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The MELD score in patients awaiting liver transplant: Strengths and weaknesses

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Adoption of the Model for End-stage Liver Disease (MELD) to select and prioritize patients for liver transplantation represented a turning point in organ allocation. Prioritization of transplant recipients switched from time accrued on the waiting list to the principle of "sickest first".

The MELD score incorporates three simple laboratory parameters (serum creatinine and bilirubin, and INR for prothrombin time) and stratifies patients according to their disease severity in an objective and continuous ranking scale. Concordance statistics have demonstrated its high accuracy in stratifying patients according to their risk of dying in the short-term (three months). Further validations of MELD as a predictor of survival at various temporal end-points have been obtained in independent patient cohorts with a broad spectrum of chronic liver disease. The MELD-based liver graft allocation policy has led to a reduction in waitlist new registrations and mortality, shorter waiting times, and an increase in transplants, without altering overall graft and patient survival rates after transplantation.

MELD limitations are related either to the inter-laboratory variability of the parameters included in the score, or to the inability of the formula to predict mortality accurately in specific settings. For some conditions, such as hepatocellular carcinoma, widely accepted MELD corrections have been devised. For others, such as persistent ascites and hyponatremia, attempts to improve MELD's predicting power are currently underway, but await definite validation.

Keywords: Liver transplantation; MELD score; End-stage liver disease; Organ allocation policy; Hepatocellular carcinoma; Complications of cirrhosis.

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Abbreviations: OLT, orthotopic liver transplantation; MELD, model for end-stage liver disease; UNOS, United Network for Organ Sharing; CTP, Child-Turcotte-Pugh; INR, international normalized ratio; HCC, hepatocellular carcinoma; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; MELD-Na, MELD and serum sodium; iMELD, integrated MELD; UKELD, United Kingdom MELD; MESO, MELD to serum sodium ratio; PT, prothrombin time.

Introduction

With very few exceptions, orthotopic liver transplantation (OLT) represents a peculiar scenario where patients with a liver disease in its terminal stage face a potential cure. Once contraindications to OLT have been ruled out, however, this apparently straightforward solution is complicated by a number of factors, namely the shortage of available organs. In other words, despite being appropriate candidates for OLT, some patients waiting for a donor will die before receiving a suitable organ. In addition, the efficacy of OLT, i.e., its capacity to prolong patient survival with respect to the natural history of the disease, is strongly influenced by the disease stage in which transplantation is carried out [1]. Too early an operation could reduce the chances of survival, whereas too late a transplant would be associated with an unbearable peri-operative and short-term mortality. Sub-optimal utilization of liver grafts in a time of scarcity would further exacerbate the harm as the transplanted patient would not benefit from having received an organ that was not offered to another possibly more suitable candidate, who may well die as a result. Thus, liver allocation policy should assign grafts to patients most in need. Hence, an ideal tool should be able to: (a) quantify the patient's chances of survival in the short to medium-term for optimum prioritization of patients awaiting OLT; (b) classify patients according to their disease stage, enabling doctors to establish whether it is too early, appropriate, or too late to suggest OLT; (c) predict outcome irrespective of the underlying liver disease; (d) be readily manageable, possibly at the bedside; (e) last, but not least for most experts, set aside subjective elements influencing the doctors' judgment, such as features of the transplant center in terms of organization and technical and human resources, the physician's individual expertise, which could be based on personal belief rather than evidence-based data, and both personal and environmental emotional pressure. The answer to the question: "Do we possess such an ideal tool?" is, unfortunately, "No". However, the model for end-stage liver disease (MELD) score has brought us close to this goal. As with all outstanding achievements, the MELD score still has to be challenged, but it will not be easy to surpass its efficacy and flexibility.

The impact of MELD on the liver allocation policy: the score demonstrates it strengths

Once its pioneering phase was over and OLT became the standard of care for patients with end-stage liver disease, it became clear

that an allocation policy based on a first-come, first-served principle, with the time accrued on the waiting list as a major prioritizing factor, was largely inadequate. Many patients most in need of transplantation because of disease severity, but only just included in the waiting list lost their chance of receiving an organ because less severely ill patients had been waiting for a long time [2]. This inadequacy was exacerbated by a lack of a standardized practice among transplant centers. The first attempt to overcome this weakness was made by the United Network for Organ Sharing (UNOS) in the United States by implementing a categorical system that stratified patients according to disease severity. However, severity was indirectly assessed according to the intensity of care the patient needed, decreasing from the intensive care unit (status 2) to home management (status 4) with emergency cases, deemed to have a chance of survival shorter than 24 h, assigned to status 1 deserving the highest priority. The vagueness of the boundaries between these categories, which could be strongly influenced by a center's organization and physicians' attitudes, is self-evident. In addition, waiting time was again a discriminant factor within each category, and this was particularly significant in the broadest categories, such as statuses 3 and 4.

