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A Comprehensive Review of Outcome Predictors in Low MELD Patients

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Abstract

Risk scoring for patients with cirrhosis has evolved greatly over the last several decades. However, patients with low Model for End Stage Liver Disease – Sodium (MELD-Na) scores still suffer from liver-related morbidity and mortality. Unfortunately, it is not clear which of these low MELD-Na score patients would benefit from earlier consideration of liver transplantation. This paper reviews the literature of risk prediction in patients with cirrhosis, identifies which patients may benefit from earlier interventions such as transplantation, and proposes directions for future research.

Introduction

Prediction and prognosis has been a quintessential aspect of the art of medicine since its inception. With increasingly modern approaches, patients can be prioritized for life saving procedures or maneuvered away from potentially dangerous ones. Nowhere has this been more apparent than in the field of end stage liver disease and liver transplantation where sparse organ availability has required careful allocation. The Model for End Stage Liver Disease – Sodium (MELD-Na) score has been repeatedly shown to accurately predict three month mortality at high scores and is currently used to prioritize recipients for liver transplant allocation.[1,2] However, though patients with lower MELD-Na scores are de-

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prioritized with regards to liver transplant, they may still have a significant burden of liver related mortality.[3] Furthermore, the vast majority of patients listed for transplant must deal with this issue, with a 2004 study finding 92% of waitlisted patients had a MELD score of 18 or less and a more recent 2014 analysis noting 73.4% of patients were initially listed with a MELD less than 16.[4,5] Although most research has been done prior to the MELD-Na score, we review the literature on historical and novel factors that might be extended to identify the group of 'low MELD-Na' patients who suffer liver related complications and may benefit from earlier liver transplant, the use of more marginal liver grafts, or more intensive nontransplant treatments.

A Brief History of Risk Scoring for Liver Disease Severity

Advancements in risk prediction for liver disease severity have been largely driven by identifying populations at high risk for complications after procedures. In the early 1950s, Child and Turcotte attempted to identify high risk patients by laboratory factors (serum bilirubin and albumin) and clinical factors (ascites, encephalopathy, nutritional status) prior to surgery for portal hypertension.[6] In 1973, Pugh et al provided a revised score which substituted prothrombin time in place of nutritional status to form the Child-Turcotte-Pugh (CTP) score.[7] With the rise of interventional radiology and placement of transjugular intrahepatic portosystemic shunts (TIPS) there was again an increase in mortality in the sub-population of patients with CTP class C cirrhosis. A logistic regression model for predicting 3-month mortality was noted to be superior to the CTP score in this group undergoing elective TIPS with further analysis validating its prognostic capability for decompensated liver cirrhosis and prediction of waitlist mortality.[1,8] This model for end-stage liver disease ('MELD score'), based on bilirubin, creatinine, and INR, was adopted for organ allocation in the United States in 2002.

Criticism of the MELD score stems from the basis of its conception as a risk prediction model for patients with Child C cirrhosis and its focus on short term, 90 day mortality. In fact, at lower scores MELD's prognostic capability has been noted to be inferior to serum sodium, ascites, encephalopathy, glomerular filtration rate (GFR), and CTP score.[9–12] In particular, hyponatremia has been established as a key predictor of mortality.[10,12] This is particularly true of patients with low MELD scores, where the effect of serum sodium is significantly greater.[10] In fact, in patients with a MELD score less than 21, only serum sodium and persistent ascites, but not MELD, were significantly associated with waitlist mortality. Furthermore, this effect is present even up until a MELD score of 38.[10,13] Ultimately, the MELD-Sodium (MELD-Na) score was officially incorporated into organ allocation in 2016. Despite these changes, it remains unclear how to identify which low MELD-Na patients will continue to suffer from liver related morbidity and mortality.

As scoring systems are improved, the patients with consistently low scores are distilled into a truly low risk group. Future work should concentrate on identifying high risk attributes of patients within this low MELD-Na cohort to help determine subgroups that would benefit from earlier transplant. The remainder of this paper describes potential candidates for these attributes

Outcome Predictors Beyond MELD-Na

Many potential candidates for predictors have been suggested and examined in the past.[14] Most center around quantification of portal hypertension and its sequelae. Hepatic Venous Pressure Gradient (HVPG)

Measurement of the severity of portal hypertension via the HVPG is an intuitive first step in identifying at-risk patients based on physiology. Multiple studies have demonstrated that elevated HVPG is a risk factor for variceal bleeding.[15] Secondary analyses on data acquired from the initial trials of beta blocker therapy have also demonstrated a correlation between lack of response to HVPG-lowering therapy and survival, renal dysfunction, hepatic encephalopathy, ascites, and spontaneous bacterial peritonitis.[16] The elevated pressures present can be decreased in patients via pharmacotherapy with beta-blockers and nitrates, through nonpharmacologic means such as TIPS, or via decreasing parenchymal inflammation through treatment of hepatitis and alcohol abstinence.

