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MANAGEMENT OF CIRRHOTIC PATIENT (A CARDENAS AND P TANDON, SECTION EDITORS)

Predicting Future Complications of Cirrhosis

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Abstract

Purpose of Review Decompensated cirrhosis and liver failure result in high mortality risk. Identifying the severity of illness and risk of poor outcomes is important for improved clinical decision making. This review serves to examine the currently in practice and developing tools for prognosticating patients with cirrhosis.

Recent Findings The Child–Turcotte–Pugh (CTP) score and Model for End-Stage Liver Disease (MELD) score are the most used prognostic tools for cirrhotic patients. More recently, however, are newly developing biochemical models and imaging tools that strive to improve upon the MELD score.

Summary Significant effort has been dedicated to revising, complementing, or replacing the MELD score for prognostication and for transplant allocation. Ongoing adjustment to current prognostication methods and the search for new paradigms promises improved ability to predict outcomes and determine the best management in the future.

Keywords Cirrhosis · Prognostic factors · Chronic liver disease · Liver transplant · Model for end-stage liver disease (MELD)

Introduction

Once patients with cirrhosis experience decompensation, early mortality risk increases sharply [1•]. Using clinical and biochemical tools to determine risk allows the identification and timely management to improve outcomes. The foremost example of this for chronic liver disease is liver transplantation, which drastically improves long-term survival. Furthermore, in accordance with the Department of Health and Human Services "Final Rule" in 2000, the US (and most countries') liver transplant allocation system is urgency-based to allow the highest risk and sickest patients' first access to life-saving organs. It is thus vitally important to accurately risk stratify patients with cirrhosis. The Child–Turcotte–Pugh (CTP) score and Model for End-Stage Liver Disease (MELD) score are the best-known prognostic tools for cirrhotic patients, though not only do several other paradigms exist but there are also continued efforts to revise existing or create new tools. Even MELD, which is the backbone for US liver transplant allocation, has been the target of revision. This review will discuss existing models as well as developing paradigms for risk stratification of patients with cirrhosis (Table 1).

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Commonly Used Prognostic Paradigms

Child–Turcotte–Pugh

Dr. Charles Gardner Child, a surgeon and portal hypertension expert, first proposed the Child–Turcotte (CT) scoring system in 1964 [2]. It included five variables: ascites, encephalopathy, nutritional status, serum bilirubin level, and serum albumin level and classified patients in class A, B, or C with increasingly poor prognosis. It was modified by Pugh et al. in 1972 in a report on surgical treatment for variceal bleeding to create the CTP score [3]. Nutritional status was replaced with prothrombin time (PT) and assigned a score ranging from 1 to 3 to each variable. CTP is frequently used clinically to appreciate the degree of hepatic dysfunction in patients with cirrhosis and to prognosticate peri-operative outcomes. When the US liver transplant community began searching for a prognostic score

