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MELD and Prediction of Post-Liver Transplantation Survival

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The model for end-stage liver disease (MELD) was developed to predict short-term mortality in patients with cirrhosis. It has since become the standard tool to prioritize patients for liver transplantation. We assessed the value of pretransplant MELD in the prediction of posttransplant survival. We identified adult patients who underwent liver transplantation at our institution during 1991-2002. Among 2,009 recipients, 1,472 met the inclusion criteria. Based on pretransplant MELD scores, recipients were stratified as low risk (≤ 15), medium risk (16-25), and high risk (> 25). The primary endpoints were patient and graft survival. Mean posttransplant follow-up was 5.5 years. One-, 5- and 10-year patient survival was 83%, 72%, and 58%, respectively, and graft survival was 76%, 65%, and 53%, respectively. In univariable analysis, patient and donor age, patient sex, MELD score, disease etiology, and retransplantation were associated with posttransplantation patient and graft survival. In multivariable analysis adjusted for year of transplantation, patient age > 65 years, donor age > 50 years, male sex, and retransplantation and pretransplant MELD scores > 25 were associated with poor patient and graft survival. The impact of MELD score > 25 was maximal during the first year posttransplant. In conclusion, older patient and donor age, male sex of recipient, retransplantation, and high pretransplant MELD score are associated with poor posttransplant outcome. Pretransplant MELD scores correlate inversely with posttransplant survival. However, better prognostic models are needed that would provide an overall assessment of transplant benefit relative to the severity of hepatic dysfunction. *Liver Transpl* 12:440-447, 2006. © 2006 AASLD.

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In 1998, the United States Department of Health and Human Services (DHHS) issued its final rule with the recommendation that a triage system be devised that ensured efficient use of donated organs. The model for end-stage liver disease (MELD) was developed earlier to assess short-term prognosis among patients undergoing transjugular intrahepatic portosystemic shunt.¹ The validity of the model as a disease severity index in patients with end-stage chronic liver disease was subsequently assessed and confirmed.^{2,3} In February of 2002, the United Network for Organ Sharing (UNOS) implemented MELD to prioritize organ allocation in patients with chronic liver disease awaiting liver transplantation. Subsequent analysis confirmed the validity of MELD for this purpose.⁴

There have been few reports of the ability of MELD to predict survival following liver transplantation. Thus far the results have been conflicting. Some authors showed no correlation between MELD and short-term posttransplantation survival.⁵⁻⁷ However, other reports suggested that pretransplant MELD predicted posttransplantation survival.⁸⁻¹¹ Still, the studies thus far reported included small numbers of patients and with limited posttransplantation follow-up. Larger studies with longer follow-up are therefore needed to confirm the prognostic value of MELD for posttransplantation outcomes.

We examined a large cohort of patients who underwent liver transplantation for end stage chronic liver

Abbreviation: MELD, model for end-stage liver disease.

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disease at our center. The aim of our study was to evaluate the predictive value of baseline MELD, calculated prior to liver transplantation, in the assessment of post-liver transplantation patient and graft survival.

PATIENTS AND METHODS

Study Population

All adult patients (age >18 years) who underwent deceased donor liver transplantation during the 12-year period between January 1991 and December 2002 at the Thomas E. Starzl Transplantation Institute, University of Pittsburgh, Pittsburgh, PA, were considered for the study. The patients were identified through the Electronic Data Interface for Transplantation, an electronic database that provided comprehensive tracking of transplant candidates and recipients at our institution. We excluded patients with acute liver failure, hepatocellular carcinoma, and other hepatic malignancies and those who received live donor liver transplantation. Other hepatic malignancies included cholangiocarcinoma, metastatic liver disease, angiosarcoma, and epithelioid hemangioendothelioma. None of the patients were excluded on the basis of race, ethnicity, sex, or human immunodeficiency virus status. Our institutional review board approved the study. All clinical and laboratory data including donor information were collected by an electronic search of the Electronic Data Interface for Transplantation and provided to the investigators by a designated honest broker after removal of patient identifiers.