Inclusion of HVPG may increase the prognostic accuracy of both death and decompensation of cirrhosis even after adjusting for MELD score and serum sodium. This was particularly true for patients with low MELD scores, where lower pressure gradients were associated with better outcomes.[17] Unfortunately despite ongoing research into correlates such as splenic elastography, the widespread use of HVPG has been limited in patients with cirrhosis due to its invasive nature.[18] That being said, the clinical utility of HVPG measurement in patients with low MELD-Na scores may be beneficial to stratify patients at higher risk for portal hypertensive complications and need for earlier transplantation.

Cardiovascular physiologic changes

Similarly, high cardiac output, low systemic vascular resistance, and hyperdynamic myocardium are among the well-known cardiovascular and hemodynamic physiologic changes in end stage liver disease (ESLD).[19] More severe diastolic dysfunction and elevated right sided heart pressures have been associated with persistent ascites, poor post-TIPS outcomes, and worse post transplant outcomes.[20–22] Even when controlling for MELD score, pretransplant diastolic dysfunction manifested as elevated left ventricular ejection fraction and sub-clinical right heart dysfunction have been associated with post transplant mortality, death, renal failure, and graft failure.[23] These physiologic changes are the hallmarks of cirrhotic cardiomyopathy, and have been implicated as a cause of renal failure in spontaneous bacterial peritonitis.[24] Therefore, in the low MELD-Na population, development of this physiologic state should be studied in order to determine if it signals impending decompensation and the need for earlier transplantation. For example, echocardiographic estimates of strain, cardiac output, and/or systemic vascular resistance might be used to distinguish trajectories of low MELD-Na patients.

In contrast, this hyperdynamic cardiovascular state may also correlate with riskier liver transplantation. Significant coronary artery disease (CAD) is common in patients with cirrhosis, and even more so in patients with nonalcoholic steatohepatits (NASH) given the overlapping risk factors for both. Further complicating the preoperative assessment, symptomatic screening for cardiac disease is difficult as patients with ESLD are often

sedentary, dyspneic, bradycardic on beta-blockers, and demonstrate signs and symptoms of volume overload with ascites and peripheral edema. All of these aspects can diminish the predictive value of noninvasive testing for underlying atherosclerotic cardiovascular disease, making it more challenging to estimate perioperative risk. In fact, assessment of CAD using noninvasive testing has a very poor sensitivity for predicting cardiac events post transplant, with the sensitivity of dobutamine stress echocardiography as low as 9–13% and SPECT as low as 51%.[25,26] This area is still undergoing intensive study, however a recent AST expert review suggests that coronary artery calcium (CAC) scoring and/or CT angiography may be useful tools to rule in or rule out significant CAD, respectively.[27] Biomarkers not included in traditional ESLD risk scores, such as cardiac troponin, may help to identify patients with cardiac dysfunction or those who are at an increased risk of poor outcomes with transplant.[28]

A major question needing further study is whether early cardiac physiologic changes could serve as a non-MELD-Na predictor and how this is balanced with operative risk stratification.

Renal Function

Another well-known effect of cirrhotic physiology is relative renal hypoperfusion and its sequelae. Renal dysfunction is common in patients with cirrhosis, occurring in 20% of hospitalized patients and 37% of outpatients followed at a median of 1.3 years.[29] It is a key determinant of survival with more than half of patients dying within a month of developing renal failure and an additional 10 – 30% dying between three months and one year, even after accounting for baseline MELD-Na or CTP Score.[30] Additionally mortality risk increases if renal failure occurs with other complications of cirrhosis such as gastrointestinal hemorrhage, hepatic encephalopathy and acute on chronic liver failure.[14,31–33] Finally, the pattern of renal dysfunction plays a key role in waitlist mortality risk – patients with acute kidney injury (AKI) have more than double the risk of mortality, as compared to those with chronic kidney disease (CKD), independent of MELD score and serum creatinine.[34] Therefore, there remains an opportunity to prioritize liver transplant among “low” MELD candidates with either co-morbid hepatic decompensation or acute renal dysfunction.

