The MELD Score: Limitations and consequences.

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***Abstract*--**The success of liver transplantation has created unexpected challenges for physicians and surgeons caring for patients with chronic liver disease or acute liver failure. Specifically, with all of these legitimate candidates for liver transplantation, how does one prioritize them given the unfortunate issue of limited donor availability? The answer to that problem has undergone several iterations which have ultimately resulted in the Model for End-stage Liver Disease (MELD) score allocation system. The MELD score, which yields a numeric value based upon serum creatinine, bilirubin and INR has been successful in prognosticating 90 day mortality for these patients, and has proven to be a just method of liver allocation. However, a careful look at the parameters of the MELD score reveals the limitations and resultant caution that should be given to ostensibly objective data. Creatinine and INR are labile especially in the setting of patients with advanced liver disease that are prone to alteration not only by the inherent disease state but also iatrogenic interventions. The implications of these interventions have significant medical and moral consequences as they not only determine immediate treatment but also which patients are allocated the precious life-extending resource of organ transplant. In this review the principles and parameters of the MELD score will be discussed, as well as their ultimate consequences upon both liver and simultaneous liver-kidney transplantation.

***Key words*--**liver transplant; liver-kidney transplant; MELD score; transplant priority.

1. INTRODUCTION.

Liver transplantation represents a definitive therapy for acute liver failure and chronic liver disease (CLD), including most commonly alcoholic liver disease or hepatitis C viral infection. The first successful liver transplant surgeries resulting in high one-year survival were in 1967 by Thomas E. Starzl [1]. Through advances in surgical technique, and importantly the implementation of cyclosporine in 1979 and tacrolimus in 1989, post-operative morbidity and mortality have been improved such that liver transplantation has become a standard and integral practice in modern medicine and surgery [1-2]. As this procedure became not only technologically reproducible but beneficial to patients, the immediate concern arose as to who should be eligible for it. Remarkably, 40 years later in the US there are about 6,000 liver

transplants per year, for approximately 16,000 patients on the 'wait-list' [3]. These numbers point to an immediate and critical disparity of vital resources and over the years methods for prioritizing these patients with CLD or acute liver failure towards transplantation have been developed. These concerns have resulted in the implementation of a quantitative estimate of 90 day mortality, the Model for End-stage Liver Disease (MELD) score [4-6].

Table 1: MELD score and effect on Liver transplantation, pre- vs post-MELD allocation (adapted from Dutkowski *et al*).

Parameter	Effect	P-value
Waiting time to transplantation (days) all groups Hepatocellular carcinoma	255 vs 192 334 vs 204	0.0693 0.036
Waiting list mortality (death/1000 pt years)	386 vs 242	< 0.0001
Transplantation of sicker patients (median MELD score)	13.5 vs 20	0.003
Recipient post-transplant morbidity for renal replacement therapy* (%)	13 vs 46	< 0.0001
Hospital mortality (%)	6 vs 9	NS
Cost of transplantation (admission to discharge) (median $)	81,967 vs 127,453	0.02

*Authors note that kidney function recovered in most cases within 6 months of transplantation.

The MELD score, despite imperfections, has been quite productive in its goals of equitable liver allocation, such as decreased waiting time and wait list mortality, as noted in table 1 [1, 3, 6-10]. Ideally it was hoped that the quantized parameters of bilirubin, creatinine and INR would not only capture the biology and trajectory of liver disease, but in a sense form an objective non-biased method of utilitarian allocation. However this latter assumption is somewhat tentative given the inherent complexity of the disease state and human interest in modifying it. These concerns are captured in the obvious question: should patient-care be maximized resulting in a reduced priority, i.e. a lower MELD score, or should the physician "neglect" transient efforts to improve a patient's health status so the MELD score and thus priority for a transplant, which appears inevitable, be advanced?

