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A validated model for predicting outcome after liver transplantation: implications on transplanting the extremely sick

Ido Nachmany,[1]* Igor Dvorchik,[2]* Michael DeVera,[1] Paulo Fontes,[1] Anthony Demetris,[3] Abhinav Humar[1] and James W. Marsh[1]

1 Department of Surgery, Thomas E. Starzl Transplantation Institute, University of Pittsburgh Medical Center, Pittsburgh, PA, USA
2 Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA
3 Department of Pathology, University of Pittsburgh, Pittsburgh, PA, USA

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Correspondence
Professor James W. Marsh MD, MBA, Department of Surgery, Thomas E. Starzl Transplantation Institute, University of Pittsburgh Medical Center, Montefiore-7 South, 3459 Fifth Avenue, Pittsburgh, PA 15213-3236, USA.
Tel.: 412-692-2033;
fax: 412-647-5480;
e-mail: marshw@upmc.edu

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Summary

Given the organ shortage, there is a need to optimize outcome after liver transplantation (LT). We defined posttransplant hospital length of stay >60 days (LOS > 60) as a surrogate of suboptimal outcome. In the first phase of the study, a 'Study cohort' (SC) of 643 patients was used to identify risk factors and construct a mathematical model to identify recipients with anticipated inferior results. In the second phase, a cohort of 417 patients was used for validation of the model ['Validation Cohort' (VC)]. In the SC, 65 patients (10.1%) had LOS > 60 days. One- and 3-year patient/graft survival rates were 81.9%/76.1% and 73.4%/67.4%, respectively. Patient and graft survival rates of those with LOS >60 days were inferior ($P < 0.0001$), while transplant cost was greater [3.42 relative units (RU) vs. 1 RU, $P < 0.0001$]. In a multivariable analysis, pretransplant dialysis ($P < 0.001$), mechanical ventilation ($P < 0.015$), MELD ($P < 0.003$), and age ($P < 0.009$) were predictors of LOS > 60 days [ROC curve – 0.75 (95% CI 0.70, 0.81)]. In the VC, 53 patients (12.7%) were expected to have adverse outcome by the model. These patients had longer LOS ($P < 0.0001$), higher cost (<0.0001), and inferior patient and graft survival ($P < 0.007$).

Introduction

Since the early days of liver transplantation (LT), one of the major challenges faced by the transplant community has been the limited availability of organs. There have been different approaches aimed at increasing the limited organ pool, including use of marginal donors, graft splitting, and living donation. Unfortunately, all these means have major drawbacks, and at the same time, the mortality rate on the waiting list is still significant. According to the Scientific Registry of Transplant Recipients (SRTR), the annual death rate per 1000 patient-years at risk on the liver waiting list was 113.1 in 2009, and in the USA, every year, around 2000 patients die while waiting for a liver transplant [1]. Therefore, the pool of transplantable organs must be used in a way that will optimize its utilization, allowing for maximal benefit of patients with end-stage liver disease.

With Merion's *et al.* [2] publication in 2005 on the survival benefit of LT, the transplant community became concerned that certain patients were undergoing transplantation

prematurely during the course of their disease. Therefore, the cut-off level of Model for End-Stage Liver Disease (MELD) ≥15 was set as a prerequisite for transplantation (excluding cases of upgrade, mainly for HCC), which was accepted throughout the United Network for Organ Sharing (UNOS) regions [3].

The current 'sickest-first' allocation policy, based on MELD alone, is oriented at prolongation of a single patient's life. Such a policy is not necessarily the most efficient, in terms of achieving the maximal gain of patient-years for the entire waiting list. Also, this allows for transplantation in extremely sick patients that theoretically may gain low benefit from transplant.

According to SRTR reports [1], the overall 1- and 5-year survival after deceased donor liver transplantation (DDLT) are 85.3% and 68.4%, respectively. This number represents all patients undergoing DDLT in the US in the years 2007–2008 (1-year survival) and 2003–2008 (5-year survival).

Nonetheless, among DDLT recipients, there are patients who achieve much inferior results. Their postoperative course is complicated, and their survival is reduced. The management of such cases is also extremely expensive. Altogether, such transplants may ultimately lead to a loss of an organ and add a significant economic burden without achieving the expected survival benefit [4].

