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Review

Mortality scoring systems for liver transplant recipients: before and after model for end-stage liver disease score

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The mortality scoring systems for patients with end-stage liver disease have evolved from the Child-Turcotte-Pugh score to the model for end-stage liver disease (MELD) score, affecting the wait list for liver allocation. There are inherent weaknesses in the MELD score, with the gradual decline in its accuracy owing to changes in patient demographics or treatment options. Continuous refinement of the MELD score is in progress; however, both advantages and disadvantages exist. Recently, attempts have been made to introduce artificial intelligence into mortality prediction; however, many challenges must still be overcome. More research is needed to improve the accuracy of mortality prediction in liver transplant recipients.

Keywords: Acute-on-chronic liver failure; End stage liver disease; Liver cirrhosis; Liver transplantation; Mortality; Organ dysfunction scores; Prognosis.

KSTA

INTRODUCTION

Since Dr. Thomas Starzl performed the first human liver transplantation (LT) in 1963, LT has been considered the only definitive treatment for decompensated end-stage liver disease (ESLD) [1]. Several scoring systems have been proposed to predict mortality in patients with ESLD [2,3], and these scoring systems have also been used as a basis for allocating livers of brain death for LT [4]. Previously, the Child-Turcotte-Pugh (CTP) classification was used as the basis for the United Network for Organ Sharing (UNOS) organ allocation system. However, some disadvantages of CTP classification exist, such as the existence of several subjective parameters, and the final result is determined by three classes (A, B, and C) [5]. Since 2002, the Model for End-stage Liver Disease (MELD) score, which consists of all objective indicators, has replaced the CTP classification for the basis of the liver allocation system in the UNOS [5]. The Korean Network for Organ Sharing changed the basis of the liver allocation system from CTP classification to MELD in 2016 [6].

The MELD score was initially developed to predict the short-term mortality of patients undergoing the transjugular intrahepatic portosystemic shunt (TIPS) procedure for liver cirrhosis (LC) in 2000 [3]. Recently, the demographics of patients, indications for LT, and treatment options for ESLD have changed a lot [4,7]. Many studies have reported that the MELD score does not accurately reflect mortality risk in specific clinical situations, such as acute-on-chronic liver failure (ACLF) [8], hepatocellular carcinoma (HCC) [7], and sex disparity [9,10].

The prediction of mortality in patients with ESLD is closely related to donor organ allocation [4,6], and a more accurate prediction of mortality can greatly influence the perioperative management of LT recipients. In this article, we re-

view notable scoring systems, past and present, related to the prognosis of ESLD.

CHILD-TURCOTTE-PUGH CLASSIFICATION

In 1964, Child and Turcotte introduced a classification that predicts the prognosis of patients undergoing portocaval shunt surgery for LC, and they suggested that their classification represents a "hepatic functional reserve" [2,5,11]. They selected five factors (serum albumin, bilirubin, ascites, encephalopathy, and nutritional status) based on their clinical experience and not on clinical trials or analysis. Finally, the classification defines each element into one of three classes (A, B, and C, Table 1) [2,5]. There was some criticism that three of the five elements (ascites, nutrition, and encephalopathy) were highly subjective, and the detailed explanation of how to integrate the five elements was ambiguous [11].

In 1972, Pugh replaced the "nutritional status," which was considered the most subjective element with "prothrombin time," adjusted limits for serum albumin, and defined the encephalopathy grading more clearly [12,13]. Pugh also calculated scores by assigning 1, 2, or 3 points to each of the five components, with a total score of 5–6 corresponding to class A, 7–9 to class B, and 10–15 to class C (Table 1) [12,13]. Pugh's modification has been widely used for CTP classification [5,13].

Despite Pugh's modification, subjective indicators (encephalopathy and ascites) remain; therefore, the attending physician can roughly grade the severity of liver disease [5]. This is often expressed by using "the gestalt method" [5,11,12]. Moreover, there are only three classes in the CTP classification, and when a certain threshold is reached, the class is fixed regardless of changes in clinical conditions [5].