Data Analysis

We examined the distribution of patient and donor age, sex, race, and ethnicity. In addition, we looked at recipient-donor sex, race, and blood group mismatch. We also noted the etiology of chronic liver disease, cold and warm ischemia time, retransplantation, Child-Turcotte-Pugh score at listing and at transplantation, and MELD score at transplantation. The diagnosis of chronic liver disease was confirmed by histopathology of the explanted liver. The etiology of chronic liver disease was categorized into 3 groups: group 1, cholestatic diseases (primary biliary cirrhosis, primary sclerosing cholangitis, secondary biliary cirrhosis, and cystic diseases); group 2, chronic hepatitis C; and group 3, all other patients. The modified Child-Turcotte-Pugh score was calculated and each patient categorized as A, B, or C. We used the modified MELD score as employed by UNOS for organ allocation: $MELD = [0.957 \times \log_e(\text{creatinine}) + 0.378 \times \log_e(\text{bilirubin}) + 1.12 \times \log_e(\text{international normalized ratio}) + 0.64] \times 10$ (Available at: <http://www.unos.org/resources>. Accessed January, 2005).

The score was calculated with available pretransplantation variables and without any correction for hemodialysis. In 88% of the patients, laboratory studies were available within a window of 3 days prior to transplantation, and almost all had tests available within 30 days. Information regarding hemodialysis was unavail-

able in our data set, and therefore MELD score was not corrected accordingly. However, more recent data indicated that only 2.5% of transplant recipients at our center had a history of hemodialysis. Actual laboratory international normalized ratio values were included in the analysis that obviated the need for derived value from prothrombin time.

Patients were initially stratified into 7 groups based on the MELD score of <10, 11-15, 16-20, 21-25, 26-30, 31-35, and ≥ 36 . Graft and patient survival were compared among the groups. Groups with similar results were merged to develop 3 larger categories as defined by pretransplantation MELD of ≤ 15 (low risk), 16-25 (medium risk), and > 25 (high risk). Graft failure was defined by retransplantation. Patient and donor age and cold ischemia time were analyzed as dichotomous variables. Patient age was categorized as either ≤ 65 years or > 65 years and donor age as ≤ 50 years or > 50 years. Cold ischemia time was categorized as ≤ 12 hours or > 12 hours. We also performed a subset analysis of the high-risk group (MELD score > 25) to identify predictors of patient survival.

Statistical Analysis

For the univariable analyses of posttransplant graft survival and patient survival, we used the Kaplan-Meier method with the log-rank or Tarone-Ware test to estimate unadjusted survival rates and to compare the survival rates of groups based on sociodemographic and clinical variables. For multivariable analyses, we used the Cox proportional hazards regression method with a stepwise procedure to determine the adjusted survival rates. To evaluate this final multivariable model, we used Cox-Snell residual goodness-of-fit plots (to measure model calibration) and c-statistics (to measure model discrimination). We used the Grambsch and Therneau test to determine whether potential risk factors satisfied the proportional hazards assumption. For all analyses, we used Stata version 8.2 (Stata, Inc., College Station, TX) and SPSS version 11 (SPSS Inc., Chicago, IL), and we considered a *P* value of < 0.05 to be significant.

RESULTS

A total of 2,009 patients underwent liver transplantation during the study period. Of these patients, 537 were excluded from the study for the following reasons: acute liver failure (41), malignancies (304), live donor liver transplantation (16), and incomplete data (176). Among patients with incomplete data, international normalized ratio values were unavailable for all, and serum bilirubin and creatinine levels were unavailable in 4 patients. Thus, 1,472 patients who had complete data sets to enable MELD calculation were included in the analysis.

Clinical Features

The mean recipient age was 51 years, compared to the mean donor age of 40 years (Table 1). A higher propor-

TABLE 1. Patient and Donor Characteristics
(n = 1,472)

Patient age (years)	51 ± 11
Donor age (years)	40 ± 17
Patient sex (male)	861 (58%)
Donor sex (male)	857 (58%)
Sex mismatch	633 (43%)
Racial mismatch	298 (20%)
Rhesus mismatch	197 (13%)
Patient race	
Caucasian	1,338 (91%)
African American	43 (3%)
Other	91 (6%)
Donor race	
Caucasian	1,260 (86%)
African American	169 (11%)
Other	43 (3%)
MELD score at transplant	18 ± 8
CTP score at transplant	9 ± 2
Cold ischemia time (hours)	12.4 ± 3.8
Follow-up posttransplant (years)	5.5 ± 3.9
Etiology	
Hepatitis C	395 (27%)
Alcohol	295 (20%)
Cholestatic diseases	270 (18%)
Indeterminate	232 (16%)
Autoimmune hepatitis	118 (8%)
Hepatitis B	53 (4%)
Metabolic diseases	58 (4%)
Miscellaneous	51 (4%)

NOTE: Values are presented as mean ± SD or proportions, as appropriate.

