

MELD Score as a Predictor of Pretransplant and Posttransplant Survival in OPTN/UNOS Status 1 Patients

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The Model for End-Stage Liver Disease (MELD) score is predictive of survival and is used to prioritize patients with chronic liver disease patients for orthotopic liver transplantation (OLT). The aims of this study are (1) to assess the ability of MELD score at listing to predict pretransplant and posttransplant survival for nonchronic liver disease patients listed with the Organ Procurement and Transplantation Network/ United Network for Organ Sharing (OPTN/UNOS) as Status 1; and (2) to compare survival associated with 4 diagnostic groups within the Status 1 designation. The study population consisted of adult patients listed for OLT at Status 1 in the UNOS national database between November 1, 1999 and March 14, 2002 (N = 720). Events within 30 days of listing were analyzed using Kaplan-Meier and Cox regression methodology. Patients meeting criteria for fulminant hepatic failure without acetaminophen toxicity (FHF-NA, n = 312) had the poorest survival probability while awaiting OLT; this was negatively correlated with MELD score ($P = .0001$). These patients experienced the greatest survival benefit associated with OLT, with an estimated improvement of survival from about 58% to 91% ($P < .0001$). Patients listed for primary nonfunction within 7 days of OLT (n = 268) did not show mortality to be related to MELD score ($P = .41$) and did not show a significant association between survival and OLT ($P = .68$). In conclusion, liver allocation within the Status 1 designation may need to be further stratified by diagnosis, and MELD score may be useful for prioritizing FHF-NA candidates. (HEPATOLOGY 2004;39:764–769.)

Because of the growing incidence of end-stage liver disease and the incommensurate growth of grafts available for transplantation, the number of people awaiting an orthotopic liver transplantation (OLT) has grown to 17,707 as of August 31, 2003.¹ In 2002, 5,315

patients received a liver transplant.² The Department of Health and Human Services issued its Final Rule that allocation be conducted according to “medical urgency.”³ In response, the Organ Procurement and Transplantation Network (OPTN), or, more specifically, the United Network for Organ Sharing (UNOS), the OPTN contractor, implemented a new policy using the Model for End-Stage Liver Disease (MELD) score for allocation of grafts to adult patients with chronic liver disease awaiting transplantation in the United States.⁴ Early reports indicate that allocation of grafts based on a medical severity score may reduce the number of deaths on the waiting list because of liver disease.⁵

However, policies for allocation of grafts to patients with acute liver failure remain essentially the same. Adults classified as OPTN/UNOS Status 1 are broadly categorized into 2 groups: fulminant hepatic failure and early graft failure following OLT requiring re-OLT. Allocation of grafts to Status 1 patients is based on waiting time, blood type of donor and recipient, and geography, with grafts from local donors allocated first to local Status 1 candidates and then to regional and national Status 1

Abbreviations: OLT, orthotopic liver transplantation; OPTN, Organ Procurement and Transplantation Network; UNOS, United Network for Organ Sharing; MELD, Model for End-Stage Liver Disease; FHF, fulminant hepatic failure; PNF, primary graft nonfunction; HAT, hepatic artery thrombosis; FHF-A, fulminant hepatic failure due to acetaminophen poisoning; FHF-NA, fulminant hepatic failure without acetaminophen toxicity.

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patients. Patients listed as Status 1 with UNOS have priority over all other patients with chronic liver disease.

In this study, we evaluate the ability of the MELD score at listing to predict pretransplant and posttransplant survival for patients listed as UNOS Status 1. Furthermore, we assess whether the different diagnostic groups of patients listed as Status 1 differ with respect to pretransplant and posttransplant survival.

