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Model for End Stage Liver Disease: End of the First Decade

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Synopsis

In February 2002 the Model for End Stage Liver Disease score (MELD) was adopted as the basis for allocation of liver allografts for transplantation (LT) in the United States. Implementation of the MELD score led to a reduction in waiting list registration and waitlist mortality and an increase in deceased donor transplants. The MELD score, as an objective scale of disease severity, has been used in the management of patients with chronic liver disease in the non-transplant setting. Several models have been proposed to refine and improve the MELD score. This includes measurement of serial MELD scores, addition of variables (e.g. serum sodium), or re weighting components of the MELD score. We believe that the MELD score will be used as a template to improve upon as an objective gauge of disease severity and a metric to optimize allocation of scarce donor organs for liver transplantation for the next decade and beyond.

Keywords

MELD; organ allocation; waitlist mortality; mathematical models; prognosis; survival

Introduction

In February 2002 the Model for End Stage Liver Disease score (MELD) was adopted as the basis for allocation of liver allografts for transplantation (LT) in the United States. Implementation of the MELD score led to a reduction in waiting list registration and waitlist mortality and an increase in deceased donor transplants.¹ Despite transplanting sicker patients (higher MELD scores), there has been no appreciable decrement in survival after LT.² Further, as a common metric of underlying severity, the MELD score has been used in management of patients with a wide spectrum of liver disease.³ The MELD score is a working model and has served as a template for further refinement to achieve the goal of equitable distribution of a scarce resource.^{4, 5} This review highlights the strengths of the current MELD score, addresses its limitations and discusses proposed modifications to successfully enrich a MELD based allocation system for the next decade of LT.

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A. Development of the MELD score

The recognition of several limitations of the existing liver allocation policy in the late 1990s provided a strong impetus to devise a more equitable and efficient system. Transplant candidates were categorized into 4 broad United Network for Organ Sharing (UNOS) statuses, which were in part defined by arbitrary descriptors of disease severity (e.g. intensive care admission). For non-intensive care patients, the Child-Turcotte-Pugh score was used to measure disease severity. The score, however, consisted of variables that were subjective (e.g., ascites, encephalopathy) or influenced by inter laboratory variability (e.g., prothrombin time, albumin) and lacked statistical validity (e.g., equal weights to all elements such as mild hyperbilirubinemia versus grade II hepatic encephalopathy). Because of the inability of this transplant status system to accurately stratify patients according to their level of sickness, there were a large number of patients within a given status for whom waiting time was used to determine priorities in allocation. Sicker candidates who were listed late in the course of disease progression were disadvantaged as they had not accrued enough waiting time despite their high risk of mortality. Under the system waitlist mortality continued to increase.⁶⁻⁸ In studies that correlated waiting time and risk of mortality, waiting time was shown to be a poor metric for disease severity.⁹ In 1999, the Institute of Medicine and the US Department of Health and Human Services issued a mandate to the liver transplant community to design an organ allocation system that de-emphasized waiting time and set allocation priorities based on the severity of liver disease and risk of mortality.¹⁰

The MELD score was initially created to predict survival in patients with complications of portal hypertension undergoing elective placement of transjugular intrahepatic portosystemic shunts (TIPS).¹¹ The model was subsequently validated as a predictor of survival in several independent cohorts of patients with varying levels of liver disease severity (e.g., hospitalized and ambulatory patients), as well as patients of geographically and temporally diverse origin.¹² In a prospective study of candidates on the waiting list, MELD was an excellent predictor of waitlist mortality. The concordance (c-statistic) with 3-month mortality as the end point, for the MELD score was 0.83 indicating that when a pair of patients are randomly drawn out of the study population, 83% of the time, the model correctly predicts the first patient to die.³

Though the original derivation of the model included the etiology of liver disease, subsequent studies de-emphasized the importance of etiology of liver disease.³ Further, early studies showed that individual complications of portal hypertension such as spontaneous bacterial peritonitis, encephalopathy, variceal bleeding, or ascites did not provide further prognostic information when added to MELD.¹² Thus, when the MELD score was selected as the metric for the new allocation policy, the etiology of liver disease was removed from the score. In addition, several changes were introduced to the score.¹³ They included lower bounds for serum creatinine, bilirubin, and international normalized ration (INR) fixed at 1 to avoid negative scores and an upper bound of serum creatinine at 4 mg/dl, including patients on hemodialysis. While these modifications were made empirically, they were widely accepted and our recent study largely supported those upper and lower bounds (see below).

