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Review Article

The Development and Appraisal of MELD 3.0 in Liver Diseases: Good Things Never Come Easy

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Abstract

Since its proposal, the Model for End-Stage Liver Disease (MELD) score has been employed to predict short-term mortality among patients with chronic liver disease and those awaiting liver transplantation, serving as the primary criterion for organ allocation. However, as the demographic and epidemiological characteristics of chronic liver disease and liver transplantation have evolved, a range of MELD-related scores has emerged, including MELD-Na, iMELD, delta MELD, MELD XI, MELD-LA, and pediatric end-stage liver disease, culminating in the recently proposed MELD 3.0, which builds upon MELD-Na. This study aimed to comprehensively review and summarize relevant studies on MELD 3.0 in various scenarios, assessing its effectiveness in organ allocation, post-transplantation outcomes, and mortality prediction for patients with end-stage liver disease. Our preliminary findings indicate superior predictive performance of MELD 3.0, warranting further in-depth investigations to broaden its clinical implications.

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Introduction

Developed by Kamath *et al*. in 2000, the original MELD score served as a prognostic model incorporating three objective laboratory measures [(creatinine, total bilirubin, and international normalized ratio (INR)], with etiology as the sole subjective indicator. Initially, it aimed to predict short-term prognosis for patients with portal hypertension undergoing transjugular intrahepatic portosystemic shunt (TIPS). Subsequently, it has been broadly applied to evaluate the severity of various pathological conditions in patients with end-stage liver disease and to determine the urgency and prioritization for liver transplantation (LT).[1]

Although the MELD score has significantly improved health outcomes since its implementation in clinical practice, some inherent limitations should be acknowledged and addressed. These concerns regarding the MELD score are depicted as follows: (1) Serum bilirubin, creatinine, and INR are influenced by the underlying disease status, such as infections, vitamin K deficiency, and the administration of diuretic medications. Therefore, Kamath *et al*. suggested that to avoid extrahepatic impacts, the MELD score should be utilized under conditions of hemodynamic stabilization and adequate rehydration.[2] (2) Using serum creatinine clearance rather than serum creatinine could more accurately reflect biochemical changes related to liver dysfunction. It is highlighted that the average muscle mass is lower in females than in males, indicating more advanced renal dysfunction in females at equivalent creatinine levels.[3] (3) Given the effective spread of anti-hepatitis C drugs, the incidence of liver transplants for hepatitis C has dropped dramatically, while the proportion of patients waiting for transplants due to alcohol-associated liver disease (ALD) and metabolic dysfunction-associated steatohepatitis as major etiologies has risen substantially, altering the demographic characteristics of chronic liver disease and the indications for LT.[4] (4) The MELD score cannot promptly capture pathophysiological perturbations in patients with complications such as refractory ascites (RA), hepatic encephalopathy, hepatocellular carcinoma, and acute-on-chronic liver failure (ACLF), thus limiting its performance for long-term prognostication. (5) While the MELD score remains a reliable predictor of preoperative mortality in transplant candidates, it has limited utility in predicting post-transplant mortality.[5]

Collectively, the magnitude of liver disease severity and the allocation of liver transplant resources require more precise, comprehensive, and accurate evaluation to meet escalating healthcare demands and provide tailored treatments for improved prognoses. In this regard, a spectrum of iterative MELD scores has been constructed and is discussed in the following statements.

MELD-related score

Over the past two decades, the MELD score has been continuously modified and developed to generate versatile, rel-

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Table 1. Formula for MELD-related scores