Patients and Methods

MELD Score

The MELD score is a severity score predictive of mortality in patients with chronic liver disease. It is based on the 3 biochemical parameters total serum bilirubin, prothrombin time and creatinine:

$$\begin{aligned} \text{MELD} = & 3.78 \times \log_e(\text{bilirubin [mg/dL]}) \\ & + 11.20 \times \log_e(\text{INR}) + 9.57 \\ & \times \log_e(\text{creatinine [mg/dL]}) + 6.4. \end{aligned}$$

The MELD score derives from objective, standardized laboratory measures that are taken as part of the standard care of patients with liver disease. It was originally derived to assess the prognosis of patient who underwent transjugular intrahepatic portosystemic shunt procedure.⁶ MELD score was validated in various patient groups with chronic liver disease, including hospitalized patients, outpatients, patients with specific diagnoses, and a mix of patients irrespective of type of liver disease.^{7,8} In these patient groups, the MELD score was consistently predictive of mortality at various time points, *i.e.*, 1 week, 3 months, and 1 year. Across various patient groups and time points, concordance values for the original MELD score remained consistently in the range of 0.7 and 0.8. Based on its high predictive power, the MELD score was adapted and assessed for use in organ allocation for patients with chronic liver disease awaiting transplantation.⁴ The MELD score has also been validated prospectively in patients with chronic liver disease listed for transplant at UNOS.⁹

Patient Population. The cohort of patients included in this study are adults (≥ 18 years old) who were added to the UNOS liver waiting list at Status 1 between November 1, 1999 and March 14, 2002. UNOS Status 1 patients fall into 2 broad categories: fulminant hepatic failure (FHF) and early graft failure requiring retransplantation. For each of these categories, a patient must have a life expectancy without a liver transplant of less than 7 days. UNOS listing guidelines for FHF are as follows:

- Onset of stage II encephalopathy within 8 weeks of the first symptoms of liver disease, and asterixis, hyperbilirubinemia, and marked prolongation of the prothrombin time (INR) or hypoglycemia

- Primary graft nonfunction (PNF) within 7 days of transplantation

- Hepatic artery thrombosis (HAT) within 7 days of transplantation

- Acute decompensated Wilson's disease

For purposes of this study, FHF patients were further classified as fulminant hepatic failure due to acetaminophen poisoning (FHF-A) or fulminant hepatic failure without acetaminophen toxicity (FHF-NA) because of expected differences in survival probabilities.^{10,11} Acute Wilson's disease patients were excluded because of their small number. Information provided to UNOS on the Status 1 justification form at the time of listing was used to classify the remaining patients into 4 diagnostic groups: FHF-A, FHF-NA, PNF, and HAT.

Statistical Methods. Kaplan-Meier estimation with competing risks and the log-rank test were used to assess overall survival and survival differences between the diagnostic groups.^{12,13} Death and "candidate condition improved, transplant not needed" were treated as the 2 competing risks. Patients who underwent transplantation and patients lost to follow-up were treated as randomly censored. With improved condition included in the model as a competing risk in survival analysis, transplant recipients are assumed to be randomly selected from those patients still awaiting a transplant but dissimilar to patients who have been removed from the list because of improved condition. Patients who deteriorated and became too sick to undergo transplantation were treated as deaths.¹⁴ We censored all patients still under observation at 30 days after listing in case they had neither incurred an event nor been censored until that time. More than 99% of the patients died or had an OLT within 30 days or had 30 day follow up from the time of listing.

A Cox model with competing risks was used to assess the association between MELD score, diagnostic group, and mortality.¹⁵ Next, transplantation as a time-dependent covariate was included to assess the association between transplantation and mortality. To assess overall survival probability, we estimated the crude incidences derived from the hazard rates of the individual competing risks. Crude incidence corresponds to cumulative incidence in the presence of competing risks and accounts for censoring. The difference in the estimated crude incidence over the interquartile range of the MELD score was used to assess the relation between MELD score and overall survival. We used the jackknife method to estimate variances for this estimated difference.¹⁶

Results

A total of 836 patients ≥ 18 years were listed for OLT with UNOS at Status 1 during the study period. One

Table 1. Baseline Characteristics of 720 UNOS Status 1 Patients Listed for OLT Between November 1, 1999 and March 14, 2002

