Is the Model of End-Stage Liver Disease (MELD) Valid in Israel? A Critical Analysis of Liver Transplant Waiting List Mortality

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Abstract

Background: The model for end-stage liver disease is the best available predictor of waiting list mortality among liver transplant candidates.

Objectives: To validate the applicability of MELD in Israel.

Methods: All candidates awaiting liver transplantation in our institution were followed prospectively since 2002. We measured the concordance (c-statistic) equivalent to the area under the receiver operating characteristic curve in order to assess the predictive power of MELD. Other independent mortality risk factors were identified by a separate multivariate analysis. Mortality rates within different MELD and Child-Pugh-Turcotte scores were compared to the original (United States) MELD data.

Results: Of 86 patients listed for transplantation, 40 were transplanted (36 in Israel and 4 abroad). Of the other 46 patients, 24 are alive and still listed, and 22 died (25%, ~7%/year). The area under the ROC curve for MELD score was 0.79 (0.83 USA) compared to a CPT score of 0.71 (O.76 USA). High MELD scores, occurrence of spontaneous bacterial peritonitis, and diagnosis of hepatocellular carcinoma were independent risk factors of mortality. Death rates per mid-MELD score (20–29) were significantly higher than the USA results.

Conclusions: MELD is valid in Israel and superior to CPT in predicting waiting list mortality. Although longer waiting time due to organ scarcity is a key factor, death rates in the mid-range (10–29) MELD groups indicate further audit of the care of patients with end-stage liver disease.

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Outcome prediction of patients with chronic end-stage liver disease is problematic. There are no simple, direct quantitative measurements and the accuracy of existing scoring systems, such as the traditional Child-Pugh-Turcotte classification, is limited. In addition, their clinical parameters are subjective. In the absence of any alternatives, the CPT classification determines patient prioritization in the process of organ allocation. In 2001, the Mayo Clinic group suggested a novel model to predict the outcome of patients with ESLD, which they named model of end-stage liver disease [1,2]. Soon afterwards, the United Network of Organ Sharing conducted a multivariate analysis of mortality risk factors within the national waiting list in the United States, which validated the MELD as an accurate tool for the prediction of death while awaiting liver transplantation [3]. In 2003, MELD was formally adopted by the UNOS for allocation and quality control. It has since been validated in many other aspects of terminal liver disease, including the prediction of prognosis in viral or alcoholic hepatitis [4], risk of mortality among cirrhotic patients [5], outcome following liver transplantation [6], outcome following general surgical procedures in patients with ESLD [7], following transjugular intrahepatic portosystemic shunt procedures [8], following transarterial chemoembolization for hepatocellular carcinoma [9] and, recently, also as a prognostic tool for patients with acute liver failure [10].

The advantages of MELD include objectivity, reproducibility, simplicity and comparability. MELD was studied extensively over the past 2 years [11,12] and there is now wide agreement of its superiority over the previous allocation system [13]. It was therefore proposed as a tool for cadaveric liver graft allocation in Israel, even before its applicability to the Israeli circumstances was confirmed [Ashckenazi T, Romano Z. Board of Directors meeting, Israel Transplant, 16 June 2005; synopsis, personal communication].

Theoretically, different compositions of the waiting lists (demographic and etiologic factors, disparity of ESLD severity, etc.) and differences in the quality of management of patients with ESLD can all alter MELD suitability for Israel. The aims of this study were to compare the makeup of the waiting lists in Israel and the USA, to evaluate the validity of the MELD in Israel, to identify additional independent mortality risk factors other than the MELD, and to compare outcomes of patients with ESLD (transplant candidates) in Israel vs. the USA.

Patients and Methods

We designed this study to imitate the original MELD analysis, as performed by Wiesner et al. [3], which prospectively applied

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MELD = model for end-stage liver disease
ROC = receiver operating characteristic
CPT = Child-Pugh-Turcotte

ESLD = end-stage liver disease
UNOS = United Network of Organ Sharing

the MELD for establishing 3 month mortality of 3437 adult liver transplant candidates suffering from chronic ESLD. The size of our list (smaller) and the frequency of laboratory and clinical updates (fewer), however, mandated a modified approach. Instead of parallel analysis of a cohort of patients listed for transplantation within a defined period, we looked at all the listed patients within the last 3.5 years. To overcome the differences in follow-up, we used the MELD values and CPT scores as calculated at the last ambulatory "elective" clinic visit but not at the time of active complication or hospitalization (bleeding, infection, invasive treatment of HCC, etc.). In other words, instead of comparing the MELD values, CPT scores and prospective 3 month outcome as had been done originally, we compared the last elective MELD and last elective CPT with the outcome, which was determined after 3 months by defined endpoints (see below). By so doing, we overcame the effect of waiting time *per se* and the expected natural deterioration of the patients while awaiting transplantation.

