Model for End-Stage Liver Disease (MELD) Score as a Biomarker

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Deepika Devuni and Jawad Ahmad

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D. Devuni • J. Ahmad (✉)
Division of Liver Diseases and Recanati-Miller Transplantation Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA
e-mail: jawad.ahmad@mountsinai.org; javbob@hotmail.com

Abstract

End-stage liver disease (ESLD) due to cirrhosis carries a high mortality. Previous methods to quantify the risk of death in these patients were subjective. The model for end-stage liver disease (MELD) score was developed and is an accurate biomarker of 90-day mortality in patients with ESLD, essentially measuring how sick a patient is. The MELD score incorporates serum bilirubin, creatinine, and INR in a mathematical formula. Since 2002, the MELD score has been used to prioritize deceased donor organ allocation for patients listed for liver transplantation (LT) in the USA. The use of the MELD allocation system has resulted in sicker patients being transplanted with decreased waiting time, thereby decreasing the death rate on the LT waiting list, without an adverse effect on posttransplant outcome. The MELD score has been adopted as a biomarker with good effect in other situations where patients with ESLD have a high risk of dying such as surgery, alcoholic hepatitis, acute liver failure, and variceal bleeding. Since the MELD score was introduced, there have been several modifications that may have increased effectiveness in certain situations. The MELD score is not an accurate biomarker for the risk of death from liver cancer and some other conditions, and hence for the purposes of liver allocation on the transplant list, an exception to the calculated MELD score can be given.

Keywords

Model for end-stage liver disease (MELD) score • End-stage liver disease • Liver transplantation • Organ allocation

Abbreviations

AH	Alcoholic hepatitis
CTP	Child-Turcotte-Pugh
DF	Discriminant function
ESLD	End-stage liver disease
FHF	Fulminant hepatic failure
HCC	Hepatocellular carcinoma
HCV	Hepatitis C
HRS	Hepatorenal syndrome
ICU	Intensive care unit
LT	Liver transplantation
MELD	Model for end-stage liver disease
OPO	Organ procurement organization
OPTN	Organ procurement and transplantation network
PSE	Portosystemic encephalopathy
TIPS	Transjugular intrahepatic portosystemic shunt
UNOS	United Network for Organ Sharing

Key Facts of the MELD Score

1. The MELD score is a mathematical formula that uses readily available blood tests to predict the severity of a patient's liver disease.
2. The MELD score is used to determine where patients are on the waiting list for liver transplantation in the USA – a higher score puts you higher on the list.
3. The MELD score ensures sicker patients are transplanted first.
4. The MELD score can be used in other liver conditions to predict how sick patients are.
5. The MELD score does not predict how well patients will do after liver transplantation.

Introduction

End-stage liver disease (ESLD) due to cirrhosis is the 12th leading cause of mortality in the USA according to the Centers for Disease Control (CDC). Patients with cirrhosis can be asymptomatic for many years during the compensated phase, but patients with decompensated cirrhosis have developed complications related to portal hypertension in the form of ascites, portosystemic encephalopathy, and variceal bleeding and are at risk of developing hepatocellular carcinoma (HCC). Patients who develop complications of portal hypertension and/or HCC are candidates for liver transplantation (LT).

Liver transplantation typically leads to 70% 5-year survival, but the main restriction is the lack of deceased donor organs. In the USA the number of patients waiting for LT (approximately 15,000) and transplants performed annually (approximately 6,000) has not changed for a decade, meaning a significant number of patients that are listed for LT will not get transplanted before they die or are removed from the list for being too sick to transplant. An equitable method to prioritize deceased donor organs is therefore of paramount importance. The federal government and the transplant community recognized this in the late 1990s, and this led to the development of the model for end-stage liver disease (MELD) score which has been used to prioritize potential recipients for LT since February 2002.

This paper will illustrate the strengths and weaknesses of the MELD score as a biomarker in patients with ESLD and its adaptation and modification for use in other liver diseases.

Natural History of Liver Disease

End-stage liver disease is typically due to viral hepatitis (B or C), fatty liver disease, alcoholic liver disease, autoimmune liver disease, metabolic liver diseases, and cryptogenic cirrhosis. The disease progression is very variable with some patients only developing inflammation without significant fibrosis, but a minority of patients will develop progressive fibrosis and eventually cirrhosis. Patients with cirrhosis can

often be asymptomatic and therefore undiagnosed unless they have been followed regularly. In addition, the compensated phase of cirrhosis can last for many years even when there are laboratory abnormalities. However, decompensation, defined by the development of ascites, variceal bleeding, or portosystemic encephalopathy (PSE), usually signals a more rapid progression of disease with mortality after the first decompensating event as high as 50% at 5 years (Fattovich 1997).

The HALT-C group followed a group of 1,050 subjects with chronic hepatitis C (HCV) and advanced fibrosis and determined that the incidence of cirrhosis was 9.9% per year (Dienstag 2011). In the study by Fattovich et al. (1997), 384 chronic HCV patients with cirrhosis were followed for more than 10 years, and the 5-year probability for hepatic decompensation was 18%, and 5-year survival was 91%. In a study comparing alcoholic cirrhosis and HCV, the risk of hepatic decompensation and mortality was similar, and importantly alcohol abstinence even in patients who had already developed cirrhosis improved the survival benefit (Toshikuni 2009).

Once decompensation has occurred, standard medical therapy can alleviate symptoms such as diuretics for ascites, endoscopic management of varices, and lactulose for PSE, but it does not reverse the pathologic process of cirrhosis. Such patients are therefore candidates for LT. With the high burden of liver disease, particularly viral hepatitis in the USA, the number of potential LT candidates exceeds the number of donor organs available. Hence the policy governing the allocation of these scarce organs has been under scrutiny ever since the early days of LT.