Abbreviations: CTP, Child-Turcotte-Pugh; MELD, Model for Endstage Liver Disease.

tion of both recipients and donors were male, and both were predominantly Caucasian. Almost half of the patients had recipient-donor sex mismatch and one-fifth had racial mismatch. Among the study cohort of 1,472 patients, the mean MELD score was 18; 649 (44%) were in the low-risk MELD group (6-15), 568 (39%) were in the medium-risk MELD group (16-25), and 255 (17%) were in the high-risk MELD group (>25). Ninety-two patients (6%) were in Child-Turcotte-Pugh A category, 713 (49%) had B status, and 669 (45%) had C status. The mean cold ischemia time was 12 hours, and the average posttransplant follow-up was 5.5 years. Chronic hepatitis C was the leading indication for transplantation, followed by alcoholic and cholestatic liver diseases. In 16% of the recipients, etiology remained indeterminate.

A total of 461 liver allograft recipients died during the study period. The causes of death included sepsis (127), allograft failure (64), cardiac dysfunction (arrhythmia, myocardial infarction, cardiac tamponade; 61), multi-organ failure (46), malignancy (lymphoproliferative disorders, lung cancer and others; 37), respiratory failure (23), stroke (22), gastrointestinal hemorrhage (15), intraoperative death (11), renal failure (10), suicide (6),

trauma (4), and unknown cause (35). Among patients who died of graft failure, causes included primary non-function (8), biliary and vascular problems (7), recurrent hepatitis C (7), and chronic rejection (42).

Survival Analysis

The mean posttransplant follow-up was 5.5 years. Although graft survival declined more rapidly than patient survival during the first posttransplant year, it paralleled patient survival during subsequent years. Overall patient survival was 83%, 72%, and 58% at 1, 5, and 10 years, respectively, and graft survival was 76%, 65%, and 53% at 1, 5, and 10 years, respectively.

In univariable analyses (Table 2), we found that patient age, donor age, patient sex, MELD score at transplantation, etiology of liver disease, and retransplantation were significantly associated with patient and graft survival. When we analyzed recipient age at cutoff levels of 50 and 65 years, we found that older age correlated with diminished survival at both cutoff levels. Similarly, donor age of >50 years was associated with diminished survival. One-year patient survival in low, medium, and high MELD strata was 86%, 84%, and 75%, respectively. While 10-year patient survival declined to 65% in patients with MELD scores ≤10, it declined to as low as 40% in patients with MELD scores ≥36. Thus, pre-transplant MELD scores correlated inversely with post-transplant survival (Fig. 1). One-year and overall survival was significantly better in the low MELD group compared to the medium ($P = 0.001$) and high MELD groups ($P < 0.001$), and it was also better in the medium MELD group compared to the high MELD group ($P < 0.001$). However, there was no significant difference in survival among the 3 groups beyond the first year ($P =$ not significant). In all diagnoses (etiology categories), survival declined as the MELD scores increased (Fig. 2). Transplant recipients whose liver condition was caused by cholestatic diseases had the best posttransplant survival, and this advantage was maintained despite being in the high-risk MELD group. Recipients who underwent retransplantation had a poorer long-term outcome than those who did not undergo retransplantation, and recipients with Child-Turcotte-Pugh A disease had better survival at 1 and 5 years posttransplant than those with Child-Turcotte-Pugh B or C disease (Table 2). Patient race, donor sex and race, recipient-donor sex, race and Rhesus mismatch, and cold ischemia time did not correlate with posttransplantation survival. Overall, 183 patients (13%) underwent retransplantation. Among those patients, 81 (44%) were in the low-risk MELD group, 73 (40%) were in the medium-risk group, and 29 (16%) were in the high-risk group prior to initial transplantation. For those recipients who underwent retransplantation, the outcomes tended to be poor regardless of the MELD score at retransplantation.

