Liver Transplantation
Organ Allocation in the MELD Era

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Required SRTR notice

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Biosketch

Lafaine Grant is an Assistant Professor in the Division of Digestive and Liver Diseases. Dr. Grant is a transplant hepatologist focusing on the care of patients with end-stage liver disease and liver transplant recipients. Her other interests include general hepatology and drug induced liver injury.

Purpose

The purpose of this presentation is to understand the system of organ allocation for liver transplantation. To understand the improvements made by the system and our current status. To learn that despite great strides made in liver transplantation and allocation, disparities remain and represent opportunities for improvement in our current system.

Learning objectives

1. To understand the MELD system of liver organ allocation for transplantation
2. To understand ongoing changes being made to improve the MELD system
3. Learn that disparities remain in the organ allocation and distribution system

Historical Perspective

Liver transplantation is the sole definitive treatment for end-stage liver disease. Dr. Thomas Starzl performed the first human liver transplant in 1963. The recipient was a 3-year old male with biliary atresia who died of hemorrhage on the operating table 4 hours after revascularization of the allograft. Two patients were transplanted within the ensuing 3 months with a survival of 7 ½ and 22 days (1). Several transplants were performed over the next few years before the next "long-term" success of a patient transplanted in 1967 with survival over 1 year (2, 3). In these early years, liver transplantation continued but despite improvements in surgical techniques and patient and donor selection, survival remained poor, with 18-30% one-year patient survival (4, 5). Allograft rejection and systemic infection remained problematic and liver transplantation was still considered experimental (6). Allograft survival improved with the introduction of cyclosporine, which was finally approved for use in 1983(7-10). Tacrolimus was approved in 1994 which further improved the results of organ transplantation (11). With the growing success of maintaining liver allograft transplantation, the National Institutes of Health declared that liver transplant was no longer an experimental endeavor and was a valid treatment for end-stage liver disease. As a consequence, there was a growing demand for transplantations and the organ market was being commercialized. In 1984, the U.S. congress passed the National Organ Transplant Act (NOTA) outlawing the sale of human organs and establishing the Organ Procurement and Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR). It also authorized the Department of Health and Human Services (DHHS) to establish Organ Procurement Organizations (OPO). In 1986, the United Network for Organ Sharing (UNOS), a private, non-profit organization, received the first federal contract to operate the OPTN and continues to do so today.

Table 1

Date	Event
1954	First successful kidney transplant performed.
1967	First successful liver transplant performed.
1968	First successful isolated pancreas transplant performed. First successful heart transplant performed. The Southeast Organ Procurement Foundation (SEOPF) is formed as a membership and scientific organization for transplant professionals.
1977	SEOPF implements the first computer-based organ matching system, dubbed the "United Network for Organ Sharing."
1981	First successful heart-lung transplant performed.
1983	First successful single-lung transplant performed. Cyclosporine introduced.*
1984	National Organ Transplant Act (NOTA) passed.** The United Network for Organ Sharing (UNOS) separates from SEOPF and is incorporated as a non-profit member organization.
1986	UNOS receives the initial federal contract to operate the Organ Procurement and Transplantation Network (OPTN).
1988	First split-liver transplant performed.
1989	First successful living donor liver transplant performed.
1990	First successful living donor lung transplant performed.
1998	First successful adult-to-adult living donor liver transplant performed.
2000	U.S. Department of Health and Human Services publishes Final Rule (federal regulation) for the operation of the OPTN.
2001	For the first time, the total of living organ donors for the year (6,528) exceeds the number of deceased organ donors (6,081).

Source: www.unos.org

Indications

The most common etiology of liver disease leading to transplantation in the United States is chronic viral hepatitis, mostly hepatitis C. Other important causes are alcoholic liver disease and cryptogenic cirrhosis. We are now realizing that a high portion of patients with cryptogenic cirrhosis likely had non-alcoholic steatohepatitis (NASH). As the obesity epidemic continues to grow, the proportion of patients with underlying NASH requiring liver transplant is also anticipated to increase. Other less common causes of chronic liver disease include primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis, and metabolic liver diseases. Acute liver failure (ALF) is a less common but well-established indication for liver transplantation. Causes of ALF include viral liver disease, autoimmune hepatitis, acute

decompensation of Wilson's disease or drug induced liver injury, particularly acetaminophen toxicity.

Early experience in liver transplant for primary liver cancer was dismal with unacceptable 90-day mortality rates and tumor recurrence exceeding 80% (4). There was a change in philosophy when it was noted that small, incidentally found hepatocellular carcinoma (HCC) tumors on explanted livers did not significantly affect survival. In 1996, Mazzaferro *et al*. published their landmark study showing that selected patients undergoing liver transplantation for small HCCs had an overall survival of 85% at 4 years. These benefits were similar to those of patients being transplanted for non-malignant causes (12). This resulted in the adoption of the Milan Criteria into clinical practice. Other less common indications include hepatopulmonary syndrome, portopulmonary hypertension, polycystic liver disease and metabolic disorders, such as primary hyperoxaluria and familial amyloidosis. These require special exception points as agreed upon by the regional review board.

Contraindications

There are several contraindications to liver transplant including severe cardiopulmonary disease, uncontrolled infection, active extra-hepatic malignancy, and severe neurologic disease, anatomical and psychosocial issues. Carefully selected patients with hilar cholangiocarcinoma may undergo liver transplant as outlined by the Mayo clinic protocol (13, 14). A number of U.S. transplant centers perform liver transplantation in patients that are HIV positive. Advanced renal disease is now only a relative contraindication as some patients may qualify for combined liver and kidney transplantation. Likewise, patients over age 65 years may be considered for liver transplant if they are otherwise in healthy.