To enhance the role of disease severity in the organ allocation policy, UNOS adopted a new classification by merging the presence of certain clinical features with the Child-Turcotte-Pugh (CTP) score [3,4], which is based on two discrete clinical variables (ascites, encephalopathy) and three continuous laboratory variables (serum albumin and bilirubin, and prothrombin time) to which a score from 1 to 3 is given according to the magnitude of their derangement. Specific cut-offs for serum bilirubin are employed for cholestatic diseases. First conceived to assess the outcome of cirrhotic patients undergoing porto-caval shunt surgery [5] or esophageal transection for bleeding varices [6], this score system had become the most popular tool for estimating the severity of chronic liver disease and patient prognosis. However, this classification had not been validated as a tool to predict mortality on the waiting list for OLT, a setting where shortcomings blunted its full efficacy. The CTP score components had been selected empirically, as had the cut-off values for each variable. It was also assumed that each variable possesses the same weight, which has not been demonstrated, and that variables were independent of each other, which may not be the case for serum albumin concentration and prothrombin time. In addition, clinical variables have to be judged subjectively, and the assignment to the three classes results in categories that certainly differ in terms of prognosis, but are broad enough to accommodate patients with substantially different disease severities. Such a ceiling effect is particularly important for patients belonging to class C. Nor was the CTP-based UNOS system able to overcome this problem, as it included only four categories, again resulting in many patients being grouped into each category. Thus, patients who most needed OLT in the short-term, ended up competing with those that could wait longer because of a less severe disease on the basis, once again, of the time spent on the waiting list. Nonetheless, an initial reduction in waitlist mortality ensued (Fig. 1).

In 2000, Malinchoc and coworkers from the Mayo Clinic in Rochester [7] devised a mathematical model to predict the outcome of elective placement of transjugular porto-systemic shunt in patients with cirrhosis and portal hypertension, named the Mayo End-stage Liver Disease (MELD) score. This model proved

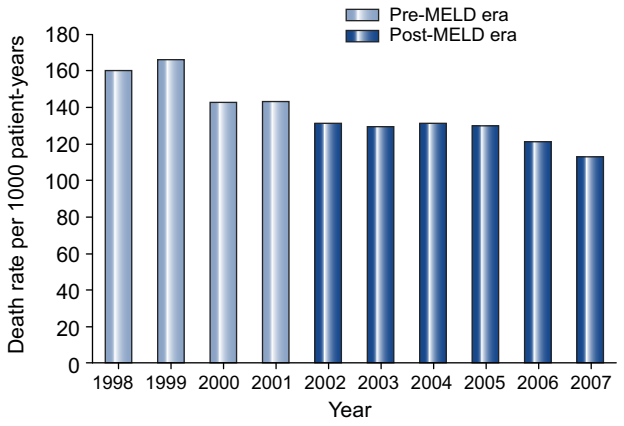

Fig. 1. Unadjusted death rates per 1000 patient-years of OLT candidates on the waiting list in the pre-MELD era (light blue) and in the post-MELD era (dark blue) in the United States (data from Ref. [16]). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

to predict the probability of death within three months after the procedure. Subsequently, the model name was changed to Model for End-stage Liver Disease and it was successfully validated in patient cohorts with different liver disease severity, and different geographical and temporal origin [8]. The original model incorporated three simple laboratory parameters, serum creatinine, serum bilirubin, and international normalized ratio (INR) for prothrombin time, along with the etiology of cirrhosis as the fourth variable. Further studies showed that the accuracy of MELD was preserved after eliminating the variable related to the etiology of cirrhosis [8] that could allow some degree of subjective freedom in its definition, thus leaving a score based only on objective laboratory parameters. Concordance ("c") statistics demonstrated the high accuracy of MELD in stratifying patients according to their risk of dying in the short-term (three months), as many studies reported c-statistics close to or even higher than 0.8, a value reflecting a predictive power of high clinical significance, and usually superior to that of the CTP score [8–10]. Further validations of MELD as a predictor of survival at various temporal end-points were obtained in independent cohorts of patients with a broad spectrum of chronic liver disease [11–13].

MELD has several features of an ideal prognostic model to predict the probability of survival: it only incorporates simple and objective variables readily determined in all laboratories, and each variable is weighted according to its influence on prognosis. The score is independent from the etiology of liver disease, and, hence, does not need adjusting in this respect. It also possesses a high predictive power and provides a continuous ranking of disease severity, thereby overcoming the ceiling effect of the CTP score. Thus, the time came for a sickest-first policy to be reliably fulfilled, and the MELD score became the means to allocate liver grafts in the United States of America from February 2002. The organ allocation system had at last got rid of the influence of accrual time on the waiting list, and patients were unchained from rigid categorizations that had often under- or overestimated their actual priority. In the OLT setting MELD is calculated differently from the original formula that directly incorporated the measured values of the variables, by fixing their lower limit at 1 to avoid negative scores; in addition, serum creatinine value is capped at 4 mg/dl.