Strengths of the MELD score include that it is an objective metric utilizing a continuous scale, which lends itself to ranking patients based on disease severity. It incorporates laboratory parameters that are easily available and reproducible. Its validity as a robust mathematical model to assess mortality risk in patients with end stage liver disease has been shown in multitude of studies.³ In fact, MELD has been shown to be superior to clinical judgment in identifying patients at risk of mortality.¹⁴

B. Components of the MELD score

Bilirubin

In patients with end stage liver disease, serum bilirubin concentration is a well-established marker of the 'hepatic synthetic function,' although in the strictest sense, it represents excretory function. Of the three MELD variables, serum bilirubin carries the most weight. It has essentially linear relationship with 90 day mortality in patients waiting for LT (Figure 1), despite lack of consideration for inter-laboratory variability in the measurement serum bilirubin.¹⁵

In the MELD score, the serum total bilirubin concentration is used for the bilirubin variable. In theory, direct bilirubin is expected to be a better physiologic marker of liver function than total bilirubin, because indirect fraction of bilirubin is susceptible to other processes in the body, such as hemolysis and genetic variability in the bilirubin metabolism. In reality, however, in our evaluation of direct bilirubin as an alternative to total bilirubin, we did not find the former to be a superior predictor than the latter (unpublished data).

Creatinine

It is common to see a substantial degree of variability in renal function in patients with end stage liver disease. More importantly, diminished renal function is an important predictor of survival in those patients.^{16–19} Incorporation of serum creatinine in the MELD score as a predictor of survival affords considerable advantage over other measures of liver disease such as the Child-Pugh score. In Figure 1, serum creatinine has a sigmoid pattern in that the increase in mortality is relatively linear within a range of creatinine, in partial support of the current lower and upper bounds of 1 and 4, respectively.

However, accuracy of non-invasive measurement of renal function, including serum creatinine has been shown to be suboptimal among cirrhotic patients.^{20–22} True, measured glomerular filtration rate (GFR, e.g., by iothalamate clearance measurement) is better at assessing prognosis than creatinine and mathematic equations containing creatinine.^{20, 21} A multivariable model that incorporates calculated GFR and/or serum sodium is superior to the MELD score (See below for MELDNa).²²

There has been a recent push for standardizing creatinine measurement in laboratories. The traditional colorimetric alkaline picric Jaffe method has several limitations, one of which is interference with bilirubin in high concentrations.²³ In patients with high serum bilirubin (>25 mg/dL), serum creatinine can be overestimated, leading to imprecise calculation of the MELD score. Accordingly, the new standard is an enzymatic method for measuring serum creatinine. Preferential use of the latter method and standardization of measurement processes has been proposed, especially in patients with serum bilirubin >25 mg/dL.³

INR

Prothrombin time and the INR reflect coagulopathy associated with synthetic dysfunction in patients with end stage liver disease. The liver plays an important role in the coagulation pathways by generating most of the clotting factors. In patients with end stage liver disease, decreased production of factors along the intrinsic pathway prolongs prothrombin time. Figure 1 shows that after adjusting for bilirubin and creatinine, INR is associated with a steep increase in mortality risk. However, once it reaches approximately 3, the risk does not seem to increase any further.