Allocation of Organs Prior to MELD

The allocation of deceased donor liver allografts was based on a system that emphasized patients' waiting time and hospitalization status separated into three main categories. Patients admitted to the intensive care unit (ICU) received priority over admitted patients in the hospital followed by patients who were ambulatory. The transplant community met to formulate the minimal criteria for placing adult patients on the LT waiting list (Lucey et al. 1997). They suggested that patients with all causes of cirrhosis with a Child-Turcotte-Pugh score of ≥ 7 or the presence of portal hypertensive gastrointestinal bleeding would qualify to be on the waiting list. The assessment of severity of liver disease was based on the Child-Turcotte-Pugh score.

Child-Turcotte-Pugh (CTP) Score

The CTP score was initially developed for assessing the severity of liver disease. In 1964, Child and Turcotte published a classification system as a tool to determine the preoperative risk of portosystemic shunt surgery for patients with variceal bleeding. It included five factors – encephalopathy, serum bilirubin, nutritional status, ascites, and serum albumin (Child and Turcotte 1964). Pugh et al. (1973) modified the score by replacing nutritional status with prothrombin time. They also added scores

Table 1 Child-Turcotte-Pugh scoring system for patients with ESLD

	1 point	2 points	3 points
Serum bilirubin	<2 mg/dl	2–3 mg/dl	>3 mg/dl
Serum albumin	>3.5 g/dl	2.8–3.5 g/dl	<2.8 g/dl
Ascites	Absent	Controlled with medications	Refractory
Encephalopathy	Absent	Medically controlled	Poorly controlled
INR	<1.7	1.7–2.2	>2.2

Table 2 Minimal listing criteria for liver transplantation prior to the MELD score

Status	Definition
1	Life expectancy of less than 7 days without transplantation:
	1. Fulminant hepatic failure
	2. Primary graft nonfunction within 7 days of LT
	3. Hepatic artery thrombosis less than 7 days after LT
	4. Acute decompensated Wilson disease
2A	In ICU with a CTP score >10 with unresponsive active variceal hemorrhage or hepatorenal syndrome or refractory ascites or hepatic hydrothorax or stage 3 and 4 encephalopathy
2B	Inpatients with a CTP score of ≥10 or a CTP score of ≥7 and either unresponsive active variceal hemorrhage or hepatorenal syndrome or spontaneous bacterial peritonitis and refractory ascites or hepatic hydrothorax
3	Patients needing continuous medical care, with a CTP score of 7 but not meeting criteria for status 2B
7	Temporarily inactive due to various reasons

ranging from 1 to 3 for each factor based on severity. They used the modified score to classify patients into A (5–6 points), B (7–9 points), or C (10 or more points) categories based on the cumulative points (Table 1). This scoring system was then used to assess the outcomes of surgery in patients with cirrhosis undergoing esophageal transection for bleeding varices. Patients with CTP class C had the highest mortality. The CTP score was included in the liver organ allocation as part of minimal listing criteria (Table 2).

The main disadvantage of using the CTP score was that the severity of ascites and encephalopathy are subjective, and it does not take into account renal function which is often abnormal in patients with more severe ESLD.

Development of MELD

The allocation of donor organs for LT is based on the availability of organs at the local organ procurement organization (OPO). There have always been geographic disparities in waiting time within the different areas in the USA which have increased as the number of transplant centers has increased despite the National Organ Transplant Act of 1984 which was meant to ensure equitable distribution of organs.

In 1998, the United States Department of Health and Human Services issued the "Final Rule" regulation (OPTN 1999). The principles of the "Final Rule" mandated that the sickest patients should get transplanted first without limitation of geographic area. It also recommended that a system be developed to standardize the criteria to place a patient on the waiting list and use factors to assess severity of liver disease with less subjective variability. The effect of disease severity and waiting time had been illustrated in a study by Freeman and Edwards (2000), which reviewed the 16,414 patients that were added to the waiting list from January 1997 to December 1997. They demonstrated that disease severity at the time of listing had a significant impact on mortality whereas waiting time did not. What was required was an accurate biomarker of liver disease severity that could measure the risk of dying with ESLD.

The precursor of the MELD score was based on article by Malinchoc et al. (2000) in which they were developing a statistical model to predict patient survival in patients undergoing elective transjugular intrahepatic portosystemic shunt (TIPS). A total of 231 patients were included from four transplant centers in the USA. The median survival time post TIPS was 1.4 years. In univariate analysis increasing levels of ascites, hepatic encephalopathy, Child-Pugh class and Child-Pugh score, bilirubin, creatinine, and INR significantly had a negative effect on survival. Increasing albumin level had a positive effect on survival. In multivariate analysis, they found serum creatinine, serum bilirubin, INR, and the cause of cirrhosis to be independent risk factors for mortality. These factors were then weighted to come up with a disease severity index that was termed the model for end-stage liver disease (MELD) score. The same group then examined the disease severity index in patients waiting for LT (Kamath et al. 2001). The formula for the modified MELD score is $3.8[\log_e$ serum bilirubin (mg/dL)$] + 11.2 [\log_e$ INR$] + 9.6 [\log_e$ serum creatinine (mg/dL)$] + 6.4$. The study initially included 282 patients hospitalized for complications of liver disease. Patient survival was assessed as the interval from the day of hospitalization to the last day of follow-up or death. The C-statistic for prediction of 3-month survival by MELD score was 0.87. They studied patients in the ambulatory setting and found a C-statistic of 0.87 and 0.8, respectively. The study also demonstrated that complications of portal hypertension such as ascites, variceal bleeding, or encephalopathy did not add to the C-statistic of the MELD score. In conclusion, the group felt that MELD score was better than CTP score and had less variability. They suggested that it followed the principle of the "Final Rule."