Table 1 Summary of multiple prognostic tests for chronic liver disease

Metric	Variables/staging	Strengths	Weaknesses
Child–Turcotte–Pugh score	Ascites encephalopathy prothrombin time serum bilirubin serum albumin	1. Assesses morbidity and mortality after surgery with those with liver disease	1. Variability in measuring degree of ascites and encephalopathy 2. Medications can significantly alter classification 3. Does not assess response to medical management 4. Arbitrary constraints of variables
Model for end-stage liver disease (MELD)	Serum bilirubin serum creatinine INR serum sodium	1. Uses objective parameters not subject to inter-observer variability 2. More continuous and dynamic discrimination 3. Standard lab work to attain variables 4. Less influenced by medical treatments	1. Affected by non-hepatic factors 2. Does not include some known prognostic variables 3. Gender bias—females with lower creatinine compared to ales but equivalent renal function
Hepatic venous pressure gradient	Hepatic vein free pressure and hepatic vein wedged pressure	1. Considered gold standard for measuring portal circulation 2. Ability to stratify cirrhosis stage with defined outcome, prognosis and management strategy	1. Invasive 2. Operator dependent
D'Amico stages	Stage 1: compensated cirrhosis without varices Stage 2: compensated cirrhosis with varices Stage 3: bleeding without other disease complications Stage 4: first non-bleeding decompensating event Stage 5: any second decompensating event	1. Identify prognostic clinical stages of cirrhosis and expected complications specific to stage 2. MELDs < 20, can improve risk stratification of transplant candidates based on stage	1. Stages only validated in alcohol, virus related, and cryptogenic cirrhosis, not in HCC 2. Insensitivity to improvement in liver disease (i.e., treatment for HCV)
Chronic Liver Failure-Sequential Organ Failure Assessment	Respiratory (PaO2/FiO2) coagulation (platelet #) liver (bilirubin) cardiovascular (MAP or pressor) nervous (GCS) renal (Cr or urine output)	1. Independent short-term mortality predictor 2. Accuracy and discriminatory power was superior to SOFA 3. Outperformed CTP, MELD, SOFA, and APACHE II in acute liver failure	1. Numerous variables to collect 2. Subjectivity determining GCS in hepatic encephalopathy
Acute Physiology and Chronic Health Evaluation III	Physiology (0–252), chronic health (0–23), age (0–24)	1. Comprehensive 0–299 objective scoring system to provide probability estimates for critically ill ICU patients	1. Can only be used in homogeneous disease categories and for severity stratification, not risk prediction 2. In rare conditions or unusual presentations for common conditions, risk may not be accurately estimated 3. Estimates based on ICU selection criteria not after ICU treatment
Acute on Chronic Liver Failure	Grades I–III	1. Weighs other organ system failure into classification system for liver disease	1. Definition of acute on chronic liver failure continues to evolve amongst governing bodies
Protein C	Serum protein C concentration	1. Non-invasive 2. Ability to predict 3-month mortality in cirrhotic patients	1. Anticoagulation therapy can alter levels 2. Difficulty with bioassays to measure readily and routinely
Cysteine C	Serum cystatin C concentration	1. May predict renal function more accurately than Cr 2. Addition of CysC to MELD predicted AKI and mortality vs MELD and CTP scores alone	1. Assay not readily available
99mTc-phytate	99mTc-phytate uptake, graded I–V	1. Useful to measure extrahepatic uptake 2. Good correlation to CTP score survival	1. Cost associated with scintigraphy 2. Increased radiation to patient 3. Subjective nature of scoring system

Table 1 (continued)

Metric	Variables/staging	Strengths	Weaknesses
Neutrophil to lymphocyte	Ratio = (neutrophil/lymphocyte)	1. Independent predictor of mortality for stable liver cirrhosis and patients with liver failure listed for transplant 2. High neutrophil count and lower lymphocyte count predictors of waitlist death	1. Not accurate in infection 2. Not accurate in leukemia
Indocyanine green	Indocyanine green disappearance rate, (%/min)	1. Non-invasive QLFT 2. Sensitivity 85% and specificity 90% in predicting outcomes from cirrhosis 3. Can be combined with MELD for MELD-ICG scoring system and found to be more accurate with prognosis than MELDNa	1. Not accurate for predicting short-term prognosis in patients with MELD > 35
Cholate test	Portal circulation clearance Systemic circulation clearance Systemic shunt	1. Non-invasive QLFT 2. Can be used to calculate the disease severity index which has been modeled for direct clinical outcome 3. May offer safety advantage over liver biopsy for fibrosis staging	1. No FDA approval 2. Not yet determined if practical or ready for routine use
Sarcopenia	Cross-sectional area of psoas at L3 vertebrae	1. Associated with mortality in patients with cirrhosis 2. May identify patients who benefit from nutritional interventions	1. Depends on cross-sectional imaging and method of measuring
Frailty	Time—6-min walking test	1. Predicts waitlist mortality and transplant outcomes	1. Requires sufficient time to conduct, which may be preclusive in busy clinical settings

