CHAPTER X
Improving Liver Allocation: MELD and PELD

INTRODUCTION

The application of a statistical model to liver allocation represents a sea change in the evolution of organ allocation policy. In the past, most organ allocation policy was developed using a consensus of opinion regarding the issues at hand, with little in the way of statistical analysis, mathematical derivation, or validation of principles. As organ allocation has become more scrutinized, a more transparent and justifiable method has become necessary. In this chapter, we report on the rationale and development of the new continuous disease severity scale based on the Model for End Stage Liver Disease (MELD) and Pediatric End Stage Liver Disease (PELD) scores. We outline the early results of liver allocation under this new system and address the regional variation that still exists. Lastly, we describe additional analyses performed by the Scientific Registry of Transplant Recipients (SRTR) that illustrate the utility of this system for measuring results and analyzing transplant center behavior.

DEVELOPMENT AND VALIDATION OF MELD

In the early 1980s, as liver transplantation became an increasingly successful procedure in the United States, donor livers were shared on a voluntary ad hoc basis. The growing number of successful liver transplant programs suggested the need for a more formal organ allocation system — for all solid organs. In 1987, the US Government responded by establishing the Organ Procurement and Transplantation Network (OPTN), which has been operated under Federal contract. Since 1987, attempts to improve and standardize organ allocation have been ongoing and evolving.

The earliest system of liver allocation employed a "sickest-first" principle, with some priority also given to time spent on the transplant waiting list. Initially, the allocation scheme was based on patient location. Patients in an intensive care unit (ICU) received first priority, followed by patients requiring continuous hospitalization, and lastly patients who were being cared for at home. As the waiting list for liver transplantation continued to grow, waiting time became a major factor among patients in any given location, determining who received an organ and who did not. One problem with this allocation system was its lack of standards for what constituted appropriate criteria for admission to the ICU or continuous hospitalization. Indeed, many makeshift ICUs were established merely for the purpose of advantaging patients for transplantation. In addition, because waiting time was a determinate factor, patients were added to the waiting list years before they actually needed a transplant merely to accrue waiting time.

These issues led to the convening of a consensus development conference in 1996 organized by the American Association for the Study of Liver Disease, the International Liver Transplant Society, and American Society of Transplant Physicians, to establish minimal listing criteria for liver transplantation and to design a new allocation system based on disease severity (1). Following the conference, the Child-Turcotte-Pugh (CTP) scoring system was adopted as the measure of liver disease severity to be utilized in allocation (2-5). In addition, a separate Status 1 category was created for patients with fulminant hepatic failure, primary nonfunction of a liver transplant, or hepatic artery thrombosis diagnosed within seven days of transplantation, as well as patients with acute decompensated Wilson's disease. Status 1 candidates were given the highest priority for donor organs (5). Patients with chronic liver disease were grouped into three categories: Status 2A (CTP score ≥ 10 and less than seven days predicted survival), Status 2B (CTP score ≥ 10 or CTP score ≥ 7 with major complications of portal hypertension), and Status 3 (CTP score ≥ 7). However, the waiting list continued to grow to nearly 19,000 patients, leading to ever-increasing waiting time for transplant candidates. With only three defined categories for patients with chronic liver disease, waiting time became a dominant factor in organ allocation. Waiting time as an allocation factor became less acceptable when two published studies documented conclusively that waiting time was not associated with increased death on the waiting list (6,7). Waiting time and the CTP score were imperfect components of the allocation system. Waiting time was not reflective of medical need for transplantation, and the CTP score, which had subjective elements that could be manipulated and had never been validated for predicting mortality on a waiting list, led to a failure of the system to accurately prioritize large numbers of patients waiting for donor livers.

In 1998, the Government published a Final Rule clearly stating that waiting time should be de-emphasized as a major component of organ allocation. The Final Rule requires that the allocation policies be based on sound medical judgment using defined criteria to achieve the best use of donated organs and avoid wasting of organs (8).

In response to this mandate, the OPTN appointed a subcommittee of the Liver and Intestinal Transplantation Committee to develop and carefully assess an appropriate model to meet these criteria. Following a careful review of the literature and examination of existing liver disease survival models, the committee decided to further assess the Mayo End-stage Liver Disease model (later renamed Model for End-stage Liver Disease, or MELD) as a basis for a liver allocation policy. MELD, which had been developed to assess the short-term prognosis of patients undergoing transjugular intrahepatic portosystemic shunt (TIPS) procedures (9), was based on four simple variables, including three biochemical values (serum creatinine, serum bilirubin, and international normalized ratio, or INR, of prothrombin time) and the etiology of the liver disease.

Since it had been previously shown that survival following portosystemic shunt surgery is mainly determined by the severity of the underlying liver disease, it was hypothesized that the MELD model could be used as a prognostic indicator for all patients with advanced chronic liver disease, and potentially could be applied to prioritize patients on the waiting list for a liver transplant (10). The model had the advantage that it relied mainly on objective and standardized laboratory tests, which are readily available and reproducible throughout the country. None of the parameters in the model were subjective or had political overtones, such as age or race, that might make implementation controversial.

Since the MELD model was developed to determine the short-term prognosis of patients undergoing a TIPS procedure, its prognostic value needed to be validated across a wide spectrum of liver disease etiology and severity. The questions regarding MELD and its validation included the following: 1) Would it predict who would live and who would die in patients with decompensated and compensated cirrhotic stage disease? 2) Was the model valid across all liver disease etiologies? 3) Was it dependent on other important factors involved in chronic liver disease, such as complications of portal hypertension? 4) Would it predict who would die on the waiting list? 5) Could use of such a model for allocation reduce deaths on the waiting list and make allocation more equitable?

To validate the MELD model, 282 adult chronic liver disease patients hospitalized at the Mayo Clinic between January 1994 and January 1999 were studied retrospectively (11). Patients with advanced hepatocellular cancer and those having advanced cardiopulmonary comorbidity were excluded from the analysis. Patient survival was assessed from the day of hospitalization until death or last follow-up. Since the aim was to validate the MELD score as a severity index of liver disease to predict short-term mortality, three-month mortality was chosen as the primary outcome measure, but one-year outcomes were also assessed. The validity of the logistic regression model was determined using a c-statistic to evaluate the area under the receiving operating characteristic curve (12). In addition, overall mortality based on baseline MELD and CTP scores were assessed (Table X-1). The baseline MELD score appeared to be as good or better than the CTP score in predicting mortality, and had the advantage of employing variables that are available, standardized, reproducible, and objective. With this initial positive study, assessment of patient survival using the MELD score was validated in three other groups of patients including patients with compensated cirrhosis, cholestatic liver disease, and decompensated cirrhosis. In all instances, the MELD score was found to be an excellent predictor of three-month mortality, with a c-statistic ranging from 0.80 to 0.87 (13).

An additional question was whether complications of portal hypertension (e.g., ascites, encephalopathy, or variceal bleeding) affect the ability of the MELD score to predict mortality risk. Their inclusion in the model added little improvement in fit to predicted three-month mortality. Similarly, etiology was found to contribute very little to MELD's predictive power. The investigators concluded that a MELD score made up of the three laboratory values could be used without data on complications of portal hypertension and etiology (12).

The last and most important study to be completed to validate MELD applied the model to the national waiting list (14). In this study, the MELD equation was altered so that all laboratory values < 1 were rounded up to 1.0 to prevent coefficients with negative values. The etiology variable was removed from the original equation in response the previous study showing that this factor contributed little additional predictive value (Figure X-1). Between November 1999 and December 2001, MELD values were studied in 3,437 adult liver

Table X-1. Relationship Between MELD, CTP Score, and 3-Month Mortality in Hospitalized Cirrhotics (Group A)

MELD Score	≤9	10-19	20-29	30-39	≥40
3-Month death rate	4 (6/148)	27 (28/103)	76 (16/21)	83 (5/6)	100 (4/4)
CTP Score		**A**	**B**		**C**
3-Month death rate		4 (3/77)	14 (13/93)		51 (35/69)

Note: Values expressed as percent (number/total). Source: Weisner et. al., 2001 (13).

transplant candidates with chronic liver disease who were added to the waiting list at status 2A or 2B. Of this cohort, 412 (12%) died during the initial three months of follow-up. Waiting list mortality increased directly in proportion to the MELD score at listing (Figure X-2). As shown in Figure X-3, the c-statistic with three-month mortality as the endpoint was 0.83 for MELD, compared to 0.76 for the CTP score ($P < 0.001$); a larger area under the receiver operating characteristic (ROC) curve indicates better identification of illness. These data suggested that the baseline MELD score accurately predicts three-month mortality among patients with chronic liver disease on the liver waiting list, and therefore could be applied usefully for allocation of donor livers (Table X-2).