2. PROLOGUE to the MELD SCORE.

The First steps were taken in 1986 when the Organ Procurement and Transplant Network (OPTN) was established through the National Organ Transplant Act of 1984 to be managed under the United Network for Organ Sharing (UNOS) [1, 11-12]. UNOS is divided into 11 regions across the US, with organs allocated within each region in most circumstances. A number of methods have evolved to properly allocate livers to appropriate recipients based on a utilitarian ethic: the liver graft should go to those patients who not only most need them medically, but also who would benefit most from them. Initially, "time on the waiting list" was utilized to prioritize patients, however it was quickly recognized that the time on this transplantation list was not a good marker of necessity, but rather was more a consequence of the willingness of transplant centers to accept patients for listing. As a result, patients referred early (for various non-standardized reasons), without hepatic decompensation, who were placed on the waiting list might have a greater listing priority than another decompensated liver disease patient, or one with hepatic cancer. Allocation was not uniformly based on the extent of pathology and prognosis, but rather the proclivities of patients, physicians and institutional policies.

Noting these inequities, UNOS subsequently revised the priority listing procedures to be based upon the location of the patient at the time of donor availability, designated as status levels. status level 1 implied acute liver failure and moribund state, level 2 was a patient in the intensive care unit (ICU), status level 3 was a non-ICU hospitalized patient, and status 4 was a patient well enough to be non-hospitalized. Within that system status 7 was for a patient taken off the transplant list (inactive). These

levels were subsequently divided further by disease severity based on the Child-Pugh score and other variables. The Child-Pugh score comprised five variables of graded severity: ascites, albumin, bilirubin, nutrition and encephalopathy [13]. Subsequently given the somewhat nebulous assessment of nutrition, this parameter was replaced by the INR level in the Child-Turcotte-Pugh score, and yet the subjective parameters of both of ascites and encephalopathy remained [14]. Furthermore, the bilirubin level is given a maximal score of 3 mg/dl, thus inappropriately grouping together a spectrum of patients with significant differences in decompensation, reflected in higher bilirubin levels, and affecting true prognosis. The rationale of status and its disease state modifications, although imperfect, was sensible: those with more illness/advanced disease would be located either in a hospital, or in an ICU, as opposed to being at home waiting for a transplant [2, 15]. Quickly it became evident that these status levels were not as objective for disease severity as had been hoped. The allocation in the hospital for patients to be in an ICU or non-ICU setting relied not just on objective clinical criteria, but bed space availability, the hospital's perception of what constitutes ICU level care, and ultimately the aggressiveness of the physician in managing the patient's condition. At each level these criteria are not standardized and thus allow for a variety of outcomes not entirely expected based upon the initial admission. In the current era the status level 1 is still kept to designate those patients with acute liver failure, e.g. caused by Tylenol toxicity, requiring urgent liver transplantation [15].

Given persistent concerns for misallocation of these precious livers and the significant material and financial costs attendant to them, further research was initiated into better and more quantitative alternatives. As a result in 2002, the MELD score allocation system was adopted as the criteria utilized to prioritize patients on liver transplant waiting lists [4-5, 15]. The original score arose from the Mayo Clinic in 2000 and was utilized to stratify patients undergoing transvenous intrahepatic portosystemic shunt (TIPS) procedure in the setting of variceal hemorrhage. Given its success in this domain, it was extrapolated more widely and was found to be quite successful at predicting 90 day mortality for non-transplanted liver disease patients generally. The initial MELD score for transplantation included the INR, serum creatinine, serum bilirubin level (see figure 1) and a disease etiology correction factor for alcoholic liver disease and cholestatic liver disease. The correction factor was ultimately removed upon further analysis as it was not observed to affect mortality prognosis [6, 16-18].

Figure 1: The MELD score equation.

MELD Score = 10 {0.957 Ln(Cr) + 0.378 Ln(Tbil) + 1.12 Ln(INR) + 0.643}*

*Ln = logarithm; Cr = creatinine; Tbil = total bilirubin.

