

Variation of the MELD Score as a Predictor of Death on the Waiting List for Liver Transplantation*

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Abstract

Background. Currently, the most recent MELD score available for each waiting list patient is used to prioritize organs. **Aim.** The aim of our study was to identify the predictive value for death on a waiting list (WL) for the variation of MELD scores at specific time intervals. **Methods.** During 2004-2006, 208 consecutive adult patients were listed for liver transplantation in our Center. To identify the potential predictors of patient death, the univariate and multivariate Cox's proportional hazards regression model was used. To assess the ability of MELD score variation to correctly rank order patients according to risk of death while on the WL, c-statistic was used. **Results.** The 12 months actuarial survival was 81%. MELD score variation in the last three months was found as the only independent predictor of death on our WL ($p=0.03$). The c-statistics for prediction of death on the WL are 0.73 for MELD score at listing, 0.85 for MELD score at last evaluation, 0.62 for MELD variation from inclusion on WL, 0.86 for MELD variation within the last three months. **Conclusion.** Dynamic evaluation of MELD scores with its recalculation within the last three months has the best predictive value for death on the WL.

Key words

Liver transplantation - MELD score - outcome - delta MELD

Introduction

Liver transplantation (LT) represents the only curative therapy for patients with end-stage liver disease, giving

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excellent long-term survival (1). In addition to longer survival, LT recipients are now experiencing improved quality of life, including resumption of active social and professional life, as well as reproductive capacity (2). However, the increasing discrepancy between the number of cirrhotic patients on waiting lists (WL) and the number of available donor livers has a major impact on the WL mortality. A large proportion of cirrhotic patients still die while on the WL because of organ shortage and inaccurate prediction of life expectancy (3-5).

Many prognostic models have been developed in the last two decades to predict mortality in cirrhosis and the variables included in these models are indicators of end-stage liver disease (6-8). Until recently, by far the most frequently used both in clinical practice and in clinical research, is the Child-Pugh score (9, 10). Recently, the model for end stage liver disease (MELD) has replaced the Child-Pugh score in the United States for prioritizing donor liver allocation (11). A recent large systematic review (7) showed that in clinical practice the Child-Pugh score can be currently used in all cirrhotic patients, while the MELD score is more useful in patients with decompensated cirrhosis. The introduction of the MELD system for graft allocation in the United States resulted in a 3.5% reduction in WL mortality while early survival of liver transplant recipients remained unchanged despite the selection of more ill patients for transplantation (12).

Although MELD eliminates subjective assessments and has shown accuracy for outcome prediction in patients with decompensated cirrhosis, it has also several limitations (13, 14). One of the limitations of MELD score is that the components of the MELD score were found to independently and individually predict death on the WL. These laboratory parameters can be influenced by various complications of cirrhosis or other external factors such as nutrition status, medication etc. Another disadvantage of this prognostic model is that some important variables such as portal hypertension are not taken into account. Furthermore, the MELD scoring system can not accurately predict death on the WL in patients with cholestatic liver diseases, as well as in patients with hepatocellular carcinoma.

In addition to the initial MELD score, the changes in MELD score over time (last MELD, delta MELD and cut-off MELD) have been proposed as additional predictive factors for negative outcome (15-17). Huo et al (16) show that delta MELD may be a more accurate predictor of death risk than initial MELD and Child-Pugh score. Another study (17) demonstrated that delta MELD was predictive of mortality in univariate analysis, but less predictive when current MELD was included and not predictive when considered with both current and serial number of MELD scores.

Due to these contradictory results and to the imperfect nature of this prognostic score, the aim of our study was to prospectively analyze the prognostic value of the different MELD variations in comparison with MELD score at the inclusion on the WL, in a program characterized by a long waiting time.

Patients and methods

Waiting list registrants and data collection

A prospective study was conducted gathering data from 208 consecutive adult patients with end-stage liver disease (2B or 3 United Network for Organ Sharing – UNOS – status fulfilling the minimal listing criteria Child-Pugh score of =7; or one of the following complications no matter what the Child Pugh class was: variceal upper digestive bleeding, spontaneous bacterial peritonitis, hepatocellular carcinoma) listed for LT at the referral center between October 2004 and June 2006. All patients had complete data required for MELD calculation in the liver transplantation file. For patients with hepatocellular carcinoma the MELD score was not assigned to be 20 or 24 as proposed by UNOS, but calculated as usual. Survival analysis was conducted in December 2006, 6 months after the inclusion of the last patient. The date of the death while on the WL, the date of the last contact with our center and the date of the LT were registered. Patients transplanted during the study interval and patients still alive at the moment of the survival analysis were considered censored cases.