Figure X-1. Comparison of Original MELD and OPTN/UNOS MELD PELD Equations

Original MELD

MELD=(0.957 x LN (creatinine) + 0.378 x LN (bilirubin) + 1.12 x LN (INR) + 0.643) + 0.643 x (cause of cirrhosis*)

OPTN/UNOS MELD

MELD =(0.957 x LN (creatinine**) + 0.378 x LN (bilirubin**) + 1.12 x LN (INR**) + 0.643)

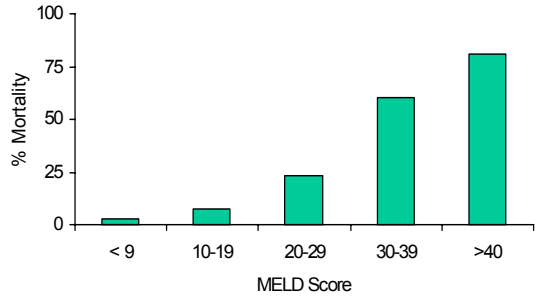
PELD

PELD= (0.436 x age†) - (0.687 x log (albumin)) + (0.480 x log (bilirubin)) + (1.857 x log (INR)) + (0.667 x growth failure‡)

* Cholestatic liver disease = 0; all others = 1
** Values < 1.0 rounded up to 1.0
† Age < 1 year = 1; all others = 0
‡ Values > 2 standard deviations from the norm = 1; all others = 0

Source: Wiesner et al, 2003. (14)

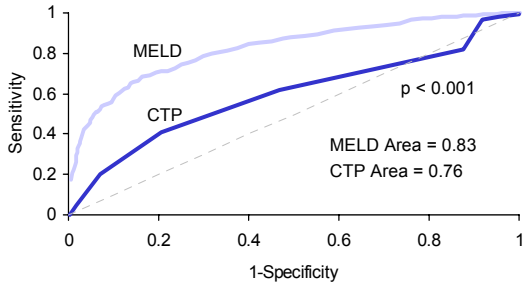
Figure X-2. Three-Month Mortality Based on Listing MELD in Patients on the OPTN Waiting List



Source: Wiesner et al, 2003. (14)

Policy developers recognized that the MELD and PELD scores would not serve all candidates for liver transplantation equally well. The most important "exceptional" diagnosis was hepatocellular carcinoma (HCC). Recent studies had suggested that excellent results could be achieved for liver transplant candidates

Figure X-3. Area Under the Receiver Operating Characteristic (ROC) Curve for the MELD and CTP Models



Source: Wiesner et al. The model for end-stage liver disease (MELD) and allocation of donor livers.Gastroenterology, 2003.Reprinted with permission.

with early-stage HCC (15-17) but that prolonged waiting times increased the dropout rate and diminished these results when liver transplantation was assessed in an intention-to-treat approach (18,19). Most of these candidates face a risk of tumor progression that is greater than their risk of death and therefore some estimate of the risk of tumor progression was necessary to incorporate these patients into the new system. By equating this risk of progression with the risk of death as defined by the MELD score, a similar priority score could be assigned for these patients (20). Initially, OPTN policy estimated this risk at 15%, corresponding to a MELD score of 24 for candidates meeting Stage I criteria, and 30% (MELD score of 29) for Stage II patients (21). Early experience with the new system

Table X-2. Comparison of MELD and CTP Allocation Schemes

	MELD Allocation Scheme	CTP Allocation Scheme
Development & rationale	TIPS Outcome	Surgical shunt outcome
Assessment	Prospective	Empiric
Parameters	Objective	Some are subjective
Variability	Minimal	Center-to-center interpretation
Spectrum	Continuous	Ceiling effect, categorical
Validation	Yes	No
Allocation emphasis	Disease severity	Waiting time

Source: SRTR.

revealed that the dropout rate for HCC candidates was extremely low and that candidates without HCC but with similar MELD scores had higher mortality rates compared with the HCC patients. (Table X-3 and Table X-4) For this reason, in April 2003 the HCC

Table X-3. 90-Day Transplant and Mortality Rates After Waitlisting for Liver (Only), by Calculated MELD/PELD Lab Score

Calculated Score	N	Mean Lab (Match) Score	Death Rate[1]	Median MELD/PELD at Death	Transplant Rate[2]	Median MELD/ PELD at Transplant
Adult Status 1	387	31.3	38.3%	38	68.0%	35
MELD: Lab (No Exceptions)						
6-10	1,277	8.4	1.6%	10	5.6%	9
11-10	3,219	14.8	3.9%	20	14.4%	17
21-25	524	23	13.7%	30	42.2%	24
24	*(104)*	*24*	*14.8%*	*30*	*44.2%*	*24*
26-30	241	28	34.0%	31	62.1%	30
29	*(47)*	*29*	*47.6%*	*36*	*64.8%*	*29*
31-40	363	36.3	63.3%	40	79.6%	37
Overall	5,624	16.0	8.2%	33	22.1%	22
MELD: HCC						
24	77	12.6	5.9%	24	43.9%	24
29	388	11.9	5.6%	29	76.1%	29
Overall	465	12.0	5.6%	29	70.7%	29
Other non-HCC Exceptions						
Adult	106	15.2 (28.1)	14.8%	32	65.1%	29
Pediatric	43	5.1 (29.7)	2.6%	39	67.3%	30
Pediatric Status 1	156	25.6	22.5%	31	66.7%	22
PELD: Lab (No Exceptions)						
(-11)-(-1)	60	-4.8	0.0%	.	16.5%	-3
0-10	115	5.0	1.8%	5	15.3%	7
11-20	113	15.0	3.2%	16	34.1%	17
21-30	62	24.5	13.9%	25	43.7%	25
31-40	13	34.8	19.2%	33	42.3%	29
41+	9	56.8	33.3%	46	66.7%	49
Overall	372	12.0	7.8%	25	37.0%	18

1: Censored at removal from the waiting list for reasons other than death. 2: Censored at removal from the waiting list for reasons other than cadaveric transplant.

Notes on Table X-3: Table X-3 shows the 90-day outcomes by the MELD/PELD distribution for all patients including the average MELD/PELD score at death and transplant. Similarly, Table X-4 shows the 30-day outcomes by MELD/PELD distribution. The study population includes all patients on the liver waiting list that were added between 2/27/02 and 11/28/02 for the 90-day outcome tables and 2/27/02 and 1/27/03 for the 30-day outcome tables. Patients waiting for a liver-intestine were excluded from the analyses.

Non-Status 1 patients granted an exception within 30 days of date of listing had the exception score used for calculation of their match MELD/PELD. Similarly, the first exception MELD/PELD score granted within 30 days of wait-listing for patients listed between 2/27/02 and 1/27/03 (or 11/28/02 for 90-day outcomes) was used for calculation of the match MELD/PELD score. Follow-up time (start date) began on the listing date for non-exception patients listed between 2/27/02 and 1/27/03 (or 11/28/02 for 90-day outcomes), and on the date of the exception for patients receiving an exception score. Patients with automatically assigned MELD/PELD score of 6 were allowed to have their start date delayed for up to 30 days if an updated score became available during this time. All patients were followed for 30 and 90 days from the start date.

Unadjusted Cox regression models were used to model 30-day and 90-day rates of transplantation and death on the waiting list. Time to transplant models were censored at the earlier of waiting list removal for reasons other than cadaveric transplant (including death) or 30 days (or 90 days). Time to death models were censored at removal from the waiting list for reasons other than death (including transplant) or 30 days (or 90 days). Modeling the transplantation and death rates in this manner addressed the problem of the competing risks of transplantation and death. Status 1 patients were analyzed separately.

Source: SRTR Analysis. Data as of August 1, 2003.

Table X-4. 30-Day Transplant and Mortality Rates After Wait-Listing for Liver (only), by Calculated MELD/PELD Lab Score

Calculated Score	N	Mean Lab (Match) Score	Death Rate[1]	Median MELD/PELD at Death	Transplant Rate[2]	Median MELD/ PELD at Transplant
Adult Status 1	471	31.4	35.1%	38	66.8%	34
MELD: Lab (No Exceptions)						
6-10	1,487	8.5	0.4%	17	2.3%	9
11-10	3,807	14.8	1.0%	19	6.2%	17
21-25	636	23	4.1%	29	20.7%	24
24	*(126)*	*24*	*5.4%*	*32*	*22.8%*	*24*
26-30	305	28	19.7%	31	45.0%	29
29	*(60)*	*29*	*29.1%*	*29*	*42.7%*	*29*
31-40	458	36.2	43.1%	40	64.9%	37
Overall	6,693	16.2	4.8%	36	14.4%	26
MELD: HCC						
24	94	12.9	1.2%	24	25.9%	24
29	489	12.0	1.3%	29	47.1%	29
Overall	583	12.2	1.3%	29	43.7%	29
Other Non-HCC Exceptions						
Adult	124	15.1 (27.8)	8.5%	32	39.5%	29
Pediatric	47	5.5 (29.7)	2.3%	39	33.3%	29
Pediatric Status 1	195	26.2	22.8%	31	53.8%	23
PELD: Lab (No Exceptions)						
(-11)-(-1)	71	-4.9	1.5%	-3	4.6%	-3
0-10	134	5.1	1.5%	5	6.8%	7
11-20	142	15.1	2.9%	16	16.3%	17
21-30	74	24.4	4.6%	29	22.4%	25
31-40	15	34.7	17.5%	33	13.3%	26
41+	11	55.1	40.0%	32	54.5%	49
Overall	447	12.1	7.1%	18	23.7%	19

1: Censored at removal from the waiting list for reasons other than death. 2: Censored at removal from the waiting list for reasons other than cadaveric transplant.