The MELD score allowed for point adjustments for the presence of hepatocellular carcinoma (HCC) based upon tumor staging as defined by the Milan criteria [19-20]. For instance, these patients receive a score of at least 22 at baseline with additional points added every 3 months. In addition to HCC, optional additional points were allowed based upon UNOS regional board approval for the hepato-pulmonary syndrome, amyloidosis, portopulmonary syndrome and primary hyperoxaluria [21]. The average MELD score nationally at the time of transplantation is 20. MELD score listing is further indexed by blood type, thus the patients with type AB blood are more quickly transplanted than those with type O, given the more common frequency of the former. Additionally for patients who have the same MELD score, and all other clinical variables constant, allocation of the organ then goes to the patient longer on the list.

3. MELD SCORE and CREATININE.

The benefits of the MELD score and its subsequent modifications have been dramatic and include the items identified in table 1 [7-9]. Nevertheless, manipulation of the MELD score, composed seemingly of objective data, has been

identified as a problem [22-26]. Ultimately rules for transplant listing using the MELD score were adopted [27]. The MELD score is unitless, ranging from 6 to 40, and utilizes whole numbers. For instance a patient with a score of 10 has a 6% 90 day mortality, whereas a patient with a score of 40 has a 89% 90 day mortality. Individuals with a MELD score < 7 should not be listed. Patients with a MELD score < 15 have shown not to derive net benefit from liver transplantation. For those with a MELD score greater or equal to 25, weekly recalculation of score is required; between 19 and 24, a monthly recalculation; between 11 and 18, recalculation at 3 month intervals is recommended, and with scores 10 or less, a yearly calculation. Individuals on hemodialysis (HD) were given an initial score of 20, beyond which bilirubin and INR can contribute. For patients not on HD but with altered kidney function either from acute kidney injury (AKI) or chronic kidney disease (CKD) the serum creatinine was topped out at a value of 4 mg/dl [2-4, 15, 20].

The utilization of serum creatinine has raised critical questions regarding its true role in measuring accurately renal function and ultimately it's significant impact on the MELD score [27]. Creatinine is a spontaneous breakdown product of creatine, a phosphate carrier for ATP replenishment in muscle. In stable states, whether healthy or diseased, it can be produced at a constant rate, and is subsequently filtered at the renal glomeruli and excreted. It is not re-absorbed, but a fraction is secreted from the proximal tubule. Creatinine was hoped to represent a marker of not just glomerular filtration rate (GFR), but by extension kidney function in a stable state [28-29].

However, this simple assumption has a significant number of limitations that are in general practice not uniformly addressed. Creatinine production is dependent on nutritional intake of creatine and it's amino acid building blocks, which are variable and/or impaired in patients with liver disease [30]. Creatinine production is known to be decreased in septic states, a common occurrence in decompensated cirrhotics with impaired immune function [31]. The serum creatinine level is dependent on volume of distribution, which is significantly altered given changes in oncotic protein concentration, vascular wall permeability and overall fluid retention given the consequences of portal hypertension and activation of the renin-angiotensin-aldosterone system. Furthermore there is direct chemical interference upon creatinine at a number of levels. Medications such as trimethoprim and cimetidine compete for secretion in the proximal tubules with creatinine thus raising its serum level, while simultaneously implying that a decrease in GFR and kidney function has occurred. [32]. Furthermore, the assays utilized to measure serum creatinine can be interfered upon by keto-acids and bilirubin, the latter causing significantly depressed reported values of creatinine. The chemical assays themselves are not uniform across hospitals. There are not simple or standard ways to correct for these variables [33-37].

In so far as creatinine is a reflection of kidney function and systemic processes like volume status it has become a target for physician analysis and intervention. Beyond short term gains in patient care, such parameters can be altered and strategically manipulated towards a higher MELD score and thus eligibility for transplantation. For instance, aggressive (or inadequate) diuresis and mobilization of third space fluid like edema, ascites, and pleural effusions result in not only significant changes in the serum level of creatinine but also morbidity and mortality for the patient. Additionally, as was noted with the negative interference of bilirubin upon creatinine, which has a larger effect at higher bilirubin levels, a number of patients who should be higher on the transplant list are in fact given lower priority. Indeed, it is readily seen that either by commission or omission, patients may not be properly stratified for liver transplantation; that in fact, further misallocation of this limited resource is occurring with the attendant medical-surgical risks and significant cost.

