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The evolution in the prioritization for liver transplantation

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Abstract

Policies for organ allocation can be based on medical urgency, utility or transplant benefit. With an urgency policy, patients with worse outcomes on the waiting list are given higher priority for transplantation [based on the Child–Turcotte–Pugh score or the Model for End-stage Liver Disease (MELD) score, or United Kingdom model for End-stage Liver Disease (UKELD) score]. The MELD and UKELD scores have statistical validation and use objective and widely available laboratory tests. However, both scores have important limitations. Adjustments to the original MELD equation and new scoring systems have been proposed to overcome these limitations; incorporation of serum sodium improves its predictive accuracy and is part of the UKELD score. The utility-based systems are based on post-transplant outcome taking into account donor and recipient characteristics. MELD and UKELD scores poorly predict outcomes after liver transplantation due to the absence of donor factors. The transplant benefit models rank patients according to the net survival benefit that they would derive from transplantation. These models would be based on the maximization of the lifetime gained through liver transplantation. Well-designed prospective studies and simulation models are necessary to establish the optimal allocation system in liver transplantation, as no current model has all the best characteristics.

Keywords MELD score, UKELD score, liver transplantation, allocation, survival benefit

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Introduction

Prioritization for liver transplantation (LT) has evolved over the past 20 years [1]. Until 2002 transplant candidates were prioritized to undergo LT based on their United Network of Organ Sharing (UNOS) status (2A, 2B and 3) based on their Child–Turcotte–Pugh (CTP) scores [2] and the waiting time on the list. The UNOS status 2A, 2B and 3 (Table 1) was replaced by the model for end-stage liver disease (MELD) score adopting the "sickest first" policy for organ allocation [3,4]. In 2006, MELD was adopted by Eurotransplant, (https://www.eurotransplant.org), which allocates organs in seven countries of central Europe: Austria, Belgium, Croatia, Germany, Luxemburg, the Netherlands

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Table 1 Classification of candidates for liver transplantation according to the old UNOS system

Status	Characteristics
1*	They have fulminant (sudden) liver failure or their newly LT did not function (life expectancy <7 days without a LT).
2A	They have chronic liver disease and are in the hospital's critical care unit with a life expectancy <7 days without a LT. They have a CTP score ≥10 and meet other medical criteria
2B	They have chronic liver disease and are becoming more urgently in need of a LT but do not meet the criteria for Status 2A. They have a CTP score ≥10, or a CTP score ≥7 and meet at least 1 of the medical criteria
3	They have chronic liver disease and are under continuous medical care, but are not in the hospital, except for possible short stays. These patients do not meet the criteria for Status 2B

**These patients are the most critical and include patients with fulminant hepatic failure, acute decompensated Wilson's disease; primary non-function or hepatic artery thrombosis in a LT within 7 days of implantation. This category was not affected by the new allocation system.*
LT, liver transplantation; CTP, Child-Turcotte-Pugh score

and Slovenia. In the United Kingdom, the UKELD score (www.uktransplant.nhs.uk) has been adopted for several years and recently published [5].

The use of MELD and UKELD scores reflect the adoption of mathematical models of prognosis for decompensated cirrhosis. However, as not all patients can be transplanted due to the shortage of available organs, prioritization of patients is necessary, but it strongly depends on the policy that is used for allocation of donor organs (Table 2). There are three possible policies for organ allocation [6]: a) medical urgency: patients with highest waiting list mortality have the higher priority for transplantation, b) utility system, based on expected post-transplant outcomes, and c) transplant benefit, in which both the waiting list and post-transplantation outcomes are taken into account. In the latter 2 policies, donor quality is an additional parameter for assessing transplant outcome [7]. In the following sections, we summarize the advantages and limitations of the current systems.

Urgency-based allocation systems (Table 3)

The CTP score

The CTP score [8] is based on 5 empirically selected variables (ascites, encephalopathy, serum bilirubin, albumin and prothrombin time), with a range of 5 to 15 points derived originally for predicting the outcome of portal-caval shunt surgery and later transported to assess prognosis of cirrhosis across all etiologies. Although the CTP-based system represented a great improvement, its use for prioritization of candidates for LT had several drawbacks [9,10]. Firstly, ascites and encephalopathy are subjective variables. Secondly, patients were not sufficiently differentiated so that waiting time had great impact on prioritization; this was due to a "ceiling and floor effect" (minimum and maximum of laboratory values used in the scores). Thirdly, there was no variable reflecting renal function, a well-established prognostic marker in end-stage cirrhosis [11].