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Source: SRTR Analysis. Data as of August 1, 2003.

"exceptional" MELD points were reduced to 20 and 24 for Stage I and Stage II candidates, respectively.

The OPTN also recognized that other rarer diagnoses and special circumstances might also arise in which MELD score would not be a good determinant of the need for a liver transplant. The new policy provided for the other "exceptional" cases by developing a regional peer-review process. These regional peer-review boards (RRBs) were assigned the responsibility of reviewing centers' applications for increased priority for these exceptional cases. If the RRB finds that the clinical circumstances of an individual case represent greater need as determined by the center's application for a higher MELD score, then the candidate is assigned that higher score. In cases where the RRB does not agree with the center's assessment, the center is free to appeal the RRB decision or reapply for a different MELD score.

At the time of organ offer, candidates are prioritized by their "match score." For patients without RRB-approved requests for an increased MELD score, the match score is simply the MELD score as calculated by laboratory values alone. For patients with RRB-approved MELD score requests, their match score is the new RRB-approved score. A full description of the OPTN policy has been published (21) and current policy language can be found at www.optn.org.

PEDIATRIC END-STAGE LIVER DISEASE (PELD) SCORE

Development and Validation of PELD Criteria

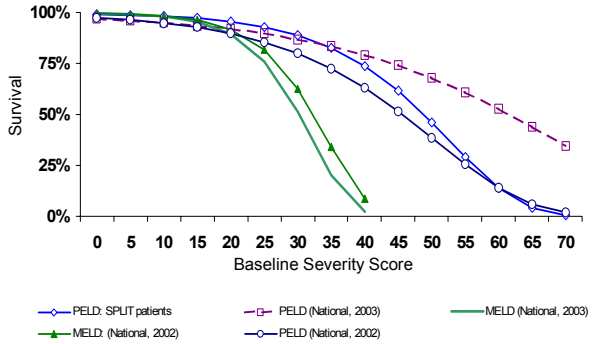
Concurrent with the development of MELD, the pediatric hepatology community developed a similar scoring system relevant to the unique characteristics of children with chronic liver disease. In contrast to the MELD score, which was originally developed in a selected population of adult patients with end-stage liver disease requiring a TIPS procedure (10), the PELD score was developed from data representative of a cross-section of children awaiting liver transplantation (22). These data derived from the Studies of Pediatric Liver Transplantation (SPLIT), a consortium of 38 pediatric liver transplant centers that has been enrolling children who are eligible for liver transplantation in the United States and Canada since 1995 (23). At the time of development of PELD, the SPLIT database was enrolling approximately 50% of all children placed on the waiting list for a liver transplant in the United States.

There was general agreement between the pediatric and adult hepatology groups that the basic principles underlying the development of MELD and PELD should be the same, and that only objective verifiable parameters would be included to avoid the possible bias of subjective assessments such as ascites or encephalopathy (13). Events such as variceal bleeding and spontaneous bacterial peritonitis would not be included in the scoring system, based on previous studies showing that the outcome of such events was dependent on the severity of the underlying liver disease, rather than the events themselves in children (24) and adults (25). It was also agreed that the number of parameters in the model would be limited so that calculations of the score would be straightforward. Development and testing of both models would use a similar statistical methodology (c-statistic). Like MELD, death at three months on the waiting list was the primary endpoint. A second composite endpoint of death or moving to the ICU before transplant was also examined, as described elsewhere (22), but was not incorporated into the PELD score.

The SPLIT data analyses included Kaplan-Meier estimates of the probability of death on the waiting list for 18 different variables. For the development of PELD, six variables were selected based on statistical significance and agreed-upon principles of model development. These were bilirubin, INR, calculated glomerular filtration rate (GFR), serum albumin, age, and growth failure. There were 884 children evaluable for the endpoint of death on the waiting list. From the multivariate analyses, the significant factors that were incorporated into the PELD score were bilirubin, INR, albumin, age < 1 year, and growth failure (defined as height or weight more than two standard deviations below normal for age and gender). The c-statistic for death at three months on the waiting list was 0.92 (95% confidence interval 0.85 - 0.99) (22). Mazareigos et al. independently validated the PELD score and confirmed its ability to predict death on the waiting list in a large single-center data set (26).

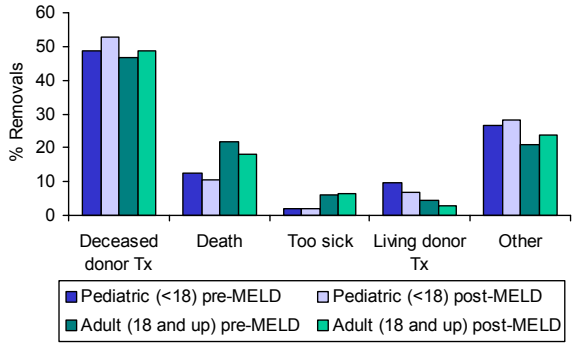
A comparison of the probability of death at three months for a given PELD or MELD score is shown in Figure X-4. The figure shows the initial curve generated from the SPLIT database for PELD, as well as curves based on national waiting list data since the implementation of MELD and PELD. Note that the PELD curves fall to the right of the MELD curves at higher scores, meaning that for a given score in this range the probability of death on the waiting list is less for a child than for an adult. In contrast, at lower scores the mortality risk associated with PELD is higher than associated with MELD. However, it was decided to accept the PELD score without an adjustment factor that would attempt to equate the probability of the death on the waiting list for a given score between children and adults. This has the effect of giving children who are somewhat less ill than

Figure X-4. Predicted Probability of Waitlist Death at Three Months, by Severity Score



Source: SPLIT and SRTR analyses, October 2003.

Figure X-5. Reasons for Removal from the Liver Waiting List Before and After Implementation of MELD/PELD



Source: SRTR Analysis. Data as of August 1, 2003.

adults with the same score the same level of priority, potentially directing appropriate organs to children at a less severe stage in their disease. In addition, the new policy respects the previous policy of trying to direct pediatric organs to pediatric recipients and maintains the stipulation that pediatric patients with chronic liver disease who require ICU care may be designated Status 1.

Effects on the Liver Waiting List

Since the implementation of MELD and PELD, the pediatric transplant community has been studying their effects on wait-listed children. With the increasingly dominant number of adults on the liver waiting list, access of pediatric patients to transplants under the new allocation system is of concern. Figure X-5 shows the reasons for removal from the waiting list for pediatric and adult patients before and after the implementation of PELD and MELD (2/27/01 - 2/26/02 and 2/27/02 - 2/26/03, respectively). In the period before MELD/PELD, 10,944 patients were added to the liver waiting list, of which 1,035 (10%) were children, compared to 856 (9%) in the MELD/PELD period. Overall, 47% of adults were removed for deceased donor transplant in the pre-MELD/PELD era compared to 49% in the MELD/PELD era. For children, the comparable figures are 49% pre-MELD/PELD and 53% post-MELD/PELD. These data suggest that under the new allocation system, the percentage of children and adults on the waiting list who received a deceased donor organ increased slightly between the two periods. From Figure X-5 it can also be seen that the number of children who died or became too sick to transplant dropped in the MELD/PELD period, and that for both children and adults, there was a reduction in living donor transplants between the two periods. There was also an increase in removals from the list for "other" reasons in the MELD/PELD period. This increase in removals for "other" reasons likely occurred because when centers were required to re-examine wait-listed patients when the MELD/PELD system was first implemented, they may have then found patients who were not appropriate candidates for transplantation.