	Diagnostic Group				Total (N = 720)	P Value*
	FHF-A (N = 76)	FHF-NA (N = 312)	HAT (N = 64)	PNF (N = 268)		
Age, years						
Mean (SD)	34.4 (12.1)	40.3 (13.1)	48.6 (7.7)	50.7 (10.2)	44.3 (12.9)	0.0001
Median	32	39	48	50	45	
(Min, Max)	(20, 69)	(19, 73)	(29, 65)	(19, 74)	(19, 74)	
Males, N (%)	15 (19.7)	103 (33.0)	45 (70.3)	270 (63.4)	333 (46.3)	0.0001
MELD score						
Mean (SD)	36.8 (10.7)	35.9 (11.7)	20.2 (12.0)	30.3 (10.1)	32.5 (12.0)	0.0001
Median	37.1	35.4	18.6	29.5	31.6	
(Min, Max)	(11.2, 63.9)	(2.8, 82.7)	(1.2, 71.8)	(10.2, 68.5)	(1.2, 82.7)	

Abbreviations: OLT, orthotopic liver transplantation; FHF-A, fulminant hepatic failure; acetaminophen; FHF-NA, fulminant hepatic failure other causes; HAT, hepatic artery thrombosis; PNF, primary graft non function; SD, standard deviation.

*P-value is for the T-test of same mean for age and MELD score, and χ^2 -test of same proportion for male.

hundred three (12.3%) patients did not formally meet the criteria for Status 1 and were therefore excluded from analysis. There were 13 patients with acute decompensated Wilson's disease. The remaining 720 patients were classified into the 4 diagnostic groups FHF-A, FHF-NA, PNF, and HAT.

Characteristics of the Study Population

The mean age of the study cohort was 44.3 years (SD 12.9 years), and about half of the patients were male (Table 1). The majority of the patients were Caucasian (66.2%), followed by 14.9% African-American and 12.4% Hispanic. The most common diagnostic groups of patients were FHF-NA (312, 43.3 %) and PNF (268, 37.2%). The FHF-A and FHF-NA patients were younger and had higher MELD scores at listing than the HAT and PHF patients (Table 1).

Survival of Patients Awaiting OLT

The 30-day survival probability of patients awaiting OLT according to the Kaplan-Meier estimates with competing risks are depicted in Fig. 1. Differences in the overall survival between groups were significant ($P = .0001$). The FHF-NA group had the worst observed outcome awaiting OLT, the HAT group the best, and the FHF-A and PHF groups intermediate. Comparisons between the groups showed that the FHF-NA group had statistically significant lower survival rates in this 30-day period than the PNF group ($P = .0002$). The FNF-A group did not differ significantly from the FHF-NA group ($P = .31$) but did differ significantly from the PNF group ($P = .039$). The HAT group differed significantly from the FHF-A ($P = .015$) and FHF-NA ($P = .0019$) groups but not from the PNF group ($P = .24$). There was no significant survival difference between males and females after adjusting for diagnostic group ($P = .51$).

Cox Model for Patients Awaiting OLT

Model building for the competing-risks Cox model for patient survival was based on data from the FHF-NA and PNF groups because there were too few events in the FHF-A and HAT groups.¹⁷ The relationship between MELD score and survival varied significantly between groups, as indicated by the significant interaction between diagnostic group and the MELD score ($P = .012$). Therefore, separate models were fit for the different groups. For the FHF-NA group, MELD score was a statistically significant predictor of mortality (hazard ratio [HR] = 1.048, $P = .0001$). MELD score was associated with a lower but nonsignificant rate of removal for improved condition (HR = 0.985, $P = .48$). For the PNF group, MELD score was not a statistically significant predictor of mortality (HR = 1.013, $P = .50$), and it was marginally

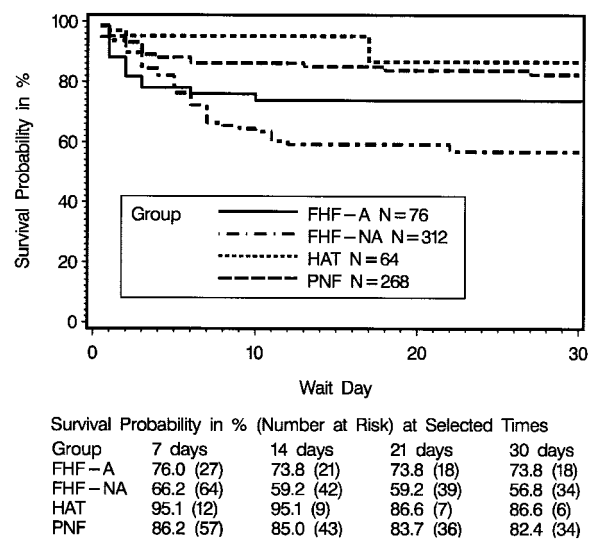


Fig. 1. Kaplan-Meier analysis of 30-day survival probability according to diagnostic group of the 720 UNOS Status 1 patients awaiting OLT.