For the purposes of deceased donor organ allocation, patients with ESLD waiting for LT are each given a MELD score based on their laboratory parameters. The score increases as the severity of their disease worsens and so is checked periodically so that they can move up the list. The score starts at 6, since the lowest value of each integer is set at 1, and is typically capped at 40 since the 3-month mortality at this score is more than 80% (Fig. 1).

The MELD score was adopted as the method for prioritizing organs for deceased donor liver allocation on February 27, 2002. After the application of the MELD score, several studies showed a decrease in transplant waiting list mortality. Weisner et al. (2003) examined 3,437 liver transplant patients added to the list between

Fig. 1 Three-month mortality based on listing MELD in patients on the OPTN waiting list (From SRTR/OPTN annual report 2003 (www.srtr.org))
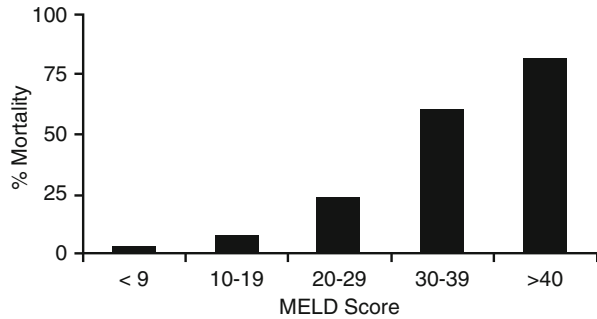

Fig. 2 Graph comparing MELD score and CTP score in assessing 90-day mortality in patients with ESLD
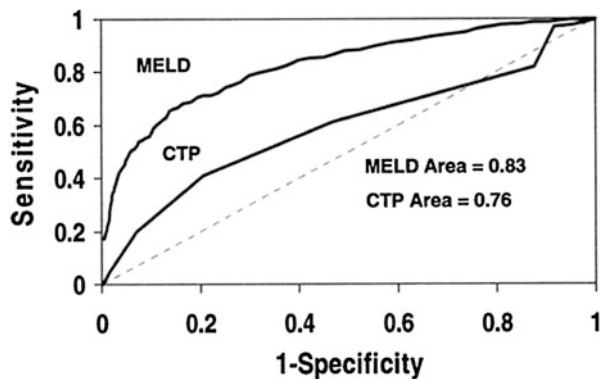
November 1999 and 2001. Four hundred twelve patients died during the 3-month follow-up period. Patients with MELD ≥ 40 had a mortality of 71%. The C-statistic for MELD score was 0.83 as compared to CTP score which was 0.76 (Fig. 2).

Data from the United Network for Organ Sharing (UNOS) had demonstrated that the number of patients waiting for LT had been steadily increasing for the 8 years prior to introduction of the MELD score (Fig. 3). Freeman et al. (2004) compared the rates of transplant listing, transplants, deaths, and removals between the year of MELD implementation and the year before. They observed a 12% decrease in the waiting list registrants as patients did not get an advantage of time on the list. There was also 3.5% decrease in waiting list mortality in the MELD era as compared to the year before as the sickest patients were transplanted first. Ahmad et al. (2007a) studied the impact of MELD allocation on US veterans undergoing LT in the Veterans' Healthcare System. A total of 207 patients were included in the study with 83 patients transplanted pre-MELD and 124 in the MELD era. The mean waiting time decreased from 461 days (pre-MELD) to 252 days (MELD era) ($P = 0.004$), and the mean MELD score at LT increased to 23.4 (MELD era) compared to 20.3 (pre-MELD) ($P = 0.01$), concluding that implementation of the MELD system led to sicker veterans being transplanted with shorter waiting times.
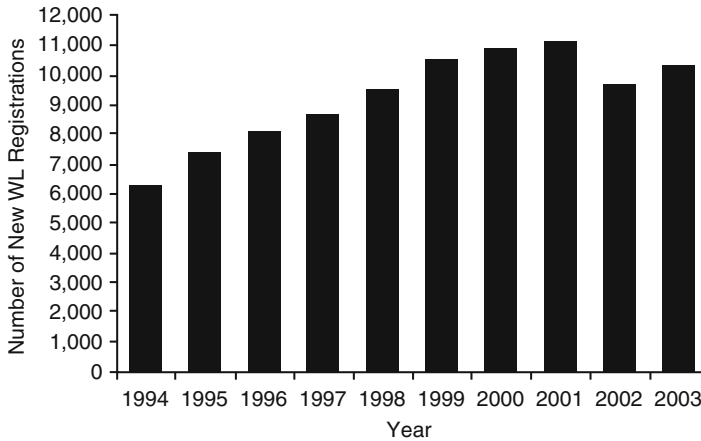
Fig. 3 New liver waiting list registrations in the USA from 1994 to 2003 (From 2004 OPTN/SRTR annual report, Table 1.5)

This shorter waiting time of sicker patients should translate into reduced death on the waiting list. In a study from Germany, Quante et al. (2012) reviewed the effect of MELD on wait list mortality. Wait list mortality was decreased from 18% to 10% ($p = 0.04$). The mean MELD score at allocation increased from 16.4 to 22.7 ($P = 0.007$), and the 90-day and 1-year survival post LT was found to remain stable at 90%.