In multivariable analyses, using the Cox proportional hazard model and after adjustment for the year of transplantation (Table 3), we found that patient age >65 years, donor age >50 years, male sex of recipient,

TABLE 2. Factors Associated With Patient and Graft Survival (Univariable Analysis)

Variables	Patient Survival (%)				Graft Survival (%)			
	1 Year	5 Years	10 Years	P Value	1 Year	5 Years	10 Years	P Value
Overall	83	72	58		76	65	53	
Patient age				<0.001				<0.001
≤65 years	84	73	60		77	66	55	
>65 years	75	57	33		71	53	32	
Donor age				<0.001				<0.001
≤50 years	85	75	61		81	70	57	
>50 years	81	66	51		68	55	43	
Patient sex				0.001				0.005
Female	86	76	63		79	68	58	
Male	82	69	54		75	63	49	
MELD score at OLT				<0.001				<0.001
6–15	86	75	62		79	68	55	
16–25	84	73	59		77	66	55	
>25	75	62	45		69	57	42	
Diagnosis				0.016				0.007
Cholestatic diseases	89	78	64		83	73	59	
Hepatitis C	83	71	58		76	63	51	
Others	82	70	55		74	64	51	
Retransplantation				<0.001				<0.001
No	85	74	60		85	74	60	
Yes	72	57	40		16	3	1	
CTP status				0.01				0.06
A	96	81	62		90	75	64	
B	83	72	58		75	65	52	
C	82	70	57		76	65	52	

Abbreviations: OLT, liver transplantation; CTP, Child-Turcotte-Pugh; MELD, Model for Endstage Liver Disease.

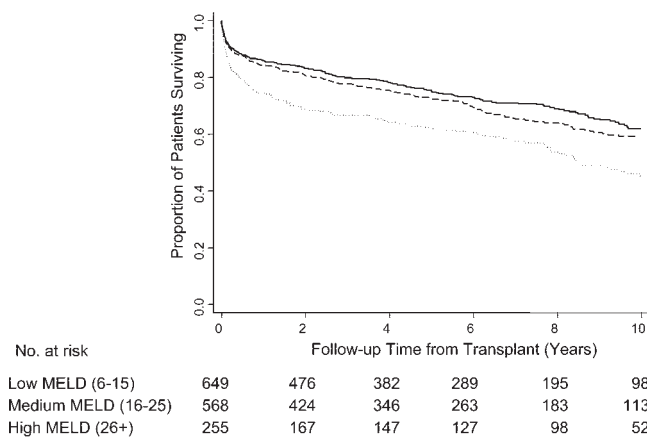


Figure 1. Patient survival based on MELD scores at liver transplantation. The solid line indicates the low-risk MELD (6–15) group, the dashed line indicates the medium-risk MELD (16–25) group, and the dotted line indicates the high-risk MELD (≥26) group. Kaplan-Meier analysis with comparison among groups by log-rank test was carried out. Log-rank: $\chi^2 = 22.52$; $P < 0.001$.

retransplantation, and pretransplant MELD score of >25 were significantly associated with poor patient and graft survival. The c-statistics for patient survival and graft survival were 0.63 and 0.73, respectively. We also determined independent predictors of patient and graft survival at 1 year posttransplantation (Table 4). Recip-

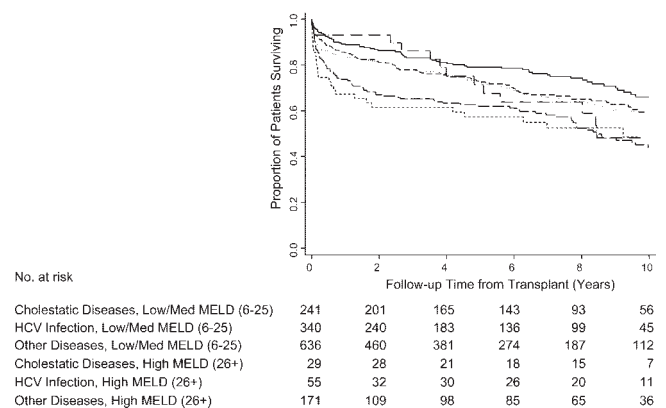


Figure 2. Posttransplantation patient survival and etiology of chronic liver disease in low/medium- and high-risk MELD groups. For the low/medium MELD (6–25) group: The solid line indicates cholestatic diseases, medium dashes indicate hepatitis C virus infection, and the small dots indicate other diseases. Log-rank: $\chi^2 = 5.21$; $P < 0.072$. For the high MELD (≥26) group, the dash-dot line indicates cholestatic diseases, small dashes indicate hepatitis C infection, and the large dashes indicate other diseases. Tarone-Ware: $\chi^2 = 1.61$; $P < 0.448$.