Organ Allocation

Pre- MELD Era

A system for procuring and distributing large numbers of donor organs was not necessary in the early years of organ transplantation. Prior to 1968, the concept of death as defined by the cessation of a heartbeat and breathing was generally accepted. However, modern intensive care life support could prolong such activity delaying the declaration of death. In 1968, the Harvard Commission introduced the concept of brain death as irreversible coma. Further support was added in 1981

when the President's Commission agreed with the concept of brain death leading to the Uniform Determination of Death Act (15, 16). These legal decisions regarding the concept of brain death meant that there was an increased availability of organs compared to the earlier years. In 1977, the Southeast Organ Procurement Foundation (SEOPF) implements the first computer-based

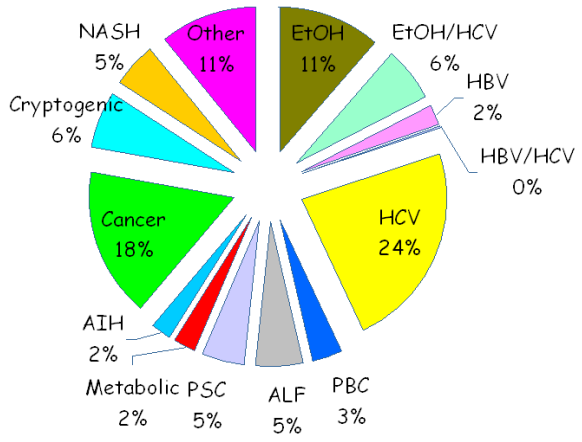


Figure 1. Transplantation by etiology

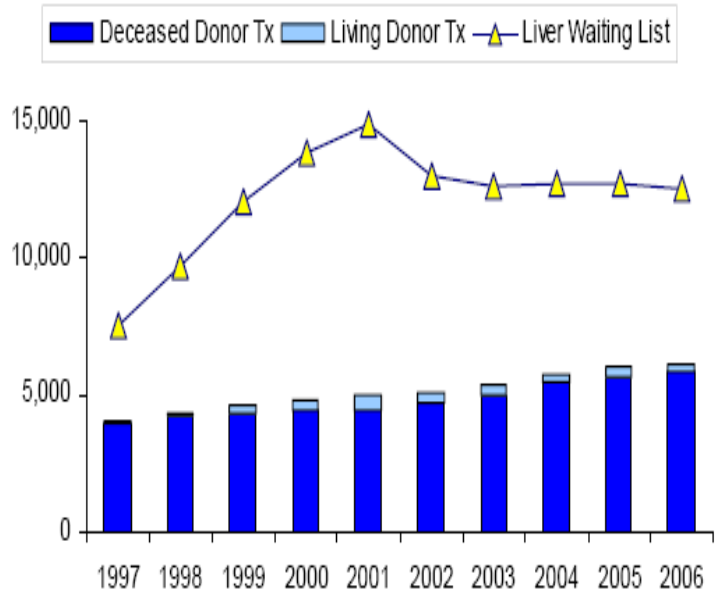
organ matching system, called the United Network for Organ Sharing (UNOS). UNOS later separates from the SEOPF and forms a private non-profit organization that was later contracted to operate the Organ Procurement Transplantation Network. The nation was arbitrarily divided into 11 geographical regions in an effort to organize procurement and distribution. Organs were distributed locally, then regionally and then nationally. Points were allocated in 6 categories of illness severity depending on the condition. Patients were stratified according to their hospitalizations status with those in the intensive care unit receiving a higher priority than hospitalized non-ICU patients and outpatients receiving the lowest priority. Point allocation favored local use of the organ in part to minimize cold ischemia time. Severity points could be overridden by declaring a "UNOS STAT" category. This was a subjective designation based on the judgment of the transplant center. Thus, the early organ allocation and distribution system was based on subjective medical parameters and the probability of transplant depended on the patient's location and time waiting for transplantation. Later versions of the plan sought to place an increased emphasis on medical urgency. Patients were listed as status I to III in order of decreasing urgency according to their medical condition. **(See appendix A for detailed definition of status levels).** However, they were all grouped together based on the Child-Turcotte-Pugh (CTP) score **(Table 2)** that often failed to distinguish disease severity in a large group of patients. Those with a CTP score of 7-9 were designated as status 3, those with a CTP score of ≥10 were status 2B and patients with pending death in the next 7 days were designated as status 2A. Therefore, the major distinguishing factor became the wait time. The increase in graft and patient survival in the 1980s and 1990s with the introduction of calcineurin inhibitors, helped establish liver transplantation as an accepted standard of care for end-stage liver disease. This led to a rising demand for organs compared to the static organ supply. As the number of candidates waiting for transplantation grew, there was an increase in waitlist mortality. **(Figure 2)**

Table 2 Child-Turcotte-Pugh calculation

	Scoring Points		
	1	**2**	**3**
INR	**<1.7**	**1.7-2.3**	**>2.3**
Bilirubin, mg/dl	**<2.0**	**2.0-3.0**	**>3.0**
Albumin, g/dl	**>3.5**	**2.8-3.5**	**<2.8**
Encephalopathy grade	**None**	**1-2**	**3-4**
Ascites	**None**	**Mild**	**Moderate**
Total points	**5-6 points**	**7-9 points**	**≥ 10**
CTP class	**A**	**B**	**C**

Child CG, Turcotte JG. Surgery and Portal Hypertension in:
The liver and Portal Hypertension. Philadelphia, PA: WB Saunders Co.; 1964.50-64.

Figure 2. Rising waiting list with static organ supply



Source: 2007 OPTN/SRTR Annual Report, Table 1.5

MELD Era

Adopting MELD

Despite modifications of the deceased donor liver transplant allocation system, inequities persisted. Sicker patients were being bypassed for transplantation in favor of patients with more compensated liver disease simply because the latter had been waiting longer. Gravely ill patients did not have access to organs based on a pre-determined geographical boundary, the donor service area (DSA). In 1998 the Department of Health and Human Services issued a mandate called the "final rule" that deceased donor livers for transplantation be allocated in a more equitable manner with a de-emphasis on time spent on the waiting list (17).