INR, international normalized ratio; *HCC*, hepatocellular carcinoma; *HCV*, hepatitis C virus; *PaO2*, partial pressure of oxygen in arterial blood; *FiO2*, fraction of inspired oxygen; *MAP*, mean arterial pressure; *GCS*, Glasgow coma scale; *Cr*, creatinine; *SOFA*, sequential organ failure assessment; *CTP*, Child–Turcotte–Pugh; *MELD*, model for end-stage liver disease; *MELDNa*, model for end-stage liver disease with sodium incorporation; *APACHE*, acute physiology and chronic health evaluation; *ICU*, intensive care unit; *CysC*, cysteine C; *AKI*, acute kidney injury; *Tc*, technetium; *QLFT*, quantitative liver function test; *ICG*, indocyanine green; *Na*, sodium; *FDA* , Food and Drug Administration

to transition liver transplant from a predominantly waiting time-dependent allocation system to an urgency-based system, it first trialed using CTP [4].

There are, however, limitations to the CTP score. It is subject to inter-observer variability as both the degree of ascites and encephalopathy are subjective assessments determined by physical examination alone. The use of imaging has led to a more consistent diagnosis of ascites, but it is unclear how ascites detected by imaging alone should be categorized. Hepatic encephalopathy (HE) can be assessed by psychometric testing or slowing of frequency on an electroencephalography (EEG), but access to these tests is limited. Additionally, both ascites and HE are influenced by medications such as diuretics, albumin infusion, and lactulose, and the CTP score does not discriminate between improvement in hepatic function and the impact of medical management.

The remaining variables in the CTP scoring system are categorized with arbitrarily defined limitations that may or may not reflect the true severity of their disease and result in poor discriminatory power. For example, in severe cases of bilirubin elevation, the CTP score assigns the same value for a bilirubin of 3.1 mg/dL as it does for 31 mg/dL despite likely different prognoses [5]. Similarly, the CTP classification for serum albumin does not differentiate between patients with serum albumin levels below 2.8 g/dL. The use of intravenous albumin may confound the value and interpretation of the scoring system. Furthermore, PT varies between laboratories depending on the sensitivity of the thromboplastin reagent used. The International Normalized Ratio (INR) mitigates this by using a standardized thromboplastin reagent. However, INR was intended to standardize the anticoagulation effect of warfarin and is not rigorously validated in coagulopathy related to liver disease [6]. CTP also excludes renal function, a well-established prognostic marker in advanced cirrhosis. While still clinically useful in the cirrhotic population, the CTP score's weaknesses disqualified it for liver transplant allocation [7].

MELD

The MELD scoring system was developed to predict mortality using a cohort of patients with decompensated cirrhosis undergoing transjugular intrahepatic portosystemic shunt (TIPS) placement [8]. It uses three objective laboratory parameters selected from many variables. The model was based on observations that serum bilirubin, creatinine, INR, and cause of the underlying liver disease were predictors of survival in patients undergoing elective TIPS placement for portal hypertensive complications. The cause of underlying disease was excluded in a revised model. The addition of individual complications of portal hypertension, such as ascites or variceal bleeding and hepatic encephalopathy, did not alter the model's predictive ability. The advantage of the MELD score is that it uses objective parameters that are not subject to inter-observer variability like is the case with the CTP score. Additionally, with a range from 6 to over 40, the MELD offers a more continuous and dynamic discrimination compared with the CTP score and requires only a standard lab for blood work to attain the necessary variables to calculate. With some notable exceptions, the MELD score is less influenced by various treatment modalities [4, 9].