ient age >65 years, retransplantation, MELD score >25, noncholestatic etiology of primary disease, and Child-Turcotte-Pugh C status were significantly associated with diminished patient survival at 1 year. On the other hand, recipient age >65 years, donor age >50

TABLE 3. Factors Associated With Patient and Graft Survival (Multivariable Analysis), With Adjustment for the Year of Transplant

Variables	Patient Survival*		Graft Survival†	
	Risk Ratio (95% CI)	P Value	Risk Ratio (95% CI)	P Value
Patient age				
>65 years	1.00		1.00	
≤65 years	0.47 (0.37,0.61)	<0.001	0.44 (0.34,0.56)	<0.001
Donor age				
>50 years	1.00		1.00	
≤50 years	0.77 (0.64,0.92)	0.005	0.74 (0.62,0.87)	<0.001
Patient sex				
Male	1.00		1.00	
Female	0.74 (0.61,0.88)	0.001	0.78 (0.66,0.93)	0.004
Retransplantation				
Yes	1.00		1.00	
No	0.53 (0.42,0.67)	<0.001	0.08 (0.06,0.09)	<0.001
MELD scores at transplant				
>25	1.00		1.00	
16-25	0.59 (0.47,0.75)	<0.001	0.68 (0.54,0.84)	<0.001
6-15	0.65 (0.52,0.82)	<0.001	0.76 (0.61,0.95)	0.016

Abbreviation: CI, confidence interval.

*C-statistic for patient survival model = 0.63.

†C-statistic for graft survival model = 0.73.

TABLE 4. Factors Associated with 1-Year Patient and Graft Survival (Multivariable Analysis), with Adjustment for the Year of Transplant

Variables	Patient Survival*		Graft Survival†	
	Risk Ratio (95% CI)	P Value	Risk Ratio (95% CI)	P Value
Patient age				
>65 years	1.00		1.00	
≤65 years	0.53 (0.36,0.79)	0.001	0.50 (0.35,0.72)	<0.001
Donor age				
>50 years			1.00	1.00
≤50 years			0.75 (0.60,0.93)	0.01
Patient sex				
Male			1.00	1.00
Female			0.80 (0.64,0.99)	0.049
Retransplantation				
Yes	1.00		1.00	1.00
No	0.51 (0.37,0.70)	<0.001	0.08 (0.06,0.10)	<0.001
MELD score at transplant				
>25	1.00		1.00	1.00
16-25	0.52 (0.34,0.77)	0.001	0.67 (0.50,0.90)	0.007
6-15	0.53 (0.37,0.74)	<0.001	0.74 (0.55,0.99)	0.043
Diagnosis				
Others	1.00			
Hepatitis C	0.97 (0.72,1.30)	0.84		
Cholestatic liver diseases	0.57 (0.38,0.86)	0.007		
CTP status				
C	1.00			
B	0.32 (0.11,0.90)	0.03		
A	1.14 (0.83,1.56)	0.42		

Abbreviations: CI, confidence interval; CTP, Child-Turcotte-Pugh.

*C-statistic for patient survival model = 0.65.

†C-statistic for graft survival model = 0.75.

TABLE 5. Factors Associated With Long-Term Patient and Graft Survival in Patients Who Survived for at Least 1 Year (Multivariable Analysis), with Adjustment for the Year of Transplant

Variables	Patient Survival*		Graft Survival†	
	Risk Ratio (95% CI)	P Value	Risk Ratio (95% CI)	P Value
Patient age				
>65 years	1.00		1.00	
≤65 years	0.40 (0.28,0.55)	<0.001	0.36 (0.26,0.51)	<0.001
Donor age				
>50 years	1.00		1.00	
≤50 years	0.71 (0.55,0.92)	0.01	0.68 (0.52,0.88)	0.004
Patient sex				
Male	1.00		1.00	
Female	0.70 (0.54,0.89)	0.005	0.75 (0.58,0.97)	0.027
Retransplantation				
Yes	1.00		1.00	
No	0.58 (0.41,0.80)	0.001	0.06 (0.04,0.10)	<0.001

Abbreviation: CI, confidence interval.