MODEL FOR END-STAGE LIVER DISEASE SCORE

In 2000, Malinchoc et al. [3] published a "Mayo End-stage Liver Disease" model to predict the prognosis of patients undergoing TIPS procedures. They used prospectively obtained patient data and calculated scores through statistical analysis [5,14]. The score was based on serum bilirubin levels, prothrombin time (international normalized ratio [INR]), and serum creatinine levels. The name of this model was later changed to "Model for End-stage Liver Disease" [5,15]. Kamath et al. [15] validated this early MELD score and reported that the 3-month death rate in patients hospitalized for hepatic decompression is as follows: 4% for MELD ≤ 9, 27% for MELD 10–19, 76% for MELD 20–29, 83% for MELD 30–39, and 100% for MELD ≥ 40.

In 2002, UNOS changed the liver allocation system from a state-based algorithm to an algorithm that uses a continuous, objective MELD/pediatric end-stage liver disease (PELD) score to prioritize patients needing LT [5,16,17].

The formula for the original MELD score was as follows (Table 2) [15]:

$$MELD = 3.8 \times \log_e(\text{bilirubin [mg/dl]}) + 11.2 \times \log_e(\text{INR}) + 9.6 \times \log_e(\text{creatinine [mg/dl]}) + 6.4 \times (\text{etiology: 0 if cholestatic or alcoholic, and 1 otherwise})$$

LIMITATIONS OF THE MELD SCORE

Innate limitations of the MELD score

Serum creatinine is not a good indicator for assessing renal dysfunction because it is influenced by extra-renal factors, such as muscle mass, sex, age, and ethnicity [14]. Severe muscle wasting in patients with ESLD can reduce serum

Table 1. Original and Modified Child-Turcotte-Pugh Classification

Components	Original Child-Turcotte classification			Child-Turcotte-Pugh classification		
	A	B	C	1	2	3
Bilirubin (mg/dl)	< 2	2–3	> 3	1–2	2–3	> 3
Albumin (g/dl)	> 3.5	3–3.5	< 3	> 3.5	2.8–3.5	< 2.8
Ascites	None	Easily- controlled	Poorly- controlled	Absent	Slight	Moderate
Neurological disorder	None	Minimal	Advanced "coma"	None	None	None
Encephalopathy (grade)	None	None	None	None	1, 2	3,4
Nutrition	Excellent	Good	Poor, "wasting"	None	None	None
Prothrombin time (seconds prolonged)	None	None	None	1–4	4–6	> 6

How to integrate the five elements is unclear in original classification. In Child-Turcotte-Pugh classification: Class A (5-6 points, total scores), Class B (7–9 points), Class C (10–15 points).

Table 2. Equations of MELD/PELD and Updated Versions

Score	Equations	Featuring
Original MELD [15]	3.8 × $\log_e$ (bilirubin [mg/dl]) + 11.2 × $\log_e$ (INR) + 9.6 × $\log_e$ (creatinine [mg/dl]) + 6.4 × (etiology: 0 if cholestatic or alcoholic, 1 otherwise)	- Etiology disappeared in later versions
MELD-Na [30]	MELD + 1.32 × (137-Na) – [0.033 × MELD × (137-Na)]	- Sodium concentrations are mEq/L, values less than 125 are set to 125, and values greater than 137 are set to 137
MELD 3.0 [19]	1.33 (if female) + [4.56 × $\log_e$ (bilirubin)] + [0.82 × (137 – Na)] – [0.24 × (137 – Na) × $\log_e$ (bilirubin)] + [9.09 × $\log_e$ (INR)] + [11.14 × $\log_e$ (creatinine)] + [1.85 × (3.5 – albumin)] – [1.83 × (3.5 – albumin) × $\log_e$ (creatinine)] + 6	- Give additional points to women - Updated interactions between parameters
PELD [31]	(0.436 × age) – [0.687 × log (albumin)] + [0.480 × log (bilirubin)] + [1.857 × log (INR)] + (0.667 × growth failure)	- Age: age < 1 year = 1, all other ages = 0 - Growth failure: values > 2 standard deviations from the norm = 1, all others = 0

