CLINICAL SCIENCE

Impact of MELD allocation policy on survival outcomes after liver transplantation: a single-center study in northeast Brazil

Thales Paulo Batista, Bernardo David Sabat, Paulo Sérgio V. Melo, Luiz Eduardo C. Miranda, Olival Cirilo L. Fonseca-Neto, Américo Gusmão Amorim, Cláudio Moura Lacerda

Department of Surgery and Liver Transplantation, Oswaldo Cruz University Hospital, University of Pernambuco, Recife/PE, Brazil.

OBJECTIVE: To analyze the impact of model for end-stage liver disease (MELD) allocation policy on survival outcomes after liver transplantation (LT).

INTRODUCTION: Considering that an ideal system of grafts allocation should also ensure improved survival after transplantation, changes in allocation policies need to be evaluated in different contexts as an evolutionary process.

METHODS: A retrospective cohort study was carried out among patients who underwent LT at the University of Pernambuco. Two groups of patients transplanted before and after the MELD allocation policy implementation were identified and compared using early postoperative mortality and post-LT survival as end-points.

RESULTS: Overall, early postoperative mortality did not significantly differ between cohorts (16.43% vs. 8.14%; p = 0.112). Although at 6 and 36-months the difference between pre- vs. post-MELD survival was only marginally significant (p = 0.066 and p = 0.063; respectively), better short, medium and long-term post-LT survival were observed in the post-MELD period. Subgroups analysis showed special benefits to patients categorized as non-hepatocellular carcinoma (non-HCC) and moderate risk, as determined by MELD score (15-20).

DISCUSSION: This study ensured a more robust estimate of how the MELD policy affected post-LT survival outcomes in Brazil and was the first to show significantly better survival after this new policy was implemented. Additionally, we explored some potential reasons for our divergent survival outcomes.

CONCLUSION: Better survival outcomes were observed in this study after implementation of the MELD criterion, particularly amongst patients categorized as non-HCC and moderate risk by MELD scoring. Governmental involvement in organ transplantation was possibly the main reason for improved survival.

KEYWORDS: Organ transplantation; Survival analysis; Mortality; Government regulation; Liver grafts.

INTRODUCTION

Initially described by Malinchoc et al.[1] as a mathematical model for predicting survival in the first three months postoperatively for patients who underwent percutaneous placement of transjugular intrahepatic porto-systemic shunt (TIPS), the model for end-stage liver disease (MELD) score was quickly validated as a predictor of mortality for a wide variety of liver diseases,[2-4] including cirrhotic patients awaiting liver transplantation (LT).[5-8]

Afterwards, to reduce mortality amongst patients on the waiting list[9,10] and to eliminate possible confounding factors, the MELD criterion was incorporated as a more transparent and objective system, based on easily measurable laboratory tests.[11-13] The implementation of this model was based on the recognition that time on the list was an inadequate criterion for prioritizing candidates for LT, since it had little relationship to mortality in these patients.[12,13]

Therefore, considering that an ideal system of graft allocation should ensure the best use of available livers for mortality reduction amongst patients on waiting lists and improvement of survival after transplantation,[5] changes in allocation policies need to be evaluated in different contexts over time. In addition, as the MELD criterion has only recently been implemented in Brazil (2006), only medium-term post-transplant survivals could be compared with those observed in the period before its introduction.[14]

Impact of MELD on post-transplantation survival
Batista TP et al.

CLINICS 2011;66(1):57-64

This current study describes a Brazilian single-center experience and provides a comparison between pre- vs. post-MELD cohorts to analyze the impact of MELD allocation policy on survival outcomes after LT at the Department of Surgery and Liver Transplantation of the Oswaldo Cruz University Hospital (HUOC), University of Pernambuco.

MATERIALS AND METHODS

Study Population and Data Collection

A retrospective cohort study was carried out on patients transplanted by the Department of General Surgery and Liver Transplantation of the Oswaldo Cruz University Hospital, University of Pernambuco, from July 15, 2003 to July 14, 2009. Using our own database, two groups of patients transplanted before and after MELD allocation policy implementation were identified: pre-MELD group—those undergoing LT from July 15, 2003 to July 14, 2006 (n = 113); and Post-MELD group—those undergoing LT between July 15, 2006 and July 14, 2009 (n = 185).

The same surgical team performed all procedures using standard technique without veno-venous bypass and with conventional or *piggyback* hepato-venous reconstruction. After LT, tacrolimus, mycophenolate (sodium or mofetil) and prednisone were used as immunosuppressive treatment, with no changes in the protocols applied from 2003 to 2009. All patients were followed for at least one year in order to determine the primary endpoint (death).

We limited our study to adults and adolescent patients (>16 years) who received deceased donor orthotopic LT. For patients who had undergone re-transplantations, data were collected from the first procedure only and recipients of *split-liver* or sequential (*domino*) transplants were not eligible for this study. We also excluded patients transplanted as a result of fulminant hepatic failure, as well as patients with incomplete data in their medical records.

Variables and Outcomes

Descriptive statistics include donor and recipient ages, cold (CIT) and warm ischemia times (WIT), amounts of red blood cells (RBC) and platelets transfused at the surgery, MELD score and monthly transplant rates as continuous variables. As categorical variables, Child-Pugh classing, ABO blood grouping, pre-transplant diagnosis, recipient gender and hepato-venous reconstruction type were studied.

Two different survival outcomes were compared between pre- vs. post-MELD groups: early postoperative mortality and patient post-LT survival. Early postoperative mortality rates were defined as the proportion of deaths in the first 30 days after LT. Patient survival, as a function of time after transplantation until the date of death or end of the study, was explored as short- (3 and 6 months), medium- (1 year) and long-term (3 years) outcomes. Data on deaths not related to liver disease or transplant procedure, and data on those patients alive at the end of the study, were ''censored'' for cumulative survival estimation.