The impact of the MELD-based liver graft allocation policy on the OLT system has been impressive: new registrations on the waiting list suddenly dropped, interrupting a growing trend that had accompanied OLT for several years. The removal rate for death or disease progression (“too sick”) also steadily declined [9,10,14–16] (Fig. 1). A slight increase in organ availability could have contributed to the reduction in waiting list mortality, but it is generally agreed that this has mostly been due to MELD implementation [17]. Further advantages associated with the change in allocation policy were a decrease in the median waiting time to OLT (Fig. 2), an increase in the number of deceased donor transplants and the steadiness in the overall patient and graft survival rate after transplantation, with the exception of candidates with extreme MELD values exceeding 30 [14,16,18–20]. These favorable results led many transplant centers worldwide to adopt the MELD-based way of ranking and prioritizing candidates for OLT. Moreover, MELD has progressively been employed as a prognostic tool for patients with chronic liver disease outside the transplant setting for conditions, such as variceal bleeding, bacterial infections, fulminant liver failure, alcoholic hepatitis, and surgery other than OLT. A detailed discussion of these applications of MELD is beyond the limits of this review; interested readers can refer to many recent fine reviews [10,21–23].

Conditions not properly accounted for by MELD: the score shows its weaknesses

The MELD score succeeds in defining the three-month death risk of patients with non-malignant end-stage liver disease and it has proved a reliable tool for prioritizing these patients in the OLT waiting list. There are conditions, however, that are not properly accounted for by the MELD score, either because they are not sufficiently “perceived” and weighted by the variables included in the score, or because their short-term risk in the waitlist is progression beyond the limit of transplant suitability, rather than death (Table 1).

Conditions implying specific end-points for prioritization

To overcome this potential shortcoming, modifications consisting in adding points to the calculated MELD score have been proposed, some of which are widely employed the world over. However, these adjustments were created arbitrarily, often without scientific evidence, with the purpose of avoiding an advantageous or disadvantageous prioritization vis-à-vis cirrhotic patients without these conditions for whom the MELD score had been validated.

Hepatocellular carcinoma (HCC)

A typical example of the conditions described above is HCC, which apparently involves a minority of patients in the waiting list. Indeed, reports from European [24] and US [16] transplant registries indicate a prevalence of 8% and 2%, respectively. These low figures, however, reflect the fact that only cases with HCC as a primary diagnosis are clearly identified, whereas data elaboration discloses that about 10–20% of patients in the waitlist have HCC.

HCC often arises in patients with fairly well-preserved liver function and low MELD score, so that their risk is more often related to tumor progression beyond the stage ensuring a favorable outcome with transplantation, than death on the waiting list because of terminal liver failure due to the underlying cirrhosis. Of course, this concept is valid irrespective of the transplant criteria for HCC [25,26] adopted by individual centers.

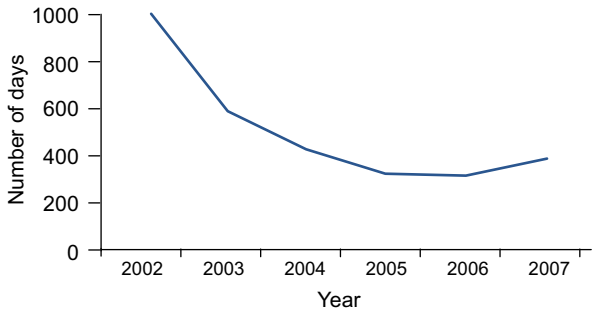

Fig. 2. Median waiting time to OLT after the implementation of MELD in 2002 in the United States (data from Ref. [16]).

At first, based on the evaluation of their three-month death probability, patients with stage T1 HCC (single tumor ⩽1.9 cm) received a MELD score of 24, while patients with stage T2 (single tumor 2–5 cm, or two to three nodules all <3 cm) received a score of 29 [27]. This system led to a sudden increase in the transplant rate of patients with HCC. More than 87% of these patients underwent OLT within three months of listing [28], raising concerns about an excessive priority given to HCC candidates with respect to patients without HCC [29]. Following studies reporting a much lower progression risk [27,29,30], the exception MELD score for HCC candidates was adjusted downward: at first, patients with T1 lesions were given a score of 20, but additional points were subsequently eliminated [31] once the inaccuracy of imaging techniques for small lesions, not confirmed in the explanted liver, had been ascertained [32]. Prioritization was also reduced for candidates with T2 lesions: at first they were given a score of 24, reduced more recently to 22. However, patients with HCC in stage T2 have their score upgraded by three points for every three months on the waiting list as long as tumor burden remains within the established criteria for OLT [33].