A well-known limitation of prothrombin time is variability in assays depending on the reagent and/or measurement technique used in the laboratory. The INR was developed to

overcome this limitation by standardizing prothrombin time results primarily for patients receiving coumadin. However, when applied to individuals with liver disease, this method of calculation for INR proves to be suboptimal.^{24, 25} In studies in which liver patients' plasma samples were tested using different prothrombin reagents, there was a substantial degree of variation in INR values.^{26, 27} In contrast, if calibration is done using standards derived for liver disease patients, inter-assay and -laboratory variability could be reduced significantly.

Based on these data, it has been proposed that incorporation of a liver-specific INR may improve the predictive ability of the current MELD. However, there are many practical issues that would need to be addressed.²⁸ Manufacturers of INR reagents would need to determine two separate measurements for derivation of the INR, leading to increased costs and confusion, and potential for laboratory error. In addition, implementation and monitoring for standardization across laboratories are expected to be costly and unlikely to be funded given the relatively low prevalence of end stage liver disease. Thus, despite the theoretical advantages of INR calibrated for liver patients, practical challenges to application of this important concept do not appear to be easily surmountable at this time.²⁵

Application of MELD scores in patients on anticoagulation therapy does present a challenge. If a high MELD score is mostly driven by an artificially high INR, the true MELD may be actually quite low (e.g., <15), making the transplantation less beneficial to the patient (see below net benefit section).²⁹ Heuman et al examined a model without INR ("MELD-XI") for liver transplant candidates on stable oral anticoagulation.³⁰ The model was still less accurate than MELD, suggesting that even in those patients, INR somehow carries prognostic information. .

In summary, there remains a strong need for a reproducible and accurate measure of coagulopathy in liver patients, which may replace INR in MELD making it even more accurate.³¹ At the current time, however, INR remains a practically useful and statistically significant correlate of mortality risk in patients with end stage liver disease.³² It is also widely available and is likely continue to be used an indicator of survival in patients with end stage liver disease and a component of the MELD score.³

C. Application of MELD in Liver Transplantation

Coinciding with the implementation of MELD-based liver allocation, there was an immediate 12% reduction in LT waiting list registrations, especially in candidates with MELD scores of less than 10.² More importantly, there was a 3.5% reduction in waiting list death rate^{2, 22, 33}, accompanied by a decrease in median waiting time from 656 days to 416 days.⁸ More recent data showed longer term benefits of the MELD system: between 2002 and 2008, the number of waitlist candidates decreased by 3.4%, while the annual dropout rate from the waiting list remained stationary.³⁴ Waiting time also decreased with a higher proportion of candidates being transplanted within 30 days (23% 2001 to 37% in 2008). Thus, the MELD score has been a pivotal element of the current allocation system, contributing to more effective allocation of the scarce donor organs and to a significant increase in the probability of receiving a LT under.^{2, 35}

An initial concern in implementing the MELD-based allocation system was that selection of patients with high MELD scores will undermine the outcome following LT. Actual data, however, have shown that the 1-year patient and graft survival did not change between the pre- and post-MELD eras, although the mean MELD score at LT did increase from 17 to 21.^{2, 36, 37} Furthermore, when the survival outcomes were controlled for appropriate covariates, adjusted one year graft survival actually improved from 79.5% to 85.6% and patient survival from 85.4% to 89.4% between 1998 and 2007. Similar benefits from implementation of the MELD score have been shown outside of the US.³⁸⁻⁴⁰

There are, however, several basic features of the MELD score that need to be recognized. First, the MELD score was created in a carefully screened population that was devoid of acute, reversible complications (e.g. infection or volume depletion). Hence, it may not accurately capture the risk of mortality in acutely decompensated cirrhotic patients.³ Second, although the MELD score applies to majority of patients with chronic liver disease, it does not address mortality associated with rare complications of end stage liver disease (e.g., portopulmonary hypertension).⁸ To assign appropriate priority in these patients beyond their native MELD score, exception scores have been increasingly used - between 2002 and 2008, MELD exception on the waiting list increased from 382 to 890. Similarly, the original MELD score derivation excluded persons with hepatocellular carcinoma (HCC). As the incidence of HCC in the US continues to rise, the number of LT candidates receiving the standard exception score for HCC has been increasing.³⁴ The LT community is still grappling with how to assign appropriate exception scores for HCC to ensure equitability between patients with HCC and those with a high 'biological' MELD score.^{34, 41-44} Lastly, pretransplant patient status in general and the MELD score in particular has a limited ability to predict post-transplant mortality. This is a result of factors such as donor characteristics, transplant factors, and random post-operative complications that have very little to do with pretransplant patient condition.