MELD score was calculated using laboratory results collected immediately prior to the LT[15] with no adjustments for malignancy or other ''special'' conditions used to prioritize these patients on the waiting list.[16] Serum markers were used to confirm viral hepatitis diagnosis. The pre-operative diagnosis of hepatocellular carcinoma (HCC) was based on the Barcelona-2000 conference diagnostic criteria[17] and confirmed by explant pathology. The Milan criteria were applied as a basis for selecting patients with HCC for LT.

Sample Characteristics

Our group performed 298 LTs in 288 patients during the period described earlier. Eighty patients were not eligible or excluded from this study, and 208 patients were included in the analysis (pre-MELD = 73 vs. post-MELD = 135). Patient characteristics, as well as transplant Center and donor variables, are summarized in Table 1. Seventy-seven percent of HCC patients had other associated diagnoses, among which viral C hepatitis was the most common disease (52.45%).

Follow-up data were available for the entire study group (n = 208). Over the 82.6 month follow-up period, 68 liver allograft recipients died (36.7%) and 7 (3.4%) underwent re-transplantations. The main causes of death were infection, malignancy recurrence and liver failure/transplant rejection.

Analytic Approach

The statistical analyses were performed using the STATISTICA Data Analysis Software System, Version 8.0 (Statsoft, Inc., Tulsa, OK, USA), and all analyses considered a two-tailed p-value of 0.05 as statistically significant. Normal distribution was not proven for the clinical variables available (Kolmogorov–Smirnov test, $p < 0.05$); then, nonparametric tests were applied to all data analysis. For descriptive analyses, we summarized the continuous variables using medians (interquartile range) and categorical variables as proportions.

Comparisons between pre- vs. post-MELD groups were conducted using the Mann-Whitney U-test for continuous variables and chi-square tests for categorical variables, including Yates's correction or Fischer's exact test as appropriate. Rates of postoperative early mortality were compared using chi-square tests and survival probabilities were constructed using Kaplan–Meier survival estimates and compared using the log-rank test.

Furthermore, as a result of the introduction of the MELD allocation policy to prioritize the sickest patients and the well-known increase in the rates of LT for HCC in the post-MELD era,[10-12,14,18-24] we also stratified the patients according to MELD score and diagnosis, in order to control for these variables. Patients were stratified according to MELD score to low-risk (<15), medium-risk (15–20) or high-risk (>20) categories.[9] According to diagnosis, these patients were stratified as HCC or non-HCC.

Additionally, we explored some potential reasons for divergent survival outcomes after implementation of the MELD-based policy, using a cross-sectional strategy. For this analysis, we applied c-statistic, univariate and multivariate analyses to check our hypothesis, as described below.

The prognostic value of MELD score in predicting post-LT survival was assessed using receiver operating characteristic (ROC) curve analysis. The c-statistic, equivalent to the area under the ROC curve (AUC), was adopted to establish the overall diagnostic accuracy of the MELD score. Usually, AUC between 0.8 and 0.9 indicates excellent diagnostic accuracy; a score with an AUC>0.7 should be

CLINICS 2011;66(1):57-64

Impact of MELD on post-transplantation survival
Batista TP et al.

Table 1 - Descriptive statistics of measured variables.

Variables	Overall Median (interquartile range) or n (%)	Study Cohorts Median (interquartile range) or n (%)		
		Pre-MELD	Post-MELD	p-value[1]
Recipient variables				
Recipient age (years)	54 (44.5-60.5)	52 (45-59)	55 (44-61)	0.207
MELD Score	15 (12-19)	15 (12-17)	15 (12-20)	0.073
HCC	13 (10-15)	13 (12-16)	13 (10-15)	0.501
Non-HCC	17 (13-20)	15 (11-17)	18.5 (14-21.5)	<0.001
Gender				0.858
Male	137 (65.86)	47 (64.38)	90 (66.66)	
Female	71 (34.13)	26 (35.61)	45 (33.33)	
ABO blood group				0.953
A	84 (40.38)	32 (43.83)	52 (38.51)	
B	24 (11.53)	7 (9.58)	17 (12.59)	
AB	11 (5.28)	2 (2.73)	9 (6.66)	
O	89 (42.78)	32 (43.83)	57 (42.22)	
Child-Pugh class				0.926
A	53 (25.48)	17 (23.28)	36 (26.66)	
B	94 (45.19)	37 (50.68)	57 (42.22)	
C	61 (29.32)	19 (26.02)	42 (31.11)	
Diagnosis[2]				
Chronic viral hepatitis	86 (41.34)	32 (43.83)	54 (40)	0.697
HCC	61 (29.32)	10 (13.69)	51 (37.77)	<0.001
Alcoholic cirrhosis	53 (25.48)	21 (28.76)	32 (23.70)	0.526
Cryptogenic cirrhosis	25 (12.01)	10 (1.36)	15 (11.11)	0.745
Autoimmune chronic Hepatitis	13 (6.25)	6 (2.88)	7 (5.18)	0.385
Cholestatic liver Disease[3]	11 (5.28)	3 (1.44)	8 (5.92)	0.750
Miscellaneous	51 (24.51)	16 (21.91)	35 (25.92)	0.636
Donor and center variables				
Monthly transplant rate	6 (4-8)	4 (3-6)	6 (5-8)	<0.001
Donor age (years)	40.5 (25.5-51)	42 (26-51)	39 (25-51)	0.974
Cold ischemia time (hours)	6.8 (5.4-8.7)	7 (5.6-8.6)	6.6 (5.4-8.7)	0.533
Warm ischemia time (minutes)	47.5 (40-55)	55 (45-60)	45 (37-51)	<0.001
Red blood cells Transfusion (units)	3 (1-5)	3 (2-5)	3 (1-5)	0.626
Platelets transfusion (units)	0 (0-9)	0 (0-7)	0 (0-10)	0.666
Hepato-venous reconstruction				0.039
Conventional	127 (61.06)	52 (71.23)	75 (55.56)	
Piggyback	81 (38.94)	21 (28.77)	60 (44.44)	

[1]Comparisons between Pre- vs. Post-MELD cohorts using the Mann-Whitney U-test for continuous variables or chi-square tests for categorical variables
[2]Categories were not mutually exclusive, so multiple diagnoses were possible.
[3]Primary biliary cirrhosis and primary sclerosing cholangitis.
MELD = model for end-stage liver disease; HCC = hepatocellular carcinoma; non-HCC = non-hepatocellular carcinoma.

considered clinically useful and AUC ≤ 0.5 is considered to be indicative of a lack of discriminating power.[9,25,26]

The association of each demographic variable with long-term post-LT survival was also tested using the log-rank test in a univariate analysis. For this approach, we categorized the continuous variables using current cut-off points.[9,21,27-31] Then, factors whose association with survival showed a p-value <0.20 were used in a multivariate Cox's proportional-hazards model to identify the independent predictors. We also adjusted this multivariate analysis for transplantation era (first vs. second transplantation era) and allocation criterion (pre- vs. post-MELD).