Score	Components
MELD	9.57*Ln(creatinine) + 3.78*Ln(bilirubin) + 11.20*Ln(INR) + 6.43 (etiology: 0 if cholestatic or alcoholic, 1 otherwise)
MELD-Na	MELD +1.32 *(137 − Na) − 0.033 *MELD*(137 − Na)
Delta MELD	Difference in MELD scores between last and first admission within 30 days
MELD-XI	5.11*Ln(bilirubin) + 11.76*Ln(creatinine) + 9.44
iMELD	MELD + 0.3*age − 0.7*Na + 100
MELD-LA	5.68*Ln (LA) + 0.64*(MELD) + 2.68
PELD	0.480 *Ln (bilirubin) + 1.857*Ln (INR) − 0.687*Ln (albumin) + 0.436 (if the patient is less than one year old), 0.480*Ln (bilirubin) + 1.857*Ln (INR) − 0.687*Ln (albumin) + 0.667 (if the patient has growth failure)
MELD 3.0	1.33 (if female) + 4.56*Ln(bilirubin) + 0.82*(137 − Na) − 0.24 *(137 - Na) *Ln(bilirubin) + 9.09*Ln(INR) + 11.14*Ln(creatinine) + 1.85*(3.5 − albumin) − 1.83*(3.5 − albumin) *Ln(creatinine) + 6

MELD, model for end-stage liver disease; Ln, natural logarithm (base e); INR, international normalized ratio; LA, lactate; PELD, the pediatric end-stage liver disease.

evant models. The generated MELD-related scores are summarized in Table 1.

MELD-Na score

In 2006, Biggins *et al*.[6] proposed the MELD-Na score, an adaptation of the original MELD score that includes serum sodium (Table 2). The Organ Procurement and Transplantation Network (OPTN) formally implemented the MELD-Na score as the standard for liver transplant allocation in 2016, resulting in a notable reduction in mortality rates among patients awaiting LT.[7] Subsequent research, including a study by Cristal Brown *et al*., utilized the largest database of decompensated cirrhotic patients in the U.S., indicating that MELD-Na has a strong predictive value concerning six-month mortality with a C-statistic of 0.83, comparable to its predictive accuracy for 90-day morbidity and mortality.[8] An assessment of three-month outcomes for 5,223 patients on the European transplant waiting list indicated that the MELD-Na score demonstrated superior prognostic accuracy.[9] The MELD-Na score was also closely linked to post-LT complications, particularly early acute kidney injury,[10] and to Accordion Severity Grades, as a MELD-Na score ≥ 25 independently predicted postoperative severe grade complications[11] and post-liver transplant mortality. Notably, the majority of studies have shown that MELD-Na significantly enhances predictive performance in patients with lower MELD scores.[12] Although the MELD-Na score surpassed the original MELD score in predicting overall mortality in cirrhosis, it was less effective in predicting short-term mortality after TIPS.[13,14]

Delta MELD score

Merion *et al*.[15] proposed the delta MELD (ΔMELD) score, which indicates temporal changes in the MELD score over a 30-day interval and demonstrated that ΔMELD accurately predicts mortality in patients with end-stage liver disease compared to the original MELD score.[16] Furthermore, ΔMELD more accurately predicted survival status in patients awaiting LT, indicating that a ΔMELD increase of >10 correlates

Table 2. Characteristics of original MELD, MELD-Na, and MELD 3.0

	MELD	MELD-Na	MELD 3.0
Variables	INR: Total bilirubin; Serum creatinine	INR: Total bilirubin; Serum creatinine; Serum sodium	INR: Total bilirubin; Serum creatinine; Serum sodium; Albumin; Sex
Value Range			
INR	Lower limit 1.0	Lower limit 1.0	Lower limit 1.0
Bilirubin	Lower limit 1.0	Lower limit 1.0	Lower limit 1.0
Creatinine	Upper limit 4.0 mg/dL	Upper limit 4.0 mg/dL	Upper limit 3.0 mg/dL
Sodium	/	Upper limit 125 meq/L, Lower limit 137 meq/L	Upper limit 125 meq/L, Lower limit 137 meq/L
Albumin	/	/	Upper limit 1.5 mg/dL, Lower limit 3.5 mg/dL
Score range	6–40	6–40	6–40
Advantages	Objective, continuous scores, inclusion of etiologic and renal function indicators	Refining the assessment of liver disease severity adding serum sodium levels	Add albumin and gender to the equation, and address sex-based disparity
Disadvantages	Susceptible to interference from laboratory testing and lack comprehensive evaluation indicators for complications	The same as MELD	Short application time and further confirmation is needed