The final rule outlined that allocation policies should include the following:

1. Shall seek to achieve the best use of donated organs
2. Shall be designed to avoid wasting organs, to avoid futile transplant, to promote patient access to transplantation and to promote the efficient management of organ placement
3. Shall not be based on the candidate's place of residence or place of listing
4. Standardize the criteria for determining suitable transplant candidates through the use of minimum criteria (expressed through objective and

measurable medical criteria) for adding individuals to and removing individuals from organ transplant waiting lists

5. Setting priority rankings to ordered from most to least medically urgent. There shall be a sufficient number of categories to avoid grouping together patients with substantially different medical urgency
6. Distributing organs over as broad a geographic area as feasible and in order of decreasing medical urgency

In reviewing the impact of the final rule, the Institute of Medicine determined that there was a need for a new system with the following characteristics: one that would rely on a few, readily available, objective variables that had general applicability to a heterogeneous group of patients with chronic liver disease. This system should be able to distinguish disease severity along a broad continuum. Wait time should be eliminated as a criterion for allocation and uniform Organ Allocation Areas (OAAs) should be established (18). The CTP scoring system did not meet these criteria. UNOS and members of the transplant community reviewed models of liver disease severity and the MELD score was the most promising. The MELD is a mathematical model that was initially created as a prognostic model after placement of TIPS, a shunt procedure for refractory complications of portal HTN (19). Cox proportional hazards regression modeling identified the serum total bilirubin, serum creatinine, and INR for prothrombin time as predictors of survival (19).

MELD = 3.78[Ln serum bilirubin (mg/dL)] + 11.2[Ln INR] + 9.57[Ln serum creatinine (mg/dL)] + 6.43

Easy to use calculation tools may be found online at mayoclinic.org or type “meld score calculator” into a search engine; supply the variables and the score will be calculated without a need to memorize the complex formula above. After plugging these variables into a MELD score calculator (or the complex formula above), it yields a score ranging from 6 to 40 in order of increasing severity of illness. The original model also included disease etiology but this is currently not a part of the MELD calculation for organ allocation. This MELD was then tested as a marker of wait list mortality and was found to be highly predictive of 3-month mortality risk on the transplant wait list and as such was acceptable for donor organ allocation(20-22). Accordingly, this was adopted as the official method of deceased donor solid organ allocation in the United States for adults (age ≥ 18 years old) since February 2002. In the new system, the status 1 (fulminant liver failure) category was retained and those patients continued to receive top priority to receive an organ. The remaining patients were ranked according to their MELD score instead of status IIA and IIB and status III ranking. Among patients with the same blood type, the patient with the highest MELD score gets the priority. Waiting times are used only to break ties when patients have identical MELD scores. ***(See figure 3 for summary)***. Additional UNOS modification to the MELD included the following:

- Any laboratory value less than 1 is given a minimum value of 1 (in order to eliminate negative scores)

- The maximum creatinine value is set at 4 mg/dL including patients on dialysis (to eliminate an unfair advantage of patients with renal disease.

Once a patient is deemed a suitable candidate for liver transplant, a MELD score is calculated and he or she is placed on the transplant waiting list. Patients typically do not receive organ offers if the MELD score is <15 as due to a lower survival benefit soon after transplant. In a study of 1130 patients with end-stage liver disease, it was shown that patients with a higher MELD score (>15) obtain an early benefit from transplantation whereas those with MELD scores of ≤ 15 showed a transplant benefit after 2 years (23). In their study of a cohort of 12, 996 patients on the wait list from 2001 to 2003, Merion *et al*. found that "at MELD scores 18 and higher, significant and progressively increasing survival benefit was demonstrated" but that the "post-transplant mortality risk for the nearly one in four recipients who received liver transplants for chronic liver disease at a MELD score less than 15 was significantly higher than for comparable candidates on the waiting list"(24). Similar results were found in a later analysis(25).

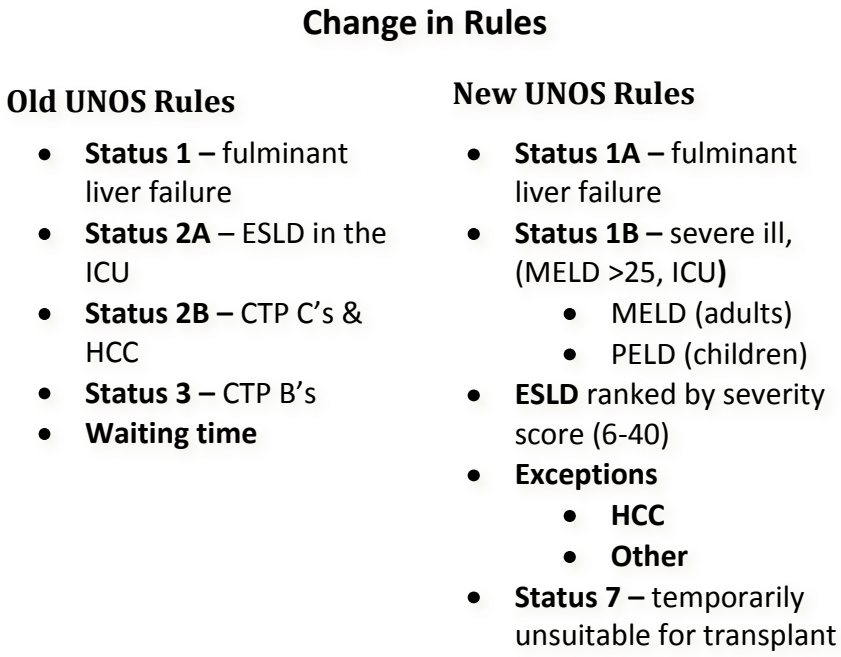


Figure 3. Highlighting the differences between the new and old allocation systems.