Renal dysfunction

Patients with renal dysfunction (serum creatinine ≥ 1.5 mg/dL) at the time of LT increased from 26.1% in 2002 to 29.8% in 2008.³⁴ However, implementation of the MELD allocation system has not been associated with an increased mortality or occurrence of stage 3 of 4 chronic kidney disease in the first 2 years after LT.^{45, 46} Since introduction of MELD, kidney transplantation, preoperative creatinine, and number of patients requiring preoperative hemodialysis have increased. These patients are older, more ethnically diverse and have received organs from older donors.^{47, 48} Despite this, patient survival within the first 2-3 years did not differ compared to the pre MELD era.^{47, 48}

These trends were also accompanied by an increase in the number of simultaneous liver-kidney transplantation (SLK) - from 100 in 1999 to 379 in 2008. This may be driven by an increased awareness of the impact of renal dysfunction on post-operative mortality as well as the importance of assessing renal function on their MELD score.³⁴ Strategies for optimal utilization of SLK continue to evolve and remain to be established in an evidence-based fashion.^{16, 17}

Benefit of LT

The MELD score has enabled the transplant community to objectively assess the benefit of LT. In their seminal paper, Merion and colleagues considered the survival benefit of LT. They showed that the benefit of LT at 1 year was highest among those with MELD scores > 18 .⁴⁹ Recipient mortality was higher among candidates with low MELD scores. For example for patients with MELD scores between 6 and 11, the risk of mortality was 3.6 times higher by undergoing LT rather than remaining on the waitlist (hazard ratio (HR) = 3.6, $p < 0.01$). For MELD 12-14, the risk remained significantly increased (HR=2.4, $p < 0.01$). Subsequently, these findings led to a change in allocation policy - an organ would need to be shared within the larger region prior to use for a local candidate with an MELD score < 15 ("SHARE 15").⁴⁹

This concept was further expanded by Volk et al who studied matching between donor and recipient in the MELD era.⁵⁰ Under the MELD system, a donated organ is prioritized to the candidate with the highest MELD score. At the time of the organ offer, whether it is accepted for the given candidate remains at the discretion of the surgeon who makes the

decision trying to achieve the best post LT outcome possible. Volk's study showed that the overall quality of organs (as quantified by the donor risk index, DRI) decreased in the post-MELD era, as more 'marginal' organs are utilized as a result of continued organ shortage. More importantly, these higher-risk organs were being transplanted in the less urgent patients (low MELD) leading to poor outcomes in these candidates. It is feared that this practice has reduced post-transplant survival in recent years among patients with low MELD scores. Similarly Schaubel et al showed that high-DRI organs were more often transplanted into lower-MELD recipients. Compared to waiting for a lower-DRI organ, the lowest-MELD category recipients (MELD 6–8) who received high-DRI organs experienced significantly higher mortality (HR = 3.70; $p < 0.01$).⁵¹ These studies highlight the advantage of the MELD score which has provided a tool with which to critically examine the organ allocation and acceptance practice as well as to shape the distribution policy to optimize the overall outcome after LT.^{52, 53}

Gender and the MELD score

Female gender has been associated with an approximate 15% increased risk of death on the wait list and a 12% decrease in the probability of receiving a LT.^{54–56} It is thought that women may be disadvantaged under the MELD system because serum creatinine is utilized in the MELD equation.⁵⁷ As a function of less muscle mass, serum creatinine may underestimate the severity of renal dysfunction in women. Hence, an inaccurate representation of their renal dysfunction may disadvantage women with lower rates of LT and higher wait list mortality for women.⁵⁸