MELD: model for end-stage liver disease, PELD: pediatric end-stage liver disease, INR: international normalized ratio.

creatinine levels. In this case, even if the serum creatinine level is normal, it cannot be concluded that the renal function is normal [9,14]. In the MELD-based allocation system, it has been frequently pointed out that women are less likely to receive LT than men, and that the mortality rate while waiting for LT is significantly higher in women than in men [9,10]. Several studies have suggested that glomerular filtration in women may be underestimated owing to their reduced muscle mass compared to that in men [9,14]. To overcome this, modified MELD with cystatin-C instead of creatinine [18] and MELD 3.0, with sex as an additional factor, was also announced [19]. Probable bias based on the inter-laboratory variability of measurement methods for serum creatinine, bilirubin, and INR has also been pointed out [14].

Specific conditions that reduce the predictive power of the MELD score

The MELD score is known to be less accurate in predicting mortality, especially in some clinical situations such as ACLF, HCC, and other serious complications of LC [4,14].

Patients with HCC often have a low MELD score because they have a well-preserved liver function. However, as with other cancers, the survival of patients with HCC is often related not only to liver function but also to cancer metastasis, and early LT enables complete resection of cancer cells [14,20]. In 1996, Mazzaferro et al. [21] reported a low cancer recurrence rate after LT in patients with small, unresectable HCC (single tumor ≤ 5 cm in diameter or no more than three tumors, each of which was no more than 3 cm in diameter), which later developed into the Milan criteria used when considering LT in patients with HCC [20]. Currently, UNOS provides additional points to patients with HCC with MELD exception regulations [22].

Huo et al. [23] reported that the mortality rate increases as complications related to LC (esophageal varix bleeding, hepatic encephalopathy [HE], hepatorenal syndrome, and spontaneous bacterial peritonitis) increase; however, this is not well reflected in the MELD score. They suggested that patients with such repeated complications may be disadvantaged by the MELD-based liver allocation system. A follow-up study by Yoo et al. [24] also reported that the MELD score did not reflect the severity of HE or ascites.

Effect of demographic and epidemiologic changes in liver disease on the accuracy of the MELD score

Since the use of the MELD score in organ allocation, the demographics, epidemiology of the liver disease, and indications for LT have changed dramatically [25,26]. The widespread use of antiviral therapy against HCV has reduced the morbidity of chronic hepatitis C. In contrast, non-alcoholic fatty liver diseases are rapidly increasing, becoming a major indication for LT along with alcoholic liver disease in the USA [7,26]. Godfrey et al. [7] reported that the predictive power of MELD decreased with these demographic and epidemiologic changes. The concordance-statistic (C-statistic) of the MELD decreased from 0.80 in 2003 to 0.70 in 2015.

UPDATED VERSIONS OF THE MELD SCORE

Attempts to overcome the weaknesses of the MELD score are ongoing. Many "new" MELD scores, such as MELD-Na,

iMELD, UKLE, MELD-AS, MELD-Plus, MELD-Cystatin C, and MELD 3.0, have been introduced as supplementary versions [4,14]. Among them, the most widely used MELD-Na and the most recently updated MELD 3.0, will be briefly described in this review.

MELD-Na

Serum sodium concentration is also known to be an important independent prognostic factor in patients with LC. For example, hyponatremia is strongly associated with hepatorenal syndrome, ascites, and liver-related death [27]. Several studies have reported that the incorporation of serum sodium concentration into MELD is beneficial for more accurate mortality prediction [27-29]. Accordingly, in 2016, the Organ Procurement and Transplantation Network/UNOS policy updated its MELD calculator to include serum sodium concentration [30]. The formula for MELD-Na used in the UNOS MELD calculator is shown (Table 2).

MELD-Na = MELD + 1.32 × (137-Na) – [0.033 × MELD × (137-Na)]

(Sodium concentrations are mEq/L, values less than 125 are set to 125, and values greater than 137 are set to 137).