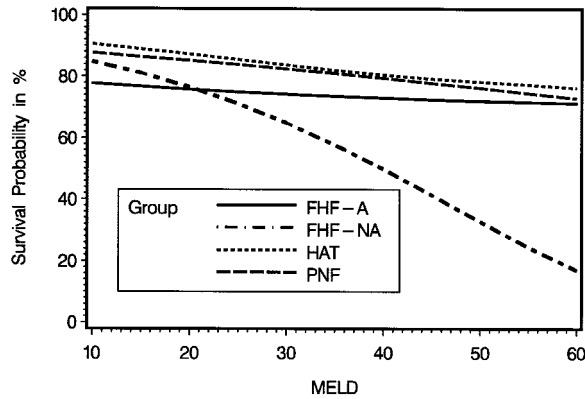


Fig. 2. Estimated 30-day survival probability of the 720 UNOS Status 1 patients awaiting OLT as a function of MELD score according to diagnostic group (from a time-dependent Cox model with death and removal from list for improved condition as competing risks).

significant for a lower rate of removal for improved condition (HR = 0.975, $P = .099$).

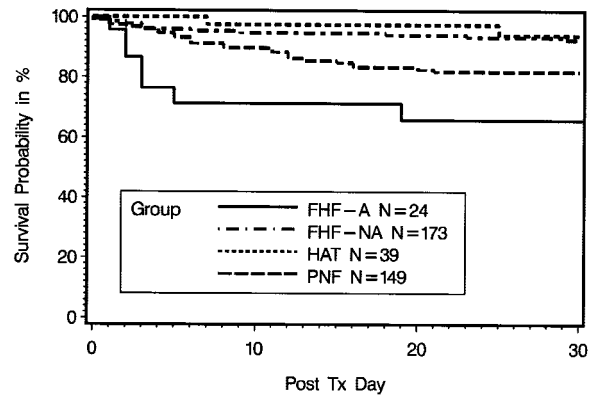
Gender and age at listing were not significant predictors of survival for both the FHF-NA ($P = .41$, $P = .29$) and the PNF ($P = .40$, $P = .54$) groups. Fig. 2 shows overall survival probability as a function of MELD score derived from the crude incidence rates for each of the four groups. For the FHF-NA group, MELD score was a significant predictor of overall survival ($P = .0001$). MELD score was not a significant predictor of overall survival for the PNF, HAT, or FHF-A groups ($P = .41$, $P = .54$, $P = .78$).

Survival of Patients Post-OLT

The 30-day post-OLT survival probability according to Kaplan-Meier estimation is shown in Fig. 3. The general test for differences between all diagnostic groups was significant ($P = .0002$). The FHF-NA and HAT patients had higher observed survival rates. These rates were slightly worse in PNF patients; FHF-A patients had the worst observed survival rates. The FHF-NA group differed significantly from the PNF group ($P = .0052$). Outcome for the FHF-A group was marginally significantly different from the PNF group ($P = .051$) and significantly different from each of the other groups ($P \leq .0026$).