The relationship between MELD and mortality in women and men remains to be fully characterized.^{59, 54, 56} Myers et al. examined the UNOS database (2002–2007) and showed that women had a lower serum creatinine but also a lower eGFR across most strata of the MELD score. In addition women also tended to have greater hepatic dysfunction as characterized by bilirubin and INR across MELD categories. In their primary analysis, after adjusting for serum creatinine, female gender was associated with a 13% increased risk of death within 90 days. Higher rates of mortality were seen between a MELD score of 21–35. However, in separate models adjusting for MELD and serum sodium, the difference in mortality was reduced to 7% and no longer significant. Using eGFR as defined by the MDRD equation conferred a 15% survival advantage to women.⁵⁶

There may be other confounders that may explain the gender-based difference in waitlist outcomes.⁶⁰ Recently, Lai et al examined the UNOS database (2002–2008) and reported that a 19% increased risk of mortality among women was decreased to 5% and was no longer significant after consideration of pertinent covariates, especially body size, namely height.⁵⁴ Transplantation rates, however, remained lower among females, even after adjustment for height (HR 0.88; 95% CI, 0.82–0.92; $p < 0.001$).

The extent to which serum creatinine is responsible for the gender disparity in waitlist outcome can only be examined by a study that includes direct measurement of GFR. The increased mortality seen in women may be multifactorial – data so far suggest that smaller body size in women, leading to lower serum creatinine and thus MELD and limiting their access only to smaller organs, may explain a large part of the observation. Women also tended to present with worse overall hepatic dysfunction increasing the urgency for LT. As discussed below (see Refit MELD), revising the lower bound of creatinine to 0.8 or addition of serum sodium may attenuate this difference in mortality.^{22, 32} Serum or urine biomarkers to accurately represent renal function in patients with end-stage liver disease may further provide improvement.²²

MELD and Retransplantation

Since implementation of MELD, the number of transplant recipients increased (4969 in 2002 and 6069 in 2008) with a decrease in re-transplantation rates. For HCV negative recipients, the rate of retransplantation decreased from 12% to 9% and for those with HCV, from 8% to 5%.³⁴ This raises a question whether the MELD score systematically disadvantages LT candidates that are waiting for repeat transplantation. We addressed this question in a recent study. The current MELD based allocation system, by and large, appeared to serve primary and re-transplantation candidates equitably.³⁵ As expected, re-transplantation candidates are listed at higher MELD scores (21 vs. 15). In the MELD score ranges where most LT is performed, there is no large difference in waitlist mortality for a given MELD score. Interestingly, the mortality risk does not increase as fast in re-transplant candidates compared to primarily liver transplant at high MELD scores (e.g. >35); alternatively in the very low MELD score ranges, the mortality trend is reversed.³⁵

D. Application of MELD score in non-liver transplant settings

The MELD score, as an objective scale of disease severity, has been used in the management of patients with chronic liver disease in the non-transplant setting. Although the initial assessment of the score was limited to survival within 90 days, the MELD score is found to be a predictor of long-term survival in patients with decompensated cirrhosis.⁶¹ The application of MELD in persons with chronic liver disease has included prognosis and treatment of variceal bleeding, infection, alcoholic hepatitis, surgical resection of hepatocellular carcinoma, placement of TIPS and management of fulminant hepatic failure and renal failure.^{3, 62–64} The MELD score is a predictor of non-transplant surgical mortality in patients with cirrhosis.^{65, 66}

E. Improving MELD

Several models have been proposed to refine and improve the MELD score. This includes measurement of serial MELD scores, addition of variables (e.g. serum sodium), or re weighting components of the MELD score.