The MELD score has been validated in patients with advanced liver disease not undergoing TIPS placement and those with compensated cirrhosis as a 3-month mortality predictor [10•]. MELD or some variations of it are used worldwide for liver transplant allocation. The original MELD calculation uses serum bilirubin, serum creatinine, and the international normalized ratio (INR) by the formula:

$$\begin{aligned}\mathrm{MELD} = {} & 9.57 \times \log\,(\text{creatinine}) + 3.78 \\ & \times \log\,(\text{total bilirubin}) + 11.2 \times \log\,(\mathrm{INR}) \\ & + 6.43.\end{aligned}$$

All the variables have a lower limit of 1. Additionally, serum creatinine is constrained between 1 and 4 mg/dL. Patients receiving renal replacement therapy at least twice within the previous week are assigned a creatinine of 4 mg/dL [9]. By utilizing MELD for allocation, patients with higher predicted mortality are prioritized over those with lower predicted mortality risk. Among liver transplant candidates, mortality and MELD score are linearly correlated with 3-month mortality estimated to be 4%, 27%, 76%, 83%, and 100% for MELD scores of < 10, 10–19, 20–29, 30–39, and 40+, respectively [11]. The C-statistic in candidates awaiting transplant MELD score is 0.87, superior to that of CTP score, 0.84 [9].

The MELD score, however, has several limitations. Serum bilirubin can be elevated in the setting of renal failure out of proportion to liver dysfunction [12]. Additionally, the MELD score does not discriminate between direct and indirect bilirubin; therefore, hemolysis or genetic variations in bilirubin metabolism result in a significant rise in indirect bilirubin and can confound the prognostic accuracy of the score [13]. Serum creatinine can vary based on the method of measurement [14]. Creatinine is also subject to gender bias because females generally have lower serum creatinine compared to males with the equivalent renal function [15]. As is the case with CTP, INR measurement with thromboplastin can vary substantially dependent upon the use of anticoagulant therapy [16], and INR is better validated in the use of anticoagulation rather than in the coagulopathy of chronic liver disease. A calculator is necessary to generate the MELD score, limiting access to areas with calculators or the internet to access online calculators. Finally, it has poorer discriminatory power in the lower ranges of the score, and there is a well-established need for a system of exception MELD points to make liver transplant more equitable for those with certain underprioritized disease states [17••, 18, 19].

In the first year of utilization of MELD for US liver transplant allocation, there was a 12% reduction in waitlist mortality. This trend continued over the subsequent years along with a reduction in waitlist time from 656 to 416 days [20]. Furthermore, MELD is predictive of other outcomes in the pre-liver transplant population, including the transplant operative time, number of packed red blood cell transfusions, length of stay in the intensive care unit, total hospital length of stay, and overall hospital stay charges [9]. MELD score and mortality are linearly correlated for preoperative patients with 3-month mortality 4%, 27%, 76%, 83%, and 100% for MELD scores of < 10, 10–19, 20–29, 30–39, and 40, respectively [21]. For in-hospital mortality, MELD scores of 15 to 19, 20–29, and > 30 showed adjusted hazard ratios of 2.52 (95% CI, 1.81–3.49; $P < 0.001$), 2.70 (95% CI, 1.89–3.84; $P < 0.001$), and 8.00 (95% CI, 3.91–16.39; $P < 0.001$), respectively [22••]. MELD scores have a non-linear response when attempting to correlate post-liver transplant survival limiting is usefulness as a post-transplant outcome predictor. However, a study by Zhang et al. attempted to compare MELD and SOFA scores vs 18 different recipient and donor variables, and MELD proved to be a better predictor of post-transplant survival [23].

Hyponatremia is an independent predictor of waitlist mortality in patients with end-stage liver disease and thus has been incorporated into the MELD score. There is an increase in mortality by 5% for each millimole decrease in serum sodium between levels of 125 and 140 mmol/L. In patients with severe hyponatremia (< 125 mmol/L) and refractory ascites, serum sodium independently was a better predictor of mortality than MELD score alone [24, 25]. The addition of serum sodium to MELD (MELDNa) improved the accuracy of the model with a C-statistic from 0.865 to 0.878 ($P < 0.01$) but in a validation data-set, MELDNa affected only 12% of the listed patients. MELDNa is a better predictor of outcome among patients with alcoholic hepatitis who had ascites but not in those without ascites [26]. However, serum sodium has limitations similar to the other variables in the MELD score. The score can be manipulated by changes in volume status with free water intake and the use of diuretics. As of January 11, 2016, the Organ Procurement and Transplant Network (OPTN) in the USA uses a modified version of MELDNa for transplant allocation after validation using the United Network for Organ Sharing (UNOS) database. If the initial MELD score is greater than 11, then the MELD score is recalculated using the formula:

$$\mathrm{MELD} = \mathrm{MELD(i)} + 1.32 \times (137-\mathrm{Na}) - [0.033 \times \mathrm{MELD(i)} \times (137-\mathrm{Na})]$$