Finally, we explored survival in consecutive transplantations eras using the Kaplan-Meier method and the log-rank test. As follow-up of patients who have recently undergone transplantation is often small, we limited this study to a one-year analysis of four successive transplantation periods (quartiles) and to a two-year analysis of two successive transplantation eras. The significant variables highlighted in the previous multivariate analysis were also compared among the transplantation quartiles using the Kruskal-Wallis test.

Ethical Comments

This study was registered in the Brazilian National System of Human Research – SISNEP (CAAE - 0003.0.106. 000/10) and approved by the HUOC Ethics Research Committee (protocol number 12/2010). All procedures complied with the standards of the Declaration of Helsinki and current ethical guidelines.

RESULTS

As summarized in Table 1, a statistically significant increase in monthly transplant rates (p<0.001), proportion of HCC patients (p<0.001) and use of the *piggyback* hepato-venous technique (p = 0.039) were found in the post-MELD cohort. A significant reduction of WIT was also observed after implementation of the MELD criterion (p<0.001) and the overall median MELD score remained unchanged after its introduction (p<0.073). In the HCC sub-group, this score was lower than among non-HCC patients (p<0.001) and displayed no change during the post-MELD era (p = 0.501). On the other hand, the median MELD score rose 3.5 points in this period in the non-HCC sub-group (p<0.001).

Impact of MELD on post-transplantation survival
Batista TP et al.

CLINICS 2011;66(1):57-64

Table 2 - Early postoperative mortality rates.

Mortality Rates	n (%)	Study Cohorts n (%)		
		Pre-MELD	Post-MELD	p-value[1]
Overall	23 (11.05)	12 (16.43)	11 (8.14)	0.112
Diagnostic Categories				
HCC	5 (8.19)	0 (0)	5 (9.80)	0.579
Non-HCC	18 (12.24)	12 (19.04)	6 (7.14)	0.054
p-value[2]	0.545			
MELD Score Risk Categories				
MELD <15	9 (9.67)	5 (14.28)	4 (6.89)	0.289
MELD 15-20	10 (12.82)	7 (23.33)	3 (6.25)	0.039
MELD >20	4 (10.81)	0 (0)	4 (13.79)	0.557
p-value[2]	0.994			

[1]Comparison between Pre vs. Post-MELD cohorts using chi-square tests.
[2]Inter-group comparisons were performed using the chi-square test.
MELD = model for end-stage liver disease; HCC = hepatocellular carcinoma; non-HCC = non-hepatocellular carcinoma.

The overall early postoperative mortality was 11.05% and showed no statistical difference between the cohorts (16.43% vs. 8.14%; p = 0.112). Similarly, the inter-group study showed no statistical difference between patients categorized according to diagnosis (p = 0.545) or MELD score (p = 0.994). However, the subgroups analysis showed a statistically significant reduction in mortality rate after introduction of the MELD criterion in the patients categorized as moderate-risk by MELD score (p = 0.039). We also found a borderline statistical significance in the non-HCC subgroup (p = 0.054) (Table 2).

Patients 3, 6, 12 and 36-months overall cumulative survivals were 85.1, 79.3, 74.5 and 67.5%, respectively. Although the difference between pre- vs. post-MELD survival rates was sometimes only marginally significant, better rates of post-LT survival were observed in the post-MELD era (Figure 1). The inter-group analysis showed no statistical

difference in survival amongst patients stratified according to diagnosis or MELD score (Figure 2), but statistically higher cumulative survivals were found in the sub-group analysis of non-HCC and moderate-risk MELD score categories in the post-MELD period (Table 3).

According to c-statistic, the accuracy of preoperative MELD score in predicting post-LT survival was 0.526, 0.524, 0.5 and 0.519, at 3, 6, 12 and 36-months, respectively. After univariate and multivariate analyses, only transfusion of RBC (≥5 units) was an independent predictor of poorer 3-year post-LT survival, although differences in CIT (≥12 hours) were also of borderline statistical significance. These findings remained unchanged after adjustment for transplantation era and allocation criterion (Table 4).

The patients transplanted with *piggyback* hepato-venous anastomosis presented significantly better post-LT survival in the univariate analysis (60.44% vs. 79.15%. p = 0.006); however, this statistical significance was lost in the multivariate analysis. This technique was also associated with lower RBC transfusion and WIT (p = 0.032 and p<0.001, respectively).

We found increased survival from first to fourth transplantation quartiles in a one-year survival analysis (61.5% vs. 73.1% vs. 75% vs. 88.5%, respectively. p = 0.027), as well as in the first vs. second transplantation era, as determined using two-year survival as an end-point (62.5% vs. 80.4%, respectively, p = 0.005). There were no significant differences in RBC transfusion or CIT into the transplantation quartiles (p = 0.177 and p = 0.608, respectively).

