Prediction of Survival After Liver Retransplantation for Late Graft Failure Based on Preoperative Prognostic Scores

Francis Y. Yao,[1,2] Sammy Saab,[3] Nathan M. Bass,[1] Ryutaro Hirose,[2] David Ly,[3] Norah Terrault,[1] Ann A. Lazar,[4] Peter Bacchetti,[4] Nancy L. Ascher,[2] and John P. Roberts[2]

The current policy for determining priority for organ allocation is based on the model for end stage liver disease (MELD). We hypothesize that severity of graft dysfunction assessed by either the MELD score or the Child-Turcotte-Pugh (CTP) score correlates with mortality after liver retransplantation (re-OLT). To test this hypothesis, we analyzed the outcome of 40 consecutive patients who received re-OLT more than 90 days after primary orthotopic liver transplantation (OLT). The Kaplan-Meier 1-year and 5-year survival rates after re-OLT were 69% and 62%, respectively. The area under the curve (AUC) values generated by the receiver operating characteristics (ROC) curves were 0.82 (CI 0.70-0.94) and 0.68 (CI 0.49-0.86), respectively ($P = .11$), for the CTP and MELD models in predicting 1-year mortality after re-OLT. The 1-year and 5-year survival rates for patients with CTP scores less than 10 were 100% versus 50% and 40%, respectively, for CTP scores of at least 10 ($P = .0006$). Patients with MELD scores less than or equal to 25 had 1-year and 5-year survival rates of 89% and 79%, respectively, versus 53% and 47%, respectively, for MELD scores greater than 25 ($P = .038$). Other mortality predictors include hepatic encephalopathy, intensive care unit (ICU) stay, recurrent hepatitis C virus (HCV) infection, and creatinine level of 2 mg/dL or higher. Analysis of an independent cohort of 49 patients showed a trend for a correlation between CTP and MELD scores with 1-year mortality, with AUC of 0.59 and 0.57, in respective ROC curves. In conclusion, our results suggest that severity of graft failure based on CTP and MELD scores may be associated with worse outcome after re-OLT and provide a cautionary note for the "sickest first" policy of organ allocation. (HEPATOLOGY 2004;39:230–238.)

The average survival after liver retransplantation (re-OLT) is inferior to that for primary orthotopic liver transplantation (OLT).[1–4] The reported 1-year patient or graft survival rates after re-OLT were typically in the 50% to 60% range.[1–6] Patients who underwent early re-OLT for primary graft nonfunction fared better.[5] Factors associated with reduced survival after re-OLT for late graft failure include advanced age,[1,3–6] renal failure,[3–6] high serum bilirubin levels,[3–5] United Network for Organ Sharing (UNOS) status 1,[3–5] mechanical ventilation before re-OLT,[4] and recurrent hepatitis C virus (HCV) infection as the indication for re-OLT.[7–9] Patients with renal failure may be predisposed to infectious complications after re-OLT because of associated deficiencies in cellular and humoral immunity.[10,11] The reason for reduced survival among patients undergoing re-OLT for recurrent HCV infection is unknown, but late referral for re-OLT[12] and infectious complications[9,13,14] have been suggested as possible factors. In the

Abbreviations: re-OLT, liver retransplantation; OLT, orthotopic liver transplantation; UNOS, United Network for Organ Sharing; HCV, hepatitis C virus; CTP, Child-Turcotte-Pugh; MELD, model for end-stage liver disease; INR, international normalized ratio for prothrombin time; HAT, hepatic arterial thrombosis; ICU, intensive care unit; HR, hazard ratio; ROC, receiver operating characteristics; AUC, area under the curve; HBV, hepatitis B virus; HBIG, hepatitis B immunoglobulin.

From the [1]Departments of Medicine and [2]Surgery, University of California, San Francisco, San Francisco, CA; [3]Division of Digestive diseases and the Dumont-UCLA Liver Transplant Center, University of California, Los Angeles, Los Angeles, CA; and the [4]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA.

Received September 25, 2003; accepted October 23, 2003.

Presented in part at the 53rd annual AASLD meeting, Boston, MA, November 2002 as an oral presentation (Hepatology 2002;36:228A).

Supported, in part, by a grant from the National Institutes of Health to the University of California, San Francisco Liver Center (P30DK26743).

Address reprint requests to: Francis Y. Yao, M.D., Division of Gastroenterology, University of California, San Francisco, P.O. Box 0538, 513 Parnassus Avenue, Room S-357, San Francisco, CA 94143-0538. E-mail: yaofyk@itsa.ucsf.edu

Published online in Wiley InterScience (www.interscience.wiley.com).

DOI 10.1002/hep.20005

largest study by Rosen et al.[5] based on analysis of UNOS data in more than 1,300 patients, advanced recipient age, elevated creatinine levels, high bilirubin levels, and UNOS status 1 at the time of re-OLT were associated with poor survival after re-OLT. Although the Rosen et al. model[5] is potentially useful in the selection of candidates for re-OLT, the authors have pointed out that an incomplete data set and limited clinical information due to the use of a registry format for data collection may have introduced bias in their analyses. Further refinements and validation of this model were recently reported based on data from six centers outside the United States.[15]

The Child-Turcotte-Pugh (CTP) classification[16] has been used widely as an index to classify disease severity in patients with end-stage liver disease. Previously, a CTP score of at least 10 was used to define two categories of patients with chronic liver failure given high priority in the organ allocation scheme (status 2A and 2B).[17] This system was replaced recently by the model for end-stage liver disease (MELD).[18] Based on serum bilirubin levels, international normalized ratio for prothrombin time (INR), and serum creatinine levels, the MELD scoring system correlates with short-term mortality in patients with end-stage, chronic liver disease.[18] Patients with the highest MELD score, which predicts the greatest risk for dying without receipt of OLT, would be given the highest priority for OLT using the "sickest first" scheme dictated by MELD for organ allocation.[19] Two of the variables included in the formulation of the MELD score (bilirubin and creatinine levels) previously have been identified to be predictive of mortality after re-OLT.[3–5] The correlation between either the preoperative CTP score or the MELD score with outcome after re-OLT has not been evaluated adequately.

