American Journal of Transplantation 2006; 6: 2470–2475
Blackwell Munksgaard

doi: 10.1111/j.1600-6143.2006.01508.x

Geographic Differences in Event Rates by Model for End-Stage Liver Disease Score

J. P. Roberts[a,*], D. M. Dykstra[b], N. P. Goodrich[b], S. H. Rush[b], R. M. Merion[c,d] and F. K. Port[b]

[a] *Surgery, UCSF, San Francisco, California, USA,* [b] *SRTR, Arbor Research, Ann Arbor, Michigan, USA,* [c] *Surgery and* [d] *SRTR, University of Michigan, Ann Arbor, Michigan, USA*
* *Corresponding author: John P. Roberts, robertsj@surgery.ucsf.edu*

The ability of the model for end-stage liver disease (MELD) score to accurately predict death among liver transplant candidates allows for evaluation of geographic differences in transplant access for patients with similar death risk.

Adjusted models of time to transplant and death for adult liver transplant candidates listed between 2002 and 2003 were developed to test for differences in MELD score among Organ Procurement and Transplantation Network (OPTN) regions and Donation Service Areas (DSA).

The average MELD and relative risk (RR) of death varied somewhat by region (from 0.82 to 1.28), with only two regions having significant differences in RRs. Greater variability existed in adjusted transplant rates by region; 7 of 11 regions differed significantly from the national average. Simulation results indicate that an allocation system providing regional priority to candidates at MELD scores ≥15 would increase the median MELD score at transplant and reduce the total number of deaths across DSA quintiles. Simulation results also indicate that increasing priority to higher MELD candidates would reduce the percentage variation among DSAs of transplants to patients with MELD scores ≥15. The variation decrease was due to increasing the MELD score at time of transplantation in the DSAs with the lowest MELD scores at transplant.

Key words: Donation service area, geographic disparities, liver transplantation, MELD, simulation modeling, SRTR

Received 24 March 2006, revised 6 June 2006 and accepted for publication 29 June 2006

Introduction

The model for end-stage liver disease (MELD) score was introduced to provide a method that expressed the risk of death in patients awaiting liver transplantation and to allow better prioritization of patients for transplantation than the previous algorithms that used combinations of waiting time, liver dysfunction and hospitalization status (1–3). The MELD score is calculated from three laboratory parameters (serum bilirubin, international normalized ratio [INR] of prothrombin time and serum creatinine) and it provides a standardized score with an excellent ability to predict the risk of death for liver transplant candidates (3).

With the establishment of a liver allocation system based on MELD, it is of interest to examine the ability of the score to predict not only the risk of death, but also other waiting list events, such as the relative rate of transplantation. Additionally, because MELD is a strong predictor of the risk of death for patients awaiting liver transplantation, it is an important tool for examining patients at a similar risk of death and for comparing their outcomes in the current organ allocation system.

A recently implemented policy change, which was based upon results by Merion et al. (4), prevents offers of donor livers to patients with MELD scores less than 15 listed with transplant centers in the same Donation Service Areas (DSA) as the donor unless no candidates with MELD scores of 15 or greater at regional DSAs accept the offer. We examined the projected effects of this policy change on the variability of MELD score by DSA at the time of transplantation using simulation modeling.

Methods

Data sources

Analyses are based on the Scientific Registry of Transplant Recipients (SRTR) database. This database contains information on all solid organ transplant candidates and recipients in the United States. It integrates information collected by the Organ Procurement and Transplantation Network (OPTN) with other sources, such as the Social Security Death Master File (SSDMF), in order to ascertain additional mortality data (5).

Outcomes by MELD score

Study population: Adult patients (age 18 or above) who were listed as candidates for only liver transplantation between February 27, 2002, and February 26, 2003, were followed until one of the following occurred: death, transplant, removal for other reasons or the end of the study on December 31, 2003. The start date was chosen to correspond with the initiation of MELD-based deceased donor liver allocation. Patients granted a MELD exception score, including those with hepatocellular carcinoma (HCC), were excluded from the analyses (6). Multiple observation periods per patient were included, beginning at each MELD update. However, periods during which a patient's waiting list status was inactive were excluded from the analyses.