DISCUSSION

Since July 2006, the MELD criterion has been adopted to guide organ allocation at the national level for LT in Brazil.[16] The implementation of this new allocation policy was followed by significant increases in the monthly rates of LT and, therefore, the total number of procedures performed by our department. This also occurred at other
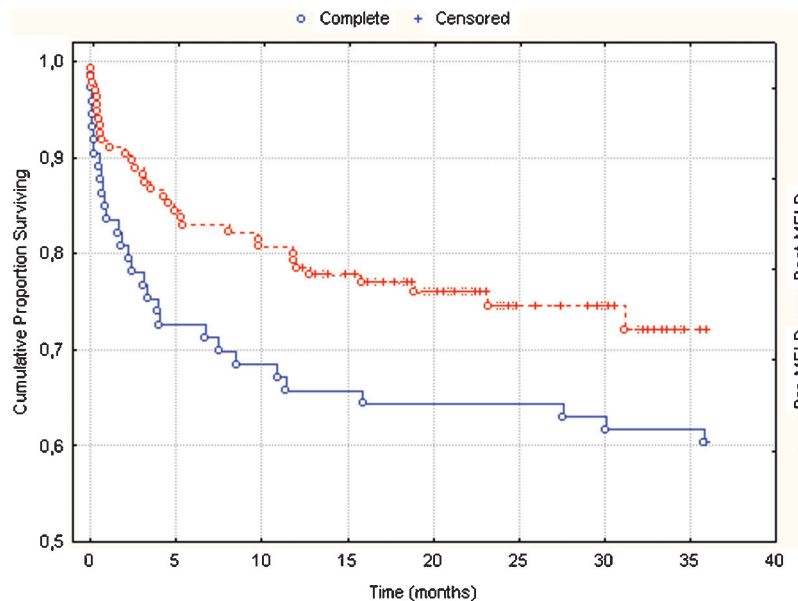

Figure 1 - Overall patient survival (Kaplan-Meier) before and after the model for end-stage liver disease (MELD) criterion implementation. There was improved patient survival at three years (with a borderline statistical significance) among the post-MELD cohort as compared to the pre-MELD cohort (60.27% vs. 72.62%, p = 0.063, by the log-rank test).

CLINICS 2011;66(1):57-64

Impact of MELD on post-transplantation survival
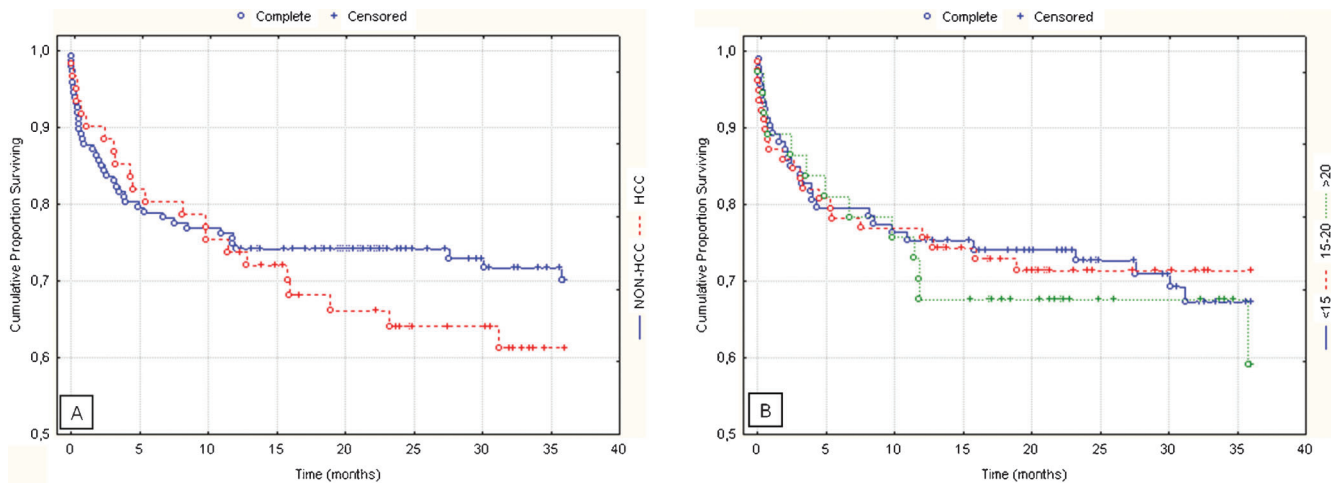Batista TP et al.

Figure 2 - Kaplan-Meier analysis of patients stratified according to diagnosis (A) and model for end-stage liver disease (MELD) score risk category (B). Inter-group analysis showed no difference in patient survival at three years (p = 0.350 and p = 0.887, respectively, by the log-rank test).

Centers,[10,11,21,32] likely reflecting recent increase in Public Health System involvement in the transplantation of organs and tissues.[10,33]

As a result of the prioritization of patients in ''special situations'' dictated by the new liver grafts allocation policy,[16] there was a significant increase in the number of patients transplanted as a result of HCC in our department, as well as around the world.[11,12,14,18-24,32,34]

Contrary to the findings of other authors, we did not find an overall increased severity of liver disease in the patients transplanted after the introduction of the MELD-based policy.[11,21,35] However, this may be as a result of the higher

proportion of HCC patients transplanted in the post-MELD period. Such patients typically have better hepatic functional reserves[10,21,36] and exhibit no change in the severity of their liver disease after adoption of the MELD criterion. Moreover, "dilution" of the MELD scores by the increase in monthly transplant rates[21] and the shorter time spent awaiting LT in our State during the post-MELD period[10] may have reduced MELD scores.

Although the difference between pre- vs. post-MELD survival has sometimes been only marginally significant, analysis of our liver transplant database reveals that the most important post-transplantation outcome—namely patient

Table 3 - Stratified cumulative proportion surviving after liver transplantation.