Delta MELD

The utility of a change in MELD (delta MELD) in predicting wait list mortality has been studied with disparate results.^{67–70} It may make intuitive sense that patients with an acutely increasing MELD may have worse outcome than those with a stable score. Indeed, in univariate analysis, a change in MELD is predictive of mortality. However, the rise in MELD is confounded by the fact that (1) patients with a sharp increase in MELD tend to have a high MELD score currently and (2) in retrospective analysis, patients acutely worsening will have frequent laboratory testing which in and of itself may represent the clinician's clinical judgment of the worsening patient's condition. These concerns were born out in multivariable analysis where once the current MELD and the number of MELD scores available were taken into account, delta MELD was no longer significant.⁷¹

Incorporation of Serum Sodium

Serum sodium concentration, as a reflection of activation of neurohumoral systems and water retention, has been recognized as an important prognostic factor in patients with liver cirrhosis.^{72–75} Hyponatremia is associated with neurologic dysfunction, refractory ascites, hepatorenal syndrome, and death from liver disease.^{76, 77} Hyponatremia, with lower sodium values portending worse outcomes, has been shown to be an independent predictor of survival at 3 and 12 months.^{78, 79}

Given the important prognostic value of sodium, its role has been evaluated as an adjunct to the MELD score in prediction of mortality in patients with end stage liver disease. After controlling for MELD, serum sodium was associated with a higher risk of mortality – each 1 mmol/L decrease in the serum sodium concentration for values between 125 and 140mmol/L was associated with 5% increase in mortality ($p<0.001$).⁷⁸ This effect was greater in patients with a lower MELD score. For 23% of the patients, the difference between the MELDNa and MELD scores was large enough to have affected allocation priority. About 7% of the deaths on the waiting list could have been prevented by using MELDNa rather than MELD. In addition to waitlist mortality, serum sodium and MELD have been shown to be closely correlated with drop-out rates among patients awaiting LT.⁸⁰

We believe that underlying event that decreases survival in hyponatremic patients is worsening renal function. As discussed above, serum creatinine is an imperfect gauge of renal function and hyponatremia may reflect an aspect of renal function that is not effectively captured by serum creatinine.²² Hyponatremia may be an earlier and more sensitive marker than creatinine to detect renal impairment and / or circularly dysfunction in patients with advanced cirrhosis.⁸¹ In predicting mortality, survival models that include directly measured GFR are superior to those with serum creatinine or creatinine based GFR estimates.²² Once an accurate measure of GFR is taken into account, however, serum sodium is no longer significant.

Like other elements of the MELD score, serum sodium assessment is widely measured objective and easily available. Potential limitations of the use of serum sodium include variability that may be altered by volume status and free water intake, making it potentially subject to willful manipulation. However, altering serum sodium to a degree to significantly alter organ allocation is difficult.^{32, 78, 79, 82} It remains unknown whether correction of severe hyponatremia into the normal range (e.g. by use of vaptans) restores the risk of mortality attributable to serum sodium. Based on our hypothesis that the underlying process of hyponatremia is progressive renal dysfunction, we predict that the effects of hyponatremia are not easily ameliorated by simple correction of serum sodium. Finally, whether transplanting patients with hyponatremia would simply shift the mortality from the waiting list to post transplant is also a potential concern. Although data about the impact of pretransplant hyponatremia on posttransplant outcome are conflicting, the largest US data showed that hyponatremia (of any degree) did not have a detrimental impact on survival 90 days after LT (HR=1.00; P=0.99). Thus, incorporating serum sodium in the organ allocation process may not adversely affect the overall outcome after LT.²²

Re weighting components of MELD

Given the origin of the MELD score in patients undergoing TIPS, re weighting the components of the MELD score using a contemporary cohort of LT candidates may improve prediction of waiting list mortality.⁸³ Recently, Leise et al examined (1) whether the mortality prediction by MELD could be improved by optimizing the coefficients of MELD based on waitlist patients and (2) whether addition of serum sodium remains important once the coefficients for the components of MELD have been optimized.³² Based on the UNOS data, a model was developed and validated that includes updated coefficients and amended upper and lower limit bounds with and without serum sodium. This model has statistically significant gain in its ability to rank LT candidates based on their risk of mortality and hence their chance of receiving a LT (See Box). The model's discrimination was also superior in candidates listed at a MELD score ≥ 15 . Implementation of the new score would affect 3.3% of all waitlist registrants and 12.0% of all transplants, with 9% fewer deaths.