MELD and Impact on Liver Transplantation

One of the main concerns and opposition of transplanting the "sickest first" was the impact it might have on early graft and patient survival since sicker patients presumably would not do as well posttransplant. In a study by Merion et al. (2005), survival benefit was assessed at various MELD levels. The survival benefit was defined as the difference between survival with or without transplant. Even if patients with a very high MELD score did not do as well after LT as patients with lower MELD scores, this would be offset by the very high mortality these patients have without LT. They demonstrated that the survival benefit at a MELD score of 40 was 96%. This suggests that high MELD score patients should get transplanted first, and the fact they did no worse than lower MELD score patients means that the MELD score is *not* a good biomarker for posttransplant outcome. Importantly, they also demonstrated that patients with MELD score <15 had worse outcomes with transplant, meaning that most patients with a low MELD score are better off waiting for LT until they become sicker.

The United Network for Organ Sharing has established 11 geographic regions for administrative purposes. There are 58 organ procurement areas which are responsible for retrieving organs and assigning them locally, then regionally, and

finally nationally depending on the MELD score of patients on the waiting list (which is subdivided by blood type). Despite the mandate that geography should not influence waiting time and MELD score at transplant, major differences still exist. Since some patients were still being transplanted in some regions at a low MELD score, with potentially worse outcomes, UNOS proposed a change in liver allocation: "Share 15" in January 2005. They proposed that the distribution sequence for a donor liver would be as follows: (1) local status 1, (2) OPTN region status 1, (3) local MELD ≥15, (4) OPTN region MELD ≥15, (5) local MELD <15, (6) OPTN region <15, (7) national status 1, and (8) national any MELD (Pomfret et al. 2007). This led to 36% decrease in transplants in MELD <15 and the proportion of transplants to recipients with MELD ≥15 increased in all geographic areas. Overall this improved the outcomes after LT, but a "MELD exception" system exists where patients with low MELD scores can be reviewed and appealed for a higher MELD score. A study by Bittermann et al. (2012) analyzed 452 MELD exceptions, 197 patients received a transplant, and 80% of these patients had MELD <15.

In spite of the Share 15, there is a disparity among various UNOS regions in terms of median MELD score at listing and transplant and time to transplant. Ahmad et al. (2007b) analyzed if MELD score at transplantation and waiting time of liver transplant recipients differs by transplantation center volume. They showed that despite having lower MELD scores, recipients at high-volume centers also experienced shorter waiting times (median waiting time, 69 days vs. 98 days, and 94 days at medium- and low-volume centers, respectively; $P < 0.001$).

In an ongoing effort to improve organ allocation, UNOS implemented "Share 35" on June 18, 2013. According to this rule, deceased donor livers are offered to regional candidates with MELD ≥35 before local candidates with MELD <35. Massie et al. (2015) compared the liver distribution and mortality in the first year of "Share 35." During this time, the proportion of deceased donor liver transplants (DDLTs) allocated to recipients with MELD ≥35 increased from 23.1% to 30.1% ($p < 0.001$). The proportion of regional shares increased from 18.9% to 30.4% ($p < 0.001$). There was a 30% decrease in wait list mortality of patients with MELD >30 but no difference in patients whose baseline MELD scores were lower. There were less discards of livers and no change in cold ischemia time.

MELD Use in Other Countries

In Europe, some countries have now adopted the MELD allocation policy including Eurotransplant in December 2006 (Germany, the Netherlands, Belgium, Luxembourg, Austria, Slovenia, and Croatia) Dutkowski et al (2010), North Italian Transplant in March 2003, Swiss Transplant in July 2007, and "l'Etablissement Français des Greffes" in France in March 2007. By contrast, several other European countries, such as Spain, Sweden, Finland, Norway, Denmark, Iceland, and the United Kingdom, still prefer to distribute their organs through a center-directed system.

In a study by Dutkowski et al. (2011), from Switzerland, they compared the first 100 transplants before and after implementation of MELD allocation. There was a decrease in waiting list mortality from 386 versus 242 deaths per 1,000 patient-years ($P < 0.0001$). It also led to transplantation of sicker patients, MELD 13.5 vs. 20 ($p = 0.003$), but the cost of transplantation was higher in the post-MELD era although patient survival was stable in both groups.

In another study from Germany, Benckert et al. (2011) studied 142 patients and found that wait list mortality had decreased, but 90-day mortality post LT did not change. They also confirmed that the MELD score is not a good biomarker of prognosis after LT. Similar findings were noted in Brazil, where MELD allocation was introduced in 2006 (Freitas et al. 2010).