Groups and Categories	n (%)	Cumulative Proportion Surviving (%) [1]			
		3 months	6 months	12 months	36 months
Overall					
Pre-MELD	73 (35.10)	77.62	72.57	65.75	60.27
Post-MELD	135 (64.90)	88.76	82.96	79.25	72.62
p-value[2]		0.036	0.066	0.028	0.063
HCC					
Pre-MELD	10 (16.39)	100.00	100.00	90.00	80.00
Post-MELD	51 (83.60)	86.00	76.47	70.58	57.27
p-value[2]		0.217	0.090	0.174	0.141
Non-HCC					
Pre-MELD	63 (42.85)	73.98	68.21	61.90	57.14
Post-MELD	84 (57.14)	90.41	86.90	84.52	83.28
p-value[2]		0.009	0.005	0.001	0.001
MELD <15					
Pre-MELD	35 (37.63)	79.41	74.28	68.57	62.85
Post-MELD	58 (62.36)	87.71	82.75	79.31	70.35
p-value[2]		0.292	0.313	0.241	0.402
MELD 15-20					
Pre-MELD	30 (38.46)	72.41	66.66	63.33	60.00
Post-MELD	48 (61.53)	91.66	85.41	85.41	78.32
p-value[2]		0.029	0.042	0.021	0.056
MELD >20					
Pre-MELD	8 (21.62)	87.50	87.50	62.50	50.00
Post-MELD	29 (78.38)	85.96	79.31	68.96	68.96
p-value[2]		0.874	0.588	0.785	0.604

[1]Kaplan-Meier method.
[2]Comparison between Pre- vs. Post-MELD cohorts using the log-rank test.
MELD = model for end-stage liver disease; HCC = hepatocellular carcinoma; non-HCC = non-hepatocellular carcinoma.

Impact of MELD on post-transplantation survival
Batista TP et al.

CLINICS 2011;66(1):57-64

Table 4 - Predictors of 3-year post-liver transplantation survival.

Variables[1]	Univariate [2]	Multivariate[3]		
		Unadjusted	Allocation Criterion	Transplantation Era[4]
Diagnostic categories[5]	0.350	–	–	–
ABO blood group	0.120	0.279	0.361	0.320
Receptor gender	0.635	–	–	–
Recipient age (<55 vs. ≥55)	0.973	–	–	–
MELD (<15 vs.15-20 vs. >20)	0.887	–	–	–
Child-Pugh class	0.400	–	–	–
Donor age (<50 vs. ≥50)	0.660	–	–	–
Cold ischemia (<12 vs. ≥12)	0.018	0.062	0.050	0.060
Warm ischemia (<45 vs. ≥45)	0.048	0.419	0.694	0.825
Red blood cells (<5 vs. ≥5)	<0.001	0.002	0.002	0.003
Platelets (yes vs. no)	0.027	0.547	0.573	0.666
Transplant rate (<5 vs. ≥5)	0.424	–	–	–
Hepato-venous Reconstruction[6]	0.006	0.119	0.135	0.128

[1]Continuous variables categorized as in parentheses.
[2]Univariate analysis using the log-rank test.
[3]Multivariate analysis using the Cox-proportional hazards model. This analysis was also adjusted to group the patients according to allocation criterion (pre-MELD vs. post-MELD) and transplantation era (first era vs. second era).
[4]First era: 7/15/2003 – 8/28/2007; second era: 8/29/2007 – 7/14/2009.
[5]HCC vs. non-HCC patients.
[6]Piggyback vs. conventional hepato-venous anastomosis.
MELD = model for end-stage liver disease; HCC = hepatocellular carcinoma; non-HCC = non-hepatocellular carcinoma.

survival—has improved since the implementation of the MELD-based liver allocation system. In order to explore these divergent outcomes,[11,14,21,37] we conducted some additional exploratory analyses to elucidate our findings further.

First, as factors related to cancer alone are not enough to predict the prognosis of patients with HCC[4] and because such patients exhibit better liver function at the time of LT,[5,10,21,36] we expected better survival for these patients and supposed it as the main reason for our improved post-LT survival during the post-MELD period.[36] However, our data have shown that HCC patient survival did not improve after introduction of the MELD criterion. Furthermore, there was no significant difference in early postoperative mortality or post-LT survival between HCC vs. non-HCC patients. Therefore, the best results observed during the post-MELD period did not result from the greater proportion of HCC patients transplanted in this period. We also noticed a trend of worsening survival after one year of LT in this patient subgroup, which probably resulted from the influence of tumor-related factors.[38]

A second possible explanation is that transplant recipients are simply not sicker in the post- vs. pre-MELD periods. Nonetheless, our data failed to confirm this hypothesis. Despite the lack of any change in liver disease severity in the HCC subgroup, the non-HCC patients exhibited a 3.5-point increase in median MELD score during the post-MELD era. This approach also demonstrated an apparent disconnect between liver disease severity and survival outcomes in the non-HCC subgroup, which presented significantly higher cumulative survival after adoption of the MELD criterion. Similarly, a lower early postoperative mortality rate, with borderline statistical significance, could also be observed amongst these patients in the post-MELD era.

Although it is plausible to hypothesize that patients transplanted with higher MELD scores had worse survival,[10,21,22] our data show there was no significant difference among patient groups with different MELD scores. This finding suggests MELD score is not a good predictor of post-LT survival. We also used the c-statistic to confirm that preoperative MELD score had poor discriminatory power in predicting post-LT survival among patients treated in our department.

Similarly, in a systematic review about the performance of MELD in the setting of LT, Colongita et al. concluded that MELD score is not a good predictor for short-term mortality after LT and that further studies were needed to assess long-term performance.[5] In addition, it has been demonstrated that this score does not have the same prognostic accuracy among patients with milder degrees of hepatic cirrhosis and that the effect of hepatic dysfunction may not be evident at MELD score values lower than 30.[5,39] This suggests only high MELD values affect post-LT survival.[21] Therefore, although statistically significant, the 3.5-point increases that represent shifts to milder degrees of hepatic dysfunction (i.e. MELD 15-20), may not translate into a clinically relevant difference in survival.

On the other hand, worse survival in recipients with higher MELD scores has been cited by some authors[9,14,35] and higher MELD scores have also been linked to greater postoperative morbidity.[40,41] However, even in patients with more severe disease, there is a clear survival benefit from LT, because of their corresponding lower survival rates on the waiting list without LT.[42-44] As demonstrated by Merion et al.,[42] the benefit of LT would become evident only in patients with MELD scores higher than 18 and the magnitude of this benefit increased with increasing MELD score. Similar results were also described by Gleisner et al., who suggested a MELD score of 15 as a transition point in terms of overall survival benefit.[44]

Although the MELD criterion was established to prioritize the sickest patients, a large proportion of transplanted recipients do not have severe liver disease, as evaluated by MELD score.[5] Accordingly, in our department the median MELD score did not change with the introduction of the MELD criterion and remained low (15 points) after implementation (HCC = 13 and non-HCC = 18.5). Similarly, only 3.4% of patients had MELD scores greater than 30 (data not shown). These low proportions of patients with high MELD scores have also been found in other studies[5,22,35,42]

CLINICS 2011;66(1):57-64

Impact of MELD on post-transplantation survival
Batista TP et al.

and probably contributed to reducing the accuracy of this score in predicting post-LT survival in our department.