This issue is further complicated by the difficulty in estimating renal dysfunction in patients with ESLD due to sarcopenia and the reliance on serum creatinine. As a result, current GFR calculators tend to overestimate measured GFR, an effect that may be especially prominent in women and cause an underestimation of disease severity. Recently, a GFR calculator was specifically developed and calibrated for patients with cirrhosis, however this has not yet been correlated with outcomes.[35] Alternatively, measurement of renal water excretion by diuresis after water load was a strong factor in mortality prediction for patients with Childs B and C cirrhosis during the pre-MELD era.[36] Of note, this test was abnormal prior to the development of renal dysfunction or hyponatremia in the studied patients.

Given the inaccuracy in using serum creatinine to determine renal function in this population, future studies should examine if other techniques, such as direct measurement, would be of benefit in predicting outcomes. This is critically important, as the proportion of patients requiring simultaneous liver-kidney transplant (SLKT) is rising rapidly in the

MELD-era, and therefore improved diagnostics may allow for earlier intervention and therefore prevention of the development of chronic kidney disease and obviate the need for SLKT.[37]

Infection

Infections are the most significant cause of morbidity and mortality in patients with cirrhosis. Spontaneous bacterial peritonitis (SBP) in particular has been long known to be associated with renal failure and subsequent mortality.[38] The exact mechanism of renal failure is unclear, with some suggesting cirrhotic patients may have inadequate cardiac responsiveness in the setting of sepsis.[24] Unfortunately, survival rates after infection remain low, with mortality as high as 63% at one year after a significant infection.[39] In one model, the development of sepsis is denoted as the last stage of cirrhosis prior to death or liver transplantation.[14] However, in patients with Child A or early Child B cirrhosis, spontaneous survival to one year was noted to be 80%.[40]

If infection was to be used as a non-MELD-Na marker of disease, although data is limited in this area, an initial serious infection in a low MELD-Na patient may be an indicator of “more to come” and warrant early transplant evaluation.

Frailty and Sarcopenia

Frailty and sarcopenia are emerging as important clinical factors associated with waitlist and post transplant outcomes independent of MELD-Na score.

The concept of frailty was originally developed in the field of geriatrics to identify a biological syndrome of increased vulnerability to health stressors[41] resulting in adverse health outcomes such as hospitalization, institutionalization, and death. Tools that measure physical frailty and its components, such as the Fried Frailty index, Short Physical Performance Battery, six-minute walk test, the Activities of Daily Living, and the clinical frailty scale, have been studied in the liver transplant population.[42–44] More recently, the Liver Frailty Index was developed in patients with cirrhosis awaiting liver transplantation out of individual components of these indices and consists of performance-based tests that capture malnutrition, muscle weakness, and poor neurocognitive coordination, three dominant domains of physical frailty.[45] While each of these tools have their strengths and weaknesses with respect to use in the liver transplant setting, they all have the common goal of operationalizing the concept of a patient’s vulnerability to acute stressors. Importantly, when tested in patients with cirrhosis, they are predictive of outcomes including hospitalizations, resource utilization, and death, independent of liver disease severity.[44–48] Furthermore, they are strongly associated with functional recovery after liver transplantation.

In contrast to a biologic syndrome, sarcopenia specifically refers to depletion of muscle mass. For a patient with decompensated cirrhosis – and therefore protein synthetic dysfunction – sarcopenia likely represents the dominant component of physical frailty. In many cases, it may be identified earlier than the clinical manifestation of physical frailty or functional impairment, and as such represents an important potential predictor of morbidity and mortality in patients with cirrhosis. Sarcopenia has been reported in 40 to 60% of patients with end-stage liver disease, has been associated with increased waitlist and post

liver transplant mortality, as well as transplant related complications such as infection and longer length of hospital stay.[49–51]