Table 2 The three possible policies for organ allocation

Medical urgency models
• Child–Turcotte–Pugh score
• MELD score
• Modifications of MELD score
• UKELD
Utility-based scores
• Donor risk index (DRI)
• D-MELD (D for donor age)
• Model based on the European Liver Transplantation Registry
Transplant Benefit models

MELD, Model for End-stage Liver Disease; UKELD, United Kingdom model for End-stage Liver Disease

The MELD score

The MELD model was first published in 2000 to predict survival in patients undergoing transjugular intra-hepatic porto-systemic shunt (TIPS) [12]. In 2001, the same group [13], slightly modified this score to predict mortality for cirrhosis: the MELD score had discriminative ability for 3-month survival of greater than 80%, regardless of the severity of liver disease, without any significant improvement by adding etiology or complications of cirrhosis. The MELD was adopted in the USA from 27 February 2002 and has evolved following close audit and validation [14]. However, as we have published, CTP and MELD are equivalent in terms of their discriminative capacity as prognostic scores whether in LT candidates [15] or for cirrhosis in general [2], even with the addition of new studies [16,17]. Recent changes in UNOS policy require liver donor offers first to patients with MELD scores ≥15 within a region, before offers to local candidates with MELD <15 (Share 15 Policy) [18]. Patients are ranked according to their MELD score and stratified by blood type. MELD score may either increase or decrease with time and individual patient scores are forwarded regularly by each transplant center (http://www.unos.org). Despite its wide spread adoption, data on calibration of MELD score have not been published.

The advantages of the MELD score are its statistical validation, in contrast to CTP score, and use of objective and widely available laboratory tests [serum bilirubin, serum creatinine and the international normalized ratio of prothrombin time (INR)] [19] (Table 3). Several online calculators are available for calculating MELD. In addition, the "ceiling effect" is minimized, since the 'upper cap' is set to 40 points. Furthermore, after adoption of MELD score, post-LT survival in the USA, remained unchanged [20], but more hepatocellular carcinoma (HCC) patients underwent LT (because of allocation of extra points) [19], and there was a small reduction in mortality on the waiting list (Table 4).

The disadvantages of MELD are firstly that it mainly reflects a "justice" system [15] (Table 4), and there are significant variations of MELD score due to different laboratory methodologies for INR [21,22], which may lead to differences of as much as 7 points in MELD score, and creatinine (Cr) measurements [23,24], leading to inequalities in prioritization of candidates, especially in those with the highest priority for LT (more jaundiced and greater renal dysfunction). Standardization of laboratory techniques would be necessary to avoid systematic biases.

Although the major advantage of MELD is the inclusion of renal dysfunction [10], Cr may weigh too heavily within the MELD score [25]. A further issue is that Cr provides only a rough estimation of renal function [i.e. glomerular filtration rate (GFR)] [26], since it is influenced by several extrarenal factors, such as total muscle mass, ethnicity and gender [27]. The latter has been highlighted by us [28], and found also by

Table 3 Prognostic models for urgency-based allocation systems

Model	Mathematical formula	Comments
Child–Turcotte–Pugh [8]	Ascites, encephalopathy, bilirubin, albumin, prothrombin time	Simple but subjective, not inferior accuracy compared to MELD
MELD [13]	9.6 x ln (creatinine mg/dL) + 3.8 x ln (bilirubin mg/dL) + 11.20 x ln (INR) + 6.4.	Lower limits of the components are bound by 1 and creatinine is capped at 4 mg/dL
MELD-Na [38]	MELD-Na–(0.025)XMELDX(140–Na)+140	Serum sodium between 125 and 140 mmol/L
iMELD [39]	MELD+ (ageX0.3)–(0.7XNa) + 100	Age of recipient was an independent factor Needs further evaluation
UKELD [40]	[(5.395Xln(INR)) + (1.485Xln(creatinine)) + (3.13Xln(bilirubin))–(81.565Xln(Na))] + 435	Minimal listing criteria: projected 1 year liver disease mortality without transplantation of >9% (UKELD >49)
MELD-XI [43]	5.11Xln(bilirubin) + 11.76Xln(creatinine) + 9.44	Exclusion of INR. Bilirubin and creatinine with different coefficients Suitable in patients under anticoagulation therapy
MELD-gender [31]	11.2Xln(INR) + 9.57Xln[(186X(Age)–0.203/female GFR(1/1.154)] + 3.78Xln[bilirubin (mg/dL)] + 6.43	Needs further evaluation
Re-weighted MELD [25]	1.266Xln(1 + creatinine, mg/dL) + 0.939Xln (1 + bilirubin, mg/dL) + 1.658Xln(1 + INR)	Lower weight for creatinine and INR coefficients and a higher weight for bilirubin coefficient No set upper and lower limits of the coefficients of each component
Re-Fit- MELDNa [47]	4.258 xLoge (bilirubin) +6.792 xLoge (creatinine) +8.290xLoge (INR)+0.652 x(140-Na) - 0.194x(140-Na)xBili+6.327	The new score had a statistically significant gain in discrimination (c statistic: 0.878 vs 0.865; $P<0$ .01) Utilization of the new score could affect up to 12% of patients