4. MELD SCORE and INR.

Similar gaming of the MELD score can be

accomplished with regard to the INR, the most heavily weighted parameter [38-41]. Any manipulation of the patient's vitamin K status whether it be at the level of dietary intake, intestinal bacterial load or therapeutic antagonists such as warfarin, will alter the INR level, significantly in some cases. The use of warfarin, given concerns for prior or active venous thromboembolism (VTE) including certain cardiac dysrhythmias, is of particular note as it too is subject to the subjective concerns of patients and providers. It is sometimes thought for instance that elevations in INR, while reflecting an inadequate synthetic apparatus necessarily reflect an "auto-anticoagulated state" such that for those patients who were perceived to have a baseline increased risk for thrombosis, their CLD in this case would be beneficial. However, the INR does not assess all the markers of coagulation, e.g. protein C, and thus does not truly reflect the baseline status of thrombosis which is certainly altered in CLD but not in one simple direction *a priori* [42]. Further is the concern for hemorrhage in the setting of a fall by an elderly patient, and in particular one with a predisposition to hepatic encephalopathy, a not infrequent occurrence in those with CLD. The real risk for fall and the more rare risk for significant hemorrhage are likely misperceived [43]. Thus at multiple levels, these patients may in fact inappropriately be assessed given false assumptions about anticoagulation and chronic liver disease pathophysiology, while the risk for complications of VTE still remains high. The physician when reflecting upon these concerns can consider warfarin in a more wholesome light, and not only effect morbidity and mortality related to VTE, but also mortality related to CLD and the use of transplantation through the resultant elevation in INR. Less well monitored, is the variability in INR resulting from differences in chemical assays by virtue of the different thromboplastin reagents utilized in it's determination [38-41]. Using a thromboplastin reagent, sometimes specific to individual hospitals, that results in a higher INR value can increase the priority score for the patients such that the now compete with a smaller group of other patients on the transplant list for a donor organ [39]. Again it is seen that objectivity of the INR value is affected by the method of measurement and the perceptions of the physicians.

With all of this in mind, one has to ask how does the utilization of the MELD score, and what MELD score numbers in particular, allow for the best results for the best candidates? For all disease indications for liver transplantation except HCC, the MELD score at listing is similar to the MELD score at the time of transplantation [7, 26]. HCC is the exception. If the MELD score at the time of initial listing (absent the added points) for HCC and time on the waiting list allowed for HCC cases are examined, the initial listing and immediate pretransplant MELD scores would be similar [7, 26]. As a result of this increase in the MELD score, the number of transplants done for HCC has increased 3-6 fold while the wait-list time has been reduced by 50% [44-45] without any adverse effects post-transplantation relative to the pre-MELD era. Thus the MELD score appears to capture fairly well the presumed biology and trajectory of liver disease, and further understanding of the mathematical parameters would seek to improve upon these results.

5. SIMULTANEOUS LIVER-KINDEY TRANSPLANT in the MELD ERA.

The maturation of transplant surgery and immunosuppressive therapies combined with better insight into liver disease and its systemic consequences have made liver transplantation a definitive practice. With this result, and the strain it places upon the liver donor pool, there has been the unexpected parallel strain upon kidney transplantation and the kidney donor pool given the weight of creatinine within the MELD score. It is important to recognize that patients who undergo solitary kidney transplant and simultaneous liver-kidney transplantation (SLKT) differ markedly in terms of their degree of renal impairment. Specifically, 100% of solitary kidney recipients are on HD at the time of transplant while only 60% of those receiving a SLKT are on HD [2]. In the MELD era, given the significance of serum creatinine, there has been a 41% increase in the number of patients