Multiple objective and reproducible measures of sarcopenia have been studied and include computed tomography (CT), magnetic resonance imaging, thigh ultrasound, dual X-ray absorptiometry, and bioelectrical impedance analysis. Although none of the modalities have been compared directly with each other in muscle mass quantitation, the preponderance of evidence in the published domain to date supports the use of abdominal CT scan to measure muscle mass in patients with cirrhosis. The total cross-sectional area of the abdominal skeletal muscles or the psoas muscle alone at the 3rd lumbar (L3) level are the two most common muscle groups measured, and when normalized to the patient's height provides the skeletal muscle index (SMI).[52] Of particular relevance for use in clinical practice, sex-specific cutoffs for SMI to define sarcopenia (less than 50 cm^2/m^2 for men and 39 cm^2/m^2 for women) have been developed for patients with cirrhosis anchored to the outcome of waitlist mortality.[52] Using these SMI cutoffs, men and women with sarcopenia experienced significantly higher risk of waitlist mortality than those without sarcopenia (Men: HR 1.7, 95% CI 1.1–2.7; Women: HR 2.8, 95%CI 1.6–5.1).

These findings demonstrate standardized methods to capture physical frailty and sarcopenia that provide risk and recovery in liver transplant patients beyond the MELD-Na score. Research in this area will be critical in determining the optimal level of frailty at which patients maintain a favorable balance of avoiding waitlist mortality and prolonged postoperative recovery.

Noninvasive functional assessments and biomarkers

Noninvasive functional assessment of the liver and biomarkers might be helpful in directly quantifying the severity of liver dysfunction and the associated risk of morbidity and mortality, particularly when clinical or laboratory parameters are insufficient. Much of this work took place prior to MELD implementation and so is worth revisiting in the context of low MELD-Na recipients. Data on the aminopyrine breath test, a rapid and noninvasive assessment of liver metabolism, are mixed in terms of predicting survival compared to CTP score with some reports suggesting improvement in prediction and others showing less benefit.[53] Similarly mixed data have been shown for other functional tests, such as indocyanine green clearance (ICGC), galactose elimination capacity, and the monoethylglucinexylidide test, all of which may independently predict survival but do not appear to add prognostic value above standard CTP and MELD scores.[54] A relatively recent report did suggest that ICGC had added value over MELD-Na in predicted survival for intermediate MELD-Na categories.[55] Lastly, the dual cholate test has the potential to quantify multiple hepatic physiological processes including hepatic uptake, systemic and portal circulation clearance, and porto-systemic shunting as well as outcomes.[56] While this test may estimate true liver 'function' most accurately, it has not yet been assessed robustly in predicting outcomes of decompensated cirrhosis or in lower MELD patients.

In terms of novel laboratory markers, one of the more promising and simple tests is the neutrophil-to-lymphocyte ratio (NLR), a biomarker associated with systemic inflammation.

The most recent study focused on low MELD patients found that this ratio was associated with liver-related death, independent of stage of cirrhosis and MELD score.[57]

Taken together, ICGC, dual cholate test, and NLR, are promising but currently do not appear superior in predicting mortality over MELD-Na in low MELD-Na patients.

Potential improvements to the MELD-Na Score

Current supplements to the MELD-Na score exist in the form of 'exception points' for standard complications such as HCC, hepatopulmonary syndrome, cholangiocarcinoma, familial amyloid polyneuropathy, cystic fibrosis, and portopulmonary hypertension. Exception points may also be awarded in special circumstances after review by a regional review board for nonstandard reasons. Despite the flexibility of this model, it requires significant coordination of efforts, suffers from regional variability, and lacks evidence for the appropriate MELD-Na correction in non-HCC conditions.[58] Thus, while any scoring system will likely require some provision for exception points, an improvement to the MELD-Na score that better identifies patients with low scores at risk for liver related death is a more mathematically elegant solution to this problem. Several candidates for improving the MELD-Na score have been proposed including albumin, sarcopenia, ascites, and alternative mathematical strategies

Low serum albumin levels have been strongly associated with increased mortality and were initially analyzed as a candidate in the calculation of the MELD score.[1] Although not demonstrated in the original MELD paper, further analysis has shown a benefit to including serum albumin with the MELD-Na score in the low MELD-Na subpopulation.[1,8,59–61] In a large cohort of waitlisted patients a five variable, '5vMELD', score was developed by incorporating of albumin and serum sodium into the MELD score.[59] This score was noted to have better predictive capability for 90 day waitlist mortality when compared to MELD and MELD-Na score equations.[62] Incorporation of albumin into risk prediction models has also been used to improve estimates of longer, one year mortality in low MELD patients above MELD-Na alone.[63]