To improve the utilization of the available liver pool, we sought to define factors that correlated with poor outcome after DDLT.

We were not concerned with patient survival only, but rather looked for a more general outcome measure that would represent survival, morbidity, and transplantation cost. To simplify the analysis, we needed a single marker that would serve well as a surrogate for the combination of the above-mentioned outcome measures (morbidity, mortality, and cost). We hypothesized that the postoperative length of hospital stay is a good surrogate marker of posttransplant course and correlates with other indicators of poor outcome, as well as cost. After preliminary data analysis, we set the cut-off at length of stay over 60 days (LOS > 60), as that correlated best with long-term graft and patient survival, organ function (liver and kidney), and cost of transplantation (data not shown).

Materials and methods

Data sources

Donor and recipient information was obtained from the electronic medical records system and the prospectively collected transplant database of the University of Pittsburgh Medical Center.

This study was approved by the Institutional Review Board.

Study design

In the first stage of the study, we tested our hypothesis by comparing graft and patient survival, organ function and transplant cost of patients with LOS > 60 to those with LOS ≤ 60 in a cohort of DDLT recipients ['Study cohort' (SC)].

Next, we defined all factors significantly associated with LOS > 60 in a multivariate analysis and constructed a mathematical model to define their quantitative effect on the risk for LOS > 60.

In the final stage of the study, we tested the performance of the model on a different cohort of DDLT recipients ['Validation cohort' (VC)]. We compared the outcome and transplant cost of patients with the highest risk according to our model to the rest of the VC.

Patient population and donated organ characteristics

Study cohort (SC)

Of the 735 adult-DDLT performed between September 2002 and March 2006, a total of 643 were primary transplants and were included in this study. Four hundred and nine (63.6%) were males and 234 (36.4%) were females. Patient age ranged from 18 to 76 years with a mean of 54.0 ± 10.6 years. MELD scores ranged from 6 to 40 with a mean of 17.3 ± 7.6.

Indications for transplantation were Hepatitis C (n = 228; 35.5%), alcoholic liver disease (n = 217; 33.7%), nonalcoholic steatohepatitis (n = 60; 9.3%), autoimmune hepatitis (n = 40; 6.2%), primary sclerosing cholangitis (n = 37; 5.7%), primary biliary cirrhosis (n = 34; 5.3%), and others (including Hepatitis B, Alpha 1 anti-trypsin deficiency, polycystic liver disease, and hemochromatosis). Thirty-five patients (5.4%) had cryptogenic cirrhosis. In 23 patients (3.6%), the indication for LT was fulminant hepatic failure.

Prior to transplantation, 52 patients (8.1%) were mechanically ventilated and 87 (13.5%) had pretransplant dialysis. Of these, 31 received 'acute dialysis' (few treatments only) and 56 were chronic hemodialysis patients.

The mean donor age, cold ischemia time (CIT), and warm ischemia time were 48.9 ± 18.5 years, 10.1 ± 3.0 h, and 29.6 ± 7.8 min, respectively.

The most common cause of donor death (74.7%) was cerebrovascular accident; 73 (11.4%) donors were donated after cardiac death (DCD).

Validation cohort (VC)

The second cohort, used for validation of the model developed on data from the SC (VC), consisted of 417 patients transplanted from April 2006 to December 2009 and followed through December of 2011. There were 263 males

(63.1%). Patient age ranged from 18 to 79 years with a mean of 55.3 years. In 139 (33%), the indication for LT was HCV-induced cirrhosis. The mean of MELD was 28.5 ± 8.6 (range 6–47; we left the calculated MELD without cutting at 40). In 86 (20.6%), there was a need for acute or chronic dialysis, and 35 (8.4%) patients were mechanically ventilated before LT. The model was used to define a group of patients with very high risk for poor outcome. This group consisted of 53 (12.7%) patients. Mean patient follow-up was 54.8 ± 1.3 months.

Outcome measures and statistical analysis

Hospital length of stay (LOS) beyond 60 days was considered an outcome measure. Graft and patient survival rates were estimated with the Kaplan–Meier test; comparison of survival between various patient cohorts was performed with the log-rank test. Categorical variables were analyzed with likelihood ratio chi-square test or Fisher's exact test when appropriate.