The primary objective of the current study is to test the hypothesis that the severity of liver disease based on either the CTP or the MELD score is important in predicting outcome after re-OLT for chronic graft failure. Although other models, including the one proposed by Rosen et al.,[5,15] may be used in prognostication and selection of candidates for re-OLT, assessing the correlation between the MELD score and survival after re-OLT is clinically relevant because this scoring system is currently used in determining the priority for organ allocation. The secondary objective is to reexamine other potential factors that may be associated with poor survival after re-OLT.

Patients and Methods

Study Cohort. Between February 1988 and February 2002, 1,162 adult patients underwent 1,242 OLT at the University of California, San Francisco. Seventy-six patients (6.5%) underwent 80 re-OLT, including four patients who received three OLT. We excluded patients who underwent re-OLT for primary graft nonfunction because these patients have a different postoperative outcome, which may introduce bias in our analysis of predictive factors for survival after re-OLT. Furthermore, to avoid the influence of primary OLT on the outcome of re-OLT, we studied only patients who underwent re-OLT at least 90 days after the primary OLT. Thirty-six of the 76 patients who underwent re-OLT within 3 months from the first OLT were excluded. The reasons for re-OLT in these 36 patients include primary nonfunction or initial poor graft function in 18 patients, hepatic artery thrombosis (HAT) in 14 patients, and refractory rejection in 4 patients. The remaining 40 patients with late graft failure who underwent re-OLT at least 90 days after the first OLT were evaluated in the current study.

Clinical and laboratory data within 24 hours preceding re-OLT were collected retrospectively from a computerized database and by review of patient medical charts. We calculated for each patient the MELD score based on serum bilirubin and creatinine levels and INR.[18] From the outset, the INR was included in the reporting of promthrombin time in all patients. We also retrospectively determined the CTP score,[16] which is based on five variables—hepatic encephalopathy, ascites, bilirubin and albumin levels, and INR. Hepatic encephalopathy was present if the patient received medical treatment including neomycin or lactulose or had clinical manifestations of at least stage 2 hepatic encephalopathy based on the criteria by Gitlin.[20] The presence or degree of ascites was assessed by diuretic requirements, as well as by abdominal imaging studies including ultrasonography or computed tomography scans.

The UNOS criteria for priority status for organ allocation evolved during the study period.[17] For the purpose of the current study, and taking into consideration several confounding variables in assigning appropriate UNOS status at the time of re-OLT, patients were classified instead into the following three groups: (1) hospitalized in the intensive care unit (ICU); (2) continuously hospitalized, not in the ICU; and (3) at home and requiring continuous medical care.

Statistical Analysis and Validation With an Independent Cohort. The Kaplan-Meier method was used to calculate survival probabilities for up to 5 years after re-OLT. Follow-up was censored at 5 years for patients who survived at least that long. Survival between subgroups was compared using the log-rank test. Among patients who underwent three OLT, follow-up was censored at the time of the third OLT. The Cox proportional hazards model was used to assess the CTP and MELD scores and

other potential predictors of mortality after re-OLT. The univariate results were reported as hazard ratios (HR) with 95% CI. The bivariate Cox model was applied subsequently for the most significant predictor identified from the univariate model to determine the impact of the other factors on mortality after re-OLT. If the standard method failed due to infinite estimates, the Firth-Cox method was used.[21] Receiver operating characteristics (ROC) curves[22] were generated for the CTP and MELD scores using 1-year mortality after re-OLT as the end point. The area under the curve (AUC) generated by connected ROC curves with 95% CI was used as a measure of the ability of each model to predict 1-year mortality after re-OLT and was compared by nonparametric methods.[23]

An independent cohort of 49 patients from the University of California, Los Angeles, was used to validate our findings in terms of the impact of the CTP and MELD scores on survival after re-OLT. These were consecutive patients who underwent re-OLT between January 1995 and August 2002 for chronic graft failure (median, 11.9 months from first OLT; range, 3.5-178 months). The ROC curves with AUC[22] were generated for CTP and MELD scores using 1-year mortality after re-OLT as the end point. Survival function based on CTP and MELD scores was compared using the log-rank test. The institutional review board from both institutions approved the current study.

Results

Baseline Characteristics. The indications for primary OLT and re-OLT are summarized in Tables 1 and 2. Graft rejection was the most common reason for re-OLT in our series (35%), followed by recurrent hepatitis B virus (HBV; 20%) and HCV infection (20%). None of the HCV-positive recipients received an organ from an HCV-positive donor. Of the 14 patients with graft rejection as the indication for re-OLT, 13 had chronic ductopenic rejection and 1 had severe acute rejection classified according to the National Institute of Diabetes and Digestive and Kidney Disease grading system.[24] More patients underwent re-OLT for rejection and HBV infection in the first period (between February 1988 and February 1995), whereas more patients underwent retransplantations for recurrent HCV infection and biliary complications in the second period (between March 1995 and February 2002). These differences, however, did not reach statistical significance (Table 2).

Table 1. Indications for Primary OLT

Indications for First OLT	Number (%)
Hepatitis C virus infection	10 (25)
Fulminant liver failure	5 (12.5)
Hepatitis B virus infection	5 (12.5)
Primary sclerosing cholangitis	4 (10)
Primary biliary cirrhosis	4 (10)
Alcoholic liver disease	4 (10)
Autoimmune hepatitis	4 (10)
Cryptogenic cirrhosis	2 (5)
Steatohepatitis	1 (2.5)
Hepatitis B and delta virus infection	1 (2.5)

Abbreviation: OLT, orthotopic liver transplantation.

Table 2. Indications for Re-OLT

Indications for re-OLT	Number in First Period* February 1988 to February 1995	Number in Second Period* March 1995 to February 2002	Total (%)
Rejection	10	4	14 (35)
Hepatitis C virus infection	2	6	8 (20)
Hepatitis B virus infection	6	2	8 (20)
Biliary causes (without HAT)	0	5	5 (12.5)
HAT	2	1	3 (7.5)
Recurrent steatohepatitis	1	0	1 (2.5)
Cryptogenic cirrhosis	0	1	1 (2.5)

Abbreviations: re-OLT, liver retransplantation; HAT, hepatic artery thrombosis.
*No statistically significant difference was found (by the Fisher exact test) when comparing the frequency of the indications for retransplantation.