MELD 3.0

Kim et al. [19] reclassified MELD to improve predictive accuracy through statistical analysis in 2021. Their final model was characterized by 1) adding sex and serum albumin, 2) considering interactions between serum albumin-sodium and albumin-creatinine, and 3) adjusting the upper bound for serum creatinine to 3.0 mg/dL. This was renamed MELD 3.0. They provided additional points to women on the basis that the MELD score of women tended to be underestimated [10]. Additionally, a significant correlation was found between bilirubin and sodium levels and between creatinine and albumin levels, which was corrected. The predictive ability for the risk of death within 90 days was slightly higher in MELD 3.0 than that in MELD-Na. The C-statistics of MELD-Na and MELD 3.0, were 0.862 and 0.869 ($P < 0.01$), respectively [19].

The formula for MELD 3.0 is as follows (Table 2):

MELD 3.0 = 1.33 (if female) + [4.56 × $\log_e$ (bilirubin)] + [0.82 × (137 – Na)] – [0.24 × (137 – Na) × $\log_e$ (bilirubin)] + [9.09 × $\log_e$ (INR)] + [11.14 × $\log_e$ (creatinine)] + [1.85 × (3.5 – albumin)] – [1.83 × (3.5 – albumin) × $\log_e$ (creatinine)] + 6

PEDIATRIC END-STAGE LIVER DISEASE SCORE

Similar to the development of MELD, the pediatric LT research group developed a scoring system tailored to the unique characteristics of children with chronic liver disease [31]. The PELD score was developed through statistical analysis based on the database of the "Studies of Pediatric Liver Transplantation (SPLIT)," a consortium that began recruiting children's data from LT centers in the USA and Canada in 1995 [32]. The PELD score uses factors different from the MELD score to identify the unique growth and developmental aspects of children. Bilirubin, INR, albumin, growth failure, and age were used as the PELD score [16,31]. The PELD score has been used to allocate donor livers for children younger than 12 years in UNOS since 2002 [33]. Chang et al. [33] reported that PELD tends to underestimate the 90-day mortality compared with MELD. They suggested that children with chronic liver disease who need LT may be disadvantaged compared to adults with similar clinical conditions.

The formula for the PELD score is as follows (Table 2) [16,31]:

PELD = (0.436 × age) – [0.687 × log (albumin)] + [0.480 × log (bilirubin)] + [1.857 × log (INR)] + (0.667 × growth failure).

Age: age < 1 year = 1, all other ages = 0.

Growth failure: values > 2 standard deviations from the norm = 1, all others = 0.

ACUTE-ON-CHRONIC-LIVER-FAILURE

ACLF is different from acute liver failure (ALF) or the progression of chronic decompensated LC [34]. ALF is defined as severe acute liver injury accompanied by coagulopathy (INR ≥ 1.5) and any degree of HE in patients without preexisting liver disease [35]. ACLF is a separate syndrome characterized by acute decompensation of chronic liver disease combined with the failure of other organs [36,37]. It has a higher short-term mortality than that predicted by the severity of the underlying chronic liver disease. It is often related to trigger events, such as exacerbation of hepatitis, bacterial infections, and active alcoholism. However, there are many cases without a definite trigger [36,38]. The systemic inflam-

matory response seems to be a critical factor in the development of ACLF [36]. The condition of the patient could be "reversible" through early intensive management of these reversible factors [38]. Patients with ACLF have a higher mortality rate than those without ACLF at the same MELD score [38,39]. Current management of ACLF is mainly based on support for organ failure; however, performing LT in advance at a critical time can improve prognosis [36,40]. Many studies on the pathophysiology, prognosis, and treatment of ACLF are in progress.

Since no common diagnostic criteria for ACLF have yet been established, several diagnostic criteria are being used interchangeably. In this review, we introduce the ACLF definition and scoring system of the European Association for the Study of the Liver (EASL), which is the most commonly used [36,37].