Continuous variables were analyzed using independent t-test with Levene's test verifying equality of variance assumption. A P-value ≤ 0.05 was considered significant. All significant variables in the univariate stage of analysis were entered into stepwise binary logistic regression analysis.

Performance of the final logistic regression model was measured by the area under receiver characteristic curve (ROC), which is an equivalent of C statistic. Financial information was reported in relative units (RU). The mean of transplantation cost for patients with LOS $\leq$ 60 days was considered equal to 1 RU. Transplant costs were obtained from the organizational financial database.

Results

Clinical outcomes and cost of transplantation—Study cohort (SC)

The mean duration of follow-up was 40.5 ± 0.8 months. During follow-up, 142 patients died and 181 grafts were lost. One- and 3-year patient/graft survival rates were 81.9%/76.1% and 73.4%/67.4%, respectively. LOS ranged from 1 to 209 days with a mean and median of 27.7 and 16 days, respectively. Sixty-five patients (10.1%) had LOS > 60 days.

When patient survival was stratified by MELD score, the analysis did not show significant differences in posttransplant survival ($P > 0.1$). The 3-year survival of patients with a MELD score over 30 exceeded 72%, this being only 10% lower than the survival of patients with a MELD score <10 (Fig. 1).

As the MELD score was not a sufficient discriminator of patient and graft survival, we looked for other parameters that would serve as better outcome predictors. We were specifically interested in a single parameter that would serve as a 'general' indicator of inferior outcome. We hypothesized that LOS would be a good surrogate marker for complicated posttransplant course and that prolonged LOS would correlate with reduced patient and graft survival, inferior graft and renal function, as well as increased transplantation cost.

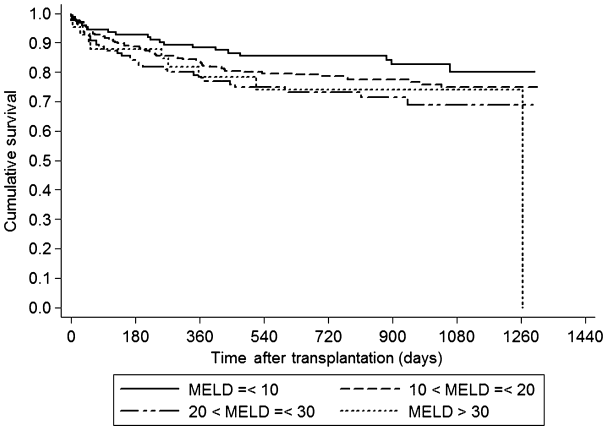

Figure 1 Patient survival stratified by Model for End-Stage Liver Disease Score.

The 1-, 2-, and 3-year graft survival rates for patients with LOS $\leq$ 60 days versus those with LOS > 60 days, were 82.0% vs. 41.9%, 75.7% vs. 37.4% and 73.2% vs. 33.2%, respectively (each $P < 0.01$) (Fig. 2). Patients with LOS > 60 days had significantly higher MELD score (22.2 ± 6.9 vs. 16.3 ± 8.5, $P < 0.0001$). Their posttransplant course was also characterized by prolonged elevation of serum total bilirubin (4.0 vs. 2.0, $P < 0.04$) and creatinine levels (2.0 vs. 1.4, $P < 0.013$) at 3 months posttransplant.

With the total estimated cost of transplantation for patients with LOS $\leq$ 60 days set to equal 1 RU, the total cost for patients with LOS > 60 days was 3.42 RU ($P < 0.0001$). In other words, the cost of transplantation was 3.42 times higher for patients with LOS > 60 days compared with those with a LOS < 60.

We next looked for factors associated with LOS > 60. Multivariable analysis revealed that four pretransplant recipient factors were independent predictors of LOS > 60 days: (i) the need for pretransplant hemodialysis, (ii) pretransplant mechanical ventilation, (iii) MELD score, and (iv) age (Table 1).

We specifically looked at infection rates in the LOS > 60, based on fever, leukocytosis (>10 000/mm^3), and antibiotic/antifungal therapy rates, as compared with the LOS < 60. In the LOS > 60, the fever and leukocytosis rates were higher, but these did not reach statistical significance (fever 3.3% vs. 0.8%, $P > 0.08$; leukocytosis 59.3% vs. 47.4%, $P > 0.13$). Antibiotics/antifungals were used more commonly in the LOS > 60 group 54.4% vs. 33.8%, $P < 0.05$).