Other potential explanations were that better survival outcomes in the post-MELD period may have resulted from our increased case volume and/or from a higher proportion of patients transplanted with the *piggyback* technique. In order to explore this hypothesis, we additionally performed a secondary statistical approach to explore long-term predictors of survival using univariate and multivariate analysis. According to this approach, transfusion of RBC alone (≥5 units) was an independent predictor of poorer three-year post-LT survival; however, CIT ≥12 hours also exhibited borderline statistical significance as an independent predictor.

In a previous study at our department, the *piggyback* technique was associated with reduced length of hospital stay, surgical time and WIT, as well as a better 30-day post-LT survival.[45] Accordingly, in our long-term univariate analysis, we found better post-LT survival amongst patients transplanted with the *piggyback* hepato-venous anastomosis. However, our multivariate analysis revealed this outcome probably resulted from the reduced RBC transfusion that accompanies this technique. The higher proportion of patients transplanted with this technique in the post-MELD era also served to explain our lower WIT observed during this last period.

As our department changed from a medium case volume center (20-50 LT /year) in the pre-MELD period of the study to a high case volume center (>50LT/year) in the post-MELD era,[21] as well as the better outcomes observed at LT Centers performing more than 20 procedures per year,[46] we hypothesized that increased LT volume was a plausible reason for better survival after implementation of the MELD allocation plan. Nevertheless, our monthly transplantation rates did not correlate with patient survival in this study. Furthermore, because our study started after more than 40 LTs had been performed by our department, center- and team-related factors (i.e. case volume and transplantation experience) appear to not have significantly influenced patient survival at our department. Similarly, Northup et al. explored the impact of transplant center case volume on survival of 9909 adult liver transplants performed in the USA since the beginning of the MELD allocation system.[47] After adjusting for disease severity and multiple donor and recipient factors, transplant center volume was no longer a significant predictor of post-LT survival, according to these authors.

As alternative reasons for our better survival outcomes in the post-MELD period, we finally hypothesized that involvement of the Public Health System in the transplantation of organs and tissues played a role.[10,33] To support this hypothesis, we explored our analysis of patient survival to include successive transplantation periods. Using this approach, we found increased survival from first to fourth transplantation quartiles in a one-year survival analysis as well as in the first vs. second transplantation era, using two-year survival as the end-point. Moreover, we also confirmed there were no differences in RBC transfusion or CIT among successive transplantation quartiles.

Notably, in the post-MELD period, governmental efforts to encourage organ transplantation improved the logistics of the donation-transplant process, allowing for an increase in the number of potential donors in brain-death notifications and in the amount of donations and transplants in the State of Pernambuco.[10,33] Furthermore, governmental involvement also included some educational, structural and financial improvements that gradually impacted on regional medical assistance[33] and may have contributed to better survival during the most recent periods of our LT activity.

Our analysis has three main strengths: firstly, whereas a previous report[14] with similar methods measured medium-term post-LT survival (1-year), we provided a 3-year survival analysis. This approach ensured a more robust estimate of how the MELD policy affected post-LT survival outcomes in Brazil; secondly, we were the first center to show significantly better survival after the implementation of a MELD-based policy.[11,14,21,37] Similarly, although MELD-based policy has not significantly reduced waiting list mortality throughout the country,[48,49] our State presented lower waiting list mortality after adoption of this new system;[10] and lastly, we explored potential reasons for our divergent survival outcomes after LT.

However, there were also limitations with our study. Firstly, few patients in the HCC and MELD >20 subgroups underwent transplantation during the pre-MELD era at our department, which limited their subgroup analyses to comparisons between the pre- vs. post-MELD periods. Secondly, a small proportion of our patients had high "calculated" MELD scores [i.e. only 3.4% had MELD scores >30 and just 8.2% had MELD scores ≥25 (data not shown)]. Notably, a low proportion of patients with high MELD scores probably minimized the accuracy of this score in predicting post-LT survival, as well as the impact of MELD-based policy on our post-LT survival outcomes. Lastly, analysis of additional donor-related variables could provide additional information, because a large proportion of extended-criteria donors were used at our department.[28,50]

CONCLUSION

In conclusion, better survival outcomes were observed in our department after implementation of the MELD allocation policy, particularly amongst patients categorized as non-HCC and moderate-risk, as determined by MELD score (15-20 points). Gradual involvement of the Public Health System in organ transplantation was possibly the main reason for the improvement in survival outcomes.

CONFLICTS OF INTEREST

All the authors declare that there are no conflicts of interest, financial support or disclaimers related to this study.

REFERENCES

1. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, RanK J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology. 2000;31:864-71, doi: 10.1053/he.2000.5852.
2. Said A, Williams J, Holden J, Remington P, Gangnon R, Musat A, et al. Model for end stage liver disease score predicts mortality across a broad spectrum of liver disease. J Hepatol. 2004;40:897-903.
3. Boursier J, Cesbron E, Tropet AL, Pilette C. Comparison and improvement of MELD and Child-Pugh score accuracies for the prediction of 6-month mortality in cirrhotic patients. J Clin Gastroenterol. 2009;43:580-5, doi: 10.1097/MCG.0b013e3181889468.

Impact of MELD on post-transplantation survival
Batista TP et al.

CLINICS 2011;66(1):57-64

4. Huo TI, Hsia CY, Huang YH, Lin HC, Lee PC, Lui WY, et al. Selecting a short-term prognostic model for hepatocellular carcinoma: comparison between the model for end-stage liver disease (MELD), MELD-sodium, and five cancer staging systems. J Clin Gastroenterol. 2009;43:773-81, doi: 10.1097/MCG.0b013e31818dd962.