Patient population
The patient cohort included adults (age > 18 years) with chronic ESLD (UNOS status 2A or 2B) who were referred and listed for liver transplantation in the Tel Aviv Sourasky Medical Center between January 2002 and June 2005. We excluded all status 1 cases (acute hepatic failure or failure of recent transplant, n=10), patients who were transplanted from living donors (n=7), and off-list patients with extended criteria of HCC who were waiting for or received extremely marginal organs (n=4). The age limit for listing in Israel is 65 years and the Milan criteria are applied for HCC cases [14].

Outcome
Outcome endpoints included transplantation (by us or abroad), death (by any cause), being dropped from the list ("too sick" or tumor progression beyond the Milan criteria), or alive and registered – all within 3 months after the last elective assessment.

Follow-up
All patients were periodically seen in the referring hepatology units, and a summary that included clinical and laboratory data was filed in our transplantation unit. The patients were also seen by our physicians (hepatologist and/or transplant surgeon) at registration, every 6 months thereafter, or following any significant medical event or change in their baseline clinical condition.

Data collection
All the demographic, clinical, laboratory and imaging data were systematically recorded in the patient's pre-transplant charts and retrieved into an electronic database by the transplant coordinator. The evaluated parameters are summarized in Table 1.

The MELD
The MELD score was determined by using the UNOS Internet site MELD calculator [15]. The MELD equation used to calculate the severity score is: MELD score = $(9.57 \log_e$ creatinine mg/dl

Table 1. Demographic, clinical and laboratory factors evaluated as mortality risk factors of liver transplant candidates in this study

Demographics	
Age	yrs
Gender	Male / Female
Marital status	Married / single
Clinical data	
Etiology of ESLD	HCV / HBV / ETOH / cholestatic disease / other
Ascites	1–3 (mild / moderate / severe)
Encephalopathy	1–5 (minimal changes / confusion / drowsiness / somnolence / coma)
Event of SBP	Yes / no
Event of gastrointestinal bleeding	Yes / no
Diagnosis of HCC	Yes / no
Laboratory results	
Hemoglobin	g/dl
Platelets count	x103 / µl
Albumin	g/dl
INR	Units
Bilirubin	mg/dl
Creatinine	mg/dl
Scores	
CPT	Points, 1–15
MELD	Points, 1–50

HCV = hepatitis C viarus, HBV = hepatitis B virus, ETOH = ethanol hepatitis

$+ 3.78 \log_e$ bilirubin mg/dl $+ 11.20 \log_e$ INR $+ 6.43$ [constant for liver disease etiology]).

Organ allocation
The policy of cadaveric liver allocation for transplantation in Israel was modified during the study period (January 2002 to June 2005). Until June 2003, allocation was between the transplant centers in proportion to the size of waiting lists, but it was the center's prerogative to choose the recipient. Since June 2003, the Israel Transplant Authority managed a national waiting list based on the New England modification of the old UNOS allocation system in which disease severity was measured by CPT classification with additional scoring for complications, such as intractable ascites, hepatorenal syndrome, HCC, and others [16]. Given the scarcity of donors and organs in Israel, other centers and hepatologists liberally refer transplant candidates to transplantation abroad [17]. For reasons beyond the scope of this analysis, we did not use this route systematically; we also never denied it to our patients.

Statistical analysis
To compare the predictive power of the MELD vs. CPT scores, we measured the concordance (c-statistic) equivalent to the area under the receiver operating characteristic curves [18]. A separate multivariate logistic regression with outcome as the dependent variable was conducted for the scores and other factors [Table 1] to identify other independent mortality risk factors. Mortality rates of the recipient candidates in Israel vs. the USA per each

HCC = hepatocellular carcinoma

MELD or CPT category were compared using the chi-square or Fisher's exact test as applicable. The statistical analysis was performed with the SAS for Windows version 9.1 conducted by the statistical service of the Tel Aviv Sourasky Medical Center.

Results

Listing and transplantation

Between January 2002 and June 2005, 86 patients were listed for transplantation in our institution, representing approximately 20% of all listings for liver transplantation in Israel. Forty were transplanted (36 in Israel and 4 abroad). Of the remaining 46 patients, 24 are alive and are still listed, and 22 have died (overall mortality, 25%, ~7%/year).