As it emerges from these subsequent adjustments, adaptation of the MELD score to “special” conditions consists of an ongoing revision, where further refinements emerge from an analysis of clinical outcomes. As examples, the current MELD adjustment for prioritizing HCC patients at our center consists in adding three points to the real MELD for T1 lesions and six points for T2 lesions, then adjusting the score by 0.5 or one point, respectively, for each month spent on the waiting list [34]. The potential advantage of this approach is to maintain the prediction of the waitlist mortality risk due to the worsening of liver failure (the real MELD score), and give an adequate weight to the additional risk of drop-out related to the tumor. An alternative method, whose main advantage is to compute the risk of drop-out on a continuous basis as for candidates without HCC, was pursued by devising a new equation including maximum tumor size and alfa-fetoprotein level besides the MELD score [35].

Other conditions

There are several other conditions in which application of the original MELD would not allow an adequate patient prioritization because of the risk of dropping out of the waitlist as disease pro-

Table 1. Conditions not properly accounted by MELD score.

Conditions implying specific end-points for prioritization	Impact on outcome in the waitlist	Potential solutions
Hepatocellular carcinoma	Progression beyond the Milano criteria	Added points to MELD to allow OLT before progression
Hepatopulmonary syndrome	Progression to severe hypoxemia	Added points to MELD to allow OLT before PaO_2 <50 mmHg on room air and/or a-v shunt fraction ≥20%
Portopulmonary hypertension	Progression to severe pulmonary hypertension	Added points to MELD to allow OLT before mean pulmonary artery pressure >35 mmHg despite ongoing treatment with vasodilators
Familial amyloidosis	Progression to polyneuropathy, cardiac involvement, poor nutritional status	Added points to MELD to allow OLT before critical progression Combined heart / liver transplantation
Conditions potentially underweighted by MELD score		
Complications of portal hypertension*	Increased risk of waitlist mortality	Integration of new variables into the MELD model (see: MELD-AS)
Hyponatremia	Increased risk of waitlist mortality	Integration of serum Na into the MELD model (see: MELD-Na)
Malnutrition	Increased risk of waitlist mortality	Integration of variables related to nutritional status into the MELD model; not yet proposed
Viral (hepatitis B and C) cirrhosis	Potentially higher mortality risk than alcoholic cirrhosis	Further studies needed. No solutions proposed
Female gender	Higher mortality risk than males	Serum creatinine corrected by gender (see: MELD modified by gender)
Patients listed with low MELD score (<21)	Reduced predictability of waitlist mortality	New scores with extended (≥1 yr) prediction ability

OLT, orthotopic liver transplantation; a-v: artero-venous; MELD-AS, MELD-ascites-Na score.
*Includes: ascites, hepatic encephalopathy, hepatorenal syndrome, esophageal variceal bleeding; spontaneous bacterial peritonitis.

gression reaches specific stages contraindicating OLT (Table 1). Just a few examples are patients with hepatopulmonary syndrome showing an unmodifiable PaO_2 <50 mm Hg [36], patients with portopulmonary hypertension exceeding 35 mm Hg even after treatment [37], and patients with familial amyloidosis having developed significant cardiac involvement or autonomic neuropathy [38]. The answer to the needs imposed by these conditions remains unstandardized among transplant centers worldwide [39–41]. However, the number of patients with these conditions currently in the waitlists is below 3% [16,24].

Thus, MELD can also serve to prioritize patients listed for OLT when their transplant needs differ from those of the original MELD criteria, even though adjustments are necessary. This adaptation process has to be seen as a progressive refinement of the adjusted MELD, and data suggesting that the probability of removal from the waitlist are higher for standard MELD cases than for exceptional cases [42] show that further work has to be done in this field. Nevertheless, this does not invalidate the usefulness and versatility of the MELD score.

Conditions potentially underweighted by the MELD score

Advanced cirrhosis is jeopardized by complications, most of which directly or indirectly related to portal hypertension, such as hepatic encephalopathy, esophageal variceal bleeding, refractory ascites, hepatorenal syndrome, severe malnutrition, and bacterial infections. All these complications imply a poor prognosis and a high risk of death [23]. However, the variables included in the MELD formula are not always influenced by these conditions, so that the disease severity of patients awaiting OLT can be underweighted.

Complications of portal hypertension

Huo et al. [43] investigated the association with MELD of complications related to portal hypertension (hepatic encephalopathy, hepatorenal syndrome, ascites, esophageal variceal bleeding, and spontaneous bacterial peritonitis), and their impact on survival in a large cohort of patients with non-cholestatic cirrhosis. As expected, they showed that these complications are time-dependent prognostic predictors of mortality, and found that the mortality risk increased for each additional episode of complications. However, patients developing complications did not necessarily have a higher MELD score and could be overlooked during the process of organ allocation. These results have been confirmed to some extent, as MELD score did not correlate with the severity of ascites and hepatic encephalopathy in a further study [44]. Thus, it appears that such high-risk patients need to

be identified better and earlier, and this may help to decrease waitlist mortality. An answer to this need, however, is currently lacking.