90-Day Outcomes on the Waiting List by Laboratory MELD/PELD Score

Table X-3 shows the 90-day outcomes for adults and children on the waiting list. Relative rates of death, and deceased donor transplant were examined for all patients added to the list between 2/27/02 and 11/28/02. Mean and median laboratory PELD and MELD scores at time of deceased donor transplant or death were included. (Laboratory MELD/PELD scores are based on laboratory data and do not include additional points assigned by regional review boards.) Separate unadjusted Cox regression models were used to model death and transplant by which MELD/PELD category or Status 1, and liver-intestine candidates were excluded. Comparing adult patients (N = 5,624) to the pediatric patients (N = 372) 90 days after listing, the rates of death were nearly the same (both approximately 8%), whereas 37% of children compared to 22% of adults received a deceased donor transplant, and 5.9% of children compared to 0.9% of adults received a living donor transplant. Removal from the list for being too sick for transplant was 0.5% for children compared to 1.2% for adults. The median lab MELD/PELD score at deceased donor transplant was 18 for children and 22 for adults, whereas a larger difference was found in the median MELD/ PELD score at death for adults and children (33 and 25, respectively). Overall, compared with adult candidates, a higher proportion of children received deceased and living donor transplants and a lower proportion of children were removed for death or being too sick. In general, children received their deceased donor transplants at lower PELD scores than the adults. These results suggest that children's

transplantation rates or removal rates were not adversely affected by the new system.

PELD Score at Listing and Time of Transplantation

Table X-5 shows the mean and median laboratory PELD scores at listing by age range for children listed between 2/27/02 and 3/30/03 and by transplant number (no previous transplant versus previous transplant). At listing, children younger than 1 had the highest PELD scores and those between 6 and 10 years had the lowest. Children with a previous transplant tended to have a higher PELD score at listing. The mean and median PELD scores comparing blood type are relatively similar, as is shown in Table X-6.

For the period 2/27/02 - 2/26/03, the mean and median allocation MELD or PELD score (the score at the time of allocation, or "match score," which includes scores by exception) is shown for adult and pediatric patients in Table X-7. This is compared to the lab MELD/PELD score. For both Lab and allocation (match) scores, pediatric candidates are receiving their transplants at lower values compared with adults. But the scores are similar for removal due to death or too sick for children compared with adults, as seen in Table X-8. Figure X-6 shows deaths adjusted per 1,000 patient years on the waiting list comparing adults and children before and after the implementation of MELD and PELD. In both periods, the death rate for all children was lower than for adults. However, for children <1 and <2 years of age at listing, the death rate was considerably higher than for adults. Currently, there are 224 deaths per 1,000 patient years for children <2 years, compared to 137 for adults. This is an increase from 183 per 1,000 patient years death rate for young children prior to the implementation of PELD and MELD.

Table X-5. Mean and Median PELD at Listing by Age and Previous Transplant

Categories	Mean PELD	Median PELD
Age at listing		
<1 Year	19.3	18.0
1-5 Years	14.3	13.0
6-10 Years	10.8	7.0
11-17 Years	12.5	10.0
Previous liver transplant		
No	15.0	14.0
Yes	18.2	17.0

Source: OPTN/SRTR Data as of August 1, 2003. Includes all listings between 2/27/02 and 3/30/03.

Table X-6. Mean and Median PELD at Listing by Blood Type

Blood Type	Mean PELD	Median PELD
A	14.4	14.0
AB	13.2	11.0
B	14.9	16.0
O	16.6	16.0

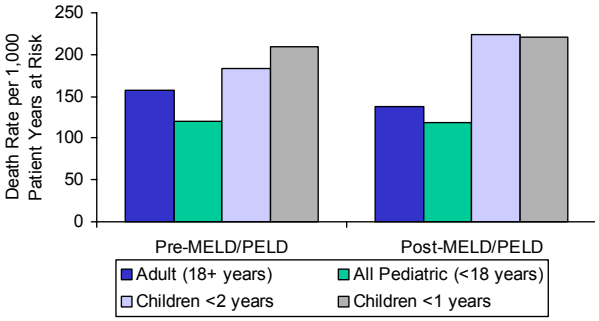
Source: OPTN/SRTR Data as of August 1, 2003. Includes all listings between 2/27/02 and 3/30/03.

Table X-7. Mean and Median Lab and Match MELD/PELD Scores by Status and Age, Deceased Donor Transplants

Age Group	Mean MELD/PELD	Median MELD/PELD
Adult		
Lab score	19.3	17.0
Match score	21.0	24.0
Pediatric		
Lab score	9.9	9.0
Match score	17.6	17.0

Source: OPTN/SRTR Data as of August 1, 2003. Includes all transplants between 2/27/02 and 2/26/03. Lab scores are based on laboratory values alone; match scores include points from RRB-approved exceptions.

Figure X-6. Deaths per 1,000 Patient Years on the Liver Waiting List Before and After Implementation of MELD/PELD



Source: SRTR Analysis. Data as of August 1, 2003.

Table X-8. Mean and Median Lab and Match PELD Scores by Removal Reason and Age

Categories			Mean PELD	Median PELD
Removed for:	Adult	Lab score	23.5	21.0
Death		Match score	18.8	19.0
	Pediatric	Lab score	21.8	23.0
		Match score	22.3	23.0
Removed for:	Adult	Lab score	21.6	19.0
Too sick		Match score	20.0	20.0
	Pediatric	Lab score	21.0	22.5
		Match score	24.2	23.5

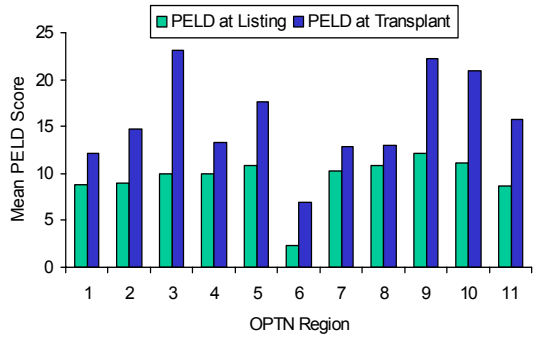
Source: OPTN/SRTR Data as of August 1, 2003. Includes all transplants between 2/27/02 and 2/26/03. Lab scores are based on laboratory values alone; match scores include points from RRB-approved exceptions.

Table X-9. Percentage of Children Listed and Transplanted at Match PELD Score Ranges

PELD Groups	Percentage at Listing	Percentage at Transplant
<10	47.4	32.1
10-14	18.7	11.4
15-19	15.8	11.7
20-24	10.1	14.3
25-29	4.6	11.0
30-34	1.4	4.2
35-39	0.6	4.9
40+	1.3	10.4

Source: OPTN/SRTR Data as of August 1, 2003. Includes listings between 2/27/02 and 3/30/03 and transplants between 2/27/02 and 2/26/03.

Figure X-7. Mean PELD Score at Listing and at Transplant, by Region



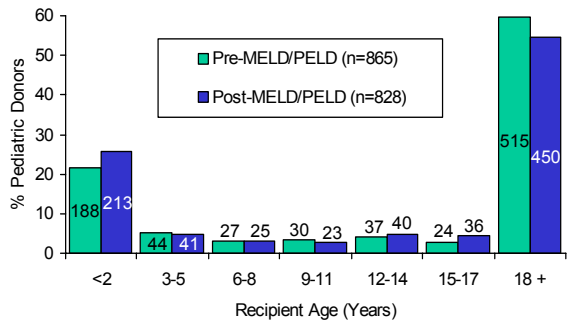
Source: SRTR Analysis. Data as of August 1, 2003.

Table X-9 shows the percentage of children listed (excluding Status 1) for ranges of the allocation PELD score, and the percent of children transplanted at ranges of the allocation PELD score. The highest proportion of children are listed and transplanted at a PELD score of <10. Figure X-7 shows the considerable variation in distribution of allocation PELD scores (excluding Status 1) by region at the time of listing and at the time of transplant. Some of this variation is due to the small number of pediatric transplants performed in some regions.

Pediatric Donor to Pediatric Recipient Policy

A previous study from the SRTR showed that the odds of graft failure were reduced significantly if pediatric recipients received livers from pediatric donors (<18 years of age) (27). This study resulted in a change in liver allocation policy in 2000 to preferentially allocate pediatric donor livers to pediatric recipients within medical urgency status and according to the usual geographic distribution rules. In order to preserve this concept under the MELD/PELD allocation policy, it was decided that livers from pediatric donors would be allocated first to those pediatric candidates with probability of death within 90 days greater than 50%. This policy was established without data to assess its effect. A preliminary analysis compared recipient age for 865 pediatric donors prior to MELD/PELD to 828 pediatric donors since its implementation (Figure X-8).