Survival Benefit Associated With Transplant

The Cox model with competing risks and time-dependent covariate for OLT demonstrated that OLT was significantly associated with better survival for the FHF-NA group ($P < .0001$). This is shown in Fig. 4. For an FHF-NA patient with a MELD score of 35.6 (mean MELD score in FHF-NA group), the estimated 30-day survival probability was 91% if the patient underwent



Survival Probability in % (Number at Risk) at Selected Times				
Group	7 days	14 days	21 days	30 days
FHF-A	71.3 (14)	71.3 (13)	65.8 (11)	65.8 (11)
FHF-NA	95.3 (155)	94.7 (140)	94.0 (134)	92.6 (128)
HAT	97.4 (37)	97.4 (34)	97.4 (30)	94.0 (28)
PNF	91.1 (130)	85.4 (120)	81.8 (109)	81.8 (102)

Fig. 3. Kaplan-Meier analysis of the 30-day posttransplant survival probability according to diagnostic group of the 385 UNOS Status 1 patients who received a transplant within 30 days of listing and for whom follow-up information was available. (Only patients with post-transplant follow-up information are included in this analysis.)

transplantation immediately upon being listed. The estimated 30-day survival probability was 58% for a patient awaiting OLT. This corresponded to a survival probability difference of 33%. The benefit associated with OLT was greater for patients with higher MELD scores.

In the PNF group, OLT was associated with a lower estimated survival probability, though this was not statistically significant ($P = .68$). For a PNF patient with a MELD score of 30.31 (mean MELD score in PNF group), the estimated 30-day survival probability was 75% for a patient who underwent retransplantation immediately upon being listed. The estimated 30-day survival probability was 82% for a patient awaiting re-OLT.

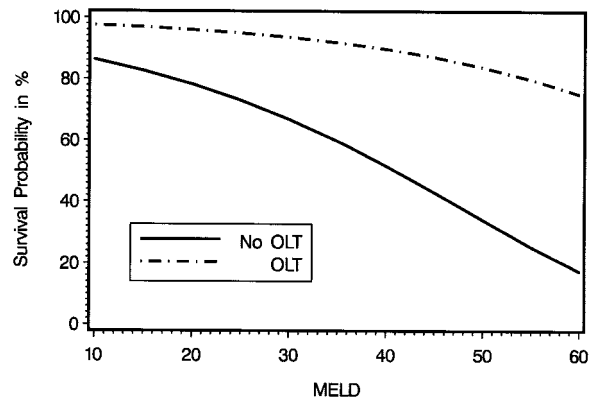


Fig. 4. Estimated 30-day survival probability from a competing-risks Cox model with transplantation as a time-dependent covariate for FHF-NA patients receiving transplant (OLT) immediately upon listing and patients awaiting OLT (No OLT) as functions of MELD scores.

Table 2. Thirty-Day Outcomes by Diagnostic Group Among the 720 UNOS Status 1 Patients Awaiting OLT

N (column %)	Diagnostic Group				Total
	FHF-A	FHF-NA	HAT	PNF	
Survive on list, no OLT	18 (23.7)	34 (10.9)	7 (10.9)	36 (13.4)	95 (13.2)
Improved	17 (22.4)	18 (5.8)	9 (14.1)	52 (19.4)	96 (13.4)
OLT	24 (31.6)	187 (59.9)	44 (68.8)	151 (56.3)	406 (56.4)
Too sick	5 (6.6)	19 (6.1)	1 (1.6)	4 (1.5)	29 (4.0)
Died waiting	12 (15.8)	54 (17.3)	3 (4.7)	25 (9.3)	94 (13.1)
Total (Row %)	76 (10.6)	312 (43.3)	64 (8.9)	268 (37.2)	720 (100)

Discussion

We have shown that for those awaiting OLT, there are significant survival differences between the diagnostic groups. For the 2 largest groups, which comprise over 80% of all Status 1 cases, the FHF-NA group had a significantly lower survival probability than the PNF group. Furthermore, MELD score was a significant predictor of overall survival for the FHF-NA group. Therefore, both the MELD score and the diagnostic group are important factors in judging the medical urgency for Status 1 patients awaiting OLT. Neither the MELD score nor the diagnostic group alone is sufficient for estimating survival probabilities for Status 1 patients.