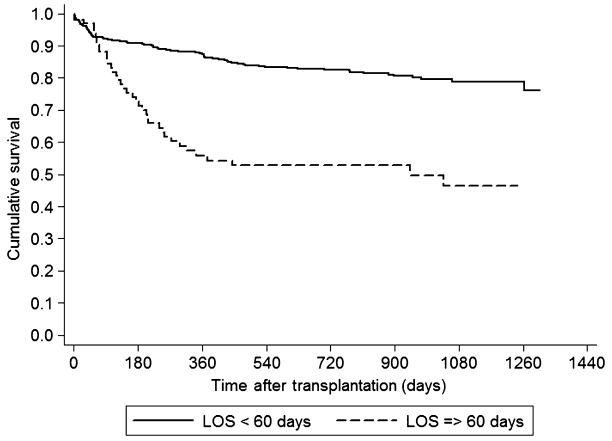

Figure 2 Patient survival stratified by hospital length of stay.

A comparison of donor characteristics between the two groups failed to reveal any significant differences in age, degree of macrosteatosis in the donor biopsy, body mass index, cold and warm ischemia times, length of donor hospital stay, or proportion of DCD donors (data not shown).

A model predicting suboptimal outcome

The analysis of estimated probabilities of suboptimal outcome (manifested by LOS > 60 days) yielded the following formula:

$$\text{Estimated Probability of Suboptimal Outcome (EPSO)} = 0.3 + \frac{1}{1+e^{-z}}$$

where:
$Z = -4.68 + 3.64 \cdot$(Pre-transplant Hemodialysis) + $2.96 \cdot$(Pre-transplant Mechanical Ventilation) + 1.06 (MELD) + A (Patient Age Group).

Hemodialysis and mechanical ventilation are categorical variables (1 or 0).

$A = 0$ when patient age ≥18 and <40, $A = 3.98$ when patient age ≥40 and <60, and $A = 8.3$ when patient age is more than 60 years.

The area under ROC curve of this model was 0.75 ± 0.03, (CI 95%; 0.69–0.81).

With the EPSO cut-off point set at 0.5, the model selected 69 patients as having higher than 50% chance of LOS > 60 days. The selected patients had significantly higher MELD score (29.1 ± 7.0 vs. 15.7 ± 6.2, $P < 0.0001$), total cost (2.1 RU ± 1.2 RU vs. 1.2 RU ± 0.9 RU, $P < 0.0001$), and LOS (52.6 ± 35.8 vs. 24.8 ± 27.3, $P < 0.0001$). Their graft ($P < 0.006$) and patient ($P < 0.009$) survival rates were significantly inferior compared with the remainder of the patients (Fig. 3).

During the posttransplant course, patients with LOS > 60 days had significantly higher serum creatinine levels than their counterparts (3.0 ± 2.5 vs. 1.3 ± 0.7) at 3 months posttransplant ($P < 0.0001$).

With the EPSO cut-off point set at 0.8, the model selected 28 patients with higher than 80% chance of having LOS > 60 days. These 28 patients had significantly higher MELD score at transplantation (33.4 ± 6.6 vs. 16.4 ± 6.7, $P < 0.0001$), total transplantation cost (2.7 RU ± 1.2 RU vs. 1.2 RU ± 0.9 RU, $P < 0.0001$), and LOS (72.8 ± 37.0 days vs. 25.7 ± 27.6 days, $P < 0.0001$). Their graft ($P < 0.001$) and patient ($P < 0.001$) survival rates were significantly inferior compared with the remainder of the patients (Fig. 4).

Thus, survival of the selected patients at 1 and 2 years was 59.2% and 46.6%, while, for the remainder of the group, it was 83.3% and 78.9%, respectively. During the posttransplant course, the serum creatinine levels of patients with LOS > 60 days were significantly higher than their counterparts (2.5 ± 2.0 vs. 1.5 ± 1.2 at 3 months posttransplant, $P < 0.0001$).

Table 1. Variables included in the model [the area under ROC curve of this model was 0.75 ± 0.03, 95% CI (0.69, 0.81)].