The baseline clinical, demographic, and laboratory characteristics of the 40 patients are summarized in Table 3. Of the 16 patients (40%) with clinically significant hepatic encephalopathy, none had grade 3 or 4 hepatic encephalopathy[20] at the time of re-OLT. Four patients (10%) received a transjugular intrahepatic portosystemic shunt 4 days to 6 months before re-OLT. The indications for this procedure included both variceal bleeding and massive ascites in two patients, variceal bleeding in one patient, and an attempt to reduce intraoperative blood loss in one patient. Five patients (13%) received combined liver and kidney transplantation.

Of the 5 patients (13%) hospitalized in the ICU, none required mechanical ventilation within 1 week before re-OLT. More than one-half of the patients were hospitalized without requiring ICU stay. Using the system of organ allocation that was in place between July 1997 and February 2002,[17] 7 of 11 patients in our cohort who received re-OLT during this period were upgraded to status 2A but did not require ICU stay upon approval of a petition process by the regional UNOS review board. All except one of these patients were hospitalized at the time of re-OLT. The other four patients were status 2B and were not hospitalized at the time of re-OLT.

Eleven patients (28%) experienced 14 episodes of serious infections within 30 days before re-OLT. The types of infection and organisms identified by cultures are summarized in Table 4. Minor infections of the urinary tract or venous catheter without bacteremia were not included.

Table 3. Baseline Clinical, Laboratory, and Demographic Data of 40 Patients Undergoing Liver Retransplantation

Clinical Data Before Re-OLT	Number (%)
Ascites	20 (50)
Hepatic encephalopathy*	16 (40)
Renal insufficiency (creatinine >2 mg/dL)	13 (33)
Variceal bleeding	5 (13)
TIPS	4 (10)
Status of patient before re-OLT	
ICU	5 (13)
Hospitalized, not in ICU	23 (58)
At home	12 (30)
Length of hospital stay before Re-OLT (wk)	
0	12 (30)
≤1	10 (25)
1–2	4 (10)
2–3	2 (5)
>3	12 (30)
Infections within 30 days before re-OLT	11 (28)
Laboratory data before re-OLT	Median (range)
Bilirubin level (mg/dL)	25.0 (1.5–57)
Albumin level (g/dL)	2.6 (1.6–3.8)
INR	1.6 (1.0–4.4)
Creatinine level (mg/dL)	1.6 (0.5–4.6)
Platelet count ($\times 10^3$)	91 (16–556)
MELD score	26.5 (8–47)
CTP score	11 (6–14)

NOTE. The median age of the patients was 45.5 years (range, 19–65 years). There were 21 men and 19 women. The median time from primary OLT to re-OLT was 2.7 years (range, 0.25–10.7 years).

Abbreviations: re-OLT, liver retransplantation; TIPS, transjugular intrahepatic portosystemic shunt; ICU, intensive care unit; MELD, model for end-stage disease; CTP, Child-Turcotte-Pugh.

*Based on the criteria of Gitlin.[20] None of our patients were in stage 3 or 4 coma before re-OLT. Subtle signs of encephalopathy (stage 1) were not included in our definition.

Table 4. Infectious Complications Within 30 Days Before Liver Retransplantation

Type of Infection and Organisms Isolated	Number
Pneumonia	5
*Streptococcus pneumoniae**	1
Xanthomonas multophilia	1
Staphylococcus aureus	1
Cryptococcus	1
Unknown organism	1
Spontaneous bacterial peritonitis	3
Escherichia coli†	2
Enterobacter cloacae	1
Bacteremia without confirmed primary source	3
Streptococcus sanguis	1
Enterococcus faecum + *S. aureus*	1
Pseudomonas aeruginosa	1
Cholangitis	1
*Enterococcus faecum**	
Candida esophagitis	2

*With bacteremia.

†One of the two cases was associated with bacteremia.

The laboratory data within 24 hours before re-OLT are also shown in Table 3. The median MELD score was 26.5 (range, 8-47). The median CTP score was 11 (range, 6-14). Twenty-four patients (60%) had a CTP score of at least 10, corresponding to Child's class C cirrhosis.

Survival. No patients were lost to follow-up. The Kaplan-Meier survival functions after re-OLT at 1 and 5 years were 69% and 62%, respectively, for the entire cohort (Fig. 1). There were 14 deaths within the first 5 years after re-OLT, including 7 deaths within the first 90 days and 12 deaths in the first year after re-OLT. The causes of death are shown in Table 5. Seven of 12 deaths in the first 6 months were due to multiorgan dysfunction associated with sepsis or poor graft function. Two deaths within the first 6 months were due to aggressive, recurrent HBV infection before the use of prophylactic intravenous hepatitis B immunoglobulin (HBIG). Another patient who did not receive HBIG prophylaxis remained alive 11 years after re-OLT. After excluding these three patients who did not receive HBIG after re-OLT, the Kaplan-Meier 1-year and 5- year survival rates were 72% and 64%, respectively. The remaining five patients with recurrent HBV infection who underwent re-OLT received a fixed dosing schedule of intravenous HBIG prophylaxis as described previously,[25] including one patient who received a combination of intravenous HBIG and oral lamivudine.

For two patients, the causes of late mortality beyond the first year and within 5 years after re-OLT were recurrent HCV infection and cryptogenic liver failure, respectively (Table 5). Four patients underwent three OLT. The time intervals between re-OLT and the third OLT were 17 days, 12 months, 61 months, and 86 months. The respective indications for third OLT were HAT, chronic rejection (two patients), and cryptogenic liver failure.

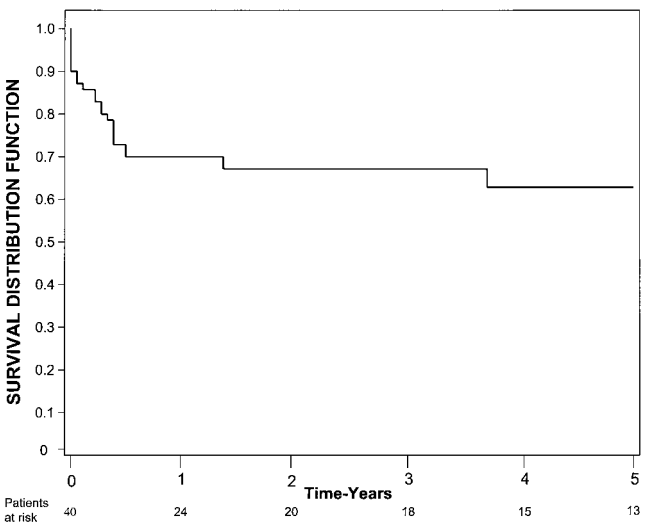

Fig. 1. Kaplan-Meier survival for up to 5 years after re-OLT for the entire cohort of 40 patients. The number of patients remaining at each time point is shown below the horizontal axis.