The sodium value range for the formula has low constraint of 125 mmol/L and a high constraint of 137 mmol/L.

Similar to the addition of sodium, further refinements have been made to MELD in an effort to further improve the accuracy of the scoring system. The UK end-stage liver disease score (UKELD) is similar to MELDNa and is used for listing patients for liver transplantation in the UK [27]. Small changes to the existing MELD model were made. The updated MELD assigns lower weight to creatinine and INR and higher weight to bilirubin [28]. Refit MELD reassigns lower and upper limits of 0.8 and 3.0 for serum creatinine with 1 and 3 for INR, respectively. ReFit MELDNa uses the refit MELD model incorporating serum sodium [29]. Integrated MELD includes sodium and age [30••]. MESO is a function of the ratio of MELD to serum sodium [31]. MELD-XI excludes INR from calculations of MELD in patients on anticoagulation therapy and is comparable to the standard MELD score [32]. In one study, comparing these models, UKELD and updated MELD were inferior in predicting mortality when compared with the MESO, MELDNa, ReFit MELD, and ReFit MELDNa [9, 33].

HVPG

Hepatic Venous pressure gradient (HVPG) is considered the gold standard for quantifying portal circulation by directly measuring the pressure difference between the hepatic vein and a wedged hepatic vein as a surrogate for portal vein pressure. As further liver damage occurs due to fibrotic change, greater resistance to flow across the liver sinusoids occurs, and HVPG increases. HVPG pressures greater than 6 mmHg indicate portal hypertension and greater than 10 represent clinically significant portal hypertension. The efficacy of HVPG, MELD, and MELDNa in predicting patient survival with decompensated liver failure was examined in a small study of 57 patients. In this study of patients with decompensated liver failure, it was concluded that HVPG was superior to MELD and MELDNa. HVPG enables the physician to stratify cirrhosis stage with a defined outcome, prognosis, and management strategy [34, 35]. Limitations associated with HVPG include the highly invasive nature of the procedure with the risk for significant complications. In addition, the validity of the measurements is highly dependent on the experience of the operator.

More Recent and Evolving Prognostic Paradigms

D'Amico's Stages of Cirrhosis

D'Amico et al. identified and organized prognostically useful clinical stages of cirrhosis. Clinical complications of cirrhosis defined distinct prognostic disease stages. A prognostic staging system of cirrhosis was proposed at the Baveno IV consensus conference using D'Amico's preliminary work [36]. Four stages were proposed: stage 1, compensated cirrhosis without esophageal varices; stage 2, compensated cirrhosis with varices; stage 3, ascites with or without varices; and stage

4, bleeding with or without ascites. The four stages notably had a significant increase in the risk of death with progression of stage. D'Amico et al. identified a total of 494 patients with biopsy-proven cirrhosis. Prognostic stages were defined according to major manifestations of decompensation of the disease [37]. Using this updated data, the Baveno IV proposal was modified to the following: stage 1, compensated cirrhosis without varices; stage 2, compensated cirrhosis with varices; stage 3, bleeding without other disease complications; stage 4, first non-bleeding decompensating event; and stage 5, any second decompensating event [36]. Patients were assigned to a stage until a decompensation occurred which marked transition to a new stage. Hepatocellular carcinoma (HCC) was not considered a separate stage as it can occur in all proposed stages of the disease and may be associated with compensated and decompensated cirrhosis. While subjective aspects exist in the D'Amico stages of cirrhosis, they are mitigated by the binary nature of the clinical inputs and the unidirectional aspect of the paradigm. Limiting the validity of the system is that only alcohol, viral, and cryptogenic cirrhosis were included, and applicability of the proposed prognostic stages to other diseases needs further investigation. Additionally, the D'Amico stages paradigm is insensitive to any improvement in liver disease that might occur after removing its cause (e.g., alcohol cessation or viral therapy) [38]. Assessing cirrhosis stage in patients with low MELD (less than 20) can improve risk stratification of transplant candidates who have increased the risk for death but otherwise low priority on a transplant waiting list [39].