MELD and Prognosis of Cirrhosis

Since the initial studies to develop MELD, multiple studies have evaluated the validity of the MELD score to assess the prognosis of liver disease. Botta et al. (2003) reviewed 129 patients with cirrhosis, and they found that the MELD score was a good predictor of short- and long-term survival and was equivalent to the CTP score. Papatheodoridis et al. (2005) compared MELD, CTP score, and creatinine modified CTP scores in decompensated cirrhosis. The accuracy of MELD was similar to the modified CTP score to predict short-term mortality, and MELD was better for long-term mortality. A large study of 1,611 patients with a spectrum of liver diseases found that patients with alcoholic liver disease had a higher 1-year and 5-year mortality than patients with alcoholic liver disease with hepatitis C, hepatitis C, or other causes of liver disease. The MELD score predicted increased mortality, with each unit increase in the MELD score predicting a 4–9% increase in mortality ($P = 0.0001$). The ROC curve C-statistic for the MELD as a predictor of 1-year mortality was 0.80 for all patients. They also found hepatic encephalopathy to be an independent predictor of mortality (Said et al. 2004). Similar findings were noted in 312 cirrhotic patients admitted to an intensive care unit. The overall mortality was 65.1%. The SOFA score (AUC 0.83) and MELD (AUC 0.81) were better predictors of mortality than traditional scores used in critically ill patients such as APACHE II (0.78) or Child-Pugh score (AUC 0.72). The authors concluded that cirrhotics with ≥ 3 organ system failure had 90% mortality (Cholongitas et al. 2006). In a study from India, 102 patients with cirrhosis were studied. They compared MELD, CTP score, and creatinine modified Child-Pugh score (CrCTP). The MELD was superior to CTP for predicting 3-month [C-statistic and 95% confidence interval, 0.967 (0.911–0.992) vs. 0.884 (0.806–0.939)] and 6-month [0.977 (0.925–0.996) vs. 0.908 (0.835–0.956)] mortality ($P = 0.05$), while CrCTP [0.958 (0.899–0.988)] was better than CTP for predicting 3-month mortality ($P = 0.02$). Serum creatinine (hazard ratio 4.43, $P < 0.0001$) was a strong independent predictor of mortality (Chawla et al. 2011).

Variability in MELD Calculation

The advantage of the MELD score over the CTP score is the objective measure in the variables that make up the MELD score. However, several studies have demonstrated that there can be interlaboratory differences in the calculation of MELD. Trotter et al. (2004) first demonstrated this when they compared the same blood sample in three different laboratories. They found that there was a statistical difference in MELD in one laboratory compared to the other two (MELD of 14 versus 17, $P < 0.03$). Most of the difference in the MELD score was due to the measurement of INR. This led to patients being listed with higher priority points. The same group looked at a larger number of laboratories and analyzed the interlaboratory variation in INR and if the differences would translate into clinically relevant changes in MELD score. They divided the samples in five different groups and INR ranged from (1.2–2) in sample 1 to (2.4–5.1) in sample 5. The variability of INR increased as the mean INR increased ($p = 0.0174$). Differences in MELD score were as high as 7 points (Trotter et al. 2007).

A similar effect on MELD scores with creatinine levels using different assays has been noted. Analysis of 403 samples from 158 patients concluded that the variability in creatinine measurement increased with rising serum bilirubin concentration, with a MELD variation of 3–7 points. A MELD score ≥ 25 was associated with the greatest variability. The authors concluded that there was poor correlation in creatinine scores with rising bilirubin and this may affect the MELD scores (Cholongitas et al. 2007a). These differences were also noted by two other studies (Schouten et al. 2012; Kaiser et al. 2014) as have gender differences since women with liver disease have a lower glomerular filtration rate for the same creatinine value. This may lead to women not getting priority on the waiting list (Cholongitas et al. 2007b).

MELD in Other Conditions

Since the adoption of the MELD score for prioritizing deceased donor liver allocation, it has been studied in various other situations involving patients with liver disease.

Surgical Risk in Patients with Cirrhosis

Patients with cirrhosis have a high risk of morbidity and mortality with any surgical procedure. Surgeons several decades ago were aware that the risk of mortality in cirrhotic patients undergoing cholecystectomy was as high as 25% (Aranha et al. 1982). Investigators then noted that several factors such as CTP score >7, presence of ascites, and elevated serum creatinine were associated with high mortality after surgery in patients with cirrhosis (Ziser et al. 1999). Teh et al. (2007) studied the short-term and long-term mortality risks in patients with cirrhosis who underwent various surgical procedures and specifically examined the effectiveness

of the MELD score as a biomarker. They looked at 772 patients undergoing abdominal ($n = 586$), orthopedic ($n = 109$), or cardiovascular ($n = 79$) surgery. The MELD score, anesthesia class, and patient age predicted mortality at 30 and 90 days, 1 year, and long-term follow-up to 20 years independent of the type of surgery. Surgery involving the liver in patients with underlying liver disease is another situation where an accurate preoperative biomarker is useful to stratify surgical risk. Cucchetti et al. (2006) studied the effectiveness of the MELD score as a biomarker on post hepatectomy outcomes in patients with HCC. One hundred fifty four patients undergoing HCC resection in a tertiary care setting were followed. Eleven patients had liver decompensation leading to death or requiring LT. A MELD score >11 was predictive of postoperative liver failure (area under the curve [AUC] = 0.92, 95% confidence interval [CI] (0.87–0.96); sensitivity, 82%; specificity, 89%). Cirrhotic patients with MELD score <9 had no postoperative liver failure and low morbidity (8.1%). Other studies have found similar results. A MELD score >8 was highly predictive of mortality in patients undergoing HCC resection (Hsu et al. 2009), and a MELD score >15 or greater had significant mortality after tricuspid repair or replacement (Ailawadi et al. 2009). Northup et al. (2005) analyzed 131 patients who underwent 140 non-transplant surgical procedures and found an overall 30-day postoperative mortality of 16.4%. They demonstrated that the mean MELD score in patients who died (24.8, 20.4–29.3) was significantly higher than survivors (16.2, 14.2–18.2), ($P = 0.0001$).