Table 5. Causes of Death in the First 5 Years After Liver Retransplantation

Patient	Re-OLT Indication	Time After Re-OLT	Cause of Death
1	HCV	44 mo	Liver failure, HCV
2	HCV	5 mo	Right heart failure
3	HCV	7 d	MOD-sepsis, IPF
4	HCV	6 d	MOD-PNF
5	HCV	3 mo	Liver failure, rejection*
6	PBC	7 d	MOD-sepsis, IPF
7	Rejection	2 mo	MOD-sepsis
8	Rejection	4 mo	MOD-sepsis
9	HBV	19 d	MOD-sepsis, peritonitis
10	HBV	4 mo	Liver failure, HBV
11	HBV	4 mo	Liver failure, HBV
12	Rejection	16 mo	Liver failure, unknown type
13	Rejection	7 d	MOD-sepsis, hemorrhage
14	HCV	6 mo	Liver failure, rejection*

Abbreviations: re-OLT, liver retransplantation; HCV, hepatitis C virus; HBV, hepatitis B virus; MOD, multiorgan dysfunction; IPF, initial poor graft function; PNF, primary graft non-function; HAT, hepatic artery thrombosis; PBC, primary biliary cirrhosis.

*Severe rejection in these two patients occurred after recurrent HCV infection treated with interferon.

Impact of CTP and MELD Scores on Mortality. Figure 2 shows the ROC curves generated for the MELD and CTP models. The AUC values were 0.82 (CI 0.70-0.94) and 0.68 (CI 0.49-0.86), respectively, for the CTP and MELD scores in predicting mortality within 1 year after re-OLT. The larger AUC value for the CTP model suggests that it is a stronger predictor of mortality compared with the MELD model, although the difference in the AUC did not reach statistical significance ($P = .11$).

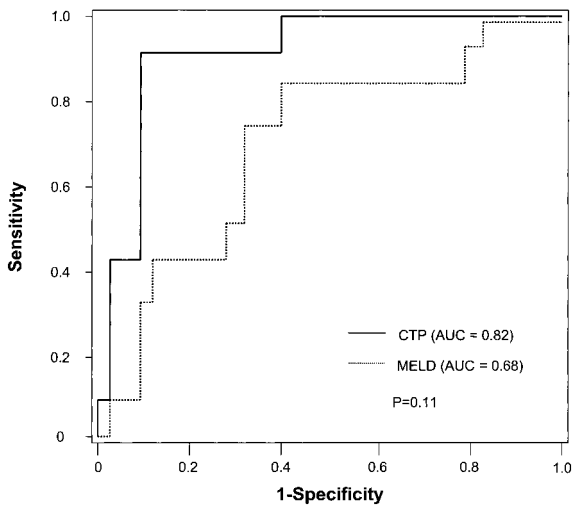

Fig. 2. The ROC curves for the MELD and CTP prognostic models in predicting 1-year mortality rates after re-OLT. (**Solid line**), CTP score; (**dotted line**), MELD score. For the entire cohort of 40 patients, the AUC values were 0.82 (CI 0.7-0.94) for CTP and 0.68 (CI 0.49-0.86) for MELD. $P = .11$ for the difference between the AUC values for CTP and MELD.

In the analysis of CTP score as a predictor of mortality, there were no deaths for 16 patients with a CTP score of less than 10 versus 12 deaths among the other 24 patients with a CTP score of at least 10. In the latter group, the actuarial survival rates were 50% and 40% at 1 and 5 years, respectively ($P = .0006$ by the log-rank test; Fig. 3). Because there were no deaths in the former group, the Firth-Cox method was used instead of the standard Cox proportional hazards model. The Firth-Cox method showed a HR of 20.5 ($P = .0007$; Table 6). A MELD score greater than 25 was also a significant predictor of mortality using the Cox proportional hazards model (HR 4.7, $P = .046$; Table 6). Patients with a MELD score of at least 25 had 1-year and 5-year survival rates of 89% and 79%, respectively. The corresponding survival figures were 53% and 47%, respectively, for patients with a MELD score greater than 25 ($P = .038$ by the log-rank test; Fig. 4).

Repeat analyses were performed after exclusion of the three patients who did not receive HBIG after re-OLT to avoid the potential bias of inadequate prophylaxis against recurrent HBV infection on survival and predictors of survival. These three patients had identical CTP scores of 12 and MELD scores ranging from 31 to 40. Two patients (MELD scores of 31 and 40, respectively) died of liver failure as a result of recurrent HBV infection (Table 5). The remaining patient (MELD score of 38) did well and remained alive 11 years after re-OLT. The 1-year and

Table 6. Univariate Analysis of Predictors of Mortality After Liver Retransplantation for the Entire Cohort of 40 Patients

Predictor Variables	Hazard Ratio (95% CI)	*P* Value
CTP score ≥10*	20.5 (2.7–2,626)*	.0007*
Hepatic encephalopathy†	10.9 (2.4–49.9)	.002†
ICU	13.0 (1.4–117)	.022
Hepatitis C virus infection	3.4 (1.08–10.7)	.037
Creatinine level ≥2 mg/dL	3.4 (1.07–10.6)	.039
MELD score >25	4.7 (1.03–21.6)	.046
Ascites	3.1 (0.84–11.5)	.089
Age	1.1 (0.99–1.1)	.089
Platelet count <60	2.5 (0.79–7.9)	.12
Infection	2.5 (0.79–7.9)	.12
INR	1.5 (0.84–2.6)	.17
Retransplant period (second half vs. first half)	0.71 (0.21–2.4)	.58
Male sex	1.3 (0.41–4.0)	.67
Bilirubin level	0.99 (0.96–1.03)	.73
Albumin level	0.84 (0.3–2.3)	.74

Abbreviations: CTP, Child-Turcotte-Pugh; ICU, intensive care unit; MELD, model for end-stage liver disease; INR, international normalized ratio for prothrombin time; re-OLT, liver retransplantation.