INR, international normalized ratio; MELD, Model for End-stage Liver Disease; UKELD, United Kingdom model for End-stage Liver Disease; Na, Sodium

others [29] and can explain in part why women have higher waiting list mortality, compared to men, in the post-MELD era [29]. In fact, the Cr values in women, represent a worse GFR than in men, for the same Cr values [30]. Thus, a score corrected for female candidates (MELD-gender) has been suggested [31]. The use of "true" GFR could eliminate any gender or race bias, but it is expensive and impractical for routine use. Cystatin-C is considered a more accurate and clinically applicable serum marker for renal function [11], but we have shown that cystatin-based formulae have poor agreement with "true" GFR in patients with cirrhosis [32].

Lastly, the MELD system does not cater for transplant candidates who have complications of cirrhosis, which affect prognosis or quality of life, such as chronic encephalopathy, resistant ascites, recurrent cholangitis, or difficult-to-treat bleeding [33,34]. Ascites, determined by CT scan, improved the discrimination of MELD in a study of 1000 patients [33]. Infection, even if resolved, does affect prognosis in cirrhosis, contrary to the original MELD formulation [34]. Many of these complications are the "MELD exceptions", which account for at least 15% of transplant candidates. The rules for accepting these patients are not standardized. The current policy for cirrhotics with HCC is no extra priority for the T1 stage, and 22 points for stage T2 (with a 3 monthly update). The justification of the extra MELD points is empirical and requires adjustment.

Proposed modifications of MELD score (Tables 3 and 5)

MELD-serum sodium score

Serum sodium has long been associated with hepatorenal syndrome, ascites and death in patients with decompensated cirrhosis [35,36]. In the LT setting, serum sodium is an independent factor of mortality, particularly for lower sodium values (120-135 mEq/L): within this range, a decrease of 1 mEq/L corresponds to a 12% increase in 3-month mortality independently of MELD score [37]. In addition, the MELD-Na, compared to standard MELD, provided better statistical performance for the risk of death among LT candidates: 7% of waiting-list deaths could be averted using MELD-Na score [38]. In Spain, MELD score, serum sodium, and recipient age were independently associated with mortality on the waiting list [39]: the new score integrating these variables into MELD (iMELD) was superior than standard MELD [39]. In 2008, the UK Liver Transplant Units developed a new scoring system (United Kingdom model for End-stage Liver Disease, UKELD score) [40], now instituted nationally. The constituent variables are serum bilirubin, Cr, sodium and INR (web-based calculator at www.uktransplant.nhs.uk). A UKELD score greater than 49 predicts a 1-year mortality of

Table 4 Advantages and disadvantages of MELD score

Advantages
• Statistically validated
• Acceptable discriminative ability
• Use of objective and widely available laboratory tests
• Inclusion of renal dysfunction
• Minimized "ceiling effect"
• Limited effect on post-LT mortality
Disadvantages
• Medical "urgency" score
• Similar discriminative ability as the CTP score
• Less convenient to use at the bedside, compared to CTP score
• Interlaboratory variations for measurement of serum creatinine and INR
• Serum creatinine provides only a rough estimation of renal function
• Systematic adverse female gender bias
• Further refinement is needed (e.g. inclusion of serum sodium, re-weighting of MELD score components)
• Exclusion of complications of cirrhosis, some of which warrant transplantation at low MELD scores (e.g. hepatic encephalopathy)
• Weak predictor of mortality after LT (exclusion of donor characteristics)
• Further statistical evaluation is needed (particularly in terms of calibration)

LT, liver transplantation; CTP, Child-Turcotte-Pugh score; MELD, Model for End-stage Liver Disease; INR, international normalized ratio

9% or more without LT, and is the minimum score for listing for LT (current 1-year post-liver transplant mortality in the UK is approximately 9%) [5,41]. The UKELD score has had calibration as part of its validation [41].