Similarly, sarcopenia has been explored as a prognostic factor to enhance prediction in patients with low MELD scores because the effect of sarcopenia appears to be most pronounced in this group.[64,65] The initial development of the "MELD-Sarcopenia" score occurred in the pre-MELD-Na era but did improve survival prediction in the low MELD population although this benefit in subsequent validation studies has been unclear.[61,65] Additionally, because sarcopenia predicts poor pre and post transplant outcomes and is not definitely reversed by transplantation, organ allocation based on sarcopenia may provide less net benefit as compared to other scoring systems.[66]

Efforts have also been made to hybridize the clinical factors in the original CTP score with the solely laboratory based MELD-Na score. A top candidate for such a factor is the presence of ascites, often one of the first clinically apparent manifestations of liver disease.[14] Moderate ascites improved prediction of survival in patients with MELD-Na <21, and on average added the equivalent of 4.5 MELD points or 3.5 MELD-Na points towards the survival of patients.[67–69]

In addition to improving the MELD-Na score, efforts have been made to use change in MELD-Na over time, often termed ‘delta-MELD’ or ‘MELD velocity’. This delta MELD was noted to be superior to either the CTP or MELD score alone at predicting 6 and 12 month mortality in patients with cirrhosis.[70] High delta MELD prior to transplant has also been noted as a negative prognostic factor for post transplant survival and graft failure.[71] Although rate of MELD change is a potential candidate for future scoring systems, the above findings should be interpreted with care as these studies were retrospective and MELD measurement was performed as part of routine care. For instance when number of MELD measurements was taken into account as a surrogate for repeated measurements in the course of an acute, end-of-life hospitalization, delta MELD was no longer superior to MELD alone.[72] Similarly, rates of change in sarcopenia and HVPG may show promise in mortality prediction for patients on the waitlist, however these reports require further validation.[73,74]

Newer statistical methods such as machine learning and artificial intelligence are starting to be applied to this important issue. For instance the burgeoning field of artificial intelligence has shown some promise in improving donor – recipient selection over conventional scores.[75,76] In the recent pre-MELD-Na era, artificial neural networks have also demonstrated a better accuracy compared to MELD in predicting three month mortality and death post hospitalization.[77,78] Given their ability to process nonparametric and nonlinear data, these artificial intelligence approaches are likely to play a significant role in the future of risk prediction and organ allocation.

Alternatives to Transplant

In the current setting of organ shortage, care for patients with low MELD-Na scores may need to be supplemented by nontransplant interventions. For instance, in the ANSWER trial and others, regular albumin infusion improved survival and reduced decompensating events.[79,80] Although this study did not specifically analyze low MELD-Na patients, approximately 80% of the patients in this trial were of CTP class A or B, with a mean MELD-Na of around 16. This intervention in the low MELD-Na setting is supported by the finding that the greatest expansion of central blood volume after albumin infusion occurred in CTP A patients.[81] Other interventions such as exercise programs targeting sarcopenia and frailty have been shown to improve HVPG, muscle mass, and quality of life measures but have not yet been linked with pre or post transplant outcomes.[82,83] In addition to the intended effect on ascites and varices, TIPS has also been shown to improve nutrition and sarcopenia.[84–86] Lastly, small uncontrolled studies have demonstrated some effect of testosterone or amino acid supplementation on improving muscle mass but patient outcomes were not studied.[87–89] Overall, despite ongoing research there are few nontransplant interventions that have high quality evidence and are effective in the waitlist population.

Discussion

Liver transplantation is a resource intensive endeavor that is a major undertaking for both patients and healthcare systems. Coupled with the relative scarcity of organs, the study of transplantation efficacy and futility is often fraught with epidemiologic and ethical

limitations due to the inability to randomize patients to liver transplantation. Comparisons of findings across decades is further limited by evolving scoring systems with different inherent biases.

Nevertheless, improving risk prediction among patients on the waitlist is essential given the scarcity of organs. The hope for any scoring system would be to identify the patients who would benefit most from transplantation and could be applied to all patients, not just those with low MELD-Na scores. This would ensure that the patients who are truly the sickest do not get inappropriately de-prioritized for transplant and if necessary can be flagged for other therapies such as living donor transplant or higher risk grafts.