*There were no deaths after re-OLT for the 16 patients with a CTP score <10. The analysis was based on the Firth-Cox method.

†Hepatic encephalopathy was the only statistically significant predictor of mortality after controlling the CTP score in the bivariate analysis (hazard ratio, 4.0; CI, 1.2–21.7, $P = .028$).

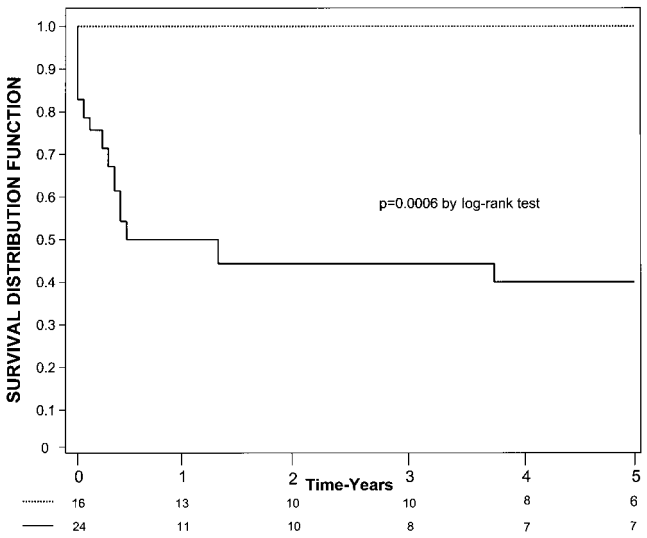

Fig. 3. Kaplan-Meier survival function for up to 5 years after re-OLT according to preoperative CTP score. (**Dotted line**), 16 patients with CTP scores less than 10; (**solid line**), 24 patients with CTP scores of at least 10. The difference in survival rates between these two subgroups was statistically significant ($P = .0006$ by the log-rank test). A CTP score of at least 10 was a significant predictor of mortality rate using the Firth-Cox method (HR 20.5, $P = .0007$). The number of patients in each subgroup remaining at each time point is shown below the horizontal axis.

5-year survival rates were 100% for the 16 patients with a CTP score less than 10 versus 54% and 43%, respectively, for the 21 patients with a CTP score of at least 10 ($P = .0024$ by the log-rank test). The 18 patients with a MELD score of 25 or less had 1-year and 5-year survival rates of 89% and 79%, respectively, versus 56% and 50% for the 19 patients with a MELD score greater than 25 ($P = .044$ by the log-rank test). The ROC curves generated after the exclusion of these three patients were almost identical, with AUC values of 0.82 (CI 0.69-0.94) and 0.67 (CI 0.48-0.87), respectively, for the CTP and MELD scores. The difference in AUC values was not statistically significant ($P = .13$).

Other Predictors of Mortality. Using univariate analysis for the entire cohort of 40 patients, in addition to the CTP score and the MELD score, other independent predictors of mortality after re-OLT included the presence of hepatic encephalopathy (HR 10.9, $P = .002$), ICU stay before re-OLT (HR 13.0, $P = .022$), HCV infection as the cause of re-OLT (HR 3.4, $P = .037$), and creatinine level of at least 2 mg/dL (HR 3.4, $P = .039$; Table 6). Statistical significance was marginal with ascites (HR 3.1, $P = .089$) and age (HR 1.05, $P = .089$). Platelet count, infection within 30 days before re-OLT, INR, sex, re-OLT period, and bilirubin level were not statistically significant. Because a CTP score of at least 10 was the strongest predictor for mortality, a bivariate model controlling the CTP score was applied to all significant predictors identified in the univariate model. Only hepatic encephalopathy remained statistically significant as a predictor for poor survival after re-OLT (HR 4.0, CI 1.15-21.7, $P = .028$; Table 6). Figure 5 shows the survival function for up to 5 years among patients with and without hepatic encephalopathy. The 1-year and 5-year survival rates for patients with hepatic encephalopathy were 38% and 30%, respectively, versus 91% and 84%, respectively, for patients without hepatic encephalopathy ($P < .0001$ by the log-rank test).

After exclusion of the three patients with HBV infection who did not receive HBIG after re-OLT, a CTP score of at least 10 was the strongest predictor of mortality (HR 19.4, $P = .001$). The same mortality predictors in the univariate analysis included hepatic encephalopathy (HR 18.5, $P = .006$), ICU stay before re-OLT (HR 20.0, $P = .01$), and HCV infection as the indication for re-OLT (HR 4.3, $P = .02$). Several differences in the results were also observed. Serious infection before re-OLT (HR 3.8, $P = .04$) was a significant predictor of mortality. Statistical significance was marginal for a MELD score greater than 25 (HR 4.3, $P = .06$) and was not achieved with a creatinine level of at least 2 mg/dL (HR 2.7, $P = .12$). After controlling the CTP score in the bivariate analysis, none of the predictors in the univariate analysis remained statistically significant as predictors of mortality.

Validation With an Independent Cohort. The overall Kaplan-Meier 1-year and 5-year survival rates after

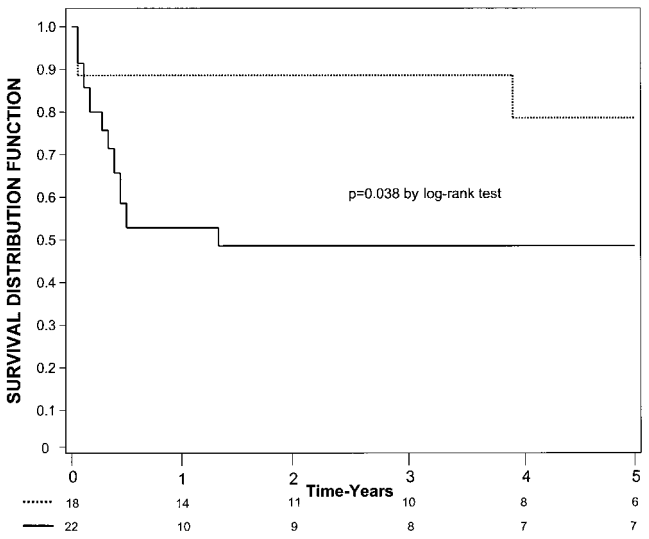

Fig. 4. Kaplan-Meier survival function for up to 5 years after re-OLT according to the preoperative MELD score. (**Dotted line**), 18 patients with MELD scores of 25 or less; (**solid line**), 22 patients with MELD scores greater than 25. The difference in survival rates between these two subgroups was statistically significant ($P = .038$ by the log-rank test). A MELD score greater than 25 was a significant predictor of mortality rate using the Cox proportional hazards model (HR 4.7, $P = .046$). The number of patients in each subgroup remaining at each time point is shown below the horizontal axis.