EASL Chronic Liver Failure Consortium (EASL-CLIF-C)

In 2013, the EASL conducted a large prospective observational study with 1343 hospitalized patients undergoing LC and acute decompensation in 29 European university hospitals to define ACLF (EASL-CLIF Acute-on-Chronic Liver Failure in Cirrhosis, CANONIC study) [37]. They modified the Sequential Organ Failure Assessment (SOFA) score into CLIF-SOFA to define organ failure in ACLF [37]. The definition of the diagnostic criteria was based on three main components (acute decompensation, organ failure, and high 28-day mortality rate) (Table 3). However, it was pointed out that the CLIF-SOFA was complex to use and did not significantly improve the prediction accuracy of MELD or MELD-Na [41]. To compensate for this, the EASL in 2014, announced the CLIF-C organ failure score (CLIF-C OFs), which simplified CLIF-SOFA [41]. The components of CLIF-C OFs are bilirubin, creatinine, the grade for HE (West-Haven), INR, mean arterial pressure, and respiratory component (PaO_2/FiO_2 or SpO_2/FiO_2) [41]. They also developed the CLIF-C ACLF score by combining the patient's age and white blood cell count (WBC) with CLIF-C OFs to predict the short-term and long-term mortality of ACLF [41]. The equation of the CLIF-C ACLF score ranges from 0 to 100 and is as follows [36,41]:

$$\text{CLIF-C ACLF score} = 10 \times [0.33 \times \text{CLIF-C OFs} + 0.04 \times \text{age} + 0.63 \times \ln(\text{WBC count}) - 2]$$

The CLIF-C ACLF score can be easily calculated using a website (http://www.efclif/com) [36]. It has been reported that the ability of the CLIF-C ACLF score to predict mortality

Table 3. Diagnostic Criteria and Grades of ACLF (EASL-CLIF-C)

Grade	Subgroups	Mortality
No ACLF	1) Pt with no OF	28-day: 4.7%
	2) Pt with a single "non-kidney" OF (a single failure of the liver, coagulation, circulation, or respiration) (sCr < 1.5 mg/dl and no HE)	90-day: 14%
	3) Pt with single cerebral failure (sCr < 1.5 mg/dl)	
ACLF grade 1	1) Pt with single kidney failure	28-day: 22.1%
	2) Pt with single failure of the liver, coagulation, circulation, or respiration (sCr 1.5–1.9 mg/dl and/or mild to moderate HE)	90-day: 40.7%
	3) Pt with single cerebral failure (sCr 1.5–1.9 mg/dl)	
ACLF grade 2	Pt with 2 OFs	28-day: 32.0%
		90-day: 52.3%
ACLF grade 3	Pt with ≥ 3 OFs	28-day: 76.7%
		90-day: 79.1%

Definition of Organ Failure (CLIF-SOFA)

1. Liver failure: serum bilirubin ≥ 12.0 mg/dl
2. Kidney failure: serum creatinine ≥ 2.0 mg/dl or the use of renal replacement therapy
3. Cerebral failure: grade III or IV HE (West Haven)
4. Coagulation failure: INR ≥ 2.5 and/or a platelet count ≤ 20 × 10^9/L
5. Circulatory failure: use of dopamine, dobutamine, or terlipressin
6. Respiratory failure: PaO_2/FiO_2 ≤ 200 or SpO_2/FiO_2 ≤ 214

ACLF: acute on chronic liver failure, EASL: European Association for the Study of the Liver, CLIF-C: chronic liver failure consortium, Pt: patients, OF: organ failure, sCr: serum creatinine, HE: hepatic encephalopathy, CLIF-SOFA: Chronic Liver Failure-Sequential Organ Failure Assessment.

was significantly higher (approximately 25 to 28%) than that of the MELD, MELD-Na, and CTP scores in patients with ACLF [41].

As ACLF is a dynamic process, the severity of ACLF can rapidly change during hospitalization. Investigators of the CANONIC study reported that ACLF resolved or improved in 49.2%, steady or fluctuating in 30.4%, and worsened in 20.4% of the patients. Most patients (81%) reached their final ACLF grade within one week of diagnosis. If patients with more than four organ failures or CLIF-C ACLF score > 64 did not undergo LT, the mortality rate was 100% after 28 days. They suggested that the assessment of patients with ACLF at 3–7 days after diagnosis provides a more accurate prediction of mortality [40].