Hyponatremia

Another powerful prognostic factor not incorporated in the MELD formula is hyponatremia. Hyponatremia is linked to impaired renal function induced by the hemodynamic abnormalities that develop in advanced cirrhosis. It is often associated with refractory ascites and hepatorenal syndrome [45,46] and implies an increased incidence of complications and a high mortality rate [47,48]. The prognostic importance of hyponatremia has been largely confirmed in the OLT setting. Indeed, three retrospective single-center studies [49–51] and a prospective multi-center study [52] agreed that hyponatremia is a strong independent mortality predictor. Interestingly, the risk of waitlist mortality appears to increase by 12% for each unit of decrease in serum sodium concentration for values between 120 and 135 mmol/L [53]. These findings have led to several attempts to integrate serum sodium into the MELD formula. The advantages and potential pitfalls of these modified scores are reported below.

Malnutrition

Cirrhotic patients are often malnourished due to poor dietary intake, intestinal protein loss, low protein synthesis, abnormalities in substrate utilization, and hypermetabolism [54]. Malnutrition is frequently under diagnosed, also because a gold standard to define nutritional status in cirrhotic patients is lacking [55,56]. Malnutrition worsens liver function in cirrhotic patients [57] resulting in higher morbidity and mortality [58,59]. The adverse prognostic significance of malnutrition has long been recognized, and this variable was included in calculating the original Child-Turcotte score [5]. Indeed, malnutrition has proved to be an independent predictor of mortality at six, 12 and 24 months in patients with cirrhosis [58], and the in-hospital mortality of malnourished patients is almost twofold higher than that of patients without malnutrition [56]. Interestingly, malnutrition enhances the risk of complications and mortality both in patients with advanced cirrhosis [56] and in those belonging to CTP class A [60]. To date, no attempts have been made to assess whether parameters related to malnutrition actually improve the MELD predictive power.

Acute complications of cirrhosis and the use of artificial liver support systems

Patients belonging to the cohorts where MELD was originally created and validated [7,8] were in stable conditions, and potentially reversible complications, such as bacterial infections, acute renal failure, and ongoing gastrointestinal hemorrhage had been resolved at the time of data collection. Thus, caution has to be exerted in calculating the MELD score during an acute, but potentially reversible, deterioration of patient conditions, as it may not accurately predict short-term mortality in such circumstances. Interestingly, the occurrence of hepatorenal syndrome type 1 effaces the predictive ability of MELD [61].

The picture can be complicated even further by artificial liver support systems. Growing attention has focused on these devices to treat specific conditions, such as severe jaundice or pruritus, or bridge patients with acute-on-chronic liver failure to OLT [62,63]. However, while it is undisputed that these devices can efficiently, but often transiently, lower at least one of the triad parameters included in the MELD score, i.e. bilirubin, it has yet to be demonstrated whether they also enhance short-term survival [64]. Thus, a consensus must be reached on when to calculate MELD in patients awaiting OLT and receiving artificial liver support.

Other potential pitfalls

As already reported, the removal of cirrhosis *etiology* from the variables employed to compute the MELD score did not appear to affect its predictive accuracy [8]. Nevertheless, Angermayr et al. found that the prediction of survival beyond three months in patients with viral cirrhosis and MELD $\geqslant 16$ is not precisely assessed [65]. Moreover, Lucey et al. demonstrated that MELD is a stronger predictor of waitlist mortality in non-alcoholic than alcoholic patients [66]. Thus, the role of cirrhosis etiology in assessing the mortality risk in cirrhotic patients cannot be seen as a definitely resolved issue.

Gender has recently emerged as a factor that can significantly influence access to OLT, as shown by a large study in the UNOS database reporting that, in the MELD era, women experienced around 30% increased probability of drop-out from the waiting list because of death or becoming too sick for transplant compared to men [67]. Although liver allocation to women could be influenced by factors such as graft size, such a disparity also depends on lower serum creatinine values. Indeed, females exhibit a worse renal function, as measured by GFR, with respect to males with similar MELD scores [68], thus being disadvantaged in calculation of the score [68,69].

Lastly, although MELD undoubtedly succeeds in predicting the short-term mortality risk in end-stage liver disease, such a risk may not be adequately assessed in patients with a *prolonged stay on the waiting list* and/or with a *less severe disease*. The superiority of MELD's predictive power with respect to CTP has been repeatedly reported. However, several studies have shown that CTP has the same ability to predict mortality or removal from the waiting list as MELD [70], or is even superior [71]. Such variant results are likely related to the inclusion of patients with a less severe liver disease [70] and/or an observation period extending up to a year [71]. Thus, the development of new scoring systems fitting these conditions may be advisable.