*C-statistic for patient survival model = 0.64.

†C-statistic for graft survival model = 0.69.

years, male recipient, retransplantation, and MELD score >25 were significantly associated with poor graft survival at 1 year. The c-statistic for patient survival was 0.65; for graft survival, it was 0.75. We examined predictors of outcome after excluding patients who died during the first year following transplantation (Table 5); patient age >65 years, donor age >50 years, male recipient, and retransplantation were significantly associated with patient and graft survival. The c-statistic for patient survival model was 0.64; for graft survival model, it was 0.69. The Cox-Snell residual good-of-fit plots (not shown) demonstrated that the models fit the data well.

Survival in High-Risk MELD Group

We performed further analyses to determine factors associated with significantly better outcomes in the high-risk MELD group (MELD score >25). In this group, we found that survival was better in younger patients (≤65 years) (Fig. 3), women (Fig. 4), and patients with cold ischemia times of ≤12 hours (Fig. 5). Transplant recipients whose liver condition was caused by cholestatic liver disease had better survival than did other transplant recipients during the first 4 posttransplant years, but survival rates were similar after that time (Fig. 2).

DISCUSSION

With the ever-increasing divergence between the availability of donor organs and the need for liver transplantation, MELD was implemented to help prioritize prospective liver allograft recipients. The model's accuracy to predict short-term mortality among patients with end-stage liver disease has been largely established.² However, an ideal selection system would incorporate predictions for survival while on the waiting list as well as following transplantation. The development of a

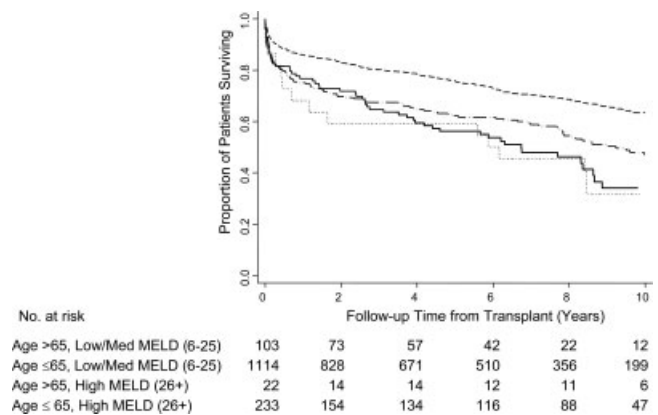


Figure 3. Posttransplantation patient survival and recipient age in low/medium- and high-risk MELD groups. For the low/medium MELD (6-25) group, the solid line indicates age >65, and the dashes indicate age ≤65. Log-rank: $\chi^2 = 26.50$; $P = 0.055$. For the high MELD (≥26) group, the dotted line indicates age >65, and the dash-dot line indicates age ≤65. Log-rank: $\chi^2 = 3.68$; $P = 0.055$.

model that could predict posttransplantation outcome based on pretransplant variables is inherently difficult because of variation in surgical skills, chance events that occur in the perioperative period, and other factors, such as graft rejection and biliary and vascular complications, that are generally independent of pretransplant events. Although it might seem plausible that the limited number of pretransplant variables that constitute MELD could probably influence the immediate posttransplant phase, their ability to predict long-term outcome would appear less likely. Recently, several investigators examined the predictive value of MELD for posttransplantation outcome, but the results were conflicting and follow-up was limited to 1-2 years, and thus a clear consensus has not yet emerged.⁵⁻¹¹ To our knowledge, the current work represents the largest

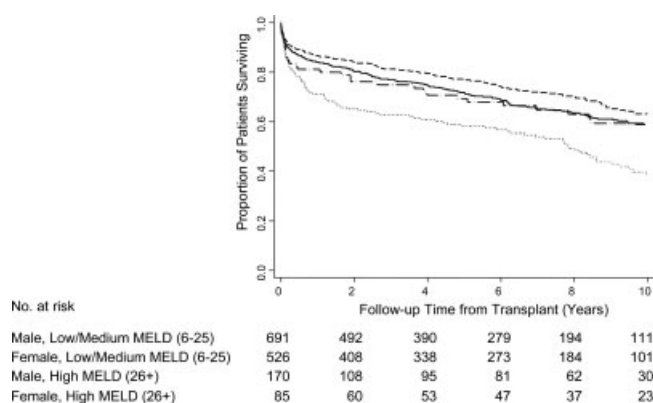


Figure 4. Posttransplantation patient survival and recipient sex in low/medium- and high-risk MELD groups. For the low/medium MELD (6-25) group, the solid line indicates males, and the dashes indicate females. Log-rank: $\chi^2 = 4.29$; $P = 0.038$. For the high MELD (≥ 26) group, the dotted line indicates males, and the dash-dot line indicates females. Log-rank: $\chi^2 = 5.72$; $P = 0.017$.