MELD score calculations

The MELD score was calculated using serum creatinine, bilirubin and the International Normalized (Prothrombin) Ratio (INR) (11) according to the following formula currently in use by UNOS (18): $\text{MELD score} = (9.57 \times \log_e \text{creatinine mg/dl} + 3.78 \times \log_e \text{bilirubin mg/dl} + 11.20 \times \log_e \text{INR} + 6.43)$.

Starting with June 2005, a computerised registry was implemented in order to prospectively register all patients listed for LT in our Center at each subsequent visit and to store in a database all MELD scores for each recalculation and all MELD score components (INR, serum bilirubin and creatinine) for each recalculation, according to currently recommended recalculation intervals (yearly if MELD score is =10, every 90 days if MELD score is between 11 and 18, every 30 days for MELD score between 19-24, every 7 days for MELD =25 according to UNOS status). For patients included on the WL before the introduction of the computerised registry, the MELD data were retrospectively

recorded in the database, although they were gathered prospectively from inclusion of that patient on the WL. The computerised registry has the ability to dynamically sort in real time the WL, showing at any given moment the transplantation priorities according to the current recorded MELD value for each patient.

Using this computerised registry, the MELD score was prospectively calculated for each patient at multiple time points, according to the disease outcome while on the WL for LT, during the study interval (June 2005-June 2006). The computer program was also able to calculate in real time and show for each subject different delta MELDs at every subsequent recalculation, taking into account previous data sets.

This study complies with the standards of Declaration of Helsinki and current ethical guidelines. All patient signed inform consent at inclusion on WL for LT.

Definitions

Initial MELD score is the MELD score calculated at baseline (time of listing).

Current MELD score is the most recent MELD score available for each patient.

The maximal variation of the MELD score was considered as the difference between the lowest and the highest value registered while on the list.

The variation of MELD score in the last three months was defined as the difference between the current MELD score and the MELD score calculated three months ago.

The variation of MELD score from the last recalculation was defined as the difference between the current MELD score and the most recent previous MELD score.

The variation of MELD score from time of listing was calculated as the difference between the current MELD score and the initial MELD score.

For variation of MELD scores the change is preserved: increase in MELD score (deterioration) is positive and decrease in MELD (improvement) is negative variation.

Non-compliant patients were defined as patients who did not comply with the established visits according to the MELD score category.

Statistical analysis

Continuous data were expressed as mean \pm standard deviation (SD). Categorical data were expressed as proportion of the subjects with a specific feature. The survival during follow-up was evaluated using the Kaplan Meier method. To identify potential predictors of patient death, univariate and multivariate Cox's proportional hazards regression models were used. To assess the ability of variation of the MELD score to correctly rank order patients according to risk of death while on the WL, our analysis was performed by measuring the concordance (c-statistic) equivalent to the area under the receiver operating characteristic (ROC) curve. The outcome we assessed was the occurrence of death while waiting on the list. A c-statistic between 0.8 and 0.9 indicated excellent diagnostic accuracy and a parameter with a c-statistic over 0.7 was considered

clinically useful. All tests were two sided and a p value < 0.05 was considered to indicate statistical significance.

Results

Waiting list characteristics

Two hundred and eight patients were listed for LT at our Center between October 2004 and June 2006. Demographic characteristics of the patient population are given in Table I. The vast majority of eligible patients (72.1%) were listed for liver cirrhosis secondary to hepatitis C virus (HCV), hepatitis B virus (HBV) or HBV- hepatitis delta virus (HDV) infection, autoimmune (6.2%) and cholestatic (4.4%) and alcoholic liver diseases (9.1%). Thirteen patients had associated hepatocellular carcinoma within Milan criteria.