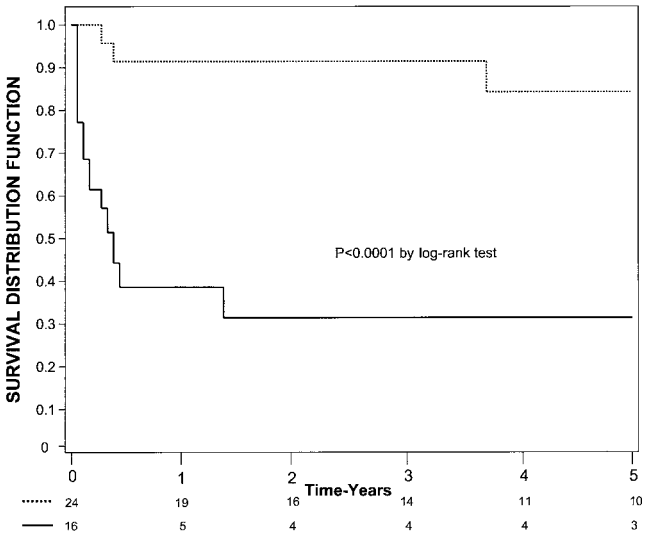

Fig. 5. Kaplan-Meier survival function for up to 5 years after re-OLT according to the presence or absence of hepatic encephalopathy. The criteria of Gitlin,[20] therapy with neomycin or lactulose, or both were used to define the presence of hepatic encephalopathy. (**Dotted line**), 24 patients without hepatic encephalopathy; (**solid line**), 16 patients with hepatic encephalopathy. The difference in survival between the two subgroups was statistically significant ($P < .0001$ by the log-rank test). The presence of hepatic encaphalopathy was a significant predictor of mortality rate using the Cox proportional hazards model (HR 10.9, $P = .002$). The number of patients in each subgroup remaining at each time point is shown below the horizontal axis.

re-OLT were 67.9 % and 56.7%, respectively, for the independent cohort of 49 patients. The median CTP and MELD scores were 11 (range, 6–15) and 22.5 (range, 6–40), respectively. The most common indications for re-OLT included recurrent HCV infection (11 patients), chronic rejection (9 patients), postnecrotic cirrhosis of uncertain etiology (9 patients), and HAT (6 patients). The AUC value was 0.59 (CI 0.43-0.76) for the CTP score and 0.57 (CI 0.39-0.74) for the MELD score ($P = .79$ for the difference in the AUC value; Fig. 6). The 1-year survival rate for the 17 patients with a CTP score less than 10 was 82.4% versus 61.4% for the 32 patients with a CTP score of at least 10 ($P = .075$). A MELD score of 22 was the cutoff that approached statistical significance in predicting 1-year mortality. The 1-year survival rate was 82.6% for the 24 patients with a MELD score of at least 22 versus 54.6% for the 24 patients with a MELD score greater than 22 ($P = .057$).

Discussion

In the era of critical organ shortage, one of the most controversial issues facing the liver transplant community is whether re-OLT should be offered to patients with chronic graft failure. A logical approach to patients with late graft failure is stratification according to the risk of dying after re-OLT. The recently implemented policy using the MELD score prioritizes organ allocation according to disease severity and the risk of death without OLT.[19] The impact of preoperative MELD or CTP score on survival after re-OLT has not been evaluated adequately.

Our results support a general theme that patients with more advanced liver disease, based on either a high preoperative CTP or MELD score, have a worse postoperative outcome than patients with less advanced disease. The analysis of an independent cohort of a similar size only showed a trend for a correlation between CTP and MELD scores with 1-year mortality, raising uncertainties regarding our findings. A prospective study based on a larger cohort of patients is needed to further address this issue. Certainly, there are complex technical and medical factors, in addition to disease severity alone, that may be associated with early mortality after re-OLT. Another weakness of the current study is related to the potential bias and subjectivity in retrospectively determining individual CTP scores, primarily with respect to the degree of ascites and hepatic encephalopathy. The association between CTP score and survival after re-OLT was evaluated by Facciuto et al.[6] who studied 48 patients with late graft failure. There was a trend towards a higher 90-day mortality rate after re-OLT among patients with a preoperative CTP score of at least 10, but the difference did not reach statistical significance ($P = .07$).[6] The correlation between a higher MELD score and increased mortality rates after re-OLT was suggested in a recent study by

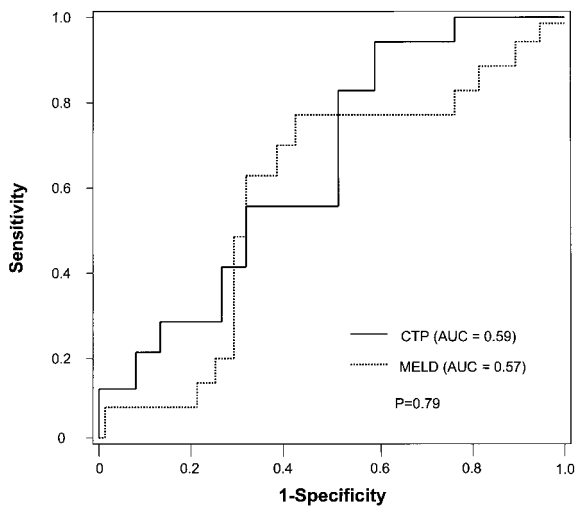

Fig. 6. The ROC curves for the MELD and CTP prognostic models in predicting 1-year mortality rtaes after re-OLT when applied to an independent cohort of 49 patients. (**Solid line**), CTP score; (**dotted line**), MELD score. The AUC values were 0.59 (CI 0.43-0.76) for the CTP score and 0.57 (CI 0.39-0.74) for the MELD score. $P = .79$ for the difference in AUC values for the CTP and MELD scores.