Chronic Liver Failure-Sequential Organ Failure Assessment and the Acute Physiology and Chronic Health Evaluation III APACHE III

Cirrhotic patients admitted to intensive care units (ICUs) have high mortality rates [40••]. The sequential organ failure assessment score (SOFA) was developed to determine organ function or rate of failure. SOFA assigns severity of organ dysfunction (0–4) for six organ systems: the respiratory, coagulation, liver, cardiovascular, CNS, and renal. The respiratory system is evaluated by the ratio of PaO2/FiO2. The coagulation system is measured by the total platelet count. The liver is evaluated by bilirubin. The cardiovascular system is measured by mean arterial pressure or administration of vasopressors. The nervous system is assessed by the Glasgow Coma Scale and the renal system is measured by creatinine or urine output [41]. The Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF-SOFA) score, a modified Sequential Organ Failure Assessment (SOFA) score, is a scoring system exclusively for patients with end-stage liver disease. It has been shown that this CLIF-SOFA, but not the original SOFA score, was an independent short-term predictor for cirrhotic patients in the ICU. CLIF-SOFA differs from SOFA because it includes West-Haven grade for hepatic encephalopathy along with bilirubin, creatinine, INR, and mean arterial pressure. Both the discriminatory and overall accuracy of CLIF-SOFA were superior to that of SOFA. The Acute Physiology and Chronic Health Evaluation III (APACHE III) was also shown to be an independent prognostic system with excellent discriminatory power and overall correctness for predicting 6-month mortality in critically ill cirrhotic patients. The APACHE III calculator incorporates information from the patient's vitals, comprehensive metabolic panel, blood counts, arterial blood gas, and Glasgow Coma Scale. In fact, CLIF-SOFA and APACHE III were both shown to have better discriminatory power than CTP and APACHE II. The CLIF-SOFA was again shown to outperform the CTP, MELD, SOFA, and APACHE II scores in a Canadian cohort of critically ill acute on chronic liver failure patients [42, 43••].

Acute-on-Chronic Liver Failure

Acute-on-chronic liver failure (ACLF) is defined as acute decompensation of cirrhosis associated with organ failure and high short-term mortality (28-day mortality > 15%) [44]. This definition was described by the EASL-CLIF Consortium who performed a multicenter European CANONIC study to look at mortality associated with ACLF at 28 and 90 days. In the study, organ failure was evaluated by the CLIF Consortium Organ Failure Score [45]. ACLF grades 1–3 were then assigned according to the number of organ system failures. Mortality of ACLF grades 1, 2, and 3 was 22%, 32%, and 73%, respectively [44]. The limitation with using ACLF is that the definition of ACLF continues to change. There have been up to 13 separate definitions within existing literature. Four organizations: The Asian Pacific Association for the Study of Liver, European Association for the Study of the Liver-chronic liver failure, North American Consortium for the Study of End-Stage Liver Disease, and the World Gastroenterology Organization have all attempted to consolidate and unify a common definition to establish further research [46••]. There continues to be significant interest in refining and advancing the use of ACLF criteria.