MELD Exceptions

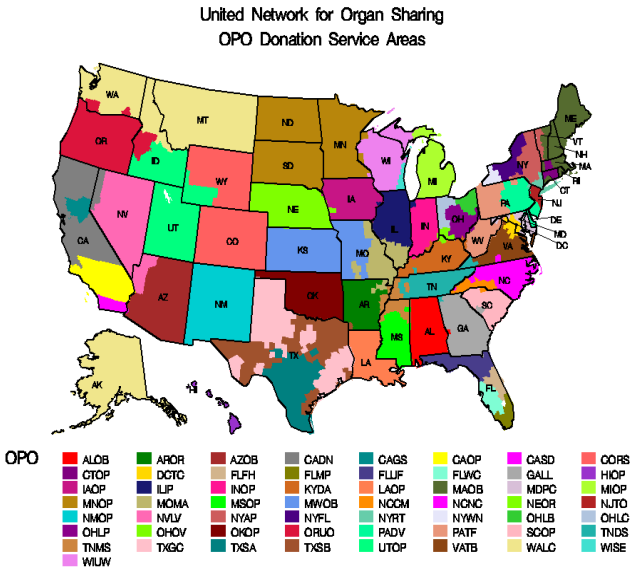
There are a number of liver conditions for which a calculated MELD score does not adequately capture the disease severity or mortality risk (26). For these conditions, patients must meet certain disease specific criteria in order to be awarded standard MELD exception points. These

conditions include the following: stage II hepatocellular carcinoma (HCC), primary hyperoxaluria, familial amyloid polyneuropathy, hepatopulmonary syndrome, portopulmonary hypertension, polycystic liver disease, hilar cholangiocarcinoma, refractory ascites or hydrothorax and recurrent bleeding ***(see appendix B for detailed description of criteria and points assigned).*** As long as patients continue to meet these criteria while on the wait list, the MELD exception points may be upgraded with additional points every three months, to reflect the patient's increased mortality while awaiting liver transplant.
Patients who do not qualify for standard MELD exception points may have their case presented by their transplant center to the local Regional Review Board (RRB). The submitting center prepares a narrative describing the medical condition, the mortality risk and how the MELD score fails to reflect this, thereby qualifying for specially assigned points.

HCC is the most common indication for standard MELD exception points. In the years immediately following the implementation of MELD exception points, transplantation for HCC increased from 4.6% in the preceding 5 years to 26% five years after MELD(27). Previously, liver transplantation for primary and metastatic hepatic malignancies was abandoned due to the high recurrence rate and poor survival (4, 28). As mentioned earlier, studies showed that patients with well-selected tumor criteria had comparable survival rates as those transplanted for non-malignant indications (12, 29). However, the traditional MELD score has poor predictability of the mortality of most patients with HCC. These patients tend to have well preserved hepatic synthetic function with normal INR and bilirubin until late in the course their disease. This would lead to a prolonged wait on the transplant list, with increasing risk of tumor progression outside of acceptable criteria for transplant. Therefore, UNOS developed a system for assigning a MELD score to reflect the 90-day mortality of 15%. Currently, patients with American Liver Tumor Study Group (ALTSG) stage II HCC (single HCC between 2 and 5 cm, or two to three lesions, none greater than 3 cm) receive 22 points. Every 3 months the points are upgraded to reflect the 10% increase in mortality. Patients with tumors <2 cm may be listed for transplant but they are not awarded exception points. These patients are listed according to their calculated MELD score. Similarly, patients with tumors outside the Milan Criteria (a tumor exceeding 5 cm or greater than 3 tumors) do not receive MELD priority points. They may be considered for transplantation by the transplant center according to regional criteria, but are listed without MELD priority points. Some regions accept extended criteria such as the UCSF criteria (1 lesion up to 6.5 cm, up to 3 lesions each <4.5 cm, and a maximal total diameter of 8 cm). Still others have regional criteria other than Milan or UCSF, under which patients are transplanted.

Organ Distribution
The current system of distribution is based on the 11 UNOS regions divided into donation service areas (DSA), each served by an Organ procurement organization (OPO). Available organs are distributed locally, then regionally, then nationally in a geographical algorithm. Once an organ is available for transplantation it is offered to the patient with the highest priority (status 1A and 1B) locally and regionally. If there are no acceptable candidates, the graft is next offered to wait list candidates with a MELD score ≥ 15 locally and then regionally. If it the organ is still not accepted, it is offered to candidates with a MELD score <15 locally and then regionally. If the

organ is still available, it is finally offered to national candidates in order of priority; first status 1A, then 1B, and others in decreasing order of calculated MELD score. With this system, it was still possible for an organ to go to a patient with a low MELD score (<15) instead of a sicker patient (example status 1A) simply because the sicker patient lived outside the region (30) . ***(See appendix C for a detailed algorithm of organ distribution)***



Source: UNOS.ORG. Geographic basis for organ distribution

The Impact of MELD on the liver allocation system

Prior to the implementation of the new liver allocation system, there were serious concerns that this would lead to transplanting sicker patients, which would result in an increase in post-transplant deaths. Early analysis of UNOS data for the first 6 months after policy implementations was encouraging as it showed an overall increase in liver transplant; fewer patients died waiting or were removed from the waiting list for being too sick for transplant. Candidates who underwent transplant were sicker with higher MELD scores, yet survival after transplant was not worse than during the period before MELD (31).

Follow up of the 1-year data showed results consistent with the early report. Freeman and colleagues and the UNOS/OPTN liver and intestine transplantation committee assessed data 1 year after the new allocation system was in place. This was compared to a similar time period 1 year prior to the MELD implementation. There was a 12% reduction in new registrants to the wait list, especially those with low MELD score. There was a 10.2% increase in cadaveric transplants and a 3.5% decrease in waiting list deaths. Patient and graft survival remained unchanged and a dramatic increase in number of transplants for malignancy was again noted (32).