Analytic approach: For each calculated (lab) MELD score, the total number of patient days spent at that score was determined. Outcomes within each MELD score category per 100 patient days were calculated. The outcomes examined included: movement to a higher or lower score, transplant, death, change to inactive status or removal from the waiting list for reasons other than death or transplant.

The effects of MELD score on transplantation and death were assessed by region and DSA using time-dependent Cox regression models. Time to transplant was modeled from the date of listing to transplantation and censored at the earliest of the following: removal from the waiting list, death or the end of the study. Time to death was modeled from the date of listing until death on the waiting list, and also censored at either removal from the waiting list, transplantation or the end of the study. All models were adjusted for candidate age, race, ethnicity, gender, MELD score and MELD by (log) time interaction.

Additional Cox regression models with individual region and DSA covariates were developed in order to compare the adjusted relative rates of transplant and waiting list death, adjusting for the patient factors mentioned above. For comparisons by OPTN region, the transplant and death models also included covariates for region and region-by-MELD interactions.

Simulation modeling

Study population: Information on 26 897 candidates on the liver waiting list and 5528 deceased donor livers available between April 1, 2002, and April 1, 2003, were used in the simulations. Although the simulation runs included pediatric (age 0–17) candidates, the analysis of the results included only adult candidates in order to focus specifically on results by MELD score (rather than pediatric PELD score).

Analytic approach: The Liver Simulated Allocation Model (LSAM) was used to compare two sets of allocation rules. LSAM was developed to compare the likely effects of alternative allocation policies on a variety of outcomes prior to implementing policy changes (7). In order to examine the effects of rules that give regional priority to candidates with MELD scores greater than or equal to 15, two sets of allocation rules were used in the simulations. After allocation to status 1 candidates, the first set of rules allocated organs initially to candidates of all MELD scores within the procuring DSA before offering the organ to candidates in the region. The second set of rules allocated organs to candidates within the procuring DSA who had a MELD score $\geq$15 then to candidates in the region of the procuring OPO with a MELD score $\geq$15, after which the organ would be offered to candidates with MELD scores below 15, first locally and then regionally. Simulation results for each set of rules were averaged over 10 iterations.

It is of interest to examine how the effects of the change in allocation policy are likely to vary by DSA. The percentage of patients who were transplanted with a MELD score $\geq$15 was compared between the two sets of simulation runs by DSA. In order to further examine the effect of the allocation change, it is useful to categorize DSAs by the median MELD score at the time of transplant. DSAs were grouped into quintiles according to their median MELD score at the time of transplant based on the simulation run, using the allocation rules that assign local priority to candidates at all MELD scores. This allowed us to compare outcomes in DSAs with a low-median MELD score at transplant (lower quintiles) to those in DSAs with a high-median MELD score at transplant (higher quintiles). Three outcomes of interest were compared among the DSA quintiles. The first was the average median MELD score among the DSAs in each quintile. The second was the number of transplants performed by DSA quintile and the third was the number of deaths observed within each DSA quintile.

Results

Table 1 exhibits the risk of several events while on the waiting list by category of MELD score. The patient days at risk for each category demonstrates the number of patients multiplied by the number of days at that score. Figure 1 shows the data on the logarithmic scale and provides better visualization of these risks. The risks of death and transplantation had similar curves and also increased logarithmically with increasing MELD scores. The risk of death for the highest MELD score group was approximately 600 times higher than that seen for the lowest MELD score group, whereas the gradient of risk from highest to lowest MELD category was 130-fold for transplantation.

The relative rates of transplantation and death (adjusted for MELD score and other patient factors) in the 11 OPTN regions are demonstrated in Figure 2. There was a relatively small range in the relative risk (RR) of death (ranging from 0.82 to 1.28). Two of the regions (Region 5 and Region 10) had RRs of death (Region 5 RR = 0.87, $p = 0.04$; Region 10 RR = 1.28, $p = 0.03$) that were significantly different than the national average. In contrast, the adjusted rates of transplantation among the regions were much more varied, ranging from 2-fold higher to more than 50% lower (RR 0.48–2.12). Seven of the 11 regions differed significantly from the nation as a whole.