Table I Characteristics of candidates on the liver transplant waiting list at Gastroenterology and Hepatology Center, Fundeni Clinical Institute

Variable	No. (%) patients
No (%) patients according to blood type	
Blood type O	64 (30.7%)
Blood type A	97 (46.6%)
Blood type B	33 (15.8%)
Blood type AB	14 (6.9%)
Mean age (\pm SD) (years)	44.8 \pm 10.9
Gender (%males)	124 (59.6%)
Underlying liver disease (%)	
Viral hepatitis	150 (72.1%)
Cholestatic liver diseases	9 (4.4%)
Autoimmune diseases	13 (6.2%)
Alcoholic liver disease	19 (9.1%)
Other (Wilson disease, Caroli disease, secondary biliary cirrhosis)	17 (8.2%)
Patients non-compliant for visits according to MELD score (%)	42 (20.1%)

The 208 study subjects generated 535 sets of concurrent laboratory data for recalculation of MELD score, with a mean of 2.5 ± 1.9 MELD score determinations per patient. The majority of the patients on the WL were status UNOS 2B and 3 with a mean Child-Pugh score of 7.2 ± 2.6 at listing and a mean MELD score at first evaluation of 13.2 ± 5.1 . The mean waiting time was 23.1 ± 7.5 months. Forty two (20.2%) patients died while on the waiting list for LT and 11 patients were transplanted during this time interval. One of the transplanted patients had hepatocellular carcinoma. The mean MELD score at transplantation was 17.3 ± 2.1 . Five patients were temporarily removed from the WL due to improvement: two patients had alcoholic liver disease and three patients had Wilson disease.

Progression of the severity of liver disease for patient while on the WL for LT

The distribution of patients according to the severity group of MELD score at listing and at last contact differs significantly ($p < 0.001$), illustrating globally the dynamics of the WL (Table II). Patients with an initial MELD score between 11-18 remained in the same category also at the

last evaluation in proportion of approximately 75%, while 11.7% of patients had an improvement of the MELD scores. Patients included in the severity category of 19-24 had a favorable evolution in 26.7% of cases, while 23.3% had a progression of the severity of liver disease. Patients in the most severe disease category, with a MELD score >25 at time of listing, regressed by adequate therapy in a lower severity category in 33.3% of cases. From all 208 patients, 40.5% of the entire population had elevation in the MELD score while on the WL, 34.7% remained stable and 24.8% improved until the end of follow-up period.

Table II Distribution of patients on the WL for LT according to MELD score severity categories at baseline (inclusion on the WL) and at last evaluation on the WL

MELD score at last recalculation	Baseline MELD score			
	< 10	11-18	19-24	>25
< 10	80.4%	11.7%	6.7%	0%
11-18	17.6%	75%	20%	16.7%
19-24	0%	5.8%	50%	16.7%
>25	2%	7.5%	23.3%	66.6%

Survival analysis

The actuarial survival rate at 12 and 24 months was 81% and 74%, respectively (Fig.1). Median survival was not reached during the follow-up. The mean follow-up interval was 14.2 months.

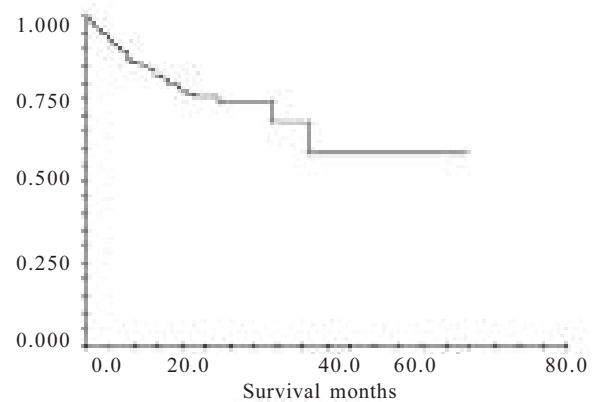


Fig.1 Kaplan Meier survival curve for patients included on waiting list for liver transplantation.

The initial MELD score, its components and its variations during certain time intervals, were evaluated as potential predictors of death while on the WL using univariate Cox regression analysis. The results of the analysis are shown in Table III. All analysed variables including the MELD score, its components (with the exception of serum creatinine at baseline) and variations are highly predictive for death on the WL. In the multivariate survival analysis performed by Cox Proportional Hazards Model, however, only MELD score variation in the last 3 months was found as independent predictor of death on our WL ($p = 0.03$, HR = 1.14).