INR, international normalized ratio; MELD, model for end-stage liver disease.

with a 1.6-fold increase in mortality risk.[17] Another study implied that ΔMELD scores were significantly higher in patients whose cirrhosis was due to alcohol consumption.[18]

MELD-XI score

The MELD-XI score, adapted for patients on anticoagulant therapy, adjusts for the effects of anticoagulation on INR values[19] and provides a more accurate assessment of patients with heart failure.[20] This score has shown prognostic relevance in patients undergoing ventricular assist device implantation[21,22] and has been validated as a predictor of early mortality following heart transplantation. Patients with elevated MELD-XI scores often present with multi-organ dysfunction, thereby exhibiting a notable correlation with increased long-term and short-term mortality in ICU settings. Moreover, the MELD-XI score is extensively utilized in patients with Fontan-associated liver disease.[23] The MELD-XI score also predicts outcomes in post-Fontan surgery patients, helping to determine the need for isolated heart transplantation or combined heart-liver transplantation. Among 596 pediatric Fontan patients undergoing isolated heart transplantation,[24] those with elevated MELD-XI scores at heart transplantation showed lower post-transplant mortality, highlighting the score's implications regarding compromised circulatory function, increased risk of liver disease, and poor outcomes.

iMELD score

Taking into account serum sodium level and age, the iMELD score was formulated.[25] Saldaña *et al*. assessed various prognostic models in 818 LT candidates regarding 90-day survival and demonstrated that the iMELD score represented greater reliability and feasibility.[26] In comparisons of three-month, six-month, and one-year mortality rates in patients with cirrhosis, iMELD outperformed both MELD and MELD-Na scores.[27,28] Additionally, in evaluations of three-month and six-month prognosis in HBV-ACLF patients, iMELD showed better predictive value compared to MELD and MELD-Na; similarly, a prospective cohort study involving Chinese HBV-ACLF patients demonstrated that iMELD displayed the highest area under the curve (AUC) for predicting mortality at both three months and five years.[29] In cases of ACLF resulting from intensive hepatic injury, iMELD proved to be the best indicator concerning 28-day mortality with the highest AUC (0.787), although Chronic Liver Failure Consortium (CLIF-C)-ACLF may be more appropriate for ACLF triggered by extrahepatic factors.[30]

MELD-LA score

A positive correlation between serum lactate levels and MELD scores led to the development of the MELD-LA score,[31] which demonstrated good predictive performance regarding short-term prognosis following LT. Meanwhile, a large-scale study indicated that MELD-LA was better at predicting mortality and sepsis in the context of CLD[32] and demonstrated strong predictive ability for variceal bleeding in cirrhosis compared to MELD.[33] The MELD-LA effectively predicted short-term prognosis in critically ill patients with cirrhosis, with an AUC of 0.808 for 15-day mortality.[34] Stratification by cirrhosis etiologies, such as alcohol and viral hepatitis (B and C), improved the score's prognostic accuracy.

Pediatric end-stage liver disease (PELD) score

The PELD score applies to children under 12, estimating the severity and prognosis of chronic liver disease in this age group. It incorporates five objective indicators: age, serum albumin, INR, bilirubin levels, and growth status.[35] The PELD score not only serves as a primary standard for organ allocation in pediatric liver transplantation but also predicts mortality among infants with end-stage liver disease awaiting LT.[36,37] However, it is unsuitable for children receiving specific treatments like artificial liver therapy, which can significantly alter serum bilirubin/albumin levels and INR. An elevated PELD score increases the risk of post-transplant mortality, and children with biliary atresia exhibit a higher mortality risk than those with other chronic liver diseases.[38] Additionally, a high PELD score is associated with increased postoperative AKI mortality in pediatric patients.[39]