Variable	Regression coefficient	Significance level (*P*)	Risk ratio (RR)	95% CI for RR lower bound	95% CI for RR upper bound
Hemodialysis					
Pre-Tx	1.29	<0.001	3.64	1.66	8.00
Mechanical					
Ventilation	1.09	<0.015	2.96	1.24	7.08
MELD score	0.61	<0.003	1.06/point	(1.02)	1.11
Patient age (years old)		<0.009			
18–40*					
40–60	1.38	<0.026	3.98	1.18	13.42
>60	2.12	<0.003	8.30	2.09	33.00
Constant†	−4.98	<0.0001	0.007	–	–

MELD, Model for End-Stage Liver Disease; ROC, receiver characteristic curve.
*Reference category.
†See formula.

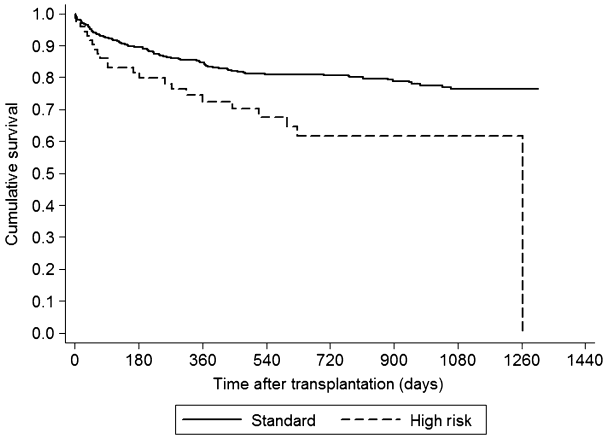

Figure 3 Patient survival stratified by model selection with cut-off at 0.5.

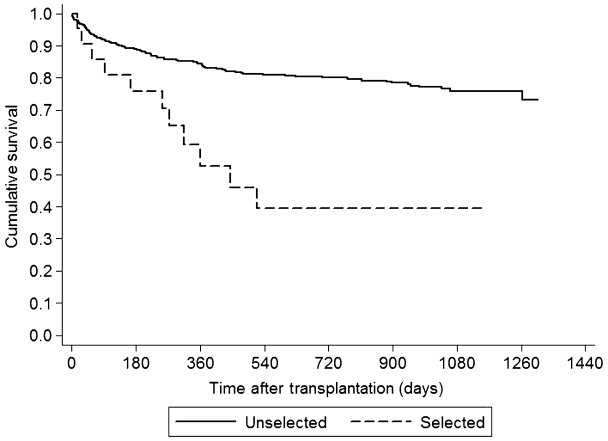

Figure 4 Patient survival stratified by model selection with cut-off at 0.8.

Validation cohort (VC)

To validate the results of the study and test the performance of the model, we used a consecutive cohort of 417 recipients of cadaveric primary LT, transplanted from April 2006 to December 2009. The patients were followed through December of 2011. Mean LOS for the entire VC was 28.5 ± 27.3 days.

Validation was performed by calculating the probability of adverse outcome (LOS > 60) by EPSO and comparing the actual hospital stay, patient and graft survival, and transplant cost of the patients with the highest score to the rest of the cohort.

The high-risk group was defined by Z value ≥40, and included 53 (12.7%) patients. This cut-off was arbitrarily set, as it yielded a group of approximately 10% of patients with the highest risk according to our identified four risk factors (age, MELD, mechanical ventilation and dialysis).

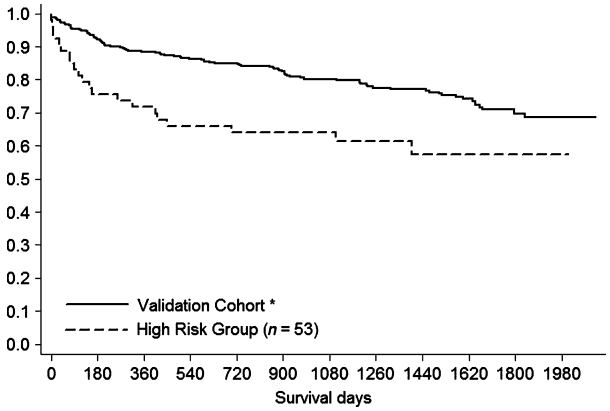

Figure 5 Patient survival in the validation cohort according to Estimated Probability Of Suboptimal Outcome (cut-off at $z \geq 40$).