Intrinsic weaknesses of the MELD score: the shortcomings of its components

The three variables included in the MELD formula were selected by a robust statistical approach [8] but each shows some limitations.

(1) *Serum creatinine.* First, serum creatinine is influenced by muscle mass, protein dietary intake, age, sex, and ethnicity [72]. Because of muscle wasting, patients with advanced cirrhosis present lower serum creatinine than the general population [72–74]. Thus, a normal serum creatinine does not exclude a significant impairment in renal function [75]. Second, serum creatinine can fluctuate considerably in the short-term in patients with massive or refractory ascites undergoing diuretic treatment, large volume paracentesis, and plasma volume expansion leading to MELD fluctuations that likely do not reflect a change in the actual

Table 2. MELD-derived models.

MELD-derived models [Ref]	Equations	Strengths	Limitations
			For all the scores including serum Na: rapid spontaneous and iatrogenic Na variability
MELD-Na [74]	MELD + 1.59 × (135 – Na)	More accurate in 6-month mortality prediction	Derived from a retrospective study, not validated, limited number of deaths during the follow-up period
MELD-Na [89]	MELD – Na – [0.025 × MELD × (140 – Na)] + 140	More accurate in 3-month mortality prediction Validated in a large population	Derived from a retrospective study, based on a non-specific database (waiting-list registry)
iMELD [90]	MELD + (age × 0.3) – (0.7 × Na) + 100	More accurate 3-, 6-, and 12-month mortality prediction	Derived from a retrospective study, validation group including HCC Advantages older recipients, who show lower post-OLT patient and graft survival
UKELD [39]	[(5.395 × ln(INR)) + (1.485 × ln(creatinine)) + (3.13 x ln(bilirubin)) – (81.565 × ln(Na))] + 435	Validated in a separate prospective cohort	Derived from a retrospective study, lack of data for comparison with MELD
MESO [94]	MELD / Na	Higher predictive value than MELD	Derived from a retrospective study, not tested on a waiting list population
MELD-AS [71]	MELD + 4.46 (if persistent ascites) + 4.53 (if Na <135)	Identifies patients with high mortality risk despite low MELD score	Derived from a retrospective study, not superior to standard MELD with scores ≥21
Updated MELD [55]	1.266 × ln(1 + creatinine) + 0.939 x ln(1+bilirubin) + 1.658 × ln(1 + INR)	More accurate 3-month and and overall predictor of mortality Derived from a large sample size	Derived from a retrospective study, based on a non-specific database (waiting-list registry)
Δ MELD [96, 97]	$MELD_2 – MELD_1$	Dynamic evaluation of disease progression	Derived from a retrospective study, time interval between assessment not defined

mortality risk [72,75]. Lastly, a significant bias in calculation of the MELD score can derive from the use of different assays for creatinine in different laboratories [76]. This variability is exacerbated by the analytical interference of bilirubin, a chromogen, when the colorimetric Jaffé method is employed. When serum bilirubin exceeds 10 mg/dl, falsely low serum creatinine readings can ensue, an effect that is enhanced in parallel with the increase in bilirubin [77]. This would underestimate the MELD score in deeply jaundiced and usually the sickest patients, who have the greatest priority for OLT. In such cases, enzymatic methods are far more accurate and their use is highly advisable [78].

The equations based on serum creatinine such as the Cockroft-Gault formula and the Modification of Diet in Renal Disease, which is considered the gold standard measure of renal function by nephrologists [79], overestimate the actual glomerular filtration rate (GFR) in cirrhotic patients [72,75]. Theoretically, creatinine clearance should be more reliable, but it also overestimates GFR in cirrhosis because of increased tubular secretion of creatinine, especially in patients with low GFR [80]. This limitation could be overcome by direct GFR measurement, but unfortunately this is inappropriate for routine use because of costs and complexity [75].

As reported above, by applying MELD to the organ allocation system, UNOS introduced changes in how the score was calculated, setting lower, as for the other variables, and upper limits for creatinine. Both these changes have been criticized. Bounding lower serum creatinine levels to 1 mg/dl to avoid negative values after logarithmic transformation implies that mortality is constant for values below 1 mg/dl. Such an assumption, however, is doubtful because all changes in serum creatinine levels reflect changes in GFR [81]. Thus, it has been proposed to eliminate the lower limit for creatinine, a change that would lead to better results with respect to the standard MELD score [81]. The 4 mg/dl capping, introduced to avoid excessively high scores in candidates with intrinsic renal disease, has also been recently challenged. Indeed, no outcome data justify this choice, and capping creatinine in patients who were not uremic or on dialysis may yield a MELD score that underestimates disease severity in the sickest patients [82].