To assess whether the predictive value of the MELD score varied by OPTN region, interactions between MELD score and the region were also tested. While the effect of MELD score on adjusted waiting list death varied modestly by OPTN region (two of 11 regions differed significantly versus the nation [Region 1 RR = 1.35, $p = 0.03$; Region 9 RR = 1.41, $p = 0.003$ vs. national RR = 1.39 per MELD point]), there was greater variability in transplantation rates by MELD score, with statistically significant differences in 5 of 11 regions (RR ranged from 1.23 to 1.28, $p = 0.02$–<0.0001 vs. the national RR of 1.26 per MELD point).

To test the effect of geography on death and transplantation, models adjusted for MELD and other factors were developed, including a covariate for each DSA. Significant differences were found among the DSAs in the adjusted rates of waiting list death and transplantation (overall DSA Wald chi-square 90, $p < 0.001$; Wald chi-square 2182, $p < 0.001$, respectively). For waiting list mortality, 6 of 50 DSAs had a RR that was significantly different from the nation. In contrast, for the RR of transplantation, 20 DSAs were

Table 1: Event rates by MELD score range (February 27, 2002 to December 31, 2003)

MELD range	Patient days at MELD range	Event rates (per 100 patient days) Higher MELD[1]	Lower MELD[1]	Transplanted	Died	Other removal	Inactive
MELD 6	85 413	0.22	-	0.02	0.00	0.10	0.01
MELD 7–11	1 024 319	0.33	0.15	0.03	0.01	0.06	0.01
MELD 12–16	1 065 630	0.47	0.38	0.07	0.02	0.06	0.01
MELD 17–21	409 095	0.86	0.71	0.20	0.05	0.09	0.03
MELD 22–26	123 151	2.04	1.67	0.52	0.13	0.16	0.05
MELD 27–29	22 112	4.07	4.02	1.17	0.37	0.27	0.15
MELD 30–34	22 063	4.25	3.17	1.74	0.60	0.36	0.24
MELD 35+	23 510	2.33	2.25	2.16	1.87	0.67	0.26

[1]Higher and lower refer to a change in MELD by ≥1.

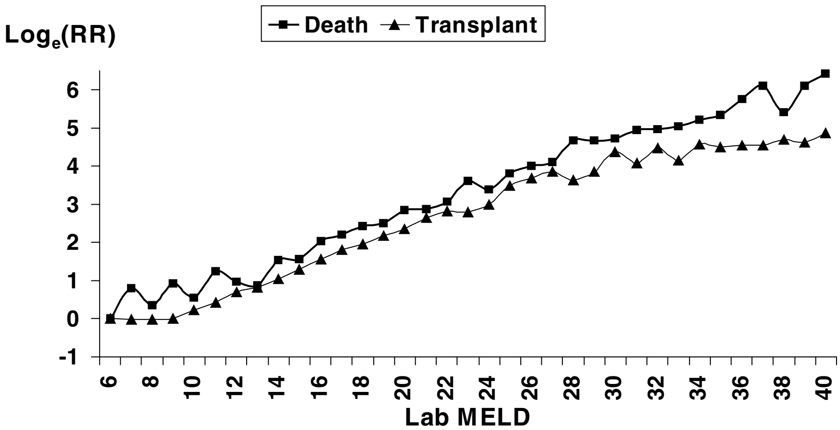

Figure 1: Relative Risk (RR) of waiting list death and receiving a deceased donor transplant while at MELD score, shown on an e-based logarithmic scale. Each increment of 1 indicates a 2.7-fold higher RR.