Areas for Improvement

The MELD allocation system has been shown to be an improvement compared to previous methods. It provides an objective, transparent and reproducible measure of organ allocation.

As in any medical management and delivery system, the MELD system must continuously be examined for areas of shortcomings and opportunities for improvement.

In 2005, the "Share 15 National" policy was implemented to minimize the inequities caused by arbitrary geographical distribution and to offer organs to sicker candidates who did not reside local to the origin of the graft. This ensured that organ offers would be extended to sicker patients nationally (status 1A, 1B, MELD score >15 in descending order of mortality risk) before being offered to more stable local candidates with a MELD score <15. In June 2012 UNOS board of directors approved the "Share 35 Regional" policy and it will be implemented on June 18 2013. This policy prioritizes organ offers to patients with a MELD score of >35 regionally before it is offered locally. Under the previous system, the graft would be available to all patients with a MELD score >15 locally before being available to a sicker patient on the regional level. For example, a patient with a MELD score of 20 could receive an offer locally before the sicker patient in the region with a MELD of 35. "Share 35 Regional" eliminates this inequity(33). The share policies are proposed to reduce mortality by 50 per year.

Another proposed amendment to the MELD includes incorporation of the serum sodium into the MELD score. This is based on data that show that a low serum sodium value is a strong predictor of mortality in cirrhotic patients, especially those with a low MELD score (34, 35) And has led to validation and development of the MELDNa score (36, 37). Based on UNOS data, liver allocation simulation modeling by the SRTR projected that MELD-Na scoring could reduce waiting list mortality by 50-60 deaths each year. The proposal has been submitted for public comment and this period closed on June 14, 2013 with plans for submission for Board review in November of 2013 if public comments are favorable. The MELD-Na score can be calculated using the formula below or placing variables of for the MELD score (INR, Creatinine, Total bilirubin) and serum sodium into an online calculator.

$$MELDNa = MELD - Na - [0.025 \times MELD \times (140 - Na)] + 140$$

Reweighting of the MELD components so that the coefficient for each variable is altered to give a lower weight to the INR and creatinine and a higher weight to the bilirubin has been proposed (38). It is proposed that this model better predicts wait list mortality than the original MELD score. This proposal requires further investigation prior to implementation.

In the initial assignment of MELD exception points for HCC, it was estimated that the risk of progression from a stage 1 tumor to stage 2 was 15% and progression from stage 2 to beyond Milan criteria and the chance for curative transplant, was 30%. MELD scores of 24 and 29 were assigned to stage 1 and stage 2 tumors respectively to reflect their associated waitlist dropout and mortality (39). There was a 6-fold increase in liver transplant for HCC with the new exception points and patients with HCC exception points appeared to be receiving an unfair advantage over patients with other diagnoses. Subsequent data showed that the initial assessment overestimated the risk of tumor progression (40, 41). Consequently, policy makers re-estimated the progression risk of tumor progression and the allocation was revised to

remove all increased priority for stage 1 tumors. Stage 2 tumors were assigned 22 MELD exception points, the equivalent of a 10% risk of tumor progression in 3 months.

Summary

Data presented in the most recent OPTN/SRTR annual report of 2011 summarize our current status. There has been an overall increase in adult deceased liver transplantation since 2002 but that number has plateaued over the last 5 years; over 5,500 annually. The number of wait list candidates has increased since 2002 (over 15,000 annually) and the median time to transplant has increased since 2006. The most concerning finding of all is the number of candidates removed from the wait list for being too sick to transplant, has nearly doubled from 2009 to 2011. Each year, more than 2000 adults die waiting for a liver transplant. Those, whom are transplanted, receive an organ at a rate and MELD score that is related to their DSA (42).

The MELD allocation system is a significant improvement over previous methods and remains a work in progress, but disparities remain. These are in part related to the arbitrary geographical divisions created years before MELD was implemented. MELD was adopted as a system for allocation and not primarily for distribution. Therefore, it was not likely that the MELD system of organ allocation alone can address the inequities currently in the system. The Share 15 and Share 35 policy adjustments are areas where allocation can impact distribution but those alone are insufficient. Distribution of organs by DSA with an emphasis on keeping the organ within that OPO is inherently biased. It has been shown that OPOs with fewer than 100 patients listed, transplant patients at a lower MELD score than those with greater than 100 patients listed for transplant(43). Therefore, more stable patients are transplanted earlier while sicker patients in the neighboring OPO wait longer or die awaiting transplantation because there is more competition for few organs. Establishing uniform Organ Allocation Areas (OAAs), each serving a population base of approximately 9 million people as recommended by the Institute of Medicine, would help mitigate this problem. Ultimately, organ allocation is a difficult issue because of increased need of a scarce resource and the ideal solution is increased organ availability. Multiple efforts to increase the organ donor pool have been undertaken including the use of organs from donors after cardiac death (DCD), older donors (>age 50) and living donor liver transplant without a significant impact on the overall donor pool. Future approaches will need to include a fundamental change in the method of identifying and recruiting potential donor families.

