to 90% (95% CI: 86-93%) for patients without this complication. Presence of early allograft dysfunction was inferior to the post-transplant MELD score for predicting a poor outcome (adjusted HR 1.8, 95% CI: 0.9-3.3).

Cause of death and re-transplantation

The underlying causes of death or re-transplantation among the 48 recipients with a MELD score at day 10 post-transplant were diverse, but there was a trend towards many graft and postoperative complications (table 3). The most common cause of this outcome was allograft or surgical complications.

Discussion

A continuously elevated MELD score with a cut-off value of 16.7 at day 10 after liver transplantation was found to be a strong and independent predictor of mortality or re-transplantation within the first year. The most obvious explanation was to assume, that the poorest prognosis and thus a high post-transplant MELD score was found in the sickest patients with a high pre-transplant MELD score, and in recipients who got extended criteria grafts. However, controlling for these and other risk factors of a poor outcome failed to affect the prognostic value of the MELD score at day 10. This indicates that yet unknown underlying causes of graft dysfunction occurs early after liver transplantation, and consequently leads to a worsened long-term prognosis.

The pre-transplant MELD score was to some extent associated with the post-transplant MELD score at day 10 (data not shown), but failed to independently predict mortality or re-transplantation in multivariate analysis. Probably due to the limited application of the pre-transplant MELD score as a predictor of outcome after liver transplantation (6-11).

Pre-transplant prognostic scores to predict post-transplant mortality have been developed, but the only score of clinical value is the Charles comorbidity index (21-23). Early post-transplant prognostic scores are of greater value, and several has previously been evaluated (12, 13, 15-17). The most easily applicable score with a good predictive value is the post-transplant MELD score. Four studies of 149, 161, 279, and 572 transplant recipients with more than 50% occurrence of hepatitis B or C, have investigated the predictive ability of the post-transplant MELD score on 3-month and some even 1-year mortality, and all found higher levels to be associated with poor clinical outcomes (12-15, 18). We evaluated the post-transplant MELD score in a cohort of 374 patients with a high occurrence of autoimmune disease. Initial poor function of the allograft not only increased the risk of a poor outcome in the immediate post-transplant period, but during the entire first year after transplantation.

It is essential to adjust for other risk factors to establish the impact of a new prognostic factor (24). In the largest study, poor outcome patients had significantly higher pre-transplant MELD score, received grafts from older donors, and were likely to have autoimmune disease (15). However, it was not established whether the post-transplant MELD score was an independent predictor of a poor outcome, or was associated with the sickest recipients, and the lowest quality grafts. In contrast to other studies on the post-transplant MELD score, we adjusted for other prognostic factors and found the post-transplant MELD to be a strong independent predictor of mortality or re-transplantation. Non-identical blood type, autoimmune liver disease, and hepatocellular carcinoma had an independent impact on outcome, but did not impair the predictive ability of the post-transplant MELD score. In conclusion, the early post-transplant MELD score does not just reflect other known causes of poor outcome after liver transplantation.

The study did not explain whether the conditions expressed by the post-transplant MELD score were the cause of later increased graft loss, or whether the high post-transplant MELD score reflected one or

more underlying factors responsible for the increased risk of poor outcome. By daily measurements we could identify the period from the 3rd to the 10th postoperative day, to be the more important period, where the MELD score indicated the risk of poor outcome. This was important, for an attempt to identify possible underlying factors, which interestingly were not related to the preoperative condition of the recipient or to the quality of the donor.

To establish these potential underlying factors that are associated with an increased post-transplant MELD score, it is important to understand that the post-transplant MELD score and its components reflect early allograft dysfunction. Both bilirubin and INR directly reflect the liver function. Creatinine does not directly reflect liver function, but can be caused by impaired kidney function due to hepatorenal syndrome. However, creatinine often reflects acute renal failure which is associated with both early allograft dysfunction and an increased risk of an inferior outcome after liver transplantation (25-28). Novel studies are needed to identify the risk factors leading to the early allograft dysfunction expressed by the post-transplant MELD score.

The early post-transplant MELD score has been suggested to be superior to the early allograft dysfunction definition among 579 liver transplant recipients, but without a statistical comparison (15). In our study the post-transplant MELD score was superior to the early allograft dysfunction definition for predicting 1-year mortality or re-transplantation by direct comparison in a multivariate model.