MELD score and its variations during certain time intervals were investigated as predictors of death on the

WL based on the c-statistic (ROC curve). The highest c-statistic value (0.86) was obtained for the MELD score variation in the last three months, which proved to be an excellent predictor of death on our WL (Fig.2), as well as current MELD score (c-statistic=0.85). Initial MELD score with a c-statistic of 0.73 may be of less clinical use, especially in our program with a long waiting time on the WL. Maximal MELD score variation (0.68), MELD score variation from time of listing (0.62) and MELD score variation from the last recalculation (0.56) were found to have no clinical usefulness in predicting death on our WL.

Table III Univariate survival Cox model. Predictors of death while on the waiting list for liver transplantation

Variable	Regression coefficient	Hazards ratio(HR)	95% CI for HR	p value
INR at time of listing	1.22	3.39	1.74-6.57	0.0002
Serum bilirubin at time of listing	0.15	1.17	1.09-1.25	< 0.0001
Serum creatinine at time of listing	0.22	1.24	-	0.1879
Initial MELD score	0.15	1.16	1.1-1.23	< 0.0001
Current MELD score	0.11	1.12	1.09-1.15	< 0.0001
Maximal MELD score variation	0.08	1.09	1.05-1.13	< 0.0001
INR variation in the last 3 months	1.15	3.15	1.8-5.5	< 0.0001
Serum bilirubin variation in the last 3 months	0.11	1.12	1.05-1.13	0.0001
Serum creatinine variation in the last 3 months	0.67	1.95	1.4-2.7	< 0.0001
MELD score variation in the last 3 months	0.13	1.14	1.08-1.2	< 0.0001
MELD score variation from the last recalculation	0.14	1.15	1.06-1.24	0.0002
MELD score variation from time of listing	0.13	1.13	1.07-1.2	< 0.0001

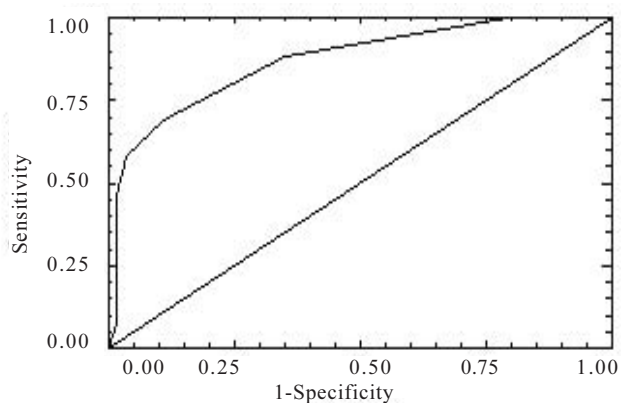


Fig.2 Area under receiver operating curve for MELD score variation in the last 3 months as predictor of death within 12 months while on the waiting list for liver transplantation (c-statistic = 0.86).

Discussion

LT has been recognized as an effective procedure of restoring health in patients who have progressive and irreversible liver injury (19). Disease severity at the time of listing has been demonstrated as an important predictor of WL death (20).

Prognostic evaluation of patients with liver cirrhosis is an important topic often challenging the clinician. The Child-Pugh score (9, 10) is by far the most largely used both in clinical practice and clinical research and has stood the test of time for nearly 40 years. Recently, MELD has replaced the Child-Pugh score in the United States for prioritizing liver donor allocation (11, 12).

According to the current UNOS policy, the most recent MELD score available is used to prioritize donor organ allocation for patients with end-stage liver disease awaiting LT (18). MELD was proven as an objective, reliable and clinically useful model for assessing disease severity and predicting survival in patients with chronic liver disease (21). There is abundant evidence suggesting that the MELD allocation system improved the outcome of patients with or without hepatocellular carcinoma on the list (22-24). As we have previously demonstrated (25), the MELD score was found to be an excellent predictor of death (c-statistic = 0.84) within 12 months on our WL, characterized by a long waiting time. Our results were in concordance with other studies (18, 23) indicating that the MELD system is better than the Child-Pugh system in predicting both 6 and 12 months mortality. In the present study we found a lower c-statistic (0.73) for the MELD score at listing for prediction of death on the waiting list. This finding can be explained by the lower mean MELD score at inclusion on the WL of 13.2 ± 5.1 in the present study compared to 17.09 ± 6.6 in our previous paper (25).