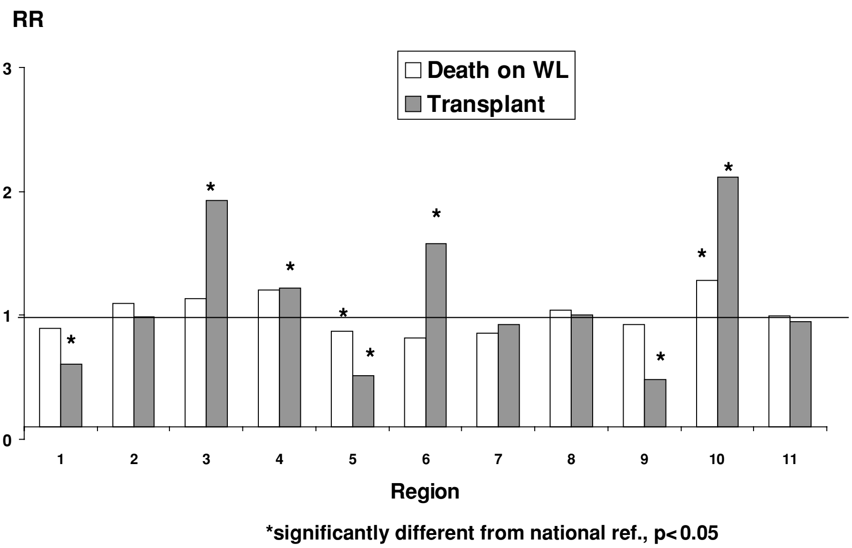

Figure 2: Adjusted relative risk (RR) of waiting list death and deceased donor transplant by OPTN region*. *Region 1: CT, ME, MA, NH, RI, VT; Region 2: DE, DC, MD, NJ, PA, WV; Region 3: AL, AR, FL, GA, LA, MS, PR; Region 4: OK, TX; Region 5: AZ, CA, NV, NM, UT; Region 6: AK, HI, ID, MT, OR, WA; Region 7: IL, MN, ND, SD, WI; Region 8: CO, IA, KS, MO, NE, WY; Region 9: NY; Region 10: IN, MI, OH; Region 11: KY, NC, SC, TN, VA.

significantly greater, and 18 DSAs were significantly lower than the national average. Rates of transplantation and death did not appear to be correlated (either directly or inversely), nor did they appear to vary at all by DSA waiting list size (results not shown).

Figure 3 displays the percentage of transplants received by recipients with MELD ≥15 for the two simulated allocation rules, ordered by percentage by DSA under the local distribution rule. The percentage of transplants received by recipients with MELD < 15 is projected to increase for each DSA under the modified rules that give regional priority to candidates with higher MELD scores. In the local priority simulation, 23 DSAs transplanted more than 30% of recipients with MELD <15, while in the regional priority simulation, only 4 DSAs transplanted more than 30% of