References

1. Starzl TE, Marchioro TL, Vonkaulla KN, Hermann G, Brittain RS, Waddell WR**.** Homotransplantation of the Liver in Humans. Surg Gynecol Obstet. 1963;117:659-76.
2. Starzl TE, Groth CG, Brettschneider L, Penn I, Fulginiti VA, Moon JB, et al. Orthotopic homotransplantation of the human liver. Ann Surg. 1968;168(3):392-415.
3. Starzl TE, Brettschneider L, Martin AJ, Jr., Groth CG, Blanchard H, Smith GV, et al. Organ transplantation, past and present. Surg Clin North Am. 1968;48(4):817-38.
4. Starzl TE, Koep LJ, Halgrimson CG, Hood J, Schroter GP, Porter KA, et al. Fifteen years of clinical liver transplantation. Gastroenterology. 1979;77(2):375-88.
5. Starzl TE, Porter KA, Putnam CW, Schroter GP, Halgrimson CG, Weil R, 3rd, et al. Orthotopic liver transplantation in ninety-three patients. Surg Gynecol Obstet. 1976;142(4):487-505.
6. Starzl TE, Ishikawa M, Putnam CW, Porter KA, Picache R, Husberg BS, et al. Progress in and deterrents to orthotopic liver transplantation, with special reference to survival, resistance to hyperacute rejection, and biliary duct reconstruction. Transplant Proc. 1974;6(4 Suppl 1):129-39.
7. Starzl TE, Klintmalm GB, Porter KA, Iwatsuki S, Schroter GP**.** Liver transplantation with use of cyclosporin a and prednisone. N Engl J Med. 1981;305(5):266-9.
8. Calne RY, White DJ, Evans DB, Thiru S, Henderson RG, Hamilton DV, et al. Cyclosporin A in cadaveric organ transplantation. Br Med J (Clin Res Ed). 1981;282(6268):934-6.
9. Starzl TE, Iwatsuki S, Shaw BW, Jr., Gordon RD, Esquivel CO**.** Immunosuppression and other nonsurgical factors in the improved results of liver transplantation. Semin Liver Dis. 1985;5(4):334-43.
10. Kahan BD**.** Cyclosporine. N Engl J Med. 1989;321(25):1725-38.
11. Starzl T, Fung J, Venkataramman R, Todo S, Demetris A, Jain A**.** FK 506 FOR LIVER, KIDNEY, AND PANCREAS TRANSPLANTATION. The Lancet. 1989;334(8670):1000-4.
12. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 1996;334(11):693-9.
13. Rosen CB, Heimbach JK, Gores GJ**.** Surgery for cholangiocarcinoma: the role of liver transplantation. HPB (Oxford). 2008;10(3):186-9.
14. Rea DJ, Heimbach JK, Rosen CB, Haddock MG, Alberts SR, Kremers WK, et al. Liver transplantation with neoadjuvant chemoradiation is more effective than resection for hilar cholangiocarcinoma. Ann Surg. 2005;242(3):451-8; discussion 8-61.
15. A definition of irreversible coma. Report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death. JAMA. 1968;205(6):337-40.
16. Barclay WR**.** Guidelines for the determination of death. JAMA. 1981;246(19):2194.
17. Organ Procurement and Transplantation Network--HRSA. Final rule with comment period. Fed Regist. 1998;63(63):16296-338.
18. *Organ Procurement and Transplantation:Assessing Current Policies and the Potential Impact of the DHHS Final Rule*: The National Academies Press; 1999.
19. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC**.** A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology. 2000;31(4):864-71.
20. Wiesner R, Edwards E, Freeman R, Harper A, Kim R, Kamath P, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology. 2003;124(1):91-6.
21. Wiesner RH, McDiarmid SV, Kamath PS, Edwards EB, Malinchoc M, Kremers WK, et al. MELD and PELD: application of survival models to liver allocation. Liver Transpl. 2001;7(7):567-80.

22. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001;33(2):464-70.
23. Gleisner AL, Munoz A, Brandao A, Marroni C, Zanotelli ML, Cantisani GG, et al. Survival benefit of liver transplantation and the effect of underlying liver disease. Surgery. 2010;147(3):392-404.
24. Merion RM, Schaubel DE, Dykstra DM, Freeman RB, Port FK, Wolfe RA**.** The Survival Benefit of Liver Transplantation. American Journal of Transplantation. 2005;5(2):307-13.
25. Schaubel DE, Sima CS, Goodrich NP, Feng S, Merion RM**.** The Survival Benefit of Deceased Donor Liver Transplantation as a Function of Candidate Disease Severity and Donor Quality. American Journal of Transplantation. 2008;8(2):419-25.
26. Biggins SW, Bambha K**.** MELD-based liver allocation: who is underserved? Semin Liver Dis. 2006;26(3):211-20.
27. Ioannou GN, Perkins JD, Carithers Jr RL**.** Liver Transplantation for Hepatocellular Carcinoma: Impact of the MELD Allocation System and Predictors of Survival. Gastroenterology. 2008;134(5):1342-51.
28. Penn I**.** Hepatic transplantation for primary and metastatic cancers of the liver. Surgery. 1991;110(4):726-34.
29. Yoo HY, Patt CH, Geschwind J-F, Thuluvath PJ**.** The Outcome of Liver Transplantation in Patients With Hepatocellular Carcinoma in the United States Between 1988 and 2001: 5-Year Survival Has Improved Significantly With Time. Journal of Clinical Oncology. 2003;21(23):4329-35.
30. Smith JM, Biggins SW, Haselby DG, Kim WR, Wedd J, Lamb K, et al. Kidney, pancreas and liver allocation and distribution in the United States. Am J Transplant. 2012;12(12):3191-212.
31. Freeman Jr RB**.** MELD/PELD: one year later. Transplant Proc. 2003;35(7):2425-7.
32. Freeman RB, Wiesner RH, Edwards E, Harper A, Merion R, Wolfe R**.** Results of the first year of the new liver allocation plan. Liver Transpl. 2004;10(1):7-15.
33. Organ Procurement and Transplantation Network. Health Resources and Services Administration.; 2013.
34. Biggins SW, Rodriguez HJ, Bacchetti P, Bass NM, Roberts JP, Terrault NA**.** Serum sodium predicts mortality in patients listed for liver transplantation. Hepatology. 2005;41(1):32-9.
35. Heuman DM, Abou-Assi SG, Habib A, Williams LM, Stravitz RT, Sanyal AJ, et al. Persistent ascites and low serum sodium identify patients with cirrhosis and low MELD scores who are at high risk for early death. Hepatology. 2004;40(4):802-10.
36. Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. N Engl J Med. 2008;359(10):1018-26.
37. Biggins SW, Kim WR, Terrault NA, Saab S, Balan V, Schiano T, et al. Evidence-based incorporation of serum sodium concentration into MELD. Gastroenterology. 2006;130(6):1652-60.
38. Sharma P, Schaubel DE, Sima CS, Merion RM, Lok AS**.** Re-weighting the model for end-stage liver disease score components. Gastroenterology. 2008;135(5):1575-81.
39. Freeman RB, Wiesner RH, Harper A, McDiarmid SV, Lake J, Edwards E, et al. The new liver allocation system: Moving toward evidence-based transplantation policy. Liver Transplantation. 2002;8(9):851-8.
40. Yao FY, Bass NM, Nikolai B, Davern TJ, Kerlan R, Wu V, et al. Liver transplantation for hepatocellular carcinoma: analysis of survival according to the intention-to-treat principle and dropout from the waiting list. Liver Transpl. 2002;8(10):873-83.
41. Cheng SJ, Freeman RB, Jr., Wong JB**.** Predicting the probability of progression-free survival in patients with small hepatocellular carcinoma. Liver Transpl. 2002;8(4):323-8.
42. Organ Procurement and Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR). OPTN/SRTR 2011 Annual Data Report. Rockville, MD. Department of Health