The high-risk group had significantly longer LOS (48.5 ± 4.5 vs. 25.6 ± 1.3 days; $P < 0.0001$), higher cost (1.53 RU vs. 1; $P < 0.0001$) and inferior patient and graft survival (1- and 3-year survival of 71.7% and 64.2% vs. 87.6% and 79.2%; $P < 0.007$) (Fig. 5).

Discussion

Liver transplantation is the only effective treatment for end-stage liver disease. Although LT is one of the most complex and costly surgical procedures, the main obstacle faced by the transplant community is the global and continuous imbalance between organ demand and supply. This translates into prolonged waiting time on the list, and significant morbidity and mortality while waiting. Also, the organ shortage indirectly influences posttransplant morbidity and mortality, as patients usually reach transplant in more advanced stage of their disease. This shortage has fueled efforts to maximize utilization of existing donor pools (like split liver transplant, marginal donors, etc.), and identify new donor sources (like donation after cardiac death and living donors) [5]. These efforts are not cost-free, as many of them are associated with increased complication rates and inferior outcome.

The organ allocation policy in the US and many other countries is urgency-oriented, and aimed at prioritizing the sickest patients on the waiting list ('sickest-first'). For such system, the MELD score works well because it is efficient in predicting pretransplant mortality. Indeed, the adoption of MELD as the allocation tool decreased new additions to the liver waiting list and improved waiting list mortality [6–8].

Given the persistent and significant lack of organs, the question remains: is an urgency-based approach the most efficient one, as opposed to other allocation

systems, like 'utility-based' (aimed at achieving fewer posttransplant deaths) and 'survival benefit-based' (aimed at reducing the total number of deaths – pre- and posttransplant)? Urgency-based allocation is generally at the expense of utility and vice versa, stemming from the fact that wait list and posttransplant mortality are positively correlated [9]. In this regard, not only is poor outcome disastrous to a recipient, it has severe implications for other patients on the list and the health system as a whole. Every liver utilized with poor outcome is a liver that could potentially have been used for other candidates, with different results.

The combination of 'sickest-first' system and organ shortage causes some patients to reach transplantation too late and too sick, and even though they survive the operation, they fail to thrive. At any given time, each center is responsible for deciding which of its 'leading' candidates is too sick to undergo LT. Unfortunately, there are no quantitative tools in the hands of clinicians to identify patients with predicted inferior post-LT outcomes, even if they do not present an absolute contraindication.

The aim of this study was to improve our ability to predict poor outcome after LT, and develop a prognostication tool that would enable clinicians to better identify suitable candidates for LT. To that end, we used our prospectively maintained database of over 1000 primary DDLT. All retransplant cases and all living-donor-LT were excluded. Of the 643 patients in the SC, only 23 (3.6%) underwent LT for fulminant hepatic failure.

We used the surrogate marker of LOS > 60 days as a measure of poor transplantation outcome. We hypothesized that it represents many aspects of outcome, including morbidity and cost, and not patient and graft survival only. As we did not exclude early mortality cases, those who died before 60 days were considered within the LOS < 60 group. This by itself supports the model, as these patients actually 'worsen' the results of the LOS < 60 group in every parameter excluding cost. Nonetheless, the LOS < 60 group had superior outcome in all parameters (patient and graft survival, liver allograft and kidney function, and cost).

We first validated our hypothesis by showing that that LOS > 60 days correlates well with poor survival (Fig. 2), liver allograft (total bilirubin 4.0 vs. 2.0, $P < 0.04$) and kidney function (creatinine levels 2.0 vs. 1.4, $P < 0.013$) as well as significantly higher cost (RU 3.42 vs. 1, $P < 0.0001$).

We then demonstrated that LOS > 60 depended mainly on four pretransplant characteristics: need for dialysis, mechanical ventilation, MELD score, and age. Based on these variables, patients with poor posttransplant outcome could be identified.