MELD 3.0 score

Recently, Stanford University School of Medicine and Mayo Clinic refined the MELD 3.0 score to better reflect new clinical characteristics of liver transplant candidates added to the OPTN list.[40] This score extends the MELD-Na by incorporating gender and albumin as additional variables. Considering the disadvantaged position of women under the current system, an additional 1.33 points were compensated for female candidates. The administration of albumin therapy in clinical practice may potentially lower the MELD score. Consequently, a sensitivity analysis was conducted to establish a MELD 3.0 model without serum albumin. This analysis showed that the MELD 3.0, including albumin, demonstrated superior mortality prediction and better discriminative accuracy than MELD-Na. The upper limit of creatinine was adjusted to 3.0 mg/dL to mitigate the influence of muscle mass and relevant comorbidities. Each variable in the MELD 3.0 was an independent predictor of mortality, but interactions between creatinine-albumin and sodium-bilirubin required adding corresponding interaction terms to the model. A temporal validation analysis of transplant candidates from 2019 demonstrated that MELD 3.0 reclassified a net 8.8% of deceased individuals on the waiting list into higher MELD categories, with a majority being female, suggesting that MELD 3.0 effectively reduces mortality on liver transplant waiting lists in the U.S. and partially eliminates existing gender disparities.

Next, we will elaborate on the clinical implementation of MELD 3.0 in the context of specific liver disease.

MELD 3.0 in liver transplantation

The purpose of organ allocation systems is to maximize the use of transplantable organs and minimize deaths on the waiting list. Organ allocation involves a delicate balance of three core principles: urgency, utility, and transplant benefit. Urgency prioritizes organs for patients with the shortest expected survival without a transplant, while utility focuses on those likely to have the longest post-transplant survival. Transplant benefit evaluates disparities in average survival rates before and after transplantation. The liver allocation has primarily emphasized urgency, with the MELD score serving as a biological predictor of mortality to help prioritize surgical intervention.[41] In 2023, the United Network for Organ Sharing approved MELD 3.0, which is set to replace MELD-Na in prioritizing donor selection for liver disease patients awaiting LT.

A gender adjustment within the MELD score was also deemed necessary to address the disadvantages faced by females in accessing liver transplants.[42] Since the implementation of MELD 3.0, an increase in transplantation likelihood has been observed for women compared to those evaluated with MELD-Na or the original MELD.[43]

Furthermore, the prognostic benefits of MELD 3.0 varied among different liver disease etiologies.[44] In certain cases, there were differences in the prognostic benefits of MELD

3.0. For male patients with alcohol-associated hepatitis (AH) or non-hepatitis ALD, as well as those with metabolic dysfunction-associated steatotic liver disease (MASLD), MELD 3.0 offered slight improvements in calibration compared to the MELD-Na score. However, MELD 3.0 showed lower discrimination for AH, with C-index values of 0.75, 0.86, and 0.84 for AH, non-hepatitis ALD, and MASLD, respectively. In this cohort, the most significant increase in waitlist scores under MELD 3.0 was observed among male patients with AH and female patients with either AH or MASLD. Given the rising issues related to ethanol abuse, further investigation into the application of MELD 3.0 in AH is required.

In an Asian cohort, MELD 3.0 reclassified 22.6% of patients from the original MELD to a higher grade.[45] The predictive ability of MELD 3.0 with albumin was lower than that observed in Western countries (C-index: U.S. = 0.869, Korea = 0.780), though it remained superior to other scores in predicting short-term prognosis on the LT waiting list, albeit not statistically significant overall.[45] This discrepancy may be attributed to racial differences, variations in liver disease etiologies across countries, and disparities in LT practices, such as the prevalence of living donor LT in East Asia. The effectiveness of MELD 3.0 in reducing waitlist mortality among women and patients with severe ascites was limited in regions with organ shortages.[46] However, in another Asian cohort, MELD 3.0 with albumin best stratified prognosis in relation to three-month survival, three-month transplant-free survival, overall survival, and total transplant-free survival. The MELD-Na-kidney dysfunction type derivation, which incorporates renal dysfunction type into MELD-Na, was comparable to MELD 3.0. When stratified by gender, MELD 3.0 demonstrated similar discriminative ability to MELD in males; but in the female cohort, it showed a significant prognostic impact on survival. This suggests that laboratory values related to hepatic and renal dysfunction may be more informative than renal dysfunction type in assessing short-term outcomes for hepatorenal syndrome in liver transplant candidates.[47]