Figure X-8. Comparison of Recipient Age of Pediatric Donor Organs Before and After Implementation of MELD/PELD



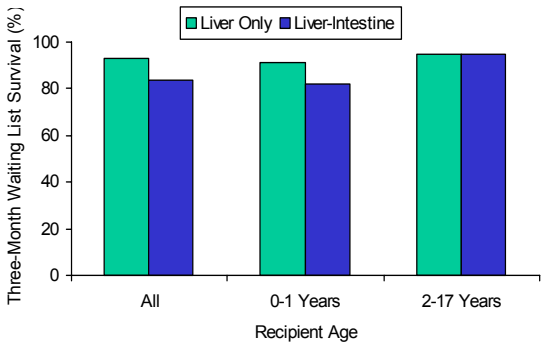
Source: SRTR Analysis. Data as of August 1, 2003.

Table X-10. Relative Risk of Waiting List Mortality by ΔPELD, Adjusted for PELD Score

ΔPELD over Prior 30 Days	PELD Changes (N events)	Relative Risk	*P*-value
Decreasing (slope <0)	268 (4)	2.36	0.219
Stable (0≤ slope ≥5)	761 (9)	1.00	(ref.)
Increasing (slope >5)	140 (8)	5.98	0.0005

Source: SRTR Final Analysis for the OPTN Liver-Intestine Committee, February 21, 2003.

Figure X-9. Three-Month Waiting List Survival Probabilities for Pediatric Liver and Liver-Intestine Candidates



Source: SRTR Analysis for the OPTN Pediatric Committee, July 24, 2002, Table 2.2.

Overall, adults received 60% of pediatric donor livers before MELD/PELD and 54% after its implementation. Organs from older pediatric donors (9 years or older) were much more likely to be placed into adult recipients than pediatric recipients: 83% before MELD/PELD and 77% afterward. This suggests either that there were no pediatric candidates in the local distribution area available at the time of the pediatric organ offer or that the system has not been successful in preferentially directing pediatric organs to pediatric recipients. Additional analyses will be required to determine the cause for these findings.

Change in PELD Score and Death Before Transplant

It has been shown that changes in the MELD score while waiting have a significant effect on the chance of dying prior to transplant. Adults with increasing MELD scores over time have a higher probability of death while waiting, and conversely adults whose MELD scores decreased over time had a decreased chance of death on the waiting list (28). An analysis was undertaken to see if the same findings applied to pediatric candidates awaiting liver transplantation (Table X-10). The change in PELD score over the prior 30 days (ΔPELD) was included in a Cox model in which the time at risk for all patients began at 30 days from time of listing. Deaths and changes to Status 1 before day 30 were not included in the mortality model. All patients were followed in a time-dependent Cox model from day 30 until the earliest of death, change to Status 1, or December 1, 2002. Despite the relatively small number of events (21 events among the 393 pediatric candidates in the study), the effect of an increasing ΔPELD was found to significantly increase the relative risk of death on the waiting list (RR = 1.10, $P < 0.0001$). The ΔPELD was also a significant predictor of waiting list mortality for an increase of greater than 5 points (RR=5.98, $P = 0.0005$). A decreasing ΔPELD also showed an adverse trend on waiting list survival, although this did not reach statistical significance. This might be explained by the finding that patients with a decreasing ΔPELD were found to have a corresponding increase in serum albumin. An increase in albumin would lower the PELD score, despite the fact that artificially increasing the albumin by infusions would indicate a worsening condition.

PELD Score and Mortality Risk, Liver Only vs. Liver-Intestine Transplant

It has been reported that up to 40% of children awaiting liver-intestine transplant die before receiving the transplant. This is particularly a problem for the youngest candidates (29). The difficulty lies in finding appropriate sized organs for candidates for liver-intestinal transplantation. Using OPTN/SRTR data, deaths on the waiting list for pediatric candidates were analyzed, comparing liver only candidates to liver-intestine candidates. Between July 1, 1997 and June 30, 2000, 2,171 children were listed for liver only, compared to 227 listed for a liver-intestine transplant. As can be seen in Figure X-9, survival on the waiting list was lower for the children requiring liver-intestine transplant, and this was particularly evident for those less than 1 year of age. A further analysis showed that for a given PELD score, death rates were 3.6 times higher for liver-intestine candidates ($P=0.01$) than for liver only patients. The PELD score itself does not predict waiting list mortality differently for liver only compared to liver-intestine patients. Using the PELD equation, the 3.6-fold increase in the average relative risk of death equated to 12 points for the "average" pediatric patient. This finding led to modification of the waiting list policy for children listed for liver-intestine transplant, who now receive additional PELD points equivalent to an incremental 10% risk of three-month mortality above what their standard PELD score would indicate. This policy was also extended to adult patients waiting on the list for liver-intestine transplants.

The Impact of PELD: Summary

Since the institution of MELD/PELD, children do not appear to be disadvantaged in their access to deceased donor livers as compared to adults. Children are handled in the organ allocation policy preferentially by directing pediatric organs preferentially to pediatric patients. Also, in contrast to adult patients, pediatric patients with chronic disease may be moved to Status 1 priority with admission to an ICU. Death or removal due to becoming too sick for transplant on the waiting list has decreased in the MELD/PELD era for both children and adults. However, children younger than 2 years of age still have a considerably higher rate of death on the waiting list than adults. There is considerable variation by region in the PELD score at listing and at transplant, suggesting that regional differences may exert important effects on pediatric patients' chances of transplant. In assessing the 90-day outcome on the waiting list, the percentage of children who receive a deceased donor organ is somewhat higher than the percentage of adults, and the proportion that die on the waiting list is somewhat lower compared to adults. Further analyses with more data and longer follow-up times are needed to determine whether or not these differences are clinically and statistically important. The change in PELD score while awaiting a transplant appears to be an important predictor of outcome for children on the waiting list, as it is for adult patients. At least from preliminary results, the percentage of pediatric donors allocated to children has risen slightly with the implementation of MELD and PELD. Children awaiting combined liver-intestine transplant have a high mortality on the waiting list, justifying the assignment of a higher PELD score than the calculated score to compensate for the increased relative risk of death on the waiting list. Finally, the important question as to the outcome of children after transplantation in the MELD/PELD era awaits further analyses.

30-DAY AND 90-DAY WAITING LIST OUTCOMES

The implementation of the MELD and PELD systems has allowed for the accurate estimation of the relative risk of 30-day mortality for patients on the waiting list for liver transplantation. The information provided herein demonstrates some of the early effects of these systems.

A logical first look at the data is to examine what the waiting list looked like at the end of 2001 and compare this to the waiting list at the end of 2002. As the MELD system was implemented in the first quarter of 2002, the year-end snapshot of the waiting list would demonstrate the combined result of reclassification of candidates using MELD/PELD.

At the end of 2001, 66% of the patients on the waiting list were Status 3 (least urgent medical status at the time) *[Table 9.1]*. Status 2B (most urgent status outside of the intensive care unit) comprised 17% of the patients, while less than one percent were Status 1 or Status 2A, usually meaning the patients were in the ICU.

In 2002, the percentage of patients listed at Status 1 at the year end was unchanged, an expected result since the definition of Status 1 did not change. The total percentage of patients listed in the lowest MELD ranges total close to the patients in the lowest statuses in 2001, suggesting that there was not a marked change in characteristics of patients listed or transplanted during the first nine months after MELD/PELD implementation.

An interesting finding is that the number of patients waiting for transplantation decreased by more than 1,000 in 2002. This is primarily due to a decrease in new waiting list registrations, as there were approximately 1,500 fewer registrations than in either of the previous two years *[Table 9.2]*. It may be speculated that the change in the system to MELD/PELD, which markedly de-emphasized waiting time, may have led centers to list patients more slowly as there is little to be gained by pre-emptive listing. Although there was an increase in the number of transplants in 2002 (approximately 300), this was not a major contributing factor to the shrinking waiting list *[Table 9.4]*.

One unexplained finding is the dramatic increase in the number of temporarily inactive patients *[Table 9.1]*. Through the decade, the number of these patients has steadily increased, and it is unclear why MELD/PELD would lead to this change. At the time of implementation of MELD/PELD, all centers were required to submit laboratory data in order to assign a MELD/PELD score. Many centers may have found that some of these patients were lost to follow-up, had improved in condition or had died before the initiation date, and therefore were removed for "other reasons."

The MELD/PELD scores of new waiting list registrants shows that the most frequent range of MELD points was 11-20, more than twice as high as patients in the lower range *[Table 9.2]*. This is of interest when compared to the year-end waiting list, where the percentages are more similar. This difference suggests that the new registrants are more ill than the patients previously added to the waiting list. There were a substantial number of registrations for patients with hepatocellular carcinoma (HCC). A different trend was seen among

pediatric registrants, of whom the largest number of registrants had PELD scores in the lowest range.