5. Cholongitas E, Marelli L, Shusang V, Senzolo M, Rolles K, Patch D, et al. A systematic review of the performance of the model for end-stage liver disease (MELD) in the setting of liver transplantation. Liver Transpl. 2006;12:1049-61, doi: 10.1002/lt.20824.

6. Wiesner RH, McDiarmid SV, Kamath PS, Edwards EB, Malinchoc M, Kremers WK, et al. MELD and PELD: application of survival models to liver allocation. Liver Transpl. 2001;7:567-80, doi: 10.1053/jlts.2001.25879.

7. Merion RM, Wolfe RA, Dykstra DM, Leichtman AB, Gillespie B, Held PJ. Longitudinal assessment of mortality risk among candidates for liver transplantation. Liver Transpl. 2003;9:12-8, doi: 10.1053/jlts.2003.50009.

8. Wiesner R, Edwards E, Freeman R, Harper A, Kim R, Kamath P, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology. 2003;124:91-6, doi: 10.1053/gast.2003.50016.

9. Brandão A, Fuchs SC, Gleisner AL, Marroni C, Zanotelli ML, Cantisani G, et al. MELD and other predictors of survival after liver transplantation. Clin Transplant. 2009;23:220-7, doi: 10.1111/j.1399-0012.2008.00943.x.

10. Tenório AL, Macedo FI, Miranda LE, Fernandes JL, da Silva CM, Neto OL, et al. Survival on waiting list for liver transplantation before and after introduction of the Model for End-stage Liver Disease score. Transplant Proc. 2010;42:407-11, doi: 10.1016/j.transproceed.2010.01.005.

11. Freeman RB, Wiesner RH, Edwards E, Harper A, Merion R, Wolfe R, et al. Results of the first year of the new liver allocation plan. Liver Transpl. 2004;10:7-15, doi: 10.1002/lt.20024.

12. Freeman RB. Overview of the MELD/PELD system of liver allocation indications for liver transplantation in the MELD era: evidence-based patient selection. Liver Transpl. 2004;10(10 Suppl 2):S2-3, doi: 10.1002/lt.20262.

13. Freeman RB, Edwards EB. Liver transplant waiting time does not correlate with waiting list mortality: Implications for liver allocation policy. Liver Transpl. 2000;6:543-52, doi: 10.1053/jlts.2000.9744.

14. Monteiro F, Coria SA, Boni R, Pereira LA. Model for end-stage liver disease: impact of the new deceased donor liver allocation policy in São Paulo, Brazil. Transplant Proc. 2009;41:226-8, doi: 10.1016/j.transproceed.2008.09.059.

15. United Network for Organ Sharing. Available at: http://www.unos.org/resources [accessed April 1].

16. Brazil. Ministry of Health. Department of Health Care. Portaria GM n° 1.160 from May 29, 2006. Brasília: Diário Oficial da União n° 103. Published on May 31, 2006. Available at: http://dtr2001.saude.gov.br/sas/PORTARIAS/Port2006/GM/GM-1160.htm [accessed on April 12, 2009].

17. Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol. 2001;35:421-30.

18. Teixeira AC, Souza FF, Mota GC, Martinelli ALC, Sankarankutty AK, Silva OC. Liver transplantation: expectation with MELD score for liver allocation in Brazil. Acta Cir Bras. 2006;21(21 suppl 1):S12-14.

19. Ravaioli M, Grazi GL, Ballardini G, Cavrini G, Ercolani G, Cescon M, et al. Liver transplantation with the Meld system: a prospective study from a single European center. Am J Transplant. 2006;6:1572-7.

20. Ahmad J, Downey KK, Akoad M, Cacciarelli TV. Impact of the MELD score on waiting time and disease severity in liver transplantation in United States veterans. Liver Transpl. 2007;13:1564-9, doi: 10.1002/lt.21262.

21. Kanwal F, Dulai GS, Spiegel BMR, Yee HF, Gralnek IM. A comparison of liver transplantation outcomes in the pre- vs.post-MELD eras. Aliment Pharmacol Ther. 2005;21:169–77, doi: 10.1111/j.1365-2036.2005.02321.x.

22. Thuluvath PJ, Maheshwari A, Thuluvath NP, Nguyen GC, Segev DL. Survival after liver transplantation for hepatocellular carcinoma in the model for end-stage liver disease and pre-model for end-stage liver disease eras and the independent impact of hepatitis C virus. Liver Transpl. 2009 ;15:754-62, doi: 10.1002/lt.21744.

23. Ioannou GN, Perkins JD, Carithers RL Jr. Liver transplantation for hepatocellular carcinoma: impact of the MELD allocation system and predictors of survival. Gastroenterology. 2008;134:1342-51, doi: 10.1053/j.gastro.2008.02.013.

24. Wiesner RH, Freeman RB, Mulligan DC. Liver transplantation for hepatocellular cancer: the impact of the MELD allocation policy. Gastroenterology. 2004;127(5 Suppl 1):S261-7, doi: 10.1053/j.gastro.2004.09.040.

25. Xiao L, Fu ZR, Ding GS, Fu H, Ni ZJ, Wang ZX, et al. Prediction of survival after liver transplantation for chronic severe hepatitis B based on preoperative prognostic scores: a single center's experience in China. World J Surg. 2009;33:2420-6.

26. Sempere L, Palazón JM, Sánchez-Payá J, Pascual S, Madaria E, Poveda MJ, et al. Assessing the short- and long-term prognosis of patients with cirrhosis and acute variceal bleeding. Rev Esp Enferm Dig (Madrid). 2009;101:236-48.

27. Busuttil RW, Farmer DG, Yersiz H, Hiatt JR, McDiarmid SV, Goldstein LI, et al. Analysis of long-term outcomes of 3200 liver transplantations over two decades: a single-center experience. Ann Surg. 2005;241:905-16, doi: 10.1097/01.sla.0000164077.77912.98.