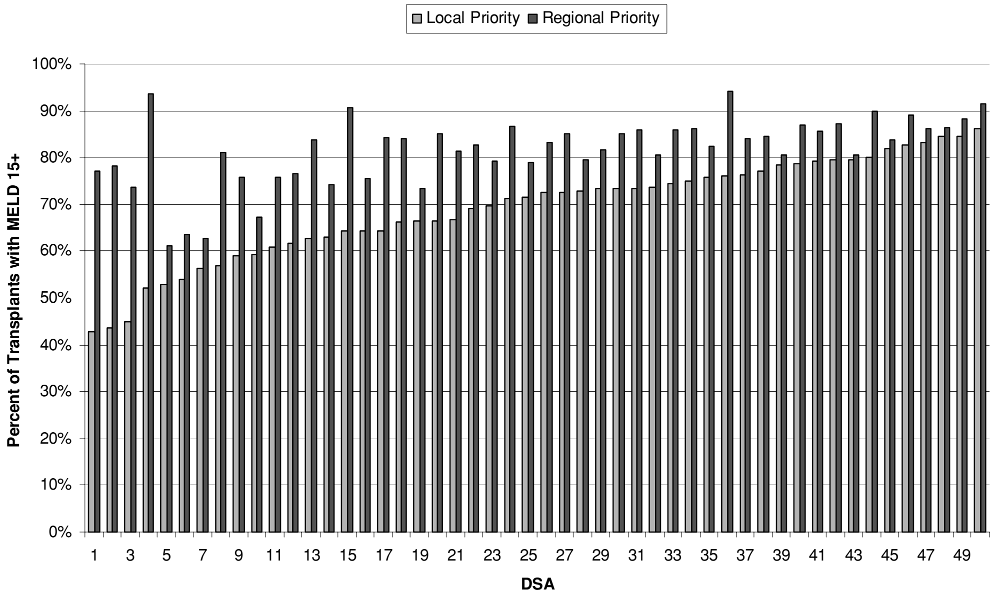

Figure 3: Percent of patients transplanted with MELD scores ≥15 at transplant during simulations comparing local (range 43–85%) and regional (range 61–95%) priority to candidates with MELD ≥15. DSAs without liver transplant programs were excluded.

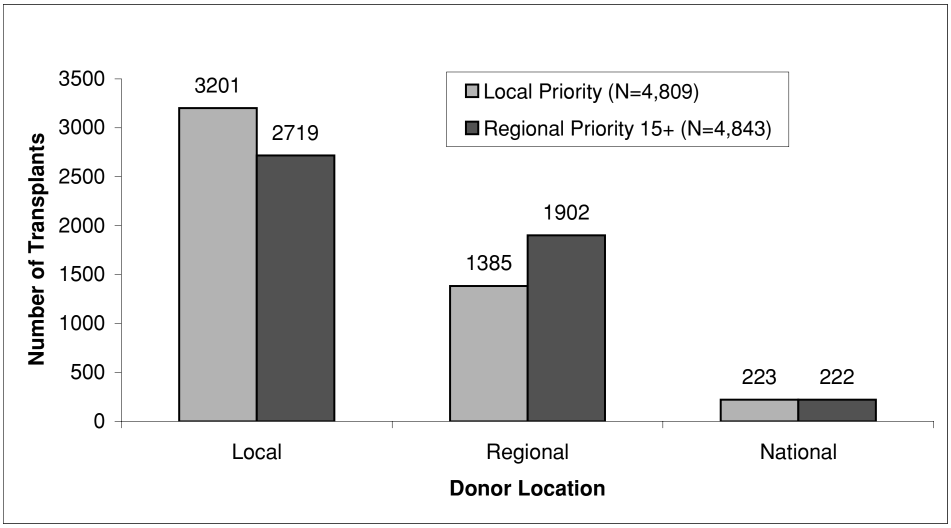

Figure 4: Number of simulated transplants by donor location and allocation policy.

recipients with MELD <15. In the local priority simulation, only 6 DSAs transplanted more than 80% of recipients with a MELD score ≥15, while in the regional priority simulation, 34 DSAs transplanted more than 80% of recipients with a MELD score of 15 or greater. The largest increases were predicted for DSAs with lower percentages of recipients transplanted with MELD ≥15 under the allocation rules without regional priority. In the local priority simulation, the median percentage of transplants to recipients with MELD ≥15 was 72% (range 42.8–86.2), while in the regional priority simulation, the median increased to just over 83% with MELD ≥15 (range 61.2–94.2).

Figure 4 shows the number of simulated transplants for the two sets of allocation rules by the location of the donor organ. As expected, there was a large increase in the projected number of regionally shared livers using the allocation rules that increased priority to candidates with MELD scores ≥15. Table 2 displays the median MELD scores at the time of transplant by DSA quintile for the two simulations. The median MELD scores were projected to be higher for each of the quintiles, with the largest increases seen in the quintiles that had the lowest median MELD scores under the allocation system that uses local priority for all MELD scores.