Table 5 Proposed modifications of MELD score

MELD and serum Sodium (Na) incorporation
• MELD-Na
• Integrated MELD score (iMELD)
• MESO
MELD-XI (without INR)
MELD-gender
Re-weighted MELD / re-Fit-MELDNa
ΔMELD (changes in MELD over time)

MELD, Model for End-stage Liver Disease; Na, Sodium; MESO, [MELD/Na] ×100

However, there are concerns with using serum sodium in allocation systems, since the new scores (except for UKELD) were validated retrospectively, and although serum sodium measurement is considered objective and is widely available, it is also subject to laboratory variation [42] just as INR and Cr and can be altered by therapeutic interventions (e.g. vaptans and diuretics).

MELD-XI (MELD without INR)

A MELD-XI score (MELD excluding INR) has been proposed, which relies only on serum bilirubin and Cr, but with different coefficients for both variables [43]. However, the performance of this score is questionable and further validation is needed. Standardization of INR with a "liver INR" is impractical [44].

Re-weighting of MELD score components

Although the major advantage of MELD is the inclusion of serum Cr [10], transplant candidates with mild hepatic synthetic dysfunction and marked renal insufficiency may have "inappropriate" priority for LT, compared to those with severe liver disease, but "normal" renal function. Indeed, a higher proportion of patients with renal insufficiency have undergone LT in the post-MELD era [45,46]. Recently, the coefficients for the MELD components were re-estimated [25]. The proposed re-weighted MELD has lower relative weight for Cr and INR coefficients, and a higher relative weight for the bilirubin coefficient, compared to the original MELD score. This new MELD score had better performance than the standard MELD score to predict overall mortality (0.68 vs. 0.64), and 3-month waiting list mortality (0.77 vs. 0.75).

The recently published re-Fit-MELDNa score is another variation on the original MELD [47]. It is the only MELD variation which uses data from patients on LT waiting lists (as does UKELD), and also incorporates serum sodium. The co-efficients are changed in particular for Cr. However, as the accompanying Editorial points out, it does not resolve some of the inherent problems of MELD as outlined above.

Delta MELD

Changes in MELD score (ΔMELD) over time may add prognostic information. Although a rapid increase in MELD might be associated with worse outcome, compared to a stable or decreasing MELD score [48-52], data in the literature have given conflicting results [49,50].

Utility-based allocation systems (Table 2)

Utility-based systems are based on the expected post-

transplant outcome. However, MELD and UKELD scores are weak predictors of mortality after LT [53-55], since post-LT outcomes depend on both the pre-LT parameters of recipient, and donor "quality". In the face of organ shortage, optimization of donor/recipient pairing would have great importance for a better outcome after LT. A MELDD score -a second D for donor- [56] has been proposed by us for a utilitarian approach, which could lead to a transplant benefit model for allocation. A simple arithmetic product [57] of donor age and preoperative MELD (DMELD) has been proposed. A cut-off value of ≥1600 was derived for high-risk donor–recipient matches. However, implementation of DMELD could lead to waiting for 'better' donors for patients with high MELD scores and could potentially lead to an increase in waiting list mortality rates.

Donor risk index (DRI) has been developed based on seven donor factors to predict post-LT outcomes [7], which ranges from approximately 0.5 to 3.0 (with 3-year graft survival rates of 81% for organs with a DRI of less than 1.0 and 60% for organs with a DRI of greater than 2.0). However, this index is complex and it is not easily translated into clinical practice. To date, it has never been used as an allocation score, but just as a clinical decision-making tool.

A large and validated model predicting post-LT survival of 34,664 undergoing a first LT was published using the European Liver Transplantation Registry database from 23 European countries [58]. The derived prognostic models (based on donor age, total ischaemic time, and other operative and recipient factors not included in MELD), significantly and independently had an impact on the outcomes post-LT with very good calibration for 3- and 12-month mortality. Thus, these models could aid the subjective decision on donor and recipient matching which occurs at the time of organ procurement, and give clinicians some robust data for allocation. Furthermore, this study emphasized that disease-specific models (along with donor characteristics) are needed because particular diseases recur, and affect medium- and long-term survival (e.g. hepatitis C and HCC), and donor characteristics, such as donor age, can affect the severity of recurrence of the primary disease [59]. These disease specific models are yet to be developed, but would be an essential component of transplant benefit models.