on HD at the time of transplantation with a resultant 177% increase in the rate of SLKT procedures occurred [36, 46-51]. Between 2002-2006 a five-fold increase in SLKT occurred with 400 such procedures performed in 2006 alone [2]. Data available on greater than 19,000 liver transplants, nearly 34,000 kidney transplants and 1,000 SLKT between 1987 and 2006 reveal no benefit of SLKT compared to liver transplant alone [48]. In fact, the SLKT survival rate actually declined from a high of 87% in 2002 to a low of 76% in 2005. Most disturbing was the finding that the kidney graft survival was worse at one year in SLKT recipients than in solitary kidney transplant recipients (77% vs. 89%) [48]. Importantly, the only sub-group of SLKT patients who benefited in terms of survival were those who had been on HD for a period of > 3 months. Furthermore, a MELD score > 23 at the time of transplant was associated with an increased kidney graft loss in those who received a SLKT [48].

Overall, significant results so far have been noted: (1) increase rate of SLKT procedures [2, 35, 46-47]; (2) a reduction in the availability of donated kidneys for those on renal transplant lists not requiring a liver transplant [2, 47]; (3) an overuse of SLKT procedures [47-50]. Obviously these problems as related to creatinine and the association with increased renal transplantation requires remediation given the limited quantity of these organs and the associated co-morbidities surgically and post-transplantation. As a result of these data, when the liver allocations committee presented their report on the use of SLKT in 2007, the consensus was that the procedure was only appropriate if the measured creatinine clearance is less than 30 mL per minute and in those who have required HD for at least 6 weeks [50].

6. LIMITATIONS in HCC DIAGNOSIS in the MELD ERA.

A major problem with the current policy relative to transplantation for HCC in the MELD era consists of the fact that a liver biopsy to document the presence of a HCC is not required [18]. Rather dynamic imaging, e.g. triple phase CT or MRI procedures, in addition to an elevated alpha fetal protein (AFP) level > 200 ng/ml, have become the standard for identifying HCC despite the fact that the positive predictive value for a HCC diagnosis utilizing imaging criteria varies substantially and has been reported to be as low as 69% [52-53]. In particular, studies have found an alarming rate of false-positive HCC diagnoses by helical CT, approximately 8% [53]. These data are confirmed by the report from the University of Colorado transplant program regarding HCC, where they failed to document a difference in the serum AFP levels between those with a true positive result for HCC as well as the number of HCC lesions identified in the explanted livers between the 2 time periods. Nonetheless, they reported that the false positive rate increased from 0/229 cases in the pre-MELD era to 3/43 cases after the introduction of the MELD criteria allocation criteria ($p < 0.001$) [45] The consequences of this policy on the small pool of available livers results in these precious liver grafts being transplanted, itself a highly complex and expensive procedure (immediate and long terms sequelae) to individuals who may not require it, while depriving those patients who would actually benefit from these liver transplants but are numerically further down the wait list.

7. ECONOMICS in the MELD ERA.

Given the nature of the MELD score, two groups of patients have seen increased access to transplantation: patients with renal disease and those with HCC. These results are expected given the mathematical properties of the MELD score, namely the weighted serum creatinine and the exception points for the appropriate HCC lesion. Regarding the first group, patients with renal disease, it is known that they can incur more costs in the setting liver transplantation. Regarding the second group, it is noted that these patients move into a higher MELD score that is usually associated with more significant and overt forms of hepatic decompensation and multi-organ failure. A number of studies, in particular that of Axelrod *et al*. have investigated the economic impact of these transplanted patients upon the transplant medical center [8, 10, 54-55]. They not surprisingly