FUTURE PERSPECTIVES OF MORTALITY PREDICTION

With the recent developments in computer science, most patient information is stored through electronic health records (EHR). Many studies have been published to introduce machine learning or (in a broader sense) artificial intelligence (AI) methods using EHR in the field of LT [4,42,43]. Banerjee et al. [44] created a prediction model using an artificial neural network technique in 2003 and published a study that predicted 1-year mortality better than the CTP score. Recently, many studies have suggested that machine learning is superior to MELD score in predicting mortality [45,46] or graft failure [42]. However, in some cases, these technologies do not show significant improvements over the current methods [47,48]. Many researchers are attempting to use AI in a wide range of fields, including optimizing organ allocation, donor-recipient pairing, and even automated immunosuppressant regimens based on transplant pathology [43,47].

Although AI enables accurate prediction, the parameters used in these studies are significantly different, and it is unclear whether the accuracy of any model can be reproduced in cohorts with different characteristics [43]. The predictive ability of these models is ultimately related to the quality of the clinical dataset [48]. AI is still considered to have limitations in comprehensively considering other clinical factors to determine the complexity, possibility, and urgency of surgery [4,43,47]. Further research is needed for the use of AI in clinical practice.

CONCLUSION

Many studies have been published to supplement the weaknesses of the MELD score, which is widely used for predicting mortality in patients with LT and organ allocation. However, the disadvantages of this approach remain. With the development of computer technology such as AI, there have been attempts to use it for prognosis prediction and organ distribution in those with LT. However, these also seem insufficient for practical use. Accurate prognosis prediction is important, as it is used not only for patient treatment but also for more efficient organ allocation. In the future, more studies should be conducted to predict mortality in patients with LT more accurately.

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CONFLICTS OF INTEREST

Yang-Hoon Chung has been an editor of the *Anesthesia and Pain Medicine* since 2019. He is a reviewer for several international journals, including *Korean Journal of Anesthesiology*, and *Journal of Korean Medical Science*. However, he was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

AUTHOR CONTRIBUTIONS

Conceptualization: Yang-Hoon Chung, Jaewoong Jung, Sang Hyun Kim. Visualization: Jaewoong Jung. Writing - original draft: Yang-Hoon Chung. Writing - review & editing: Jaewoong Jung, Sang Hyun Kim. Supervision: Sang Hyun Kim.