Rosen et al.[15] They stratified patients into three risk groups according to MELD scores less than 22, 22–31, and at least 32.

The current study is not intended to assess whether CTP or MELD scores better predict prognosis after re-OLT than the model proposed by Rosen et al.[5,15] Rather, the issue is whether there is a correlation between outcome after re-OLT and preoperative MELD score, which is currently used in determining priority for organ allocation. The finding that a higher preoperative MELD score predicts worse survival after re-OLT may have potential implications on the current organ allocation policy. The best cutoff in the MELD score in predicting mortality after re-OLT could not be assessed fully in the current study due to the small sample of patients and to the significant number of deaths among patients with a relatively low preoperative MELD score. The CTP scoring system, despite the problem with subjectivity in scoring two of the five parameters (ascites and hepatic encephalopathy), has stood the test of time for nearly 40 years as the preeminent indicator of the severity of liver disease.[26] The simplicity of the CTP score also confers a potential advantage over the MELD and Rosen models if it is confirmed to be a significant predictor of prognosis after re-OLT.

Hepatic encephalopathy, a predictor of mortality rate in the current study, did not correlate with mortality rate after re-OLT in the study by Wong et.al.[3] and was not evaluated as an individual predictor in other studies.[1,2,4–6] Our results also differed from several other studies that found advanced recipient age[1,3,5,6] and bilirubin level[3–5] to be significant predictors of mortality rate after re-OLT. The small sample of patients and possible selection bias in the current study are the most likely explanations for these differences. Prolonged intubation has been regarded as a contraindication for OLT in critically ill patients with chronic liver disease at the University of California, San Francisco. Therefore, some of the high-risk patients already might have been excluded in the current study. The true impact of preoperative hyperbilirubinemia on outcome after re-OLT might be difficult to demonstrate in our cohort because only six patients (15%) had bilirubin levels less than 5 mg/dL.

Another highly controversial issue is whether re-OLT should be performed for patients with recurrent HCV infection as the cause of failure of the first allograft.[27] The foundation of this debate is determined by whether HCV infection as the cause of graft failure *per se* is associated with increased postoperative mortality rates. The current study suggested an increased risk of death among patients with recurrent HCV infection as the indication for re-OLT, although the number of patients with HCV infection was very small and the association was no longer statistically significant after controlling the CTP score. A number of studies have suggested poor survival after re-OLT for HCV infection.[6–9] Possible explanations proposed for the poor outcome include a delay in referral until these patients have very advanced-stage disease,[12] as the current study also supports, and a higher risk of postoperative infections[9,13,14] possibly due to depression of the cellular immune response. Acute ductopenic rejection or chronic rejection leading to graft loss has been reported in some patients receiving interferon alfa treatment for recurrent HCV infection after OLT,[28–30] although the overall incidence of rejection does not appear to be increased by interferon treatment.[31] Conversely, the number of rejection episodes and the cumulative exposure to steroids have been linked to accelerated progression of HCV infection after OLT.[32–37] In the current study, two deaths were due to liver failure associated with severe ductopenic rejection while patients received interferon treatment for recurrent HCV infection and one death was related to severe recurrent HCV infection of the second allograft (Table 5). These observations highlight the dilemma in the management of immunosuppressive strategies, rejection, and recurrent HCV infection in these patients,[37] which may also contribute to significant morbidity and mortality after re-OLT.

In conclusion, the results of the current study suggest that patients who are more severely ill tend to have a worse outcome after re-OLT. In an era when there is a critical shortage of organs, the general principle underlying organ allocation policy for OLT, utilizing either the CTP model or the newly implemented MELD scoring system, is to help the sickest patients first who are at greatest risk of dying without OLT. This strategy seems justified by the increasing number of deaths among patients on the UNOS waiting list and the disparity between the demand and supply of donor organs, even if survival after primary OLT is marginally lower for the sickest patients.[19] The allocation of a scarce resource to patients needing re-OLT, however, is much more controversial when the overall poor survival rates after re-OLT are scrutinized.[38] Our results provide a cautionary note in applying the sickest first organ allocation scheme for re-OLT, but also underscore the dilemma in many transplant centers where only patients with a high MELD score can realistically undergo re-OLT. Finally, the results from an independent cohort did not provide confirmatory support of our findings. Consequently, prospective validation based on a much larger number of patients is needed.

Acknowledgment: The authors thank Linda Gibbons for providing technical support in the preparation of this article.