The existing upper and lower bounds of each variable set by the UNOS were empiric and not evidence-based. We re-examined these bounds in an iterative fashion with final

determination of the bounds based on statistical relevance (goodness of fit) as well as physiological interpretation (e.g., the upper limit of normal) of the cut-off values. A lower limit for serum creatinine (0.8) would effectively capture persons with renal dysfunction that is not adequately represented by a falsely low serum creatinine due to decreased muscle mass. An upper limit cutoff of 3.0 fits the data better and allays the purported emphasis on renal dysfunction and transplantation of patients with intrinsic liver disease. A cutoff for INR would limit the impact of outliers, many of whom may be taking coumadin. The impact of hyponatremia is greatest in persons with a low bilirubin; hence to reflect the interaction between sodium and bilirubin an upper limit of bilirubin (20mg/dL) is introduced.

Conclusion

The MELD score has been an important contribution to the field of hepatology given its ability to accurately gauge the severity of liver disease and effectively form assess the risk of mortality and determine organ allocation priority in patients waitlisted for LT in the US as well as many countries around the world. It has become part of the hepatologists vocabulary inasmuch that a MELD score conveys a succinct picture of the health status of a patient with end stage liver disease. By design, it is continually evolving; it lends itself to continued refinement and improvement in a data-driven fashion. We believe that the MELD score will be used as a template to improve upon as an objective gauge of disease severity and a metric to optimize allocation of scarce donor organs for liver transplantation for the next decade and beyond.

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List of Abbreviations

LT	Liver transplantation
MELD	Model for end stage liver disease
INR	international normalized ratio
SLK	simultaneous liver–kidney transplantation
GFR	glomerular filtration rate
HCC	Hepatocellular carcinoma
DRI	Donor Risk Index
HR	Hazard Ratio
HCV	chronic viral hepatitis C
Na	Serum Sodium
TIPS	transjugular Intrahepatic portosystemic shunt
c statistic	concordance statistic

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Box 1

Proposed modification of MELD score and MELD Na score to update coefficients, change upper and lower bounds, and incorporate serum sodium levels using wait-list data from adult primary liver transplantation candidates from the Organ Procurement and Transplantation Network (2005–2008).

MELD: Model for end stage liver disease score; Na: Serum sodium; INR: International normalized ratio

$$\text{ReFit MELD} = 4.082 * \text{Log}_e(\text{bilirubin}) + 8.485 * \text{Log}_e(\text{creatinine}) + 10.671 * \text{Log}_e(\text{INR}) + 7.432$$

bilirubin=bilirubin bounded below by 1mg/dl;

creatinine=creatinine capped by 0.8mg/dl below and 3mg/dl above

INR =INR bounded by 1 below and 3 above. Renal replacement therapy=3mg/dl.

$$\text{ReFit MELDNa} = 4.258 * \text{Log}_e(\text{bilirubin}) + 6.792 * \text{Log}_e(\text{creatinine}) + 8.290 * \text{Log}_e(\text{INR}) + 0.652 * (140 - \text{Na}) - 0.194 * (140 - \text{Na}) * \text{Bilirubin} + 6.327$$

bilirubin= bilirubin bounded below by 1mg/dl and above by 20 mg/dl

creatinine=creatinine capped by 0.8mg/dl below and 3mg/dl above

INR =INR bounded by 1 below and 3 above. Renal replacement therapy=3mg/dl

Sodium (Na) =Na bounded by 125mEq/l below and 140mEq/l above

Figure 1.
The relation between risk of 90-day mortality and individual Model for end stage liver disease variables after adjustment for the other components.