Protein C

Protein C (PrC) is a physiological anticoagulant that plays a role in regulating inflammation and cell death. It is a well-known prognostic factor in sepsis, and plasma hypercoagulability leads to progression of fibrosis and formation of microclots causing end-organ dysfunction [47•]. There is a possible association between natural anticoagulants PrC, protein S (PrS), and antithrombin III (AT) and outcomes in cirrhotics [47•]. In a multivariable predictive model on 3-month survival, it was found that PrC ($P < 0.001$), PrS ($P < 0.001$), and AT ($P < 0.001$) levels were lower in cirrhotics compared

with non-cirrhotics. Consistent with these findings, patients with CTP class C had significantly lower ($P < 0.05$) functional PrC, PrS, and AT when compared with class A, class B, and non-cirrhotic patients. PrC levels less than 52% were associated with liver dysfunction, inflammation, and sepsis and predicted 3-month mortality in cirrhotic patients [47•]. While these results are promising, patients on anticoagulation therapy can have alterations in PrC levels. Additionally, biochemical testing for PrC level is not readily and routinely available [48].

Serum Cystatin C

Acute kidney injury is a frequent complication in cirrhosis; however, Cr-based estimated glomerular filtration rate (eGFR) often does not reflect true renal function in advanced liver disease because of muscle wasting and impaired liver function [49]. Conversely, cystatin C (CysC) is unrelated to muscle volume and liver function and may estimate renal function and predict outcome more accurately compared with Cr-based eGFR in cirrhotic patients [49]. The addition of CysC into the MELD score predicts the development of AKI and mortality, respectively, and performed significantly better than the MELD and CTP scores without CysC [50•]. Cystatin C immunoassay is not a readily available immunoassay, and therefore creatinine and GFR continue to be preferred.

Neutrophil to Lymphocyte Ratio

Blood indices including lymphocyte/monocyte ratio, lymphocyte count, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio, monocyte-granulocyte/lymphocyte ratio, and red blood cell distribution width are prognostic biomarkers in certain diseases [51•]. NLR has been found to be a predictor of mortality independent of CTP and MELD scores in patients with stable liver cirrhosis, particularly patients with low MELD scores [52, 53••]. Likewise, NLR is an independent predictor of mortality in patients with liver failure listed for liver transplantation. A higher neutrophil count ($P < 0.001$) and lower lymphocyte count ($P = 0.001$) are predictors of waitlist death. After adjusting for MELD, increasing increments of neutrophil-to-lymphocyte ratio were predictive of death by 3 months ($P = 0.043$) [54•]. One major criticism of NLR is the potential for reduced accuracy in the setting of infection or other disease states that influence white blood cell count.

Technetium-99m-Phytate Hepatic Scintigraphy

Liver scintigraphy using technetium-99m-phytate (99mTc-phytate) is an imaging technique used in the diagnosis of liver diseases and has been evaluated as an outcome predictor in cirrhosis [55]. Hepatic scintigraphy in cirrhosis shows delayed colloid extraction by the liver, decreased and/or heterogeneous hepatic uptake, uptake equivalent to the liver, and increased uptake by the extrahepatic reticuloendothelial system. Uptake is dependent on extraction of colloid by the liver which is related to the number of Kupffer cells and liver blood flow. Extrahepatic colloid uptake is noted because there is decreased uptake by the diseased cirrhotic liver which is responsible for clearing the colloid [56].

Ninety-four patients with biopsy-documented cirrhosis were categorized using the CTP score and followed for 2 years. They had initial scintigraphy with 99mTc-phytate complexed with calcium in vivo. Extrahepatic uptake (EHU) of 99mTc-phytate on scintigraphy was graded from 0 (absent EHU) to 5 (significant EHU) based upon the distribution of the radiotracer between the liver, spleen, and bone marrow. Survival at 2 years was 97% for an EHU equal to or less than 2.5, 62% for grades 3–4.5, and 31% for grade 5 [55]. Even so, MELD and CTP are preferentially used because of simplicity, low-cost, widespread use, and excellent validity.