References

1. Markmann JF, Markowitz JS, Yersiz H, Morrisey M, Farmer DG, Farmer DA, Goss J, et al. Long-term survival after retransplantation of the liver. Ann Surg 1997;226:408–420.
2. D'Alessandro AM, Ploeg RJ, Knechtle SJ, Pirsch JD, Stegall MD, Hoffmann R, Sollinger HW, et al. Retransplantation of the liver. A seven-year experience. Transplantation 1993;55:1083–1087.
3. Wong T, Devlin J, Rolando N, Heaton N, Williams R. Clinical characteristics affecting the outcome of liver retransplantation of the liver. Transplantation 1997;64:878–882.
4. Doyle HR, Morelli F, McMichael J, Doria C, Aldrighetti L, Starzl TE, Marino IR. Hepatic retransplantation—an analysis of risk factors associated with outcome. Transplantation 1996;61:1499–1505.
5. Rosen HR, Madden JP, Martin P. A model to predict survival following liver retransplantation. HEPATOLOGY 1999;29:365–370.
6. Facciuto M, Heidt D, Guarrera J, Bodian CA, Miller CM, Emre S, Guy SR, et al. Retransplantation for late liver graft failure: predictors of mortality. Liver Transpl 2000;6:174–179.
7. Rosen HR, Martin P. Hepatitis C infection in patients undergoing liver retransplantation. Transplantation 1998;66:1612–1616.
8. Feray C, Habasanne A, Samuel D, Farges O, Reynes M, Bismuth H. Poor prognosis of patients retransplanted for recurrent liver disease due to hepatitis C virus [abstract]. HEPATOLOGY 1995;22:135A.
9. Casavilla FA, Lee R, Lim J, Kramer D, Irish W, Rakela J, Fung JJ. Outcome of liver retransplantation for recurrent hepatitis C infection [abstract]. HEPATOLOGY 1995;22:153A.
10. Kurz P, Kohler H, Meuer S, Hutteroth T, Meyer zum Buschenfelde KH. Impaired cellular immune responses in chronic renal failure: evidence for a T cell deficit. Kidney Int 1986;29:1209–1214.
11. Goldblum SE, Reed WP. Host defenses and immunologic alterations associated with chronic hemodialysis. Ann Intern Med 1980;93:597–613.
12. Ghobrial RM, Farmer DG, Baquerizo A, Colquhoun S, Rosen HR, Yersiz H, Markmann JF, et al. Orthotopic liver transplantation for hepatitis C: outcome, effect of immunosuppression, and causes of retransplantation during an 8-year single-center experience. Ann Surg 1999;229:824–831.
13. Singh N, Gayowski T, Wagener MM, Marino IR. Increased infections in liver transplant recipients with recurrent hepatitis C virus hepatitis. Transplantation 1996;61:402–406.
14. Sheiner PA, Kim-Schluger L, Emre S, Thung S, Lau YN, Guy SR, Schwartz ME, et al. Retransplantation for recurrent hepatitis C. Liver Transpl Surg 1997;2:130–136.
15. Rosen HR, Prieto M, Casanovas-Taltavull T, Cuervas-Mons V, Guckelberger O, Muiesan P, Strong RW, et al. Validation and refinement of survival models for liver retransplantation. HEPATOLOGY 2003;38:460–469.
16. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;60:646–649.
17. Keeffe EB. Summary of guidelines on organ allocation and patient listing for liver transplantation. Liver Transpl Surg 1998;(Suppl 1):S108–S114.
18. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, et al. A model to predict survival in patients with end-stage liver disease. HEPATOLOGY 2001;33:464–470.
19. Wiesner RH, McDiarmid SV, Kamath PS, Edwards EB, Malinchoc M, Kremers WK, Krom RAF, et al. MELD and PELD: application of survival models to liver allocation. Liver Transpl 2001;7:567–580.
20. Gitlin N. Hepatic encephalopathy. In: Zakim D, Boyer TD, eds. Hepatology: a Textbook of Liver Disease. Volume 1. 3rd ed. Philadelphia: Saunders, 1996:605–617.
21. Heinze G, Schemper M. A solution to the problem of monotone likelihood in Cox regression. Biometrics 2001;57:114–119.
22. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982;143:29–36.
23. De Long ER, De Long DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristics curves: a nonparametric approach. Biometrics 1988;44:837–845.
24. International Working Party. Terminology for hepatic allograft rejection. HEPATOLOGY 1995;22:648–654.
25. Terrault NA, Zhou S, Combs C, Hahn JA, Lake JR, Roberts JP, Ascher NL, et al. Prophylaxis in liver transplant recipients using a fixed dosing schedule of hepatitis B immunoglobulin. HEPATOLOGY 1996;24:1327–1333.
26. Forman LM, Lucey MR. Predicting the prognosis of chronic liver disease: an evolution from Child to MELD. HEPATOLOGY 2001;33:473–475.
27. Rosen HR. Retransplantation for hepatitis C: implications of different policies. Liver Transpl 2000;(Suppl 2):S41–S46.
28. Dousset B, Conti F, Houssin D, Calmus Y. Acute vanishing bile duct syndrome after interferon therapy for recurrent HCV infection in liver-transplant recipients [letter]. N Engl J Med 1994;330:1160–1161.
29. Feray C, Samuel D, Gigou M, Paradis V, David MF, Lemonnier C, Reynes M, et al. An open trial of interferon-α recombinant therapy for hepatitis C after liver transplantation: antiviral effects and risk of rejection. HEPATOLOGY 1995;22:1084–1089.
30. Gopal DV, Rabkin JM, Berk BS, Corless CL, Chou S, Olyaei A, Orloff SL, et al. Treatment of progressive hepatitis C recurrence following liver transplantation with combination interferon plus ribavirin. Liver Transpl 2001;7:181–190.
31. Jain A, Demetris AJ, Manez R, Tsamanadas AC, Van Thiel D, Rakela J, Starzl TE, et al. Incidence and severity of acute allograft rejection in liver transplant recipients treated with α interferon. Liver Transpl Surg 1998;4:197–203.
32. Sheiner PA, Schwartz M, Mor E, Schluger LK, Theise N, Kishikawa K, Kolesnikov V, et al. Severe or multiple rejection episodes lead to increased early recurrence of hepatitis C after orthotopic liver transplantation. HEPATOLOGY 1995;21:30–34.
33. Prieto M, Berenguer M, Rayon JM, Cordoba J, Arguello L, Carrasco D, Garcia-Herola A, et al. High incidence of allograft cirrhosis in hepatitis C virus genotype 1b infection following transplantation: relationship with rejection episodes. HEPATOLOGY 1999;29:250–256.
34. Charlton M, Seaberg E. Impact of immunosuppression and acute rejection on recurrence of hepatitis C: results of the National Institute of Diabetes and Digestive and Kidney Disease liver transplantation database. Liver Transpl Surg 1999;5(4 Suppl 1):S107–S114.
35. Berenguer M, Ferrell L, Watson J, Prieto M, Kim M, Rayon M, Cordoba J, et al. HCV-related fibrosis progression following liver transplantation: increase in recent years. J Hepatol 2000;32:673–684.
36. Testa G, Crippin JS, Netto GJ, Goldstein RM, Jennings LW, Brkic BS, Brooks BK, et al. Liver transplantation for hepatitis C: recurrence and disease progression in 300 patients. Liver Transpl 2001;6:553–561.
37. Sheiner PA. Hepatitis C after liver transplantation. Semin Liv Dis 2000;20:201–209.
38. Biggins SW, Beldecos A, Rabkin JM, Rosen HR. Retransplantation for hepatic allograft failure: prognostic modeling and ethical considerations. Liver Transpl 2002;8:313–322.