found an increase in the number of transplants for HCC, increased MELD scores (21 vs 17) and increased SLKT when comparing MELD era to pre-MELD era. Also it was noted that patients with MELD scores > 15 had inpatient costs that were 49% higher compared to lower MELD scores. These higher MELD patients had increased overall length of stay (LOS) [55]. Given these features and the details noted in Table 2, income to the transplant center was 114% less in high MELD patients which resulted in a net loss. Supporting concerns alluded in the prior sections, the overall LOS for SKLT was significantly longer compared to liver transplantation (28.4 vs 11.6 days) and resulted in a 388% reduction in net income. These net deficits result in part from the structure of Medicare re-imbursement: 1) patients may not be eligible for coverage; 2) costs surpass coverage; and 3) the lack of a specific designation for SLKT, wherein it is designated and reimbursed as liver transplantation [55]. Given the nature of the MELD score with its preference for patients with renal injury, i.e. higher creatinine scores, these financial injuries are inevitable and severe. Similar concerns and overall results have been investigated and validated outside the US as well [10].

Thus the results of the MELD score are complicated in a comprehensive analysis for while it has been demonstrated that this method of allocation has led to reductions in mortality by shifting the population of patients to be transplanted, it is these same patients who will likely strain the healthcare system the most [55], in which given current practices and re-imbursements, will necessarily lead to net deficits. Interestingly, it has been noted that in the pre-MELD era, costs for liver transplantation from 1993-1998 had actually been reduced by improved medical techniques and shorter LOS, from $201,677 to $143,363 [56]. Transplant centers, functioning within increasingly more difficult economic constraints are left with the problem in which transplantation has moved from being an experimental technology to one that represents definitive treatment for CLD and acute liver failure, but who is to pay for it? It's benefits are demonstrable, relying on sound biological understanding and are in-line with advanced moral principles of beneficence and non-malfeasance. Once again the ideology of the patient and physician will run-up against the realities of administrative economic analysis and it is not obvious in the long-term which will

Table 2: Impact of the MELD score on resource utilization for liver transplantation (adapted from Axelrod *et al*.)

Parameter	Relative cost for high MELD (>15) vs low MELD (≤ 15)	P-value
Total cost	49% increase	<0.001
Room and board	135% increase	<0.001
Operating room	11% increase	0.09
Pharmacy	87% increase	0.02
Laboratory	100% increase	<0.001
Radiology	92% increase	0.007
Supplies	40% increase	0.06
Overall LOS*	108% increase	<0.001
Pre-Tx LOS*	489% increase	<0.001
Net income	114% decrease	0.02

MELD = Model for end-stage liver disease; *increase in days in the hospital.

carry the day. As has been the case in other domains of healthcare, such deficits will either have to be displaced upon other paying patients or providers and services, and/or digested by the transplant center's own funds (which is unsustainable), or these procedures will be simply curtailed or stopped. The corporate nature of transplant centers imbues a law-like gravitation towards sound financial policy and thus cost containment is of the utmost importance. These concerns should drive conversations and adjustments of third-party re-imbursements and in stream-lining inpatient medical-surgical care. These healthcare concerns are not unique and remain open with no immediate salvage.

8. SUMMARY.

a. The MELD score, while imperfect and with increased costs, has proven to be the most equitable method to date for liver allocation, especially concerning HCC, in decreasing wait-list mortality, wait list time, and maintaining robust post-transplant survival.
b. Despite the objective quality of the MELD score, its parameters, specifically the creatinine and INR, are rather dynamic entities that can in part be iatrogenically manipulated with significant effects on a patient's eligibility for transplantation.
c. An evolving concern is regards to SLKT, wherein the MELD score has ushered in an increased allocation of kidney transplantations to liver patients without consistent overall benefit. Parameters to reign in SLKT for optimal patient populations are being devised and implemented.
d. The mathematical preferences of the MELD score have shifted the populations transplanted and thus incurred increased costs with significant strains upon transplant centers. The long-term consequences of this economic dislocation remain to be seen, but are nevertheless disconcerting.
e. In understanding the inherent limitations and consequences of the MELD score on liver transplantation and the healthcare system, we may continue to better serve our patients through clinical practice and reasoned allocation of this precious and life-saving resource.

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