The MELD score was adopted in February 2002 and has since been used as the basis for liver allocation. MELD accurately predicts 3-month mortality rates among patients before LT, and is superior to the previously used Child–Turcotte–Pugh score [10]. Regarding its ability to predict posttransplant outcome, the data are conflicting. Some authors showed no correlation between MELD and short-term posttransplantation survival [11–13]. However, other reports suggest that pretransplant MELD predicts posttransplantation survival reliably [14–17]. In our study, the MELD score did not perform efficiently in predicting posttransplantation outcome (Fig. 1). Specifically, the survival of patients with high (>30) or very low (<10) MELD scores differed by only 10%. This supports the concern, brought up by others, that MELD alone, although useful in predicting pretransplant mortality, lacks sufficient prognostic power to assess outcome after LT. However, the addition of dialysis requirements, patient age, and pretransplant mechanical ventilation significantly improved the prognostic power of MELD and allowed for identification of patients expected to have poor outcome after LT. Using these four parameters, we developed a mathematical tool to predict inferior outcome after LT.

Patients in the SC segregated by the model into the LOS > 60 days category had 1- and 2-year graft survivals of 71.4% and 60.9%, respectively, while the remainder of patients had 1- and 2-year graft survivals of 83.5% and 79.5%, respectively ($P < 0.009$). The performance of the model was then evaluated on a different cohort of patients (VC). When the outcome of those with the highest EPSO value (highest chance for LOS > 60) was compared with that of the rest, it was found to be significantly inferior in every category (survival, organ function, and transplant cost).

Of the four factors independently affecting posttransplant LOS, pretransplant dialysis was the most powerful predictor of poor outcome, followed by MELD (Table 1). Each one of these four factors was found significant for LT outcome in previous studies [18,19].

Although pretransplant hemodialysis affects MELD score calculation, indicating that these variables are not independent, the actual correlation between them was low (correlation coefficient of 0.31). Thus, the inclusion of both MELD score and dialysis as 'independent' predictors greatly improved the performance of the model.

On the basis of a database linking billing claims from a large private payer with the OPTN registry, Buchanan *et al.* examined the relationship between the total cost incurred by 990 LT recipients and their MELD score at the time of transplant. The transplant admission itself represented approximately 50% of the total cost of LT. MELD score of 28–40 was associated with additional charges of nearly $350K in comparison with a score of 15–20. Pretransplant

and transplant admission charges were higher by approximately \$150K and \$64K, respectively, in the higher MELD group. Those in the highest MELD group also experienced longer hospital stays both in the pretransplant period and after LT [20]. Our data demonstrate identical findings, as patients in the LOS > 60 group cost 3.42 times more than those with shorter hospital stay ($P < 0.0001$).

It is important to stress that the EPSO represents the risk level for poor outcome. It does not indicate whether or not a given patient should be offered a transplant. That decision stays in the hand of the clinicians. It is also not possible to describe efficacy tools, like sensitivity, specificity and predictive values for the model offered, as there is no consensus over definitions of outcome for an individual patient.

Conclusion

The implementation of the MELD-based allocation policy was associated with an overall decline in waiting list mortality of about 3.5%, reduction in time to transplantation, and more than 10% reduction in new waiting list registrations. Furthermore, patient and graft survival after DDLT remained unchanged, despite the fact that sicker patients were transplanted. It therefore had a beneficial effect on organ utilization, compared with the previously used methods of organ distribution. Although it carries some inherent limitations, MELD is an excellent tool to sort out the sickest patients on the waiting list. Unfortunately, using MELD as a single tool may, under certain circumstances, lead to transplantation of extremely sick patients with poor outcomes. This may also lead to loss of organs, which could have achieved superior survival in healthier recipients, and to significantly increased cost.

Diverting a vital resource from one patient to another is problematic and ethically challenging. It is relatively easy for the clinician to identify an acute setting in which LT is not acceptable (e.g. septic shock). Chronic progression of the liver disease, with secondary complications, increases the beneficial effect of LT to a certain extent, but there comes a point when the patient is too sick to achieve that benefit. As we and others have shown, this point is not well identified by MELD, as MELD is efficient in predicting pre- and not posttransplant outcome. We believe that because of the limited availability of organs, a consideration should be given to outcome prediction and better patient selection for LT. This may optimize the usage of this scarce resource. Using models such as the offered EPSO should minimize the risk of sub-optimal outcomes. If MELD is used as an 'inclusion criteria' (patient has to be sick enough), other tools should be used as an 'exclusion criteria' (patient should not be too sick).

Authorship

IN: wrote the manuscript. ID: designed and performed the research, analyzed data. MD, PF, AD and AH: collected data. JWM: designed and performed the research.

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Drs Marsh and Dvorchik had full access to all of the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis.

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