Our study had the obvious limitations of an observational study. This was the first study in which the post-transplant MELD score was adjusted for other prognostic factors of an adverse outcome, but we did not have the possibility to confirm the results in a validation cohort. Our study was sufficient to detect any meaningful impact of the background variables on the post-transplant MELD score. We adjusted for prognostic factors that corresponded partly with those identified in a large European study: fulminant hepatic failure, primary biliary cirrhosis, recipient age, donor age >60 years, compatible and

incompatible donor recipient AB0 blood type, split or reduced grafts, and total ischemia time >13 hours (2). To assess donor quality we used the donor risk index modified to the Eurotransplant region for which high scores are associated with inferior outcome for the recipient, but with a low predictive ability (20, 22, 29, 30). Data were retrospectively collected, but with a low frequency of missing data, for example biochemistry data were only missing for 10 patients (3%) at day 10 after transplantation. The study was underpowered to fully establish the impact of the post-transplant MELD score on 3-month mortality. However, no patients were lost to follow-up. Patients had to survive to the day prior to MELD score measurement to be included in the statistical analysis. However, last observation carried forward showed very similar result.

We recommend validation of our results in an independent and larger cohort (24).

Conclusion

In conclusion, an early continuous elevated post-transplant MELD score was a good and easily applicable tool to predict a high risk of mortality or re-transplantation within the first year of liver transplantation. Interestingly, we found that the post-transplant MELD score cannot be explained by donor quality or known recipient risk factors. The post-transplant MELD score reflected early allograft dysfunction and was superior to the early allograft dysfunction definition. If further validated, the post-transplant MELD score can be used to assess allograft dysfunction and thus optimizing risk stratification management with focus on patients with a high MELD score. An adverse outcome was unlikely for patients with a low MELD score.

The cause of the early allograft dysfunction has yet to be established, but our data suggest that the damage to the liver occurs within the first few days after liver transplantation. Novel studies are needed to establish the cause of the early allograft dysfunction.

Acknowledgements

We would like to thank the MATCH steering committee and the PERSIMUNE executive committee for contributing with data for this study. Furthermore, we thank Jesper Qvist Thomassen from the department of Clinical Biochemistry at Rigshospitalet for extracting biochemical test results and for quality ascertainment of the data. Funding was obtained from the Research council at Rigshospitalet, University of Copenhagen and from the Danish National Research Foundation [grant 126].

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Table 1: Characteristics of the recipients and donors at time of transplantation overall and according to clinical outcome within first year

	All patients (n = 374)	Survivors Good outcome (n = 314)	Death or re-LTx Poor outcome (n = 60)
Age, median years (IQ range)	51 (42-59)	50 (42-58)	56 (47-61)
Male, n (%)	215 (57 %)	178 (57 %)	37 (62 %)
Body mass index[1], median (IQ range)	25 (22-28)	25 (22-28)	25 (23-28)
Bloodtype non-identical, n (%)	46 (12 %)	31 (10 %)	15 (25 %)
Acute rejection[2] from day 8-12, n (%)	30 (11 %)	26 (11 %)	4 (9 %)
Hospitalized pre-transplant[3], n (%)	50 (20 %)	39 (18 %)	11 (28 %)
Pre-transplant MELD[4], n (%)			
<15	180 (48 %)	154 (50 %)	26 (43 %)
15-24.9	130 (35 %)	116 (37 %)	14 (23 %)
25-34.9	29 (8 %)	23 (7 %)	6 (10 %)
≥35	32 (9 %)	18 (6 %)	14 (23 %)
Primary liver disease[5], n (%)			
Alcoholic cirrhosis	75 (20 %)	62 (22 %)	13 (20 %)
Autoimmune liver disease	119 (32 %)	113 (36 %)	6 (10 %)
Hepatitis C	29 (8 %)	20 (6 %)	9 (15 %)