However, as any predictive score, MELD has been useful in stimulating a resurgence of interest in assessing prognosis in cirrhosis (26), but a recent review (27) demonstrates that it is imperfect and it has raised several concerns such as lack of intra- and inter-individual variation (28). Our study tried to address these concerns.

In the present study we confirmed the prognostic ability and accuracy of the current MELD score. Because the MELD scoring system was proved to be correlated with the degree of functional impairment (23), this result is logical. Facing the severe shortage of cadaveric organ donors in Romania (29) leading, in turn, to a long waiting time list (mean waiting time of 22 months) (30) there is a critical need for better predictors to allow us to select more accurately the most unwell patients for allocation of livers from deceased organ donors.

Delta MELD (Δ MELD) measures the dynamic change of residual liver function over time. Increasing delta MELD was proved to have a high predictive accuracy and may be superior to initial MELD in assessing the outcome. This is in line with our findings showing a lower predictive value for the initial MELD score for death on the WL. Serial

determination of MELD score provides updated information of disease severity that could alter the ranking status in patients awaiting transplantation. A negative direction of Δ MELD probably indicates correction of a reversible factor and is likely to predict a subsequent lower risk of mortality. These situations were encountered in our study in 11.7% of patients in the group with MELD score <18 , in 26.7% of patients in the group with MELD between 19-24 and in 33.3% of patients in the group with MELD >25 . The fact that the group with the most severe MELD scores had the highest proportion of patients with improvement in MELD shows that adequate therapy of certain complications of cirrhosis can control the negative evolution of the patient. There is a need for a prognostic factor other than the current MELD to better identify the patients most likely to have the worst prognosis, although current MELD score proved to be useful for predicting mortality also on our long WL (c-statistic = 0.85).

Merion et al (31) have further suggested in a retrospective evaluation of 760 patients, that the change in MELD score while waiting is a better predictor for mortality on WL than the absolute score at listing. For a given score, a more important predictor of WL mortality maybe the magnitude and direction of change during the previous 30 days. Patients with a positive Δ MELD > 5 during a 30-day period had more than a threefold greater waitlist mortality risk than patients for whom MELD scores increased more gradually. This was the first study to show that repeated MELD scores over time are a significantly better predictor of WL mortality than WL status level or baseline MELD scores. Each point of the 40-point MELD score was proved to be associated with a 22% increased risk for WL death. In comparison, in our study, a prospective one in which MELD-based system was used for organ allocation, the variation of MELD score in the last three months proved to be the best predictor of death while on the WL (c-statistic=0.86). This most likely reflected intrinsic decompensation of pre-existing liver disease rather than an acute superimposed event such as infection or bleeding causing further liver decompensation, which can be controlled by treatment during one month. Also patients within terminal phase who can have daily changes of the MELD scores, with high delta MELD within one month can alter the results of the Merion's study (31) and in this case the utility for organ allocation is extremely low because these patients are too ill to be transplanted anymore.

In contrast, the study of Bambha et al (17), another retrospective study, suggests that the predictive value of delta MELD is limited and that is premature to use it in the organ allocation decision, current MELD still being the most significant parameter predictive of mortality on the liver transplant waiting list. A bias factor influencing this result is the high proportion of cholestatic liver diseases (35%) in which MELD score has a low value in comparison to our study where this subgroup of patients is low (4.4%).

Our prospective analyses can help to better choose between patients with similar current MELD scores when a

liver became available, especially in the case of WL with long waiting time. Further prospective studies, maybe incorporating Δ MELD as another component of a modified MELD score, are required.

A limitation of our study is the small number of transplanted patients within the study period, making difficult the extrapolation of our findings in other transplant programs with a faster dynamic of the WL. Anyway, the majority of the LT programs have a waiting time of at least 6 months and the discrepancy between the number of waiting patients and the number of available organs remains an important issue in the vast majority of them. Thus, the variation of MELD score in the last three months can be a useful tool also in this type of LT programs.

In conclusion, the variation of MELD score during the last three months is superior to initial (baseline) MELD, to MELD score variation from time of listing, to maximal MELD variation and to MELD score variation from the last recalculation in predicting the negative outcome. It therefore should be strongly considered along with current MELD as an additional prognostic predictor for patients with end-stage liver disease awaiting LT, especially programs with a long waiting time.

Conflicts of interest

There are no conflicts of interest.

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