Table 2: Simulated median MELD at transplant by DSA quintile for two allocation policies

MELD quintile	Allocation system	N DSA	N Tx	Median MELD at Tx among DSAs in quintile	Range of simulated medians for DSAs in quintile
1	Local priority	10	652	15.0	(13.6—16.7)
	Regional priority ≥15	10	585	17.4	(15.8—18.8)
2	Local priority	10	504	17.4	(16.8—17.9)
	Regional priority ≥15	10	468	19.2	(17.5—20.6)
3	Local priority	9	1012	18.9	(18.1—19.8)
	Regional priority ≥15	9	1029	19.8	(18.8—20.9)
4	Local priority	11	1096	20.4	(19.8—21.4)
	Regional priority ≥15	11	1123	21.6	(20.4—23.9)
5	Local priority	10	1545	23.1	(21.7—24.6)
	Regional priority ≥15	10	1638	23.3	(21.1—24.1)

Results were averaged over 10 simulation runs.

Table 3: Number of simulated deaths and percent change comparing regional priority to nonregional priority for MELD ≥15 by quintile of median MELD at transplant by OPO

MELD quintile	Type of death	Local priority	Regional priority ≥15	Difference	% change
1 ($n = 2716$)	Post Tx	54	51	−4	−6.6%
	Post WL removal	48	47	−2	−3.1%
	Waitlist	140	135	−5	−3.5%
	Subtotal	242	232	−10	−4.1%
2 ($n = 1908$)	Post Tx	45	44	−1	−2.4%
	Post WL removal	43	41	−2	−4.2%
	Waitlist	120	114	−6	−4.9%
	Subtotal	208	199	−9	−4.2%
3 ($n = 4686$)	Post Tx	90	95	6	6.6%
	Post WL removal	62	60	−2	−3.4%
	Waitlist	257	249	−8	−3.1%
	Subtotal	408	404	−4	−1.0%
4 ($n = 5278$)	Post Tx	105	106	2	1.4%
	Post WL removal	83	82	−2	−2.0%
	Waitlist	377	356	−21	−5.5%
	Subtotal	565	544	−21	−3.7%
5 ($n = 12\,300$)	Post Tx	155	168	13	8.2%
	Post WL removal	166	160	−6	−3.8%
	Waitlist	762	745	−17	−2.3%
	Subtotal	1083	1072	−11	−1.0%
Total		2506	2451	−55	−2.2%

n = number of candidates listed in the MELD quintile group.
Excludes DSAs without liver transplant programs.

Table 3 shows the number of simulated deaths on the waiting list, post-transplant and after removal from the waiting list for the two allocation policies. The overall number of simulated deaths decreased by 2.2% for the simulated allocation system with regional priority to patients with MELD ≥15 compared to local priority. Some of the quintiles were predicted to have more post-transplant deaths under the new system due to performing a larger number of transplants. However, these small increases were always outweighed by larger decreases in the number of simulated deaths on the waiting list. The total number of deaths decreased for each of the DSA quintiles with the allocation system that transplants more patients at higher MELD scores.

Discussion

The MELD scoring system provides an effective representation of the risk of death while on the waiting list for transplantation. The risk of death increases exponentially with increasing MELD score, with a large difference between the risk of death for patients at the lowest versus highest score. As would be expected with a prioritization system that preferentially allocates livers to those patients with the highest MELD scores, the probability of a patient receiving a transplant also increases with increasing MELD scores.

The current organ allocation system in the United States is divided into 11 regions and within these regions there are 50 DSAs with one or more liver transplant centers. The number of liver transplant centers within a DSA ranges from one to eight. Organs are first allocated at the DSA level, and DSAs with more than one center use a common list for all patients. Organs that are not used within the DSA are then shared, first regionally and then nationally (8).

It appears that there are very few differences among regions with respect to the risk of death, after controlling for the effect of the MELD score. Only 2 of the 11 regions had a risk of death that was significantly different from the other regions (Regions 5 and 10, $p < 0.05$). At the level of the 50 DSAs, there was naturally a wider range of mortality risk (controlling for MELD score and other factors), but only 10% of the DSAs had a RR of death that was significantly different from the nation as a whole. The reasons behind these death risk differences for some DSAs and regions are not clear. Medical care practices for patients on the waiting list, unmeasured patient differences and referral patterns for transplantation may create variability in death risk that is not explained by the MELD score. It does appear that for the majority of the DSAs and regions, there is little difference in the probability of death when controlling for the MELD score.