Cryptogenic cirrhosis	30 (8 %)	23 (7 %)	7 (12 %)
Fulminant hepatic failure	47 (13 %)	32 (10 %)	15 (25 %)
Hepatocellular carcinoma	48 (13 %)	35 (11 %)	13 (22 %)
Metabolic liver disease	18 (5 %)	17 (5 %)	1 (2 %)
Other	40 (11 %)	34 (11 %)	6 (10 %)
Prior LTx	10 (3 %)	8 (3 %)	2 (3 %)
Donor			
Age, median years (IQ range)	52 (40-60)	52 (40-60)	54 (44-63)
Cold ischemia time[6], median hours (IQ range)	11 (9-13)	11 (9-13)	11 (10-14.0)
EuroTransplant Donor Risk Index[6], median (IQ range)	1.6 (1.4-1.8)	1.6 (1.3-1.8)	1.7 (1.5-2.0)
Operation time[7], median minutes (IQ range)	6.5 (5.5-7.8)	6.4 (5.6-7.6)	6.7 (5.5-8.4)

[1] Weight was not reported for one patient

[2] A subgroup analysis was performed for patients transplanted after 1st of January 2007 who survived past 8 days, n = 284

[3] A subgroup analysis was done, n = 252

[4] A pre-transplant MELD score just prior to transplantation were not available for 3 patients.

[5] Patients are classified according to all diagnoses, for example hepatitis C and alcoholic cirrhosis.

[6] Cold ischemia times were not available for 5 patients of which 2 patients did not die in close relation to the liver transplant procedure.

[7] A subgroup analysis was done, n=251.

Table 2: The MELD score's independent predictive ability when adjusted for risk factors of death or re-transplantation

Variable	Univariate analysis Hazard ratio (95% CI)	Multivariate analysis Hazard ratio (95% CI)
MELD score day 10 q4 versus q1-3	5.1 (2.8 – 9.0)	5.3 (2.9 - 9.5)
Bloodtype non-identical	3.3 (1.8 – 6.2)	3.0 (1.6 - 5.6)
Autoimmune liver disease	0.3 (0.1 – 0.6)	0.4 (0.2 – 0.9)
Hepatocellular carcinoma	2.1 (1.1 – 4.2)	2.4 (1.2 – 4.9)

The table illustrates the hazard ratio of risk factors for mortality or re-transplantation using a step-wise Cox regression model.

Table 3: Underlying cause of death or re-transplantation stratified by MELD quartiles at day 10

	Number (% of total in column) of recipients that died or were re-transplanted according to quartile of MELD score level at day 10 post-transplant				
	1st	2nd	3rd	4th	**Total**
Postoperative and graft complications[1]	0 (0%)	3 (50%)	7 (88%)	19 (68%)	**29**
Infection and multi-organ dysfunction syndrome[2]	1 (17%)	3 (50%)	0	5 (18%)	**9**
Malignancy[3]	3 (50%)	0	1 (12%)	1 (4%)	**5**
Miscellaneous and unknown[4]	2 (33%)	0	0	3 (11%)	**5**
Total	**6**	**6**	**8**	**28**	**48**

The table describes the underlying cause of death or re-transplantation stratified according to MELD quartile at day 10 post-transplant. Thirty-five patients died. Twelve patients were re-transplanted, all due to graft complications.

[1] Includes a diverse set of complications including arterial thrombosis and stenosis, biliary strictures, entero-entero anastomosis leak surgical hemorrhage, humoral rejection, ATIN, large-for-size syndrome, veno-occlusive disease, and primary poor-function.

[2] Includes *Cytomegalovirus* disease, *Pneumocystis jirovecii* pneumonia, neutropenia related infection, endocarditis, unknown infection, septic shock, and multi-organ dysfunction syndrome of unknown etiology.

[3] Included early hepatocellular carcinoma recurrence, small-celled lung cancer, acute myeloid leukemia, and angiosarcoma from a donor.

[4] Includes stroke, polyneuropathy, overdose of morphine medication, and cardiac arrest of unkown cause.

Figure legends

Figure 1

Median MELD score from prior to 21 days after transplantation according to poor (mortality or re-transplantation) and good outcome (alive without re-transplantation) within first year.

Figure 2

The predictive ability of the daily MELD score was assessed by comparing the hazard of experiencing a subsequent poor outcome for recipients with the highest quartile of the MELD score with the hazard among those in the lower three quartiles.

Figure 3

Time to death or re-transplantation according to MELD quartiles at day 10 post-transplant. Log rank test: $P<0.0001$

Figure 4

MELD score levels from the day before transplantation until day 10 post-transplant by quartiles of the MELD score at day 10 post-transplant.