Transplant-benefit allocation systems

An allocation scheme based on transplant benefit represents the balance between waiting list and post-LT outcomes, i.e. a liver graft is donated to the patient who is predicted to have neither the greatest post-LT lifetime nor the lowest waiting list lifetime, but the greatest difference between the two. Hence, patients are ranked according to the net survival benefit that they would derive from the transplant.

Recently, Schaubel et al confirmed [60] that a "transplant benefit" system should take into account donor and/or operative factors, and matching of donor to recipient characteristics for optimal outcomes. Subsequently, the same group [61] showed that "matching" could have a great impact on survival benefit from LT. The authors created a waiting list survival model (utilizing recipient characteristics) with reasonable discriminative ability (c statistic 0.74), but the post-LT survival model (consisting of donor and recipient characteristics) had a poorer performance (c statistic 0.63). This suggests that accurate evaluation of risk of death before LT is more important than after LT, presumably because the risk of death is always higher without a transplant. Indeed, in a recent paper from a single center [62], patients with MELD scores higher than 20, always had a survival benefit with LT, regardless of any donor or recipient factors. Although further studies are needed, it is encouraging that a "transplant survival benefit" allocation system is currently under serious consideration in the USA in order to maximize lifetime gained through LT [61].

Conclusions

An ideal donor liver allocation model should not only be able to allocate according to the highest probability of dying before LT, but should also be able to predict which patients have the lowest post-LT mortality in order to improve utility (i.e. a survival benefit system) [56]. This policy is currently under serious consideration for LT in the USA, while it is already used for lung allocation in the USA [63]. MELD score was instituted in 2002 for liver organ allocation in the USA, and has been adopted in several European, Asian and South America countries. Although there is no clear evidence that MELD is superior to CTP score for prognosis (the latter remains more convenient to use at the bedside), MELD score is more suitable for liver allocation [2,15]. Scores that incorporate serum sodium such as UKELD and MELD-sodium have better prediction than the standard MELD [64,65].

However, the MELD score has several drawbacks. The accuracy of MELD score has been based on its discriminative ability, but the evaluation of its calibration (i.e., the observed versus predicted outcome), which is a better index of model performance, has seldom been performed [65]. This is in contrast to UKELD score which has had its calibration evaluated as part of its validation [41]. In addition, although the three components of the MELD score were selected statistically, the initial variables entered in the model were selected empirically. The application of an artificial neural network also needs further consideration [66-68]. In addition, end-points other than survival may also be important. The MELD score at the time of LT is not related to quality of life during the first months after LT [69]. Thus, quality of life requires different modeling to incorporate into well-designed prospective studies to optimize decisions about allocation [70-72].

Urgency-based allocation systems (such as MELD and UKELD scores) are weak predictors of mortality after LT, as they do not take into account donor characteristics or quality, which influence post-LT outcomes. In fact, MELD use may have adverse effect on post-LT outcomes, as has been shown

in a recent study from a Eurotransplant center [73], possibly due to accepting "any donor" for the top of the list recipients. A similar issue is the increase in resource utilization as a consequence of the use of MELD score, an important consequence as cost-effectiveness becomes even more important in health care systems. Foxton et al [74] found that patients with MELD score higher than 24 at LT had significantly longer post-LT stay in the intensive care unit (ICU) ($p<0.0001$), total post-LT hospital stay ($p=0.008$) and more frequently need for renal replacement therapy ($p<0.001$) [74].

The utility-based systems take into account the expected post-LT outcome based on donor and recipient characteristics. Although their performance has not been evaluated officially, in clinical practice many transplant surgeons have generally utilized organs with a higher than average risk of failure for candidates with the least risk of death without transplant. The D-MELD [57] seems very attractive, but potential limitations must be taken into account, particularly for HCV-related cirrhosis, where age is of great importance with respect to recurrent disease, such that D-MELD may need to be developed for each liver disease etiology.

The transplant benefit models are based on the difference between expected lifetime with a transplant versus without a transplant, and they have already been used for lung transplantation in the United States since 2005. In LT, a recent study has presented interesting results [61], but the proposed benefit model was based on complex statistical analysis and its performance in terms of discrimination was relatively poor (c-statistic between 0.63 and 0.74). In addition, the net survival gain mainly depends on the waiting list mortality and much less on mortality after LT diminishing the utility but not the fairness of the transplant benefit model. Thus, more data are needed before changing the current urgency-based allocation policy, but clinicians should be aware of their limitations, and allocation systems should allow for flexibility according to clinical judgment and experience [75].

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