The FHF-NA group, along with the HAT group, had the highest observed posttransplant survival probability. The lower survival probability while awaiting transplant, and the greater survival probabilities following transplant, support consideration of a new allocation mechanism that prioritizes FHF-NA patients. This is further supported by our analysis incorporating pretransplant and posttransplant survival probabilities. FHF-NA patients benefited from transplantation, and the benefit was greater for patients with higher MELD scores. A similar benefit of transplantation was not observed for the PNF group. We do not contend that transplantation is not beneficial for the other Status 1 groups. However, for the 30-day time frame and number of patients available for analysis considered here, a significant relationship between transplant and survival was not observed. This may indicate that retransplantation for some recipients with PNF may not be so urgent that it must occur within 30 days to yield improved survival. Importantly, all survival benefit analyses can be confounded by the selection bias of centers treating extremely ill candidates. A survival benefit is evident here for FHF-NA patients who were selected by the centers for transplantation, but this does not necessarily mean that a survival benefit exists for all FNF-NA patients.

The primary focus of our survival analysis has been the comparison of one diagnostic group to another or the comparison of patients with different MELD scores. The analyses, however, also provide numerical estimates of absolute survival probabilities for patients as functions of

diagnostic group and MELD score. Three-month survival probabilities for chronic liver disease patients listed for transplantation have been described previously,⁹ and, assuming constant risk of mortality, one can derive 30-day survival probabilities for comparison. With this rescaling, the estimated survival probability for the FHF-NA group up to a MELD score of 40 is the same or less than the estimated survival probability for the chronic liver disease group. This inequality is dependent on the 30-day time frame. A shorter time frame would show an even smaller survival probability for the FHF-NA group compared with the chronic liver disease patients. The smaller survival probability for FHF-NA patients indicates a higher medical urgency and supports the continued prioritization of this group over the chronic liver disease patients. Furthermore, the Status 1 classification for patients with early graft failure is necessary as a backup mechanism to encourage use of marginal grafts, many of which will benefit recipients with only a small percentage requiring retransplantation.

In the PNF group, the estimated survival probability without transplantation was about 86% at day 7 and 85% at day 14—much greater than that implied by the policy requirement of “life expectancy without a liver transplant of less than 7 days.” Diagnosis of PNF is often associated with alanine aminotransferase > 2500 IU/L,¹⁸ glucose < 60 mg/dL, INR > 2.5,⁴ or bile flow < 50 cc/day.¹⁹ UNOS policy, however, states no such requirement. Given the high estimated survival probabilities for the PNF group, it may be beneficial to revisit the formal criteria for PNF patients listed as Status 1. Stricter definition of PNF for classification as Status 1 may mitigate the observed differences in survival between the groups.

In the group of patients with HAT, which is typically confirmed by angiogram or ultrasound, the observed high survival probabilities pretransplant and posttransplant are in part expected because HAT generally leads to graft failure over a period of weeks or months, but not days, despite the UNOS stated policy for Status 1 listing of “life expectancy without a liver transplant of less than 7 days.”

Despite the strong numerical relationship, caution must be exhibited in interpreting the findings. This is observational data, especially poignant when considering transplantation as a censoring mechanism. We have used competing-risk models in order to achieve a model more closely resembling medical practice. However, recipient factors relating to patients' suitability for transplantation beyond their continued Status 1 listing and initial MELD score may also play a role in a center's decision to take or reject a graft offer. This is especially important because about 60% of the patients listed for FHF-NA and PNF received a transplant. We had no data on these important factors and, therefore, they are not accounted for in the analysis. Still, the strength of the association between MELD score and waiting-list mortality, and the benefit associated with OLT for the FHF-NA group (especially in contrast to the PNF group), argue for further assessment of the current practice of retransplantation and organ allocation.

In addition to being predictive of survival, the MELD score is practical (being based on standardized laboratory parameters), is used in the routine evaluation of patients, and currently is routinely collected on all listed patients.

Conclusion

This study is based on a large sample of the target population, including all patients listed as Status 1 over a one-and-a-half year period. The marked survival differences between the FHF-NA group and the PNF and HAT patients suggest that it may be necessary to redefine criteria for the highest urgency Status 1 candidates. Our data suggest that FHF-NA patients may warrant a higher priority that can be stratified by MELD scores. Furthermore, more objective measures predictive of mortality for PNF and HAT patients should be sought in an effort to improve the fairness of the system.

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