Alcoholic Hepatitis

Alcoholic hepatitis (AH) is characterized by acute or acute on chronic inflammation in the liver due to current alcohol consumption. Symptoms are variable but range from asymptomatic to fever, profound hyperbilirubinemia, and fatigue. Mortality can be as high as 50% (Menon et al. 2001). The earliest biomarker in this disease is the discriminant function (DF) which has been used to predict short-term survival in patients with AH and is calculated by the following equation: $DF = 4.6[\text{Prothrombin Time in seconds} - \text{control Prothrombin Time}] + \text{serum bilirubin}(\text{mg/dL})$. Maddrey et al. (1978) demonstrated that a DF score ≥32 predicts significant mortality and was an indication for the use of corticosteroids in this group of patients with improvement in survival. Several studies have used the MELD score as a biomarker to prognosticate in patients with AH. Dunn et al. (2005) conducted a retrospective study of 73 patients with AH and found MELD was the only independent predictor of mortality, with a MELD score of 21 having a sensitivity of 75% and a specificity of 75% in predicting 90-day mortality. The C-statistic comparing the prognostic validity of MELD and DF in AH was comparable for 30-day as well as 90-day mortality. The MELD score was better than the CTP score and DF in predicting mortality in patients with AH in a study of 202 patients. MELD scores were recorded at two time points, including admission and at the first week, along with the interval change in score. All three of these factors were found to be independently associated with in-hospital mortality. The first week MELD score cut

off of 20 had the best sensitivity and specificity in predicting mortality (Srikureja et al. 2005). A more recent study by Goyal et al. (2014) compared MELD, DF, CTP, and the Lille score for predicting the short-term mortality in patients with AH. A MELD score >14 at admission and >12 at day 7 had high sensitivity and specificity in predicting short-term mortality.

Acute Liver Failure

Patients with acute liver failure who are candidates for LT in the USA are listed as status 1. This means they get priority over the entire list of patients with a MELD score. According to UNOS, patients listed as status 1 must fulfill one of the following criteria: (1) fulminant hepatic failure (FHF), defined as the onset of hepatic encephalopathy within 8 weeks of the first symptoms of liver failure with no pre-existing liver disease; (2) nonfunction of a transplanted liver within 7 days of implantation; (3) hepatic artery thrombosis in a transplanted liver within 7 days; and (4) acute decompensated Wilson disease. Patients must fulfill one of the above criteria in addition to being hospitalized in the ICU with a life expectancy to be less than 7 days to be qualified for the emergent listing (Table 2). The transplant-free survival in patients with FHF is only 43% (Ostapowicz and Lee 2000).

A large study evaluated the ability of the MELD score at listing to predict pretransplant and posttransplant survival for patients listed as status 1 (Kremers et al. 2004). The investigators examined 720 patients listed for LT with FHF. They were divided into two groups, FHF associated with acetaminophen (FHF-A) and FHF associated with non-acetaminophen (FHF-NA) causes. There were two other small diagnostic groups: patients with primary nonfunction (PNF) and hepatic artery thrombosis (HAT). They demonstrated that patients with FHF-NA had the poorest survival and the MELD score had a negative correlation with survival. These people demonstrated most benefit from transplant.

Yantorno et al. (2007) compared the efficacy of King's College criteria, Clichy's criteria, and MELD score in adults with FHF. In the 120 study patients, MELD had the highest C-statistic of 0.95 and was superior to King's College criteria. A MELD score >18 on day 2 of acetaminophen ingestion was associated with development of hepatic encephalopathy (C-statistic 0.92) in patients in the US acute liver failure study group. The difference in MELD on the first day and at the onset of encephalopathy (ΔMELD) was associated with poor prognosis, and MELD itself was not a predictor of survival (Schmidt and Larsen 2007); however, this was not seen in an Indian cohort of FHF patients (Dhiman et al. 2007).

In a more recent study of the UNOS database, ESLD patients with the highest MELD scores were compared to patients listed as status 1. The study included 52,459 candidates (status 1 candidates, $n = 2,128$; ESLD candidates, $n = 50,331$) aged ≥18 years who were listed for deceased donor LT between September 1, 2001, and December 31, 2007. Out of the 2,128 patients listed as status 1, 485 had acetaminophen-induced liver failure, and the remaining 1,643 were non-acetaminophen induced. The study showed that patients with MELD scores

>40 had significantly higher wait list mortality risk than status 1 candidates. The authors suggested that patients with ESLD with MELD >40 should get priority over status 1 patients. ESLD patients with MELD scores 36–40 had similar wait list mortality risk as status 1 candidates, and hence they concluded that they should be prioritized equally rather than sequentially. Post-LT survival was similar among status 1 and all groups of ESLD candidates. MELD was a significant independent predictor of wait list mortality in the acetaminophen status 1 subgroup (Sharma et al. 2012).

Variceal Bleeding

Gastroesophageal varices develop in about 50% of patients with cirrhosis and typically correlate with severity of the disease. The annual rate of esophageal variceal bleeding (EVB) is 5–15% (Garcia Tsao et al. 2007) with a 6-week mortality of 15–20% and as high as 30% patients with severe decompensated liver disease (CTP score C) (Villanueva et al. 2006). Chalasani et al. (2002) conducted a study to compare the MELD score with the CTP score as a prognostic marker in patients with acute variceal bleeding. In-hospital and 1-year mortality rates were 14.2% and 27%, respectively. The C-statistic for MELD score to predict mortality was 0.82, significantly higher than the CTP score.

Decompensation During Interferon Therapy of HCV Cirrhosis

A recent study of patients receiving pegylated interferon and ribavirin treatment for HCV-related cirrhosis demonstrated that hepatic decompensation was seen in 36.8% of patients during treatment and the MELD score was independently predictive of decompensation with a MELD score >14 associated with 83% chance of worsening of liver disease while on treatment (Dultz et al. 2013).