There is a marked association of increasing death rates on the waiting list with higher MELD scores *[Table 9.3]*. There is a 58-fold higher rate of death for patients listed with a score of >30 as compared to patients listed in the lowest MELD range. This near-logarithmic progression is a reflection of the steepness of the curve of 30-day survival plotted against MELD score. A similar trend is seen in the death rates in the pediatric population, but the small number of patients, particularly with the highest scores, may hide a more dramatic increase. The death rate among Status 1 candidates demonstrates a decade-long decrease. The death rate in patients listed with HCC is relatively low, which may hide the true risk of these candidates, who are more likely to be removed from the waiting list prior to death.

Table X-4 presents a snapshot of what occurs within 30 days after listing for various ranges of MELD (using lab MELD scores). While this table does not take into account changes in MELD score that occurred during this period, it does show the effect of the MELD system. The strong predictive gradient effect of the MELD score is seen with increasing mortality as the MELD score increases. Fortunately, it also appears that the 30-day transplant rate is also strongly affected by MELD: as the MELD score at the time of listing increases, the percentage of patients transplanted rises. This is a very strong suggestion that the MELD system works as designed. It appears to prioritize patients for transplantation.

The PELD system does not appear to be faring as well in terms of 30-day outcomes. There is not the steep gradient of death rates that is seen in the MELD system, as the slope is relatively flat and increases sharply only at the higher scores. A similar trend is seen for transplant rates, which do not rise continuously with increasing scores. Some of the effects of the PELD score may be hidden among Status 1 transplants. While Status 1 among adults is restricted to candidates without chronic liver disease, there is no such limitation among pediatric candidates. Some of the pediatric recipients with the highest PELD scores may have moved into the Status 1 category, effectively hiding the effect of the PELD score on prioritizing these patients in the Status 1 designation. The results of the PELD system at 90 days (Table X-3) are more reassuring about the effectiveness of the PELD system. Here, the death rates demonstrate a better gradient and the transplant rates increase as expected.

A striking finding of these analyses is the transplantation rates among patients with exception MELD/PELD scores, primarily those with HCC. These patients are given MELD points to match a predefined risk of death in this patient population. While the death rates for this group (Table X-4) are low, the major risk for these patients is that their tumors may progress to a stage that would prevent transplantation. These patients were given a MELD score of 24 or 29 depending upon tumor stage. The effect of these exception scores is better demonstrated in Table X-3, which shows that nearly 71% of candidates received a transplant within 90 days. Given these high rates of transplantation, the exception points given to these candidates were decreased to 20 and 24 early in 2003 to lessen the advantage and disparity. A preliminary review of 796 cases of candidates with increased priority due to their HCC meeting criteria identified 666 cases for whom a pathology report of the explanted liver was received by the OPTN. Review of these pathology reports identified 2 (0.3%) cases of cholangiocarcinoma, 11 (1.65%) cases of mixed hepato-cholangiocarcinoma, 161 (25%) benign or indeterminate lesions, and 488 (73.3 %) with HCC. Three hundred eighty three (43%) cases were treated with some form of ablative therapy prior to transplant. Micro- or macro-vascular invasion was present in 7% and 3% of cases respectively. The distribution of lesions by stage was: 23% stage 0, 8% stage 1, 37% stage 2, 10% stage 3, 8% 4a, and 12% 4b. Relative to the pre-operative staging, 34% of cases had a more advanced stage on the pathology report, 36% had no change and 8% had a histologic stage less than pre-operative stage. Twenty-two percent had no cancer and 68 (10%) cases had no nodule and no evidence of HCC. Of the 383 cases treated with ablative therapy, 99 had no HCC in the pathology report. Of the 32 cases for which Stage I was requested who had ablation, 7 had no tumor, 3 had Stage I, and 22 had > Stage I histologically. Of the 269 cases for which Stage II was requested and ablation was indicated 78/269 were histologically > Stage II, 115/269 were histologically = Stage II and 76/269 were histologically < Stage II and therefore downstaged. Overall, a total of 83 cases were downstaged by ablative treatment in this cohort.

REGIONAL VARIATION IN MELD SCORES

Table X-11 shows substantial regional variation in the MELD score at which patients are transplanted among the 11 OPTN regions. For example, in Region 6, 48% of recipients had scores in the 11-20 range, more than twice the percentage of patients transplanted in this range in Regions 1, 5, 7, or 9. This disparity is seen in the higher ranges also. This difference in transplantation is not seen in living donor transplantation, where there appears to be little difference between the regions.

Table X-11. Waiting List Status at Transplant for Deceased Donor Liver Recipients, by Region

WL Status at Transplant (%)	Region										
	1	2	3	4	5	6	7	8	9	10	11
Status 1	5.1	8.5	9.2	7.3	15.1	6.0	9.5	8.0	16.9	5.7	7.1
MELD 6-10	2.8	8.0	5.5	3.1	3.3	2.7	1.6	3.2	3.6	7.1	3.2
MELD 11-20	20.8	31.3	31.3	27.9	18.9	48.1	22.0	27.5	17.8	34.9	30.1
MELD 21-30	21.9	18.6	19.7	20.3	11.3	18.0	19.8	16.9	10.8	20.1	24.3
MELD >30	17.4	10.8	9.0	8.7	20.3	5.5	11.8	12.6	13.8	5.5	11.6
PELD <11	5.1	2.2	1.9	3.1	0.8	1.1	2.8	5.2	0.4	3.0	0.4
PELD 11-20	0.6	1.2	0.9	0.7	1.5	1.1	1.2	1.1	1.1	1.4	0.4
PELD 21-30	-	0.8	0.8	0.3	0.5	-	0.7	1.4	-	2.4	0.2
PELD >30	0.6	0.1	-	0.2	0.2	-	0.2	-	-	0.8	-
HCC T1	0.6	3.0	2.6	2.7	3.3	3.3	4.9	2.9	2.5	1.6	3.4
HCC T2	19.7	13.6	12.3	17.4	20.2	13.1	18.3	11.7	18.6	10.5	13.1
Other exceptions	5.6	1.9	6.7	8.3	4.6	1.1	7.1	9.5	14.4	7.1	6.0

Source: OPTN/SRTR Data as of July 1, 2003. Includes transplants between 2/27/02 and 12/31/02. WL: Waiting list.

Further data needs to be collected to examine these regional variations. It is hoped that the allocation system will in the future address these inequities of transplantation rates, using the powerful tool that the MELD system provides.

MODELING ALTERNATIVE GEOGRAPHIC DISTRIBUTION OF LIVERS UNDER THE MELD/PELD SYSTEM USING SIMULATION

Current liver allocation policy in the United States gives priority to Status 1 candidates in the local distribution area (i.e., OPO service area). Donor livers are next offered to Status 1 candidates within the region, and then to local candidates by descending MELD/PELD score. This policy results in transplantation of local candidates with low MELD/PELD scores even when there are high MELD/PELD candidates in other OPOs elsewhere in the region. Modifying this geographic ordering of candidates has been discussed as a means to reduce waiting list mortality among high MELD/PELD candidates, but in the absence of a clinical trial there is a desire to predict the effects of a modified geographic distribution scheme.

The SRTR has developed a family of simulated allocation modeling tools for use in exploring the effects of proposed policy changes prior to implementation. The first of these to be developed was the Liver Simulated Allocation Model (LSAM). LSAM uses data from actual wait-listed candidates and donor organs as inputs to an event-sequenced Monte Carlo type simulation with specified allocation rules and probabilistic models for organ acceptance and transplant outcome. Using LSAM, the potential impact of a policy for regional sharing of livers for patients above defined MELD/PELD thresholds has been examined.

Data from all adult and pediatric candidates on the liver waiting list and all donor organs that became available between 4/1/02 and 10/1/02 were included in the simulation. All simulated outcomes from the LSAM runs were estimated for this six-month timeframe.

Regional sharing of livers was examined by varying the LSAM allocation rules. Two thresholds — 25 and 35 — were tested to estimate the impact of regional sharing of organs for MELD/PELD scores above each limit. The results from these LSAM runs have been summarized and contrasted with results from an LSAM simulation of regional sharing for all MELD/PELD scores, as well as with current rules. Exception allocation MELD scores as utilized in the existing national policy were set at 20 for small hepatocellular carcinomas (HCC T1) and 24 for more extensive (HCC T2) cases. Hepatocellular carcinoma patients were excluded from sharing at the regional level. Results from the simulation model for each set of rules tested were averaged over ten separate runs to generate average outcome estimates.