Composition of waiting lists

The epidemiologic characteristics of the Israeli waiting list were different from the American list. The male:female ratio was 1.2:1 vs. 2.1:1 in the USA, and the distribution of ESLD etiologies was hepatitis C virus 47% (vs. 36.4% for the USA), hepatitis B virus 19% (vs. 5.8%), alcoholic cirrhosis 10% (vs. 27.6%), autoimmune hepatitis, non-alcoholic steatohepatitis, primary sclerosing cholangitis and primary biliary cirrhosis 6% each (vs. 4.9%, 2.4%, 1.8% and 1.1%, respectively). The percentages of patients in each MELD category, however, were closer: 3.4% Israeli vs. 3.5% USA in MELD < 10, 69.7% vs. 52.3% in MELD 10–19, 22% vs. 32% in MELD 20–29, 2.3% vs. 8.5% in MELD 30–39 and 2.3% vs. 3.5% in MELD > 40 [Figure 1].

MELD vs. CPT

The MELD was superior to CPT scores in the prediction of list mortality. By using the c-statistic, the area under the ROC curve for the MELD score was 0.79 compared with 0.71 for the CPT score (vs. 0.83 and 0.76 in the original MELD study, respectively) [Figure 2].

Multivariate analysis of risk factors

In addition to high MELD scores, of all the evaluated factors [Table 1], a previous episode of SBP and the diagnosis of HCC were independent risk factors of list mortality (P values 0.002, 0.057 and 0.0015, respectively).

Cause of death

The terminal events that were documented as cause of death in the 22 deceased patients included spontaneous bacterial peritonitis in 7 (32%), gastrointestinal hemorrhage in 6 (27%), biliary sepsis in 4 (18%), HCC-related in 2 (9%), not related to ESLD in 1, and unknown in 2.

Outcomes of transplant candidates

Except for the MELD scores of < 10 and > 30, for small numbers of patients, the death rates per each MELD score were significantly higher than the original American results: 13.3% vs. 7.7% in MELD 10–19 ($P = 0.18$), 52.6% vs. 23.5% in MELD 20–29 ($P =$
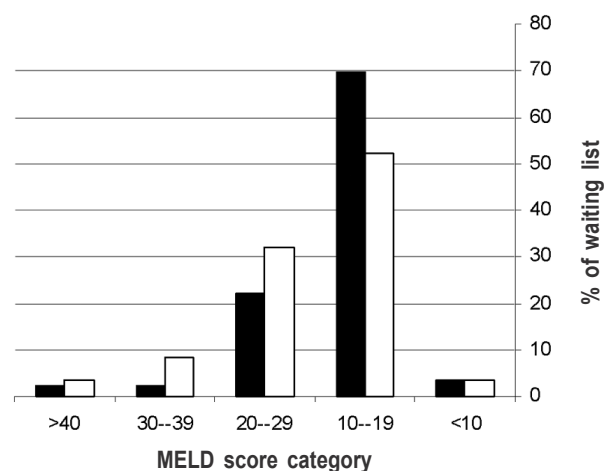
SBP = spontaneous bacterial peritonitis

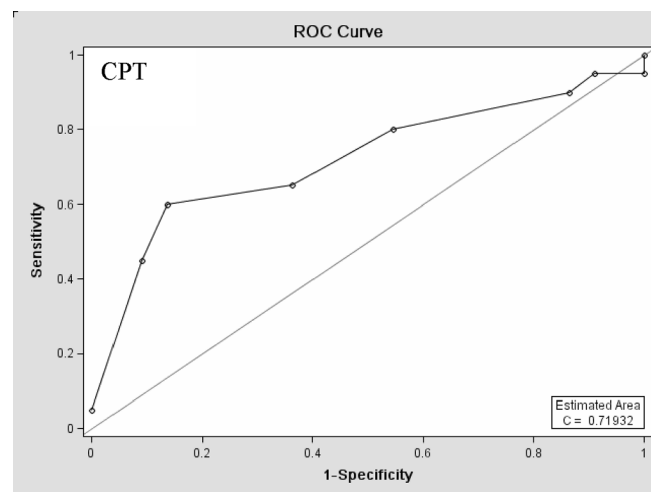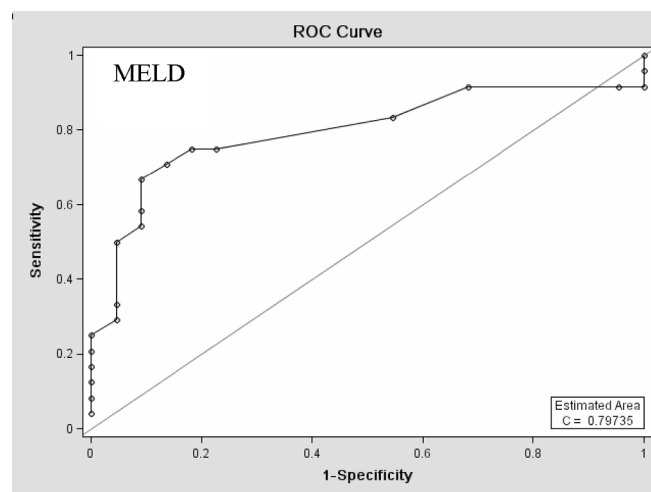**Figure 1.** The percentage of transplant candidates per each MELD category in Israel (■) vs. USA (□).