28. Macedo FI, Miranda LE, Pádua TC, Fernandes JL, Neto OL, Lacerda CM. Effects of donor age on patient survival in liver transplantation: short- and long-term analysis. Hepatogastroenterology. 2009;56:1133-6.

29. Massicotte L, Sassine MP, Lenis S, Roy A. Transfusion predictors in liver transplant. Anesth Analg. 2004;98:1245-51, doi: 10.1213/01.ANE.0000111184.21278.07.

30. Moore DE, Feurer ID, Speroff T, Gorden DL, Wright JK, Chari RS, et al. Impact of donor, technical, and recipient risk factors on survival and quality of life after liver transplantation. Arch Surg. 2005;140:273-7, doi: 10.1001/archsurg.140.3.273.

31. de Boer MT, Christensen MC, Asmussen M, van der Hilst CS, Hendriks HG, Slooff MJ, et al. The impact of intraoperative transfusion of platelets and red blood cells on survival after liver transplantation. Anesth Analg. 2008;106:32-44, doi: 10.1213/01.ane.0000289638.26666.ed.

32. Wiesner RH. Patient selection in an era of donor liver shortage: Current US policy. Nat Clin Pract Gastroenterol Hepatol. 2005;2:24-30, doi: 10.1038/ncpgasthep0070.

33. State Health Department of Pernambuco. Transplantation Center of Pernambuco. Statistics. Available at: http://www.transplantes.pe.gov.br/estatistica.htm [accessed on April 12, 2009].

34. Moonka D, Castillo E, Kumer S, Abouljoud M, Divine G, Pelletier S. Impact of model for end-stage liver disease on patient survival and disease-free survival in patients receiving liver transplantation for hepatocellular carcinoma. Transplant Proc. 2009;41:216-18, doi: 10.1016/j.transproceed.2008.09.060.

35. Yoo HY, Thuluvath PJ. Short-term postliver transplant survival after the introduction of MELD scores for organ allocation in the United States. Liver Int. 2005;25:536-41, doi: 10.1111/j.1478-3231.2005.01011.x.

36. Freitas AC, Parolin MB, Stadnik L, Coelho JC. Hepatocellular carcinoma: impact of waiting list and pre-operative treatment strategies on survival of cadaveric liver transplantation in pre-MELD era in one center in Brazil. Arq Gastroenterol. 2007;44:189-94.

37. Sharma P, Balan V, Hernandez JL, Harper AM, Edwards EB, Rodriguez-Luna H, et al. Liver transplantation for hepatocellular carcinoma: the MELD impact. Liver Transpl. 2004;10:36-41, doi: 10.1002/lt.20012.

38. Hemming AW, Cattral MS, Reed AI, Van Der Werf WJ, Greig PD, Howard RJ. Liver transplantation for hepatocellular carcinoma. Ann Surg. 2001;233:652-9, doi: 10.1097/00000658-200105000-00009.

39. Huo TI, Lin HC, Wu JC, Lee FY, Hou MC, Lee PC, et al. Different Model for End-Stage Liver Disease score block distributions may have a variable ability for outcome prediction. Transplantation. 2005;80:1414-8, doi: 10.1097/01.tp.0000181164.19658.7a.

40. Ferraz-Neto BH, Zurstrassen MP, Hidalgo R, Meira-Filho SP, Rezende MB, Paes AT, et al. Analysis of liver transplantation outcome in patients with MELD Score > or = 30. Transplant Proc. 2008;40:797-9, doi: 10.1016/j.transproceed.2008.03.016.

41. Wang ZX, Yan LN, Wang WT, Xu MQ, Yang JY. Impact of pretransplant MELD score on posttransplant outcome in orthotopic liver transplantation for patients with acute-on-chronic hepatitis B liver failure. Transplant Proc. 2007; 39:1501–04, doi: 10.1016/j.transproceed.2007.02.070.

42. Merion RM, Schaubel DE, Dykstra DM, Freeman RB, Port FK, Wolfe RA. The survival benefit of liver transplantation. Am J Transplant. 2005;5:307-13.

43. Ravaioli M, Grazi GL, Dazzi A, Bertuzzo V, Ercolani G, Cescon M, et al. Survival benefit after liver transplantation: a single European center experience. Transplantation. 2009;88:826-34, doi: 10.1097/TP.0b013e3181b26807.

44. Gleisner AL, Muñoz A, Brandao A, Marroni C, Zanotelli ML, Cantisani GG, et al. Survival benefit of liver transplantation and the effect of underlying liver disease. Surgery. 2010;147:392-404, doi: 10.1016/j.surg.2009.10.006.

45. Melo PSV. Orthotopic liver transplantation without veno-venous bypass by conventional and piggyback approaches. [Thesis]. Recife: Federal University of Pernambuco - UFPE; 2009.

46. Edwards EB, Roberts JP, McBride MA, Schulak JA, Hunsicker LG. The effect of the volume of procedures at transplantation centers on mortality after liver transplantation. N Engl J Med. 1999; 341:2049–53.

47. Northup PG, Pruett TL, Stukenborg GJ, Berg CL. Survival after adult liver transplantation does not correlate with transplant center case volume in the MELD era. Am J Transplant. 2006;6:2455-62.

48. Castro RS, Deisanti D, Seva-Pereira T, Almeida JR, Yamanaka A, Boin IF, et al. Survival before and after model for end-stage liver disease score introduction on the Brazilian liver transplant waiting list. Transplant Proc. 2010;42:412-6, doi: 10.1016/j.transproceed.2010.01.028.

49. Lima AS, Vilela EG. Efeitos da Alocação de Enxertos Hepáticos pelo Critério MELD Sobre a Lista de Espera. Prática Hospitalar. 2009;61:142-5.

50. Lucena O, Amorim AG, Sabat BD, Adeodato LCL, Miranda LEC, Lacerda CM. Liver transplantation from non-heart-beating donors: initial results from Oswaldo Cruz University Hospital's liver transplantation group, Pernambuco University. Rev Col Bras Cir. 2005;32:270-2, doi: 10.1590/S0100-69912005000500010.