For the allocation rule of regional sharing among all MELD/PELD scores, LSAM offered livers first to Status 1 local patients, then to Status 1 regional patients. Following Status 1 patients, allocation was by MELD/PELD at the regional level according to the following order:

- Group 1: Local, non-exception by MELD/(PELD)
- Group 2: Local, exception (HCC)
- Group 3: Regional, non-exception by MELD/(PELD)
- Group 4: Regional, exception (HCC)

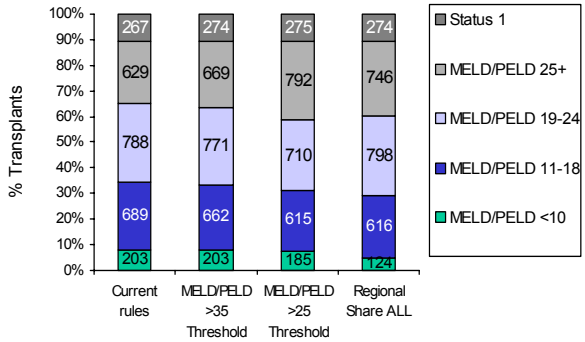
Initially the organ is offered among the pooled candidates in Groups 1-3 according to descending allocation by MELD/PELD. If there are ties at MELD/PELD, then ABO-identical patients are offered the organ before the ABO-compatible patients. If there are ties at that level, then the organ is offered first to patients in Group 1, then to patients in Group 2, and finally to patients in Group 3. Group 4 patients would then be offered the organ, in descending MELD/PELD order. Ties are broken by waiting time at or above the MELD/PELD score. Finally, the organ is offered to national patients, status 1 first, and then MELD/PELD patients in descending MELD/PELD order.

Regional sharing by MELD/PELD threshold was done as described above for patients at or above the threshold. Below the threshold, it was offered first to local patients in descending MELD/PELD order (starting at threshold minus 1), then regionally by descending MELD/PELD.

Figure X-10 shows the total number of transplants by MELD/PELD that would result under each set of allocation rules tested. Using a MELD/PELD threshold of 35 for regional sharing resulted in a 6% increase in the number of transplants done at MELD/PELD 25 or greater. When the threshold for regional sharing was lowered to 25, the number of high MELD/PELD transplants increased by 26% compared to current rules. Regional sharing for the full MELD/PELD scale was associated with an intermediate result, as more regional candidates with intermediate MELD/PELD scores would be available. Conversely, regional sharing at the 35 threshold resulted in no reduction in the number of transplants at MELD/PELD below 10, a 9% reduction at a threshold of 25, and a 39% reduction using full regional sharing. Figure X-11 shows the same data displayed by whether the transplant was allocated locally or within the OPTN region. As expected, lowering of the regional sharing threshold yields progressively more regional transplants.

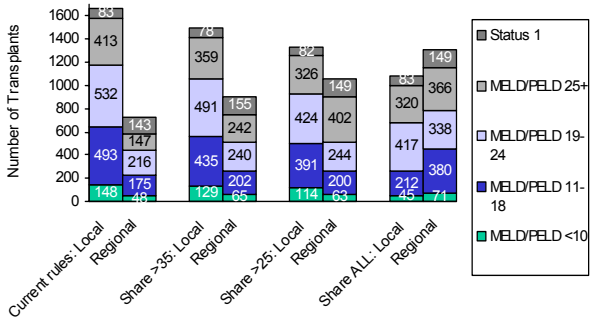
As shown in Figure X-12, simulation results suggest that regional sharing increases the number of liver transplants for pediatric recipients by approximately 10%. Overall death counts from the various regional sharing rules are given in Figure X-13. Reduction in total deaths (waiting list plus post-waiting list removal plus posttransplant) were 1%, 3%, and 4% for LSAM runs with 35 threshold, 25 threshold, and full regional sharing, respectively. Posttransplant and post-waiting

Figure X-10. LSAM Results for Regional Sharing by MELD/PELD Threshold, by MELD/PELD at Transplant



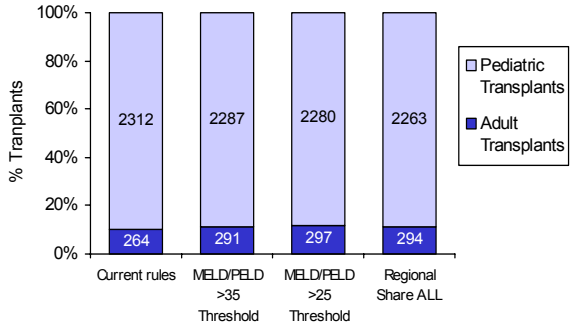
Source: SRTR Analysis. Data as of August 1, 2003.

Figure X-11. LSAM Results for Regional Sharing by MELD/PELD Threshold, Local and Regional Transplants



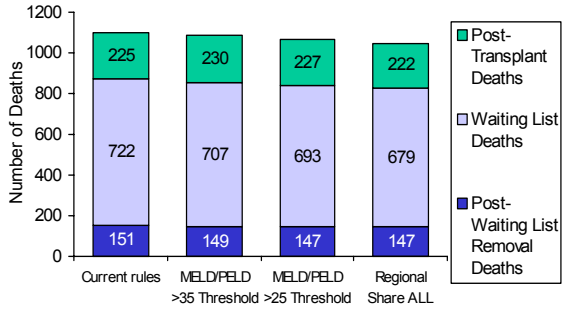
Source: SRTR Analysis. Data as of August 1, 2003.

Figure X-12. LSAM Results for Regional Sharing by MELD/PELD Threshold, Pediatric and Adult Transplants



Source: SRTR Analysis. Data as of August 1, 2003.

Figure X-13. LSAM Results for Regional Sharing by MELD/PELD Threshold, Posttransplant Deaths, Waiting List and Post-Waiting List



Source: SRTR Analysis. Data as of August 1, 2003.

list removal deaths were not predicted to change substantially, while waiting list deaths were reduced by 2%, 4%, and 6%, respectively.

While these LSAM results suggest that there may be a reduction in waiting list mortality with regional sharing by MELD/PELD, the resulting posttransplant mortality counts may be understated, since these results do not fully account for the potential adverse effect associated with increased cold ischemia time with older donor organs on posttransplant outcomes (30). Since cold ischemia time is not known at the time of organ offer, it will need to be estimated by LSAM based on transport time or geographic distance. There are plans to incorporate the predicted effects of cold ischemia time into the organ acceptance model and posttransplant survival model within LSAM. Currently, the cold ischemia time effect is partially accounted for by surrogate covariate adjustment in these models (allocation to a local, regional or national candidate). Finally, as suggested by DebRoy et al., an adjustment for the interaction between geographic distribution and donor age is made in the posttransplant survival model (30).

LSAM is a useful tool to examine new allocation policy proposals. As the model becomes more sophisticated, additional analyses of detailed output data are planned to further dissect the predicted results of LSAM modeling.

USING MELD TO IDENTIFY EXPANDED CRITERIA LIVER DONORS

In recent years, the severe shortage of deceased donor organs has driven transplant centers to broaden the characteristics by which these organs are judged acceptable. At first these donors were thought to be on the margins of acceptability and were termed marginal donors, but with more widespread use of organs from these donors, the term expanded criteria donor (ECD) has become accepted. In general, organs from such donors function less well and may carry poorer short and long-term outcomes for their recipients. As more experience is gained, medical and ethical issues arise regarding the appropriate allocation of these organs to recipients and the need to inform potential recipients of the increased risks of poorer outcome when these organs are used. For renal transplantation, these issues have been recently outlined and codified in renal allocation policy (31-33). The main driving force for implementation of such a policy was to develop a list of renal transplant candidates who are willing to accept an ECD kidney after having been informed that such an organ is at higher risk of poorer or shorter function. In particular, a renal transplant candidate whose life expectancy is less than the expected graft survival of an ECD kidney or less than the expected wait for a non-ECD kidney may be appropriate for the ECD list. Necessary for establishing policy for ECD kidneys was the requirement that a definition of ECD kidneys be characterized and donor risk factors associated with this definition identified. In a previous analysis by the SRTR, a relative risk of deceased donor kidney graft failure of 1.7 was chosen to define an ECD kidney (31). This criterion includes all deceased donors over 60 years of age and those donors over age 50 with at least two of the following: terminal serum creatinine ≥ 1.5 mg/dl, cerebrovascular accident as the cause of death, or history of hypertension. These risk factors have been incorporated into renal allocation policy and serve to accurately inform renal transplant candidates and practitioners that kidneys from donors meeting these criteria may be appropriate for candidates who are informed of and willing to accept the risks (32).