Figure 2. The area under the ROC curves for the MELD score (upper) and CPT score (lower) with 3 month mortality as endpoint.

Table 2. Dropout rates per each MELD and CPT category: our series (Israel) vs. the original MELD (USA) study

	Dropout rate (mortality + too sick)						
	Our series (n=86)					Original study (n=3437)	
	Listed	Trans-planted	N	Died	Mortality	N	Mortality	P
Class, MELD								
< 10	2	1	3	0	0%	124	2.9%	1.0
10–19	28	32	60	8	13.3%	1800	7.7%	0.18
20–29	12	7	19	10	52.6%	1098	23.5%	0.0074
30–39	2	–	2	2	100%	295	60.2%	0.52
> 40	2	–	2	2	100%	120	79.3%	1.0
Total	46	40	86	22	25%			
Class, CPT								
< 10	5	14	19	1	5%	318	5.6%	1.0
10–12	20	19	39	6	15.3%	2357	13.4%	0.9
13–15	21	7	28	15	54%	588	48.5%	0.74

0.0074), 100% vs. 60.2% in MELD 30–39, and 100% mortality vs. 79.3% in MELD > 40. When stratified by CPT classes, death rates per each class were comparable: 5% vs. 5.6% in CPT class A, 15.3% vs. 13.4% in CPT class B, and 54% vs. 48.5% in CPT class C [Table 2].

Discussion

The purposes of this analysis were to validate the MELD in the Israeli setting, to search for other mortality risk factors, and to compare the outcomes of patients with ESLD who are transplant candidates. We found that although CPT classification had a predictive value, the MELD was found to be superior (a c-statistic between 0.8 and 0.9 indicates excellent diagnostic accuracy and a model with a c-statistic over 0.7 should be considered clinically useful). Moreover, the objective and numerical nature of the MELD should preclude any conflicts between clinicians in prioritization of candidates. Previous episodes of SBP or HCC (within the Milan criteria) were also independent mortality risk factors. A major change that is being contemplated since the introduction of the MELD is extra scoring of HCC to balance the cancer- and ESLD-related death or dropout rates [19,20]. Continuous modification and reevaluation of the allocation process and the results of transplantation are essential to appropriately address this issue. Interestingly, the presence of HCC was not the direct cause of death but rather an independent predictor in patients in whom the cause of death was SBP or gastrointestinal hemorrhage – a phenomenon previously described but not fully explained elsewhere [21]. Another recently proposed modification is the usage of a change in the MELD score during the waiting time, but this needs better confirmation [22,23].

An unexpected byproduct of the current analysis is the significant disparity in the outcome of patients with ESLD between Israel and the USA. Bearing in mind that ours was a small cohort and that our study design was different, survival rates of cirrhotic patients in Israel emerged as being inferior when adjusted by

the MELD. Since the outcome measure is 3 month mortality and given that the waiting time *per se* is not a risk factor, the severe organ scarcity in Israel cannot explain this disparity, especially in the mid-high MELD patients in whom the risk of death while waiting is significantly lower in the USA cohort. Assuming that our statistical analysis is valid, a theoretical explanation should include differences in motivation, approach, expertise, resources, referral patterns and/or timing of preventive procedures (such as transjugular intrahepatic portosystemic shunt, variceal eradication, etc.). This critical subject is not within the scope of this paper. If our data faithfully reflect the Israeli reality, the care of patients with ESLD needs to be carefully and comprehensively investigated.

In conclusion, the MELD is valid for use in Israel and superior to the CPT classification in predicting mortality of liver transplant candidates. The application of the MELD for national cadaveric liver allocation is justified. The mortality rates of patients with ESLD, stratified by MELD categories, are significantly higher in Israel than the reported rates in the USA. Longer waiting time and organ scarcity cannot explain this disparity. Further audit of the care of patients with ESLD is indicated.

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