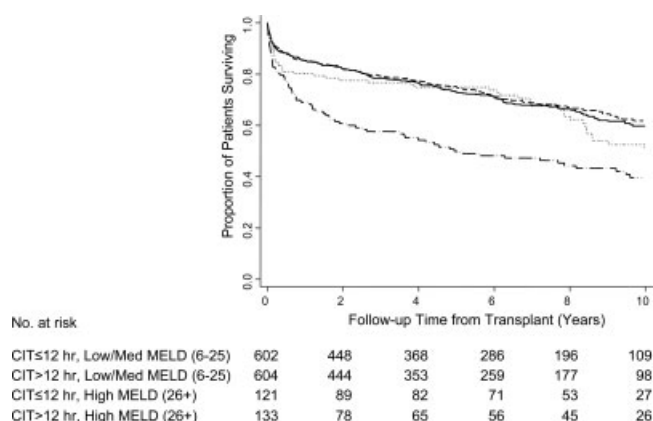


Figure 5. Posttransplantation patient survival and cold ischemia time (CIT) in low/medium- and high-risk MELD groups. For the low/medium MELD (6-25) group, the solid line indicates CIT ≤ 12 hours, and the dashes indicate CIT > 12 hours. Log-rank: $\chi^2 = 0.24$; $P = 0.624$. For the high MELD (≥ 26) group, the dotted line indicates CIT ≤ 12 hours, and the dash-dot line indicates CIT > 12 hours. Log-rank: $\chi^2 = 7.79$; $P = 0.005$.

single-center experience and provides much longer follow-up in the evaluation of MELD as a predictor of postliver transplantation survival. As our study encompassed a 12-year period, we adjusted our analysis for the year of transplantation to take into account the influence of changing clinical practices.

We found that recipient age > 65 years, donor age > 50 years, male sex of recipient, retransplantation, and pretransplant MELD score of > 25 were associated with poor patient and graft survival irrespective of the year of transplantation. The model for 1-year graft survival was similar to the overall survival model; however, factors associated with 1-year patient survival differed. Donor age and recipient sex were insignificant, but etiology of primary disease and Child-Turcotte-Pugh status were significant. To determine pretransplant variables that

influenced survival beyond the first year posttransplant, we reanalyzed the data after censoring patients who died during the first year. Our results were similar to the overall results except that the pretransplant MELD of > 25 lost its significance. This finding suggests that a high pretransplant MELD score has its greatest impact during the first year following transplantation. A high MELD score is indicative of a greater degree of hepatic and renal dysfunction. Such dysfunction is likely to influence the posttransplantation course and it is therefore not surprising that patients with MELD > 25 had inferior 1-year patient and graft survival. However, this influence is lost beyond the first year when other variables such as patient and donor age, patient sex, and retransplantation have a more profound effect on outcome. Thus, our study provides valuable information regarding the outcome of liver transplantation in relation to recipient and donor features. In particular, it assesses the value of pretransplant MELD as a predictor of patient and graft survival.

In our study, pretransplant MELD was inversely associated with posttransplant survival, particularly during the first year. This finding if validated would further establish MELD as an excellent tool in organ prioritization. However, it is also clear that sick patients with high MELD scores are unlikely to recover without transplantation. A recent study indicated that there is a distinct survival advantage with liver transplantation among such patients.¹² Our study suggests that among patients with high MELD scores, survival is better in younger and female recipients and among those with cold ischemia time < 12 hours. Such factors could be incorporated in the transplant decision-making process.

We conclude that older recipient and donor age, male sex of recipient, retransplantation, and high pretransplant MELD score are associated with poor outcome following liver transplantation. The impact of pretransplant MELD is maximal during the first year posttransplant. Better predictive models are needed to assess the survival benefit with liver transplantation.

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