and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau. Division of Transplantation;2012. . Accessed June 2013. www.srtr.org.
43. Trotter Jf OMJ. Meld scores of liver transplant recipients according to size of waiting list: Impact of organ allocation and patient outcomes. JAMA. 2004;291(15):1871-4.

Appendix A

Pre-2002 Status Designation for severity of liver disease for prioritization for organ allocation

Status 1 – fulminant liver failure

Status 2A – end-stage liver disease, in the ICU

Status 2B – hospitalized but not in the ICU, CTP C's & HCC

Status 3 – outpatient, CTP B's

Waiting time is crucial for priority.

2002 Changes to Status Designation for severity of liver disease for prioritization for organ allocation

Status 1A

1. Fulminant liver failure. Onset of hepatic encephalopathy within 8 weeks of symptoms of liver failure. No pre-existing liver disease.
   Must be in the ICU with a) ventilator dependence or b) requiring dialysis or continuous venous-venous hemodialysis. Or c) INR >2.0
2. Primary non-function of a transplanted liver within 7 days of implantation with a) AST > 3000 and INR >2.5 or arterial pH ≤ 7.3 or venous pH ≤7.25 and /or lactate ≥4mMol/L
3. Anhepatic candidate
4. Hepatic artery thrombosis in a transplanted liver within 7 days of implantation

Status 1B

1. MELD >25 (12-17 years old)
2. PELD > 25 (0-11 years old)

End-stage liver disease (ESLD)

Those not fitting criteria for status 1A or B are ranked by severity score (6-40)

Status 7

Patients designated as temporarily unsuitable for transplant

Appendix B

Region 4 Regional Review Board Guidelines revised 8/10/12

1. **Primary Hyperoxaluria:**

OPTN Policy 3.6.4.5.5 Liver Candidates with Primary Hyperoxaluria.
Candidates with AGT deficiency proven by liver biopsy (sample analysis and/or genetic analysis),
and listed for a combined liver-kidney transplant will be eligible for a MELD/PELD exception with
a 10% mortality equivalent increase every three months. Candidates must have a GFR<= 25 ml/min for 6 weeks or more by MDRD6 or direct measurement (Iothalamate or iohexol).

MELD score of 28/ PELD score of 41, with 3 point increase every 3 months

2. **Familial Amyloidosis:**

OPTN Policy 3.6.4.5.4 Liver Candidates with Familial Amyloid Polyneuropathy (FAP).
Candidates with a clear diagnosis, to include an echocardiogram showing the candidate has an ejection fraction > 40%, ambulatory status, and identification of TTR gene mutation (Val30Met vs.
non-Val30Met) and a biopsy proven amyloid in the involved organ, will be eligible for a MELD/PELD exception with a 10% mortality equivalent increase every three months.

MELD 22/PELD 28 (15% mortality risk) with 3 point increase every 3 months

3. **Hepatopulmonary Syndrome:**

OPTN Policy 3.6.4.5.1 Liver Candidates with Hepatopulmonary Syndrome (HPS).
Candidates with a clinical evidence of portal hypertension, evidence of a shunt, and a PaO_2 < 60 mmHg on room air will be eligible for a MELD/PELD exception with a 10% mortality equivalent increase in points every three months if the candidate's PaO_2 stays below 60 mmHg. Candidates should have no significant clinical evidence of underlying primary pulmonary disease.

MELD 22/PELD 28, may request a 3 point increase every 3 months

4. **Portopulmonary HTN (PPHTN):**

OPTN Policy 3.6.4.5.6 Liver Candidates with Portopulmonary Syndrome.
Candidates that meet the following criteria will be eligible for a MELD/PELD exception with a

10% mortality equivalent increase every three months if the mean pulmonary arterial pressure (MPAP) stays below 35 mmHg (confirmed by repeat heart catheterization).

- Diagnosis should include initial MPAP and pulmonary vascular resistance (PVR) levels, documentation of treatment, and post-treatment MPAP < 35 mmHg and PVR < 400 dynes/sec/cm-5.
- Transpulmonary gradient should be required for initial diagnosis to correct for volume overload.

MELD 22/PELD 28, may request a 3 point increase every 3 months

5. **Cholangiocarcinoma:**

OPTN Policy 3.6.4.5.2.Liver Candidates with Cholangiocarcinoma. Candidates meeting the criteria listed in Table 4 will be eligible for a MELD/PELD exception with a 10% mortality equivalent increase every three months.