The OPTN recommends the use of MELD 3.0 over MELD-Na for adolescents awaiting LT. Although initially developed and validated in adults, MELD 3.0 demonstrated moderate predictive performance regarding 90-day mortality in adolescents aged 12–17 on the waiting list,[48] with a C-statistic of 0.893 outperforming MELD-Na and PELD, which had C-statistics of 0.871 and 0.852, respectively. Another study indicated that incorporating weight z-scores enhanced risk stratification for LT compared to MELD 3.0 and PELD, which includes sodium and creatinine.[49] Notably, eliminating the upper limit of MELD 3.0 could improve risk stratification for mortality and potentially result in greater survival benefits from LT for critically ill patients, such as those with ACLF.[50]

MELD 3.0 in chronic liver disease

The MELD 3.0 score has been utilized as a predictor of mortality in patients with cirrhosis and other advanced liver diseases. In the context of liver cirrhosis, MELD 3.0 was significantly superior to MELD-Na for predicting both three-month and six-month mortality.[51]

In patients with hepatocellular carcinoma (HCC) categorized as Child-Turcotte-Pugh (CTP)-B, MELD 3.0 provided the most accurate mortality predictions compared to the albumin-bilirubin score.[52] The MELD 3.0 score also demonstrated improved accuracy in predicting 90-day survival for HCC patients, particularly those with scores between 21–30 and 31–37, with 90-day survival rates of 72.5% and 24.3%, respectively. These rates were lower than those of non-HCC patients, which were 82.0% and 72.3%.[53] However, MELD 3.0 performed poorly in HCC patients with renal insufficiency, where the albumin-bilirubin score was more effective, as indicated by the lowest corrected Akaike information criterion and highest homogeneity value.[54]

The prognostic value of MELD 3.0 in predicting one-year mortality in patients with ALD appears limited, showing poor performance compared to MELD-Na, with similar findings in AH.[55] Nonetheless, in AH patients, MELD 3.0 performed better for predicting 30-day and 90-day mortality and was the best predictor of the need for renal replacement therapy compared to MELD-Na.[56] Enhanced predictions for one-month and one-year mortality were also observed in patients with severe AH.[57] MELD 3.0 demonstrated a significant advantage in predicting three-month mortality among patients undergoing TIPS compared to MELD and MELD-Na[58] and accurately predicted six-week mortality risk for hospitalized patients with acute variceal bleeding.[59]

Refractory hepatic hydrothorax (RH), a serious complication of cirrhosis, was not included in the MELD model due to insufficient evidence of increased mortality. In a study by Allison Chin *et al*., RH was associated with a higher risk of liver-related death than RA at the same MELD-Na level. Although no significant differences in baseline MELD 3.0 levels were observed between patients with RH and RA, MELD 3.0 was found to provide enhanced prognostic capability for liver-related death associated with RH.[60] In 327 patients with spontaneous bacterial peritonitis, MELD 3.0 demonstrated the highest AUC for predicting in-hospital and three-month mortality, with C-indexes of 0.786 and 0.760, respectively, outperforming iMELD, MELD, CTP, and MELD-Na. However, iMELD showed the best performance in predicting six-month mortality, with an AUC of 0.752.[61] The MELD score has also been used to assess surgical risk in HCC and predict postoperative survival in patients with liver cirrhosis undergoing surgery other than LT.[62] However, this application has yet to be verified for MELD 3.0.