Hepatorenal Syndrome

Hepatorenal syndrome (HRS) is defined as the development of impaired renal function in patients with cirrhosis or other liver disorders and is characterized by renal vasoconstriction. HRS is classified into two clinical subtypes. Type 1 is defined as a doubling of the serum creatinine concentration (above 2.5 mg/dL) and reduction of creatinine clearance (CrCl) by 50% (or <20 mL/min) in less than 2 weeks. It is associated with very poor outcome with 1-month mortality exceeding 50%. Type 2 is defined by an increase in serum creatinine level to >1.5 mg/dL (or CrCl <40 mL/min) and a urine sodium level <10 mmol/L. Type 2 HRS has a less progressive course but still has a 6-month mortality of 50% (Arroyo et al. 1996).

Alessandria et al. (2005) studied 105 patients ($n = 41$ type 1, $n = 64$ type 2) with HRS. They demonstrated that the MELD score was an independent predictor of

mortality. All patients with type 1 HRS had a high MELD score (≥ 20) and had a median survival of 1 month. The survival in type 2 HRS patients correlated with their MELD score. Patients with a MELD score >20 had a median survival of 3 months and patients with MELD <20 had a survival of 11 months.

MELD Variations

ΔMELD
Variation of MELD over time has been suggested as an important biomarker in patients with ESLD as it relates to residual liver function. Merion et al. (2005) followed serial MELD scores in patients listed for transplant. Patients with MELD score increases greater than five points over 30 days had a threefold greater wait list mortality risk than those for whom MELD scores increased more gradually ($P < 0.0001$). For any MELD score, the magnitude of change in the last 30 days was considered an independent risk factor for mortality. Similar results were noted when comparing the C-statistic of MELD, ΔMELD, and CTP score in 351 cirrhotic patients. ΔMELD was superior to initial MELD and CTP scores to predict intermediate term outcome in patients with advanced cirrhosis (Huo et al. 2005).

MELD Sodium (MELDNa)

Hyponatremia is a considered a poor prognostic marker in patients with cirrhosis. It is associated with ascites and HRS and predicts increased mortality in cirrhosis. Several studies have demonstrated that in patients with a relatively low MELD score (<21), hyponatremia (Na <135) and persistent ascites were independent predictors of mortality (Heuman et al. 2004; Dawwas et al. 2007). Patients with hyponatremia but a low MELD score are therefore disadvantaged by the current MELD score-based allocation system. Ruf et al. (2005) investigated the prognostic value of adding serum sodium to the MELD score in 262 patients with ESLD. The risk of death across all MELD scores was higher with hyponatremia than those without, with a C-statistic for MELD with serum sodium of 0.905. In addition, a serum sodium <126 meq/l at listing or while listed for transplantation is an independent predictor of 3- and 6-month mortality (Biggins et al. 2005), and there was a significant interaction between MELD score and the serum sodium concentration in 6,769 liver waiting list registrants, with a more pronounced effect of serum sodium on patients with a lower MELD score (Kim et al. 2008).

Based on these findings, the MELD score was modified to incorporate the serum sodium concentration (Biggins et al. 2006; Kim et al. 2008). The MELDNa is calculated by: $\text{MELDNa} = \text{MELD} - \text{Na} - [0.025 * \text{MELD} * (140 - \text{Na})] + 140$, for sodium concentrations between 125 and 140 mEq/L. The MELDNa was better at predicting mortality in patients listed for LT compared to the MELD score (Kim et al. 2008). Several other investigators found that MELDNa was a superior biomarker of mortality compared to the standard MELD score in other situations,

including acute decompensated hepatitis (Hsu et al. 2010), hepatocellular carcinoma (Huo et al. 2008), and cirrhotic patients undergoing surgery (Cho et al. 2011).

iMELD

Another modification of the MELD score is the iMELD. MELD, age, and serum sodium were noted to be independent risk factors for mortality in a cohort of patients undergoing TIPS, and these three factors were incorporated into an integrated MELD (iMELD) by a European group. The iMELD was better than the original MELD in predicting 12-month mortality and was validated in a sample of 451 patients with cirrhosis on the waiting list for LT with increased auROC (+8%) and likelihood ratio statistic (from 41.4 to 82.0) (Luca et al. 2007). The iMELD was a better prognostic model for outcome prediction in patients with decompensated cirrhosis compared to MELD and MELDNa (Jiang 2008).

MELD-XI

Cardiohepatic syndrome is described as the development of liver dysfunction which can subsequently lead to cirrhosis in patients with heart failure (van Deursen 2010). Many of these patients are on anticoagulation. Therapeutic anticoagulation will artificially increase the INR and confer an advantage to these patients under the existing system of organ allocation. Hence, an alternative score was developed, called MELD-XI (MELD excluding INR), by normalizing to the same scale as MELD but omitting INR. The formula for MELD-XI is MELD-XI = 5.112 ln (bilirubin) + 11.76 ln (creatinine) + 9.44. MELD-XI was comparable to MELD as a predictor of pretransplant 90-day mortality (Heuman et al. 2007). C-statistics for MELD and MELD-XI were comparable in patients with cholestatic liver diseases (0.905 ± 0.030 vs. 0.894 ± 0.031) as well as non-cholestatic causes of cirrhosis (0.857 ± 0.016 vs. 0.843 ± 0.016). In a study of 255 patients undergoing primary long-term left ventricular assist device placement, patients with MELD or MELD-XI <17 had improved on-device and overall survival ($p < 0.05$) with a higher predictive power for MELD-XI. The patients who demonstrated improvement in MELD-XI score during device support had similar outcomes to those without liver dysfunction (Yang et al. 2012). Kim et al. (2013) studied the effect of MELD, MELDNa, and MELD-XI in ambulatory patients with hepatic dysfunction being evaluated for heart transplant and found that increased MELD and MELDNa had an increased independent risk of transplant.