In contrast, the probability of transplantation when controlling for MELD varies widely by region and DSA. As shown in Figure 2, 7 of the 11 regions had a relative rate of transplantation that differed significantly from the nation as a whole, with a roughly 4-fold difference in transplantation rates between the highest and lowest regions. At the DSA level, the adjusted relative rate of transplantation differed 17-fold between the DSAs with the highest and lowest rates (4.9 vs. 0.28), while the risk of death varied somewhat less dramatically with a 10-fold difference between the highest and lowest rates (2.6 vs. 0.25).

The change in the allocation system to prioritize patients with a MELD score $\geq$15 should decrease the variability of MELD scores at the time of transplantation. This effect is produced by setting a partial lower limit for allocation by MELD score, which shifts the use of these organs to higher MELD candidates elsewhere in the region when there are no local candidates with higher scores. Nonetheless, the simulation results suggest that there will still be a substantial variation of the MELD scores at transplantation. Since the risk of death increases logarithmically with increasing MELD score, relatively small differences in MELD can result in larger differences in the risk of death. It is important to be cautious in extrapolating from simulation modeling, however, because changes in physician or patient behavior associated with changes in allocation policy are not accounted for in the simulation results. Thus, early observed results of the policy may not be comparable to those of the simulation when sufficient data are available.

It is clear that the MELD score offers a method that effectively prioritizes patients for transplantation based upon their risk of death without transplant. The ability of MELD to predict waiting list death seems to be relatively stable across the current allocation units used to provide organs for transplantation. However, the current allocation system results in uneven distribution of the probability of transplant and the average benefit of transplantation. Prioritizing patients with a MELD score of 15 or greater may reduce the wide variation in the geographic differences in MELD at transplant.

Acknowledgment

The Scientific Registry of Transplant Recipients (SRTR) is funded by contract #231-00-0116 from the Health Resources and Services Administration (HRSA). The views expressed herein are those of the authors and not necessarily those of the U.S. government.

References

1. Freeman RB Jr, Wiesner RH, Harper A et al. for the UNOS/OPTN Liver Disease Severity Score, UNOS/OPTN Liver and Intestine, and UNOS/OPTN Pediatric Transplantation Committees. The new liver allocation system: Moving toward evidence-based transplantation policy. Liver Transpl 2002; 8: 851–858.
2. Wiesner R, Edwards E, Freeman R et al. for the United Network for Organ Sharing Liver Disease Severity Score Committee. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology 2003; 124: 91–96.
3. Kamath PS, Wiesner RH, Malinchoc M et al. A model to predict survival in patients with end- stage liver disease. Hepatology 2001; 33: 464–470. Review.
4. Merion RM, Schaubel DE, Dykstra DM, Freeman RB, Port FK, Wolfe RA. The survival benefit of liver transplantation. Am J Transplant 2005; 5: 307–313.
5. Wolfe RA, Schaubel DE, Webb RL et al. Analytical approaches for transplant research. Am J Transplant 2004; 4(Suppl 9): 106–113. Review.
6. OPTN/UNOS Policy 3.6.4.4. Organ distribution: Allocation of livers. Liver Transplant Candidates with Hepatocellular Carcinoma. Richmond, VA: United Network for Organ Sharing, 2004. Accessed January 21, 2005, at http://www.unos.org/policiesandbylaws/policies.asp?resources=true.
7. Thompson D, Waisanen L, Wolfe R, Merion RM, McCullough K, Rodgers A. Simulating the allocation of organs for transplantation. Health Care Manag Sci 2004; 7: 331–338.
8. OPTN/UNOS Policy 3.6. Organ distribution: Allocation of livers. Richmond, VA: United Network for Organ Sharing, 2004. Accessed January 21, 2005, at http://www.unos.org/policiesandbylaws/policies.asp?resources=true.