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REFERENCES

1. Starzl TE, Marchioro TL, Vonkaulla KN, Hermann G, Brittain RS, Waddell WR. Homotransplantation of the liver in humans. Surg Gynecol Obstet 1963; 117: 659-76.
2. Child CG, Turcotte JG. Surgery and portal hypertension. In: The liver and portal hypertension. Edited by Child CG: Philadelphia (PA), Saunders. 1964, pp 50-64.
3. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology 2000; 31: 864-71.
4. Ge J, Kim WR, Lai JC, Kwong AJ. "Beyond MELD" - emerging strategies and technologies for improving mortality prediction, organ allocation and outcomes in liver transplantation. J Hepatol 2022; 76: 1318-29.
5. Forman LM, Lucey MR. Predicting the prognosis of chronic liver disease: an evolution from child to MELD. Mayo end-stage liver disease. Hepatology 2001; 33: 473-5.
6. Kim MS. Modification of emergency status in deceased donor liver allocation: evidence for Korean model of end-stage liver disease (MELD) system. J Korean Soc Transplant 2016; 30: 51-8.
7. Godfrey EL, Malik TH, Lai JC, Mindikoglu AL, Galván NTN, Cotton RT, et al. The decreasing predictive power of MELD in an era of changing etiology of liver disease. Am J Transplant 2019; 19: 3299-307.
8. Hernaez R, Liu Y, Kramer JR, Rana A, El-Serag HB, Kanwal F. Model for end-stage liver disease-sodium underestimates 90-day mortality risk in patients with acute-on-chronic liver failure. J Hepatol 2020; 73: 1425-33.
9. Myers RP, Shaheen AA, Aspinall AI, Quinn RR, Burak KW. Gender, renal function, and outcomes on the liver transplant waiting list: assessment of revised MELD including estimated glomerular filtration rate. J Hepatol 2011; 54: 462-70.
10. Allen AM, Heimbach JK, Larson JJ, Mara KC, Kim WR, Kamath PS, et al. Reduced access to liver transplantation in women: role of height, MELD exception scores, and renal function underestimation. Transplantation 2018; 102: 1710-6.
11. Conn HO. A peek at the Child-Turcotte classification. Hepatology 1981; 1: 673-6.
12. Garcia-Tsao G. The Child-Turcotte classification: from gestalt to sophisticated statistics and back. Dig Dis Sci 2016; 61: 3102-4.
13. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973; 60: 646-9.
14. Bernardi M, Gitto S, Biselli M. The MELD score in patients awaiting liver transplant: strengths and weaknesses. J Hepatol 2011; 54: 1297-306.
15. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001; 33: 464-70.
16. Freeman RB Jr, Wiesner RH, Roberts JP, McDiarmid S, Dykstra DM, Merion RM. Improving liver allocation: MELD and PELD. Am J Transplant 2004; 4 Suppl 9: 114-31.
17. Freeman RB Jr, Wiesner RH, Harper A, McDiarmid SV, Lake J, Edwards E, et al. The new liver allocation system: moving toward evidence-based transplantation policy. Liver Transpl 2002; 8: 851-8.
18. Finkenstedt A, Dorn L, Edlinger M, Prokop W, Risch L, Griesmacher A, et al. Cystatin C is a strong predictor of survival in patients with cirrhosis: is a cystatin C-based MELD better? Liver Int 2012; 32: 1211-6.
19. Kim WR, Mannalithara A, Heimbach JK, Kamath PS, Asrani SK, Biggins SW, et al. MELD 3.0: the model for end-stage liver disease updated for the modern era. Gastroenterology 2021; 161: 1887-95.e4.
20. Duffy JP, Vardanian A, Benjamin E, Watson M, Farmer DG, Ghobrial RM, et al. Liver transplantation criteria for hepatocellular carcinoma should be expanded: a 22-year experience with 467 patients at UCLA. Ann Surg 2007; 246: 502-9; discussion 509-11.
21. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996; 334: 693-9.
22. Parikh ND, Singal AG. Model for end-stage liver disease exception points for treatment-responsive hepatocellular carcinoma. Clin Liver Dis (Hoboken) 2016; 7: 97-100.
23. Huo TI, Lin HC, Lee FY, Hou MC, Lee PC, Wu JC, et al. Occurrence of cirrhosis-related complications is a time-dependent prognostic predictor independent of baseline model for end-stage liver disease score. Liver Int 2006; 26: 55-61.
24. Yoo HY, Edwin D, Thuluvath PJ. Relationship of the model for end-stage liver disease (MELD) scale to hepatic encephalopathy, as defined by electroencephalography and neuropsychometric testing, and ascites. Am J Gastroenterol 2003; 98: 1395-9.
25. Younossi ZM, Stepanova M, Younossi Y, Golabi P, Mishra A, Rafiq N, et al. Epidemiology of chronic liver diseases in the USA in the past three decades. Gut 2020; 69: 564-8.
26. Kwong AJ, Kim WR, Lake JR, Smith JM, Schladt DP, Skeans MA, et al. OPTN/SRTR 2019 annual data report: liver. Am J Transplant 2021; 21 Suppl 2: 208-315.
27. Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. N Engl J Med 2008; 359:

1018-26.
28. Biggins SW, Kim WR, Terrault NA, Saab S, Balan V, Schiano T, et al. Evidence-based incorporation of serum sodium concentration into MELD. Gastroenterology 2006; 130: 1652-60.
29. Leise MD, Kim WR, Kremers WK, Larson JJ, Benson JT, Therneau TM. A revised model for end-stage liver disease optimizes prediction of mortality among patients awaiting liver transplantation. Gastroenterology 2011; 140: 1952-60.
30. Biggins SW. Use of serum sodium for liver transplant graft allocation: a decade in the making, now is it ready for primetime? Liver Transpl 2015; 21: 279-81.
31. McDiarmid SV, Anand R, Lindblad AS; Principal Investigators and Institutions of the Studies of Pediatric Liver Transplantation (SPLIT) Research Group. Development of a pediatric end-stage liver disease score to predict poor outcome in children awaiting liver transplantation. Transplantation 2002; 74: 173-81.
32. SPLIT Research Group. Studies of pediatric liver transplantation (SPLIT): year 2000 outcomes. Transplantation 2001; 72: 463-76.
33. Chang CH, Bryce CL, Shneider BL, Yabes JG, Ren Y, Zenarosa GL, et al. Accuracy of the pediatric end-stage liver disease score in estimating pretransplant mortality among pediatric liver transplant candidates. JAMA Pediatr 2018; 172: 1070-7.
34. Sarin SK, Choudhury A, Sharma MK, Maiwall R, Al Mahtab M, Rahman S, et al; APASL ACLF Research Consortium (AARC) for APASL ACLF working Party. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the Study of the Liver (APASL): an update. Hepatol Int 2019 13: 353-90. Erratum in: Hepatol Int 2019; 13: 826-8.
35. Lee WM, Squires RH Jr, Nyberg SL, Doo E, Hoofnagle JH. Acute liver failure: summary of a workshop. Hepatology 2008; 47: 1401-15.
36. Hernaez R, Solà E, Moreau R, Ginès P. Acute-on-chronic liver failure: an update. Gut 2017; 66: 541-53.
37. Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. CANONIC Study Investigators of the EASL–CLIF Consortium. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology 2013; 144: 1426-37, 1437.e1-9.
38. Olson JC, Kamath PS. Acute-on-chronic liver failure: concept, natural history, and prognosis. Curr Opin Crit Care 2011; 17: 165-9.
39. Sundaram V, Shah P, Wong RJ, Karvellas CJ, Fortune BE, Mahmud N, et al. Patients with acute on chronic liver failure grade 3 have greater 14-day waitlist mortality than status-1a patients. Hepatology 2019; 70: 334-45.
40. Gustot T, Fernandez J, Garcia E, Morando F, Caraceni P, Alessandria C, et al. CANONIC Study Investigators of the EASL-CLIF Consortium. Clinical course of acute-on-chronic liver failure syndrome and effects on prognosis. Hepatology 2015; 62: 243-52.
41. Jalan R, Saliba F, Pavesi M, Amoros A, Moreau R, Ginès P, et al. CANONIC Study Investigators of the EASL-CLIF Consortium. Development and validation of a prognostic score to predict mortality in patients with acute-on-chronic liver failure. J Hepatol 2014; 61: 1038-47.
42. Lau L, Kankanige Y, Rubinstein B, Jones R, Christophi C, Muralidharan V, et al. Machine-learning algorithms predict graft failure after liver transplantation. Transplantation 2017; 101: e125-32.
43. Ferrarese A, Sartori G, Orrù G, Frigo AC, Pelizzaro F, Burra P, et al. Machine learning in liver transplantation: a tool for some unsolved questions? Transpl Int 2021; 34: 398-411.
44. Banerjee R, Das A, Ghoshal UC, Sinha M. Predicting mortality in patients with cirrhosis of liver with application of neural network technology. J Gastroenterol Hepato 2003; 18: 1054–60.
45. Cucchetti A, Vivarelli M, Heaton ND, Phillips S, Piscaglia F, Bolondi L, et al. Artificial neural network is superior to MELD in predicting mortality of patients with end-stage liver disease. Gut 2007; 56: 253-8.
46. Guo A, Mazumder NR, Ladner DP, Foraker RE. Predicting mortality among patients with liver cirrhosis in electronic health records with machine learning. PLoS One 2021; 16: e0256428.
47. Peloso A, Moeckli B, Delaune V, Oldani G, Andres A, Compagnon P. Artificial intelligence: present and future potential for solid organ transplantation. Transpl Int 2022; 35: 10640.
48. Miller PE, Pawar S, Vaccaro B, McCullough M, Rao P, Ghosh R, et al. Predictive abilities of machine learning techniques may be limited by dataset characteristics: insights from the UNOS database. J Card Fail 2019; 25: 479-83.