MELD Limitations

Since the implementation of the MELD score, it has proven to be a more equitable method for organ allocation. However, there are certain conditions in which the

MELD score does not adequately predict the wait list mortality or prognosis. This has led to the development of the MELD exception.

MELD and Hepatocellular Carcinoma

Patients with HCC typically have cirrhosis but may not have advanced disease (and therefore a low MELD score) and yet are still at risk for death. The seminal study on LT in patients with HCC came out of Milan, Italy, and demonstrated that LT in patients with early HCC (one lesion <5 cm or three lesions each <3 cm) had comparable survival to patients without HCC, known as the Milan criteria (MC) (Mazzaferro et al. 1996). With the introduction of MELD, it was apparent that to enable patients with HCC and a low MELD score to have a reasonable chance of getting transplanted, they would need an exception to their biological MELD score. To try and equate the risk of dying with HCC with a biological MELD score, it was initially decided to allocate a MELD score of 24 for T1 lesions (<2 cm) and 29 for T2 (>2 cm and <5 cm, or three lesions <3 cm). This improved the probability of LT for patients with HCC on the waiting list (Yao et al. 2004). Comparing pre-MELD and post-MELD era patients with HCC listed for LT, investigators noted that the 5-month waiting list survival was 90.3% pre-MELD and 95.7% post-MELD ($P < 0.001$), demonstrating that the MELD exception benefited the HCC patients (Sharma et al. 2004).

The initial MELD exception point allocation was decreased to 24 in April 2003 and 22 in January 2005 for T2 lesions with a 10% increase in risk reflected in a rise in MELD score every 3 months. Both of these decreases occurred as it was noted that the allocated MELD score did not correlate to the risk of wait list dropout for these candidates. There have however been no further changes in the allocation of incremental exception points over time. The current policy states that an HCC candidate with tumor within MC may receive an exception MELD score, "equivalent to a 15% probability of candidate death within 3 months," with additional points given every 3 months, "equivalent to a 10% increase in candidate mortality." However, several studies have suggested this MELD exception is not such an accurate biomarker of poor outcome and may favor HCC patients (Massie et al. 2011; Washburn et al. 2010) and neither the initially nor the incrementally awarded MELD exception points for HCC accurately reflect the risk of wait list removal for HCC candidates, particularly when compared to non-HCC candidates (Goldberg et al. 2012). Currently, UNOS/OPTN is reviewing new changes to MELD exceptions such as capping HCC MELD to 34 points and to delay listing for HCC by 6 months.

MELD Exceptions for Other Conditions

MELD exceptions are also given for other conditions associated with ESLD that confer a risk of death but are not accurately measured by the MELD score (Freeman et al 2006; Table 3). These include pulmonary complications of cirrhosis,

Table 3 Conditions where a MELD exception is permitted on the LT waiting list

Condition	MELD exception points	Increase in points
Hepatocellular carcinoma (T2)	22	10% increase every 3 months
Familial amyloidosis polyneuropathy	22	10% increase every 3 months
Hepatopulmonary syndrome (HPS)	22	10% increase every 3 months
Portopulmonary hypertension	22	10% increase every 3 months
Cholangiocarcinoma (meeting protocol)	22	10% increase every 3 months
Cystic fibrosis	22	
Primary hyperoxaluria	28	
Metabolic disorders	30	If no transplant in 30 days, then status 1b

hepatopulmonary syndrome (characterized by PaO_2 <60 mmHg on room air) and portopulmonary hypertension (characterized by a mean pulmonary artery pressure ≥35 mmHg at diagnosis that must be maintained at <35 mmHg with treatment), and complications of liver disorders like primary sclerosing cholangitis leading to recurrent cholangitis. Patients with rare conditions like cystic fibrosis, familial amyloid polyneuropathy, polycystic liver disease, and primary oxaluria whose liver function is usually preserved but need a liver transplant also benefit from MELD exceptions. Patients listed with the MELD exception typically receive a 10% increase in their MELD score every 3 months while on the waiting list. In certain regions, centers can appeal for extra MELD points if the natural MELD of the patient does not reflect the underlying severity of liver disorder.

MELD and Posttransplant Outcome

The success of MELD for liver allocation and prognosis of other liver disorders has led to multiple studies evaluating the effect of the MELD score on posttransplant outcomes. Most have found no association between patient or graft outcome (Santori et al. 2005; Cywinski et al. 2011; Hayashi et al. 2003) although a single study suggested that MELD >25 was associated with poor patient and graft survival (Habib et al. 2006) and a MELD >23 predicts longer intensive care stay (Oberkofler et al. 2010). However, a MELD score >19 on postoperative day 5 may predict early graft dysfunction (Wagener et al. 2013).

Summary Points

1. The MELD score is an accurate biomarker of 90-day mortality in patients with ESLD, essentially measuring how sick a patient is.

2. Since 2002, the MELD score has been used to prioritize deceased donor organ allocation for LT in the USA.
3. The use of the MELD allocation system has resulted in sicker patients being transplanted with decreased waiting time, thereby decreasing the death rate on the LT waiting list, without an adverse effect on posttransplant outcome.
4. The MELD score has been adopted as a biomarker in other conditions associated with liver disease with good effect.
5. There are modifications of the MELD score that may have increased effectiveness in certain situations.
6. The MELD score is not an accurate biomarker for the risk of death from liver cancer and some other conditions and hence for the purposes of liver allocation on the transplant list a MELD exception can be given.

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