MELD 22/PELD 28

TABLE 4. Criteria for MELD Exception for Liver Transplant Candidates With Cholangiocarcinoma (CCA)

- Centers must submit a written protocol for patient care to the OPTN/UNOS Liver and Intestinal Organ Transplantation Committee before requesting a MELD score exception for a candidate with CCA. This protocol should include selection criteria, administration of neoadjuvant therapy before transplantation, and operative staging to exclude patients with regional hepatic lymph node metastases, intrahepatic metastases, and/or extrahepatic disease. The protocol should include data collection as deemed necessary by the OPTN/UNOS Liver and Intestinal Organ Transplantation Committee.
- Candidates must satisfy diagnostic criteria for hilar CCA: malignant-appearing stricture on cholangiography and one of the following: carbohydrate antigen 19-9 100 U/mL, or biopsy or cytology results demonstrating malignancy, or aneuploidy. The tumor should be considered unresectable on the basis of technical considerations or underlying liver disease (e.g., primary sclerosing cholangitis).
- If cross-sectional imaging studies (CT scan, ultrasound, MRI) demonstrate a mass, the mass should be 3 cm or less.
- Intra- and extrahepatic metastases should be excluded by cross-sectional imaging studies of the chest and abdomen at the time of initial exception and every 3 months before score increases.
- Regional hepatic lymph node involvement and peritoneal metastases should be assessed by operative staging after completion of neoadjuvant therapy and before liver transplantation. Endoscopic ultrasound-guided aspiration of regional hepatic lymph

nodes may be advisable to exclude patients with obvious metastases before neoadjuvant therapy is initiated.

- Transperitoneal aspiration or biopsy of the primary tumor (either by endoscopic ultrasound, operative, or percutaneous approaches) should be avoided because of the high risk of tumor seeding associated with these procedures.

6. **Polycystic Liver Disease:**

Total liver volume of >3500 ml

- MELD 22 with 3 additional points every 3 months upon reapplication

Clinically significant manifestations of disease due to massive PLD including one of the following:

a) hepatic venous outflow obstruction due to cyst
b) heart failure
c) documented weight loss of at least 10% from baseline dry weight or on liquid diet and nutritional support
d) Decreased mid-arm circumference in the non-dominant arm (men<23.8 cm, women <23.1cm)

- Median MELD of the region and 3 additional points every 3 months upon reapplication

7. **Recurrent Bleeding:**

Requiring >4 units of PRBC transfusions over one month and documented portal hypertensive gastropathy. Documentation must include "Transfusion Records".

MELD score 22, may request a 3 point increase every 3 months

8. **Recipients of DCD donor liver transplants or HAT resulting in destroyed bile ducts (Strictures requiring permanent drains and/or stents.**

Patients with DCD livers or HAT who demonstrate the presence of liver dysfunction in the first 18 months after transplantation (bilirubin of 3 or higher) with cholangiopathy as evidenced by any of the following:

- Radiological study in the first 18 months after transplantation

- Document attempted surgical, endoscopic, & radiologic therapies
- Documentation of hospital admits over last 6 months
- Document number of episodes requiring ICU care
- Document blood culture results in absence of other sources

MELD score 22, may request a 3 point increase every 3 months

9. **Hepatocellular Carcinoma:**

T3 HCC that meet the following criteria will receive MELD 22:

- Single lesion up to, but no greater than 6 cm
- Two or three lesions with the largest no greater than 5 cm and the total tumor diameter no greater than 9 cm

10. **Biliary Atresia:**

Patient must meet all of the following requirements:

1. Age less than 24 months.
2. Diagnosis of biliary atresia by intra-operative cholangiogram or liver biopsy.
3. By 3 months after the Kasai procedure, evidence of failure of Kasai procedure is evidenced by either a)Total bilirubin > 6 mg/dl **;** b)Significant malnutrition (lack of maintenance/improvement of appropriate weight or height centiles) despite aggressive enteral nutritional management; or c) intractable ascites.

PELD 24 to be increased by 2 points every 3 months on reapplication.

11. **Refractory Ascites or Hydrothorax:**

Requiring thoracocentesis an average of 1 or more liters per week or paracentesis averaging 3 or more liters per week over at least one month. The patient must have contraindications to TIPS shunt or a failed TIPS. Documentation must include “procedure notes” and be updated every 4 weeks. MELD score 16 with an appeal for 3 points every 3 months (NOT automatic).

Appendix C

Combined Share 15/35/Liver-Intestine Allocation policy changes: updated 06/18/13

Adult Donor Liver Allocation Algorithm

Combined Local and Regional

1. Status 1A candidates in descending point order

2. Status 1B candidates in descending point order

Local and Regional

3. Candidates with MELD/PELD Scores >=35 in descending order of mortality risk (MELD) scores, with Local candidates ranked above Regional candidates at each level of MELD score

Local

4. Candidates with MELD/PELD Scores 29-34 in descending order of mortality risk scores (probability of candidate death)

National

5. Liver-Intestine Candidates in descending order of status and mortality risk scores (probability of candidate death)

Local

6. Candidates with MELD/PELD Scores 15-28 in descending order of mortality risk scores (probability of candidate death)

Regional

7. Candidates with MELD/PELD Scores 15-34 in descending order of mortality risk scores (probability of candidate death)

National

8. Status 1A candidates in descending point order
9. Status 1B candidates in descending point order
10. Candidates with MELD/PELD Scores >=15 in descending order of mortality risk scores (probability of candidate death)

Local

11. Candidates with MELD/PELD Scores < 15 in descending order of mortality risk scores (probability of candidate death)

Regional

12. Candidates with MELD/PELD Scores < 15 in descending order of mortality risk scores (probability of candidate death)

National

13. Candidates with MELD/PELD Scores < 15 in descending order of mortality risk scores (probability of candidate death)

Source: http://optn.transplant.hrsa.gov