Given the rapidly changing nature and prognostic fluctuations in patients with ACLF, MELD-related scores have often demonstrated limited efficacy in this vulnerable population. In this regard, Hernaez *et al*. proposed the CLIF-C ACLF model for this specific scenario.[63] In terms of predicting short-term mortality, the AUC of the CLIF-C ACLF score was 0.80, surpassing those of MELD, MELD-Na, and CTP scores. However, this score was less sensitive for early diagnosis of ACLF in patients with alcoholic and hepatitis B virus-related cirrhosis. In a 2021 study by Li *et al*.,[64] a new simplified score, COSSH-ACLF II, was developed, including INR, hepatic encephalopathy, neutrophils, total bilirubin levels, serum urea, and age. This scoring system demonstrated significantly higher C-indexes for 28-day and 90-day mortality (0.826 and 0.809, respectively) compared to CLIF-C ACLF, MELD, and MELD-Na. Data on the role of MELD 3.0 in the ACLF population remain limited, and its impact is unclear, necessitating further studies to determine the optimal time point concerning predictive efficacy.[65]

Following extensive research, MELD-related scores have been effectively employed in clinical practice to guide the rational allocation of liver donations, significantly contributing to the preservation of numerous lives of patients with acute or end-stage liver diseases. However, due to variations in etiology, precipitating factors, and ethnicity, it remains uncertain whether MELD 3.0 is universally applicable across all categories of liver disease. In summary, further investigation into MELD 3.0 is anticipated to confirm its effects in future studies.

In 2023, the Gender Equity Model for Liver Allocation Sodium was developed in the UK and underwent external vali-

dation in an Australian cohort, where it demonstrated superior performance in predicting 90-day mortality upon waitlist inclusion compared to MELD-Na.[66] However, no significant differences were found between the Gender Equity Model for Liver Allocation Sodium, MELD-Na, and MELD 3.0 in an Italian cohort, indicating the need for further validation from other regions to clarify the discriminatory ability of these models.[67]

The original MELD score encompassed three quantitative values: serum bilirubin, INR, and creatinine, later revised into the MELD-Na score with the addition of serum sodium. Numerous variations of the original MELD score have since been proposed. ΔMELD was derived by calculating the difference in MELD scores within 30 days, MELD-LA incorporated serum lactate, and iMELD added age and sodium. Removing INR resulted in MELD XI, while excluding creatinine and including albumin yielded PELD. The latest iteration, MELD 3.0, further incorporates serum sodium, albumin, and gender, and adjusts the upper limit of serum creatinine to 3.0 mg/dL, enhancing accuracy in estimating disease severity in patients with liver diseases. MELD 3.0, which fully accounts for gender differences and optimizes organ allocation systems for liver transplantation,[43] has been adopted as a new standard in the U.S. Nevertheless, MELD 3.0 may not be as precise as other scoring systems for predicting prognosis in specific liver disease etiologies (such as AH)[44] and ACLF.[65] Additionally, its predictive capacity could be influenced by ethnic disparities, differences concerning liver disease etiology across countries, and variations in the liver transplant practice. Eliminating the upper limit of MELD 3.0, currently set at 40 points, could increase survival benefits for candidates but might also lead to overestimation of severely ill patients, affecting the fairness of organ allocation.[50] Therefore, further research is needed to verify the validity and reliability of the MELD 3.0 score.

Future prospects

With advancements in technology, novel strategies and approaches are emerging that surpass conventional MELD scoring methods. The establishment and refinement of electronic health record systems[68] can facilitate access to precise, real-time shared data, providing a solid foundation for developing and evaluating comprehensive prediction models pertinent to mortality risk associated with LT. It is anticipated that artificial intelligence, natural language processing,[69] and clinical decision support[2] will leverage robust algorithmic models, potentially enhancing predictive capabilities for prognosis.

Conclusions

In conclusion, our findings indicate superior predictive performance of MELD 3.0, warranting further in-depth investigations to broaden its clinical implications.

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Conflict of interest

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Author contributions

Writing - original draft (GG), literature search (WY), visualization and data analysis (JL), visualization (ZY), writing - review and editing (JL), design and supervision (CS). All authors were involved in the writing and revision of the manuscript. All authors have made significant contributions to this study and have approved the final version and publication of the manuscript.

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