The SRTR has recently completed a similar analysis to define expanded criteria for livers from deceased donors based on the same relative risk (RR=1.7) for early graft failure or death. For this analysis, the study population consisted of 18,025 adult primary cadaveric liver transplant recipients transplanted between 7/1/97 and 1/1/02 and followed through 8/1/02. Cox proportional hazards models were fit to investigate the association of time to graft failure or death with the donor and recipient factors. Donor factors included age, sex, race, ethnicity, cause of death, size (body mass index and weight and height separately), confirmed blood infection, use of three or more inotropic agents, dopamine or dobutamine use, partial or split liver, diabetes, hypertension, creatinine, serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), sodium > 170 mEq/L, total bilirubin, and percentage of fat on donor liver biopsy. Along with year of transplant and cold ischemic time, recipient factors included age, sex, race, ethnicity, body mass index (BMI), medical urgency status at

Table X-12. Donor Risk Factors Associated with a Statistically Significant Increased Relative Risk of Graft Failure

Donor Risk Factors*	Percent of Donors	RR	*P*-value
Partial or split liver	**1.6%**	**1.52**	**0.0002**
Serum sodium prior to procurement > 170 mEq/L	**2.4%**	**1.31**	**0.0051**
Cardiac arrest since neurological event	**2.0%**	**1.33**	**0.0065**
Cause of death: cerebrovascular/stroke	**42.8%**	**1.16**	**0.0003**
Cause of death: missing	0.9%	1.19	0.3045
Cause of death: anoxia/cardiac arrest	8.2%	1.09	0.1711
Cause of death: CNS tumor	1.1%	1.25	0.1037
Cause of death: other	1.9%	1.14	0.2298
Donor weight (per 10 kg under 70 kg)		**1.03**	**0.0038**
Black race (v. white)	**11.6%**	**1.23**	**<0.0001**
Asian race	1.9%	1.00	0.9615
Other race	0.7%	1.34	0.0902
Donor age 0-9 (v. age 10-39)	**1.5%**	**1.68**	**<0.0001**
Donor age 40-49	**18.5%**	**1.18**	**0.0004**
Donor age 50-64	**21.0%**	**1.36**	**<0.0001**
Donor age 65 or greater	**8.0%**	**1.73**	**<0.0001**

Source: SRTR Analysis (34). *Cox regression model was also adjusted for cold ischemia time and the following recipient characteristics: status, BMI, NYHC functional status, age, race, PRA>10, ventilator use, and serum creatinine.

transplant, panel reactive antibody level > 10%, New York Heart Association class, muscle wasting, ventilator use, dialysis dependency, serum creatinine, serum albumin, serum bilirubin, and ABO compatibility. Additional ascertainment of death from the Social Security Death Master File (SSDMF) was integrated with available OPTN posttransplant follow-up. A relative risk of 1.7 was chosen as a cut-off for inclusion in the ECD group. Donor risk factors associated with a statistically significant increased relative risk of graft failure are summarized in Table X-12. Risk factors associated with the largest increased risk were: donor age > 65 years, donor age < 9 years, partial or split liver, and donor age 50-64 years.

Table X-13 depicts a matrix indicating which donor variables or combination of variables results in a relative risk of graft failure or death ≥ 1.7. All donors age 70 and older had a relative risk of graft failure ≥ 1.7. Donors 60-69 years of age with at least one of the following donor factors also had a relative risk of graft failure or death ≥ 1.7. Donors 40-59 years of age who had a at least two additional donor factors or were donors of split/partial grafts had a relative risk of graft failure ≥ 1.7. The only ECD donors in the 18-39 year range were those whose livers were used for split/partial grafts. Using the study cohort (transplants performed 7/1/97 - 3/1/01), this definition categorizes 15.9% of transplanted livers as ECD and 20.9% of recovered ECD livers as not transplanted, compared with 9.9% of non-ECD livers.

Defining an ECD liver donor by a relative risk of graft failure of 1.7 may be inappropriately high because graft failure after liver transplantation has more severe consequences than graft failure after renal transplantation. In the future, investigators may want to consider a lower relative risk of graft failure as more in balance with the risk that the recipient of a failed liver graft faces. However, in the absence of analyses to justify a lower relative risk definition, it is useful to apply the working definition to analyses of graft recovery and usage under the MELD/PELD system of allocation to assess which candidates are receiving these grafts.

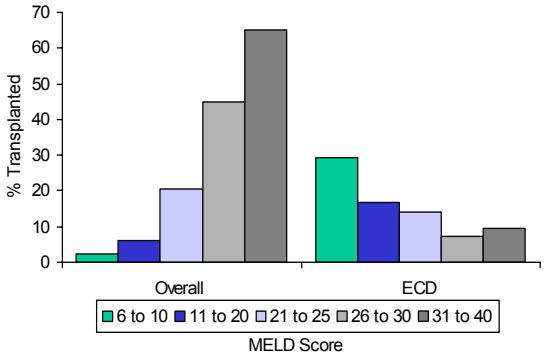
Table X-13. Expanded Criteria for Liver Donors

Donor Condition	Donor Age Categories				
	18-39	40-49	50-59	60 - 69	≥ 70
None	Ref.				X
Arrest or CVA or Na>170				X	X
Arrest and CVA		X	X	X	X
Split/partial; All other combinations	X	X	X	X	X

Source: SRTR Analysis (34).

Interestingly, the number of deceased donors increased only 3.5% in the first year of the MELD/PELD allocation compared with the year prior to implementation. Nonetheless, the transplantation rate using deceased donors increased significantly (272 per 1,000-patient years in the year prior to MELD/PELD vs. 300 per 1,000-patient years under the MELD/PELD system, $P<0.001$). This may be due to an increase in the ratio of donors recovered/donors transplanted (90.5 vs. 92.5, $P< 0.005$) under the MELD/PELD system, suggesting an increased use of ECD donor livers.

Figure X-14. 30-Day Liver Transplant Rate by MELD Score and ECD Status



Source: SRTR Analysis. Data as of August 1, 2003.

In an analysis of 30-day outcomes under the MELD/PELD system, the SRTR examined the transplantation rate for ECD donor livers among adult recipients, stratified by MELD score at the time of transplant. The results of this analysis are summarized in Figure X-14. The overall transplantation rate within 30 days of listing for all adult candidates stratified by MELD range, increases from 2% for the lowest range to 65% for candidates in the 30-40 range. However, when considering livers recovered from donors meeting the above ECD criteria, nearly 30% of all transplants performed for candidates in the lowest decile of MELD score are done with ECD livers. This rate decreases in each higher MELD range except the 30-40 category. Even for these most urgent candidates only 10% of the transplants are performed with ECD donors. This suggests that centers are utilizing livers from ECD donors preferentially for the least ill recipients.

These analyses are preliminary and future work must be done to define the criteria associated with the appropriate risk of graft failure for recipients of deceased donor livers that should be considered expanded. Once done, however, informing potential recipients of these organs of the increased risks they face will be necessary.

FUTURE DIRECTIONS

The new MELD/PELD system represents a departure from previous organ allocation policy. Waiting time, still the most important ranking criterion for kidney, pancreas, lung, and some heart candidates, has been almost entirely removed form liver allocation. The new system does not categorize patients into groups but utilizes a continuous score. These two important changes, combined with the removal of the CTP score's subjective clinical factors, have resulted in a more patient-specific system that allows for better measurement and transparence.

Hepatocellular carcinoma remains a significant clinical challenge. With more than 14,000 new cases diagnosed each year, this single indication for transplantation has the potential to overwhelm the system. Future allocation policy will require more precise diagnostic modalities and a much better understanding of the natural history of progression to more fairly assign the correct priority for these patients based on their risk of progression beyond a stage favorable for transplantation. Additional refinements in defining the favorable stage itself will also be required.

Geographic differences in transplantation rates, distribution of MELD/PELD scores at transplant and differences in RRB policies will also need to be addressed. The MELD/PELD system addresses only allocation priority; it does not affect distribution units,

defined as the smallest group of patients prioritized for a particular organ once it becomes available. In most cases, the distribution unit for liver allocation is all the patients wait-listed in all the centers served by a single organ procurement organization (OPO). There are currently many factors that make distribution units heterogeneous, such as number of brain deaths within the OPO's service area, efficiency with which the OPO identifies and retrieves the organs from these donors, the number of candidates waiting at the centers in that OPO, the number of centers within the OPO, the listing practice and organ acceptance practice of each center within the OPO (35). These all contribute to variations in MELD/PELD score at the time of organ offer. The MELD/PELD system gives the liver transplant community a precise measurement of such differences. Regional sharing for candidates with MELD scores over a certain value might be one way to help direct more organs to those most likely to die without a transplant. Also, a better understanding of the mortality risks faced by waiting candidates based on the MELD score may allow for development of minimal listing or minimal transplantation criteria based on the risk of death with or without the transplant. This potentially could reduce the number liver transplants for candidates who have a higher risk of death from the transplant surgery than they have waiting for an additional 6-12 months.

The analysis of ECD livers also opens the possibility of matching recipients based on their risks of death without a transplant and donors based on their risks of graft failure to optimize the donor pool. Combining pre-transplant mortality risk models with posttransplant survival models may also allow liver allocation policy to evolve toward maximizing the benefit of transplantation so that organs are directed to those with a high risk of dying without the transplant and with the highest net survival with the transplant.

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