Improving risk prediction in patients with low MELD-Na scores is challenging because determining which of these patients will have significant liver-related morbidity and mortality is difficult. Many of the same factors that contribute to short term mortality may be those that would also lead to poor postoperative outcomes. As noted above, measures of frailty have helped to predict waitlist outcomes but also can portend poor post transplant outcome and functional status. Similarly, pretransplant echocardiographic measures of the right ventricle have been associated with poor post transplant outcomes.[22] Other measures, such as serum albumin, creatinine, or NLR, which have strong epidemiologic relationships may be confounded by their association with non liver related acute medical events. In Figure 1, we illustrate the inter-related physiologic and clinical processes present (four way arrow) that typically lead to transplant (bottom half of Figure). In contrast, patients with sarcopenia, low creatinine, and low MELD-Na scores may be more likely to present with a sudden decompensation, becoming ‘too sick for transplant’. The cause of this sudden and severe decompensation is most commonly due to infection, multisystem organ failure, bleeding, or hepatocellular carcinoma (HCC).[3] Currently however, there is no way to predict which of these patients with low MELD-Na scores will be the ones to experience these complications.

Taking into account the above aspects of this field of study, certain patients within the lower MELD-Na group may need to be targeted for earlier transplantation, such as those with enough predictors but not too many to lead to poor outcomes in the peri or postoperative time period. In the pre-MELD-Na era, Merion et al described that UNOS patients with MELD <15 who were receiving liver transplants had a higher one year mortality than those who remained on the waitlist.[90] A second study which looked five year outcomes suggested that there was an average benefit to transplantation for patients with MELD scores >10, but that even among the patients with scores <10, approximately 20% may still derive benefit.[91] A more recent analysis incorporating the MELD-Na score may suggest an even higher threshold of 21.[92] In contrast to the above deceased donor studies, living donor transplant did benefit patients with MELD <15 when studied by the A2ALL group.[93]

The management of patients in low MELD-Na groups will be of rising importance in the years to come especially with the growing number of patients with low MELD-Na after HCV therapy.[94] The question of transplantation for this cohort is also is likely to become more frequent with increasing organ availability as the fields of donation after circulatory

death, machine organ perfusion, and living donation/split transplant continue to advance.[95,96]

Conclusion

Prediction of mortality in patients with cirrhosis is an evolving science, based initially on observational assessment of procedural complications and gradually advancing to the incorporation of biomarkers and more complex statistical scoring strategies to further enhance the accuracy of prediction and allocation. Despite these improvements, select patients with low MELD-Na scores still suffer from liver related mortality and would likely benefit from earlier liver transplantation. Identifying these patients will require new approaches that incorporate the old concepts of nutritional status, hypoalbuminemia, and progression of portal hypertensive physiology. Future research should seek to validate the testing modalities described in this review that might be otherwise passed over by the current system of organ allocation—the MELD-Na score (Table 1 and 2).

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Abbreviations:

CT	computed tomography
CTP	Child-Turcotte-Pugh
ESLD	end stage liver disease
HVPG	Hepatic Venous Pressure Gradient
ICGC	indocyanine green clearance
INR	International Normalized Ratio
GFR	Glomerular Filtration Rate
MELD	Model for End-Stage Liver Disease
MELD-Na	Model for End-Stage Liver Disease with Sodium
NLR	neutrophil-to-lymphocyte ratio
SBP	Spontaneous bacterial peritonitis
SMI	skeletal muscle index
TIPS	Transjugular Intrahepatic Portosystemic Shunt