(2) *Serum bilirubin.* Like creatinine, serum bilirubin determination can vary among different laboratories [83]. Apart from this limitation, which can hardly be resolved, it should not be disregarded that patients with cholestatic liver disease showed a lower waitlist mortality than patients with non-cholestatic

disease [14]. Thus, the original assumption that disease etiology could be avoided without altering MELD score reliability [8] may not be valid in all settings. Finally, it has yet to be investigated whether direct, rather than total bilirubin, more accurately predicts mortality in end-stage liver disease as it is less influenced by extrahepatic or benign causes of jaundice.

(3) *INR.* Prothrombin time (PT) is a long-recognized indicator of liver function and has been widely employed to assess the prognosis of patients with liver disease [23]. The recent demonstration that PT prolongation in cirrhosis does not reflect an increased risk of bleeding [84], as the synthesis of both coagulative and anti-coagulative factors is depressed, does not detract from its potential as a prognostic factor. However, it should not be forgotten that PT INR was originally developed to predict bleeding and thrombotic risk under oral anticoagulants in non-cirrhotic patients [85]. Although attempts have recently been made to modify INR to adapt it to the setting of cirrhosis [86,87], the definite validation of these new indices is still pending and this continues to represent a limitation.

Another weakness is the huge inter-laboratory variability in PT, which has not been removed by the introduction of INR [85]. Inter-laboratory INR variability in patients with liver disease leads to a median MELD score difference between the highest and lowest scoring laboratories of three to five points, with individual differences reaching up to eleven or twelve points [88–90]. The impact of such variability on the organ allocation system is self-evident.

Attempting to overcome MELD limitations: the "new" MELD scores (Table 2)

Among the prognostic factors that could be incorporated into the MELD formula in an attempt to improve its reliability, hyponatremia has received the broadest attention. Biggins et al. [52] proposed a MELD-based score, called *MELD-Na*, resulting from the integration of serum sodium into MELD, which more accurately predicted the six-month survival of cirrhotic patients awaiting OLT. More recently, a study based on a larger sample [91] modified the previous MELD-Na formula by fixing the lower and upper limits of the serum sodium concentration to 125 and 140 mmol/L, respectively, and suggested that the new score offers a better short-term mortality prediction. It also emerged that the influence of hyponatremia was mainly evident in patients with a MELD score below 30. However, the applicability of Na-based MELD scoring systems in organ allocation also has some limitations due to inter-laboratory differences and the potential variability of serum sodium concentration after simple therapeutic maneuvers, such as diuretic administration, plasma volume expansion, or hypotonic fluid infusion.

As age is strongly associated with a higher mortality in cirrhosis [23], an attempt has been made to integrate MELD variables with serum sodium and age [92]. The resulting score, called integrated MELD (*iMELD*), seems to predict three-, six- and 12-month survival more precisely than standard MELD. However, age inclusion in this setting could raise ethical issues, as OLT in older recipients is associated with lower patient and graft survivals [93,94].

Other scores that add natremia to the original MELD formula include the United Kingdom model for End-stage Liver Disease (UKELD) and the MELD to serum sodium ratio (MESO). The *UKELD*

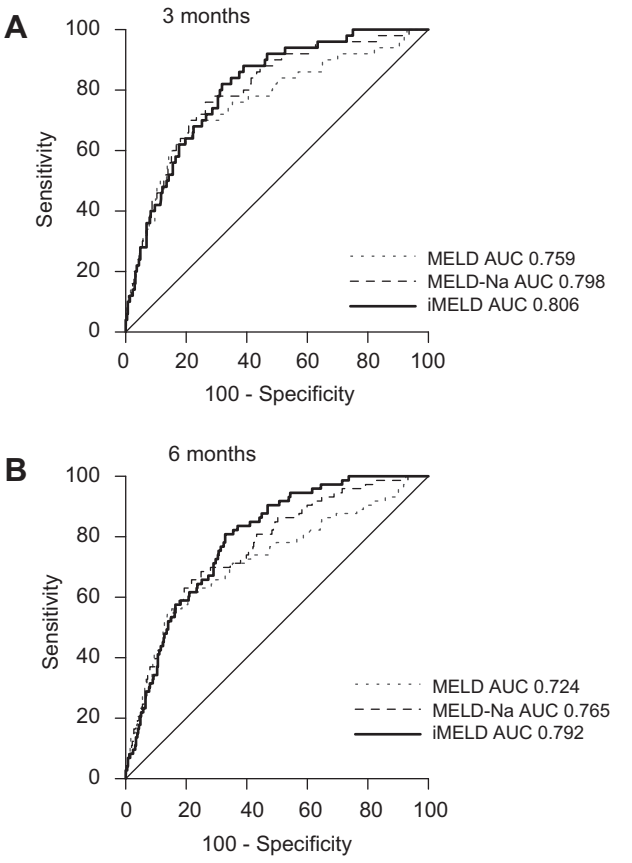

Fig. 3. ROC curves for best predictors of dropout from the waiting list with respect to standard MELD at 3 and 6 months (data from Ref. [101]). Despite both iMELD and MELD-Na showed a higher AUC in respect to standard MELD at 3 months, the comparison between AUCs showed that only MELD-Na had a significantly better prognostic power than the standard MELD, because of the very small standard error (0.018) in the difference between the areas (0.039).