Indocyanine Green

Quantitative Liver Function Tests (QLFTs) attempt to use substances normally cleared by hepatic uptake or metabolism to determine the functionality of the liver without invasive procedures. These substances can be further classified as exogenous vs endogenous. An example of an exogenous substance is indocyanine green (ICG). ICG is given intravenously and binds to albumin in the blood. It is then almost completely excreted into bile without enterohepatic recirculation. The standard of measure is the plasma disappearance rate of ICG (ICG-PDR) measured in %/min. The normal rate in a healthy liver is > 18%/min. ICG-PDR less than 6.3%/min is 85.7% sensitive and 88.9% specific in predicting outcomes in acute liver failure patients [57]. Measurement of ICG-PDR might help identify patients with ALF and predict if they will benefit from liver transplantation. The sensitivity and specificity of ICG-PDR in predicting outcomes from cirrhosis is 85% and 90%, respectively, compared to 60% and 80% for MELD, respectively. A combination MELD-ICG scoring system was more accurate in predicting prognosis in intermediate to advanced cirrhosis than MELD or MELDNa [58, 59]. There was, however, no correlation between ICG-PDR and other parameters of liver function (bilirubin, albumin, prothrombin time, ascites, and presence of varices). Rather, ICG-PDR appears to prognosticate liver performance independent of cirrhotic complications, and as such, in patients with advanced liver failure (MELD > 35) and high short-term mortality; the modified MELD-ICG was not superior to MELD [60].

Cholate Test

The dual cholate test is another QLFT that administers oral D4 cholate and IV 13C cholate simultaneously. The area under the curve of serum concentrations vs the time curve of D4 quantifies clearance from portal circulation. The area under the curve of serum concentration of 13C quantifies clearance from systemic circulation. The ratio of 13C to D4 estimates the portal-systemic shunt. These three variables can then be used to calculate the disease severity index (DSI). The DSI has been modeled and found to have a direct link to clinical outcome. A DSI greater than 19 predicted cirrhosis and risk for future clinical outcomes [61]. It is not clear if the cholate test is practical or ready for routine use in clinical practice. It is not approved by the US Food and Drug Administration for such use at this time. It does, however, identify the patients who are at risk for future clinical decompensation and also patients with adequate hepatic reserve who will have a benign clinical course. This non-invasive quantification of hepatic function and reserve may offer safety advantages over liver biopsy for fibrosis staging [62].

Sarcopenia/Frailty

Sarcopenia is the loss of skeletal muscle mass and is commonly noted in patients with cirrhosis. The skeletal muscle index is calculated to both identify and quantify sarcopenia. This can be done by measuring the cross-sectional area of the skeletal muscles of the third lumbar vertebra or the psoas muscle on cross-sectional imaging. It has been found that sarcopenia is significantly associated with mortality in patients with cirrhosis. Patients with sarcopenia are at high risk for poor outcomes and may benefit from nutritional interventions [63, 64••].

Frailty is a complex syndrome characterized by functional decline and reduced physiological reserve associated with poor clinical outcomes in patients suffering from a variety of chronic illnesses. It encompasses a large array of entities including functional decline, sarcopenia and malnutrition, physical deconditioning, impaired cognition, balance, cardiopulmonary fitness, walking speed, and muscle strength [65••, 66, 67••, 68••]. Several measurement tools for assessment of frailty are commonly used including the 6-min walk distance as defined by the distance walked in 6 min. Walking more than 300 m is considered normal, whereas walking less than 250 m is considered frail. Every 100-m reduction of the distance in the 6-min walk test is associated with 48% overall increased mortality risk ($P < 0.0001$) [69].

Frailty and sarcopenia strongly predict waitlist mortality and post-transplant outcomes even after adjustment for liver disease severity. The Frailty Assessment in Liver Transplant Candidates Study measured physiologic reserve and functional status in transplant candidates and showed a 20% rate of death or dropout related to frailty [70].

Conclusion

The MELD score remains the most commonly used method for reliably measuring the mortality risk in patients with end-stage liver disease; however, many other paradigms have been examined to either modify, enhance, or replace the MELD model. Continued efforts to better and more comprehensively risk stratify patients with chronic liver disease are necessary to optimize management of this high-risk population.

Compliance with Ethical Standards

Conflicts of Interest Joel Wedd and Kavitha Nair each declare no potential conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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