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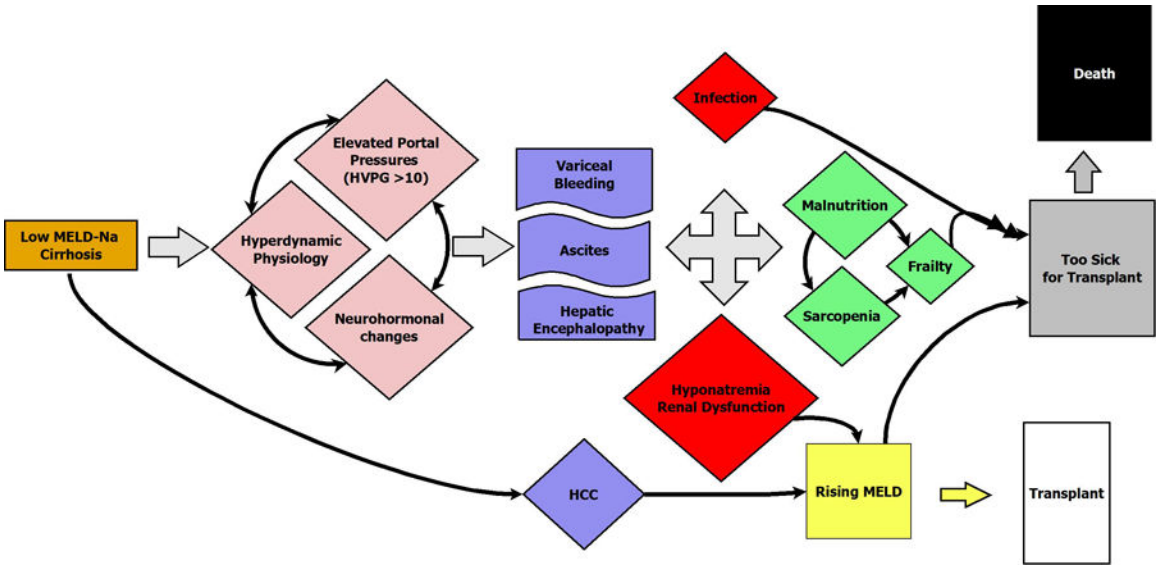

Figure 1:
Conceptual Pipeline of Events Leading to Progression and Death in Low MELD-Na Patients

Table 1.

Summary of Mortality Assessments in End Stage Liver Disease

Assessment	Relevance to Waitlist Mortality	Relevance to Post Transplant Outcomes
Frailty/Sarcopenia	• Increases mortality regardless of MELD-Na score. • Low muscle mass may falsely lower MELD-Na score	• Higher levels of sarcopenia and frailty associated with increased post transplant complications, hospital stay, and mortality.
Cardiovascular Physiologic Changes	• Decreased sympathetic responsiveness and persistent hyperdynamic physiology reduces ability to compensate and predisposes to HRS and mortality.	• Volume overload and hyperdynamic physiology may be worsened after LT and have been linked to post transplant mortality.
HVPG	• Elevated HVPG (>12 mmHg) linked to variceal bleeding and increased mortality	• Little to no data on the relationship between pretransplantation HVPG and post transplant outcome
Infection	• A leading cause of hospitalization and death in patients with cirrhosis	• A leading cause of hospitalization and death in the post transplant period
Functional Assessments and Biomarkers	• May best estimate liver function and reserve directly, little data on implications of testing on outcomes	• Little to no data on pretransplantation functional testing and post transplant outcome
Hyponatremia and Renal Dysfunction	• Hyponatremia has a disproportionate effect on low MELD patients which prompted MELD-Na • Renal function is a major prognostic indicator for mortality, however true measures of renal function are difficult to obtain	• Hyponatremia and renal dysfunction can improve with transplant but may persist in the setting of perioperative and immunosuppressive insults

Table 2.

Future directions for research

Assessment	Gaps in Knowledge/Research Questions
Frailty/Sarcopenia	• Should patients acquire MELD-Na points for frailty? • Are frailty and sarcopenia reversible with liver transplantation? • Is there a level at which they are not reversible?
Cardiovascular Physiologic Changes	• Can the presence of cirrhotic cardiovascular physiology convey a more biologically advanced state than their MELD-Na score may imply? • Can hemodynamic cardiovascular complications (heart failure, arrhythmia) be better predicted and managed after LT?
HVPG	• Does HVPG not responsive to medical therapy warrant earlier transplant evaluation? • Are there any reliable noninvasive measurements for HVPG?
Infection	• Is infection a marker of advanced disease not captured in the MELD-Na score?
Functional Assessments and Biomarkers	• Can we predict which patients with low MELD-Na scores have the least hepatic reserve? • Should these patients consider earlier transplant?
Renal Dysfunction	• Are there better predictors for renal function and patient outcomes than serum creatinine? • Are there earlier methods of detecting renal dysfunction prior to its occurrence or the presence of hyponatremia?
The future of the MELD-Na score	• Can incorporation of albumin, HVPG, sarcopenia, or other clinical variables improve the prognostic capability of the MELD-Na score? • Can assessment of the time varying nature of a patient's MELD-Na score be more informative than a single value? • How can machine learning and artificial intelligence be used to assess waitlist mortality risk among low MELD-Na patients?

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