was developed by analysis of 1103 patients and validated in a separate prospective cohort study [40,95]. The *MESO* is calculated by dividing the MELD score by the serum sodium concentration, and proved to possess a higher predictive value than standard MELD [96]. This score, however, was tested in non-waitlisted cirrhotic patients.

In general, scores resulting from the integration between serum sodium and MELD seem to enhance MELD's predictive power in patients with low MELD scores [50,52]. In this subset, point addition for the *presence of persistent ascites* (*MELD-AS*) further improved the prediction of six-month mortality when standard MELD score was 21 or lower [49]. The importance of ascites has been further confirmed as its presence in patients with MELD-Na below 21 identified those with a high one-year mortality risk independently from their MELD or MELD-Na scores [97]. Moreover, the addition of ascites to the MELD-Na formula improved its one-year mortality prediction ability [97].

The demonstration that patients with high serum creatinine have a lower waitlist mortality than those with low values, whereas patients with the highest bilirubin have the highest mortality, has led to the proposal of "*updated MELD*", assigning

a lower weight to creatinine and INR, and a higher weight to bilirubin [81]. The resulting score better predicted overall and 90-day mortality on the waiting list than standard MELD.

The MELD score is not a time-dependent model, since it is computed by a single measurement of laboratory parameters. In an attempt to weight the time-related changes, the Delta MELD ($\Delta MELD$), defined as the difference between the MELD score calculated at two time points, has been proposed [98,99]. Once again, the new score was able to predict the mortality risk of OLT candidates more accurately than standard MELD score alone. Nevertheless, its usefulness in predicting survival on the waiting list is still debated [100].

We recently compared the performance of most MELD-based scores in waitlisted patients [101]. Our data suggest that the most accurate scores to predict the drop-out rate from the waiting list are MELD-Na and iMELD. MELD-Na is the best drop-out predictor at three months, while both scores performed well at six months (Fig. 3).

Lastly, there are some clinical conditions that cannot be adequately evaluated by the standard MELD score. Patients with Budd-Chiari syndrome, or other thrombophilic syndromes, are commonly treated with oral anticoagulants [102] which improperly modify INR and, therefore, the MELD score. To overcome this problem, Heuman et al. [103] developed a score omitting INR.

Conclusions

The adoption of MELD to select and prioritize patients, and regulate organ allocation in the setting of OLT has brought substantial advantages and constituted a significant clinical turning point. The impact of MELD on the OLT system has been so strong that the period following implementation of the new score is often referred to as the "MELD era". The predictive strength of the MELD score for short-term mortality is such that it will be employed in many more settings other than the OLT waitlist for which it was conceived and validated. Like all human achievements, MELD is not perfect and has its weaknesses. Many attempts are underway to improve the applicability and reliability of the formula in specific conditions. However, virtually all these proposals continue to be based on the original MELD score, confirming its peculiar versatility, a feature that may well prove its greatest strength.

Key point 1. The strengths of the MELD score.

- Adoption of the MELD score to prioritize candidates for OLT represented a turning point in organ allocation policy as priority changed from the time spent on the waitlist to the principle of "sickest first".
- The MELD score is simple and objective and can stratify patients according to their disease severity in a continuous scale. It has been validated at various temporal end-points in independent cohorts of patients with a broad spectrum of chronic liver disease.
- MELD has a high accuracy in predicting the short term mortality risk and has led to a decrease in removal of patients from the waitlist because of disease progression and waitlist mortality, a shorter waiting time to OLT and an increase in the number of deceased donor transplants.

Key point 2. The weaknesses of the MELD score.

- Some conditions are not properly accounted for by the MELD score:
  - Conditions implying specific end-points for prioritization (hepatocellular carcinoma, hepatopulmonary syndrome, portopulmonary hypertension, familial amyloidosis).
  - Conditions potentially underweighted by the MELD score (complications of portal hypertension [ascites, hepatic encephalopathy], hyponatremia, malnutrition, gender).
- The MELD score has intrinsic weaknesses due to the shortcomings of its components:
  - Inter-laboratory variability of creatinine, bilirubin and INR assessments.
  - Reduced reliability of serum creatinine as a marker of renal function in cirrhosis.
  - Serum bilirubin influenced by extra-hepatic factors.
  - PT INR is not adapted to the setting of cirrhosis.

Conflict of interest

The authors declare that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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