

1958

A Prognostic Model for the Outcome of Liver Transplantation in Patients With Cholestatic Liver Disease

PAOLA RICCI,³ TERRY M. THERNEAU,³ MICHAEL MALINCHOC,³ JOANNE T. BENSON,³ JAN L. PETZ,³ GORAN B. KLINTMALM,¹ JEFFREY S. CRIPPIN,¹ RUSSELL H. WIESNER,³ JEFFREY L. STEERS,³ JORGE RAKELA,² THOMAS E. STARZL,² AND E. ROLLAND DICKSON³

We studied the outcome of 436 patients with primary biliary cirrhosis (PBC) or primary sclerosing cholangitis (PSC) who underwent orthotopic liver transplant (OLT) at three major liver transplant centers. Univariate predictors of outcome included age, Karnofsky score, Child's class, Mayo risk score, United Network for Organ Sharing (UNOS) status, nutritional status, serum albumin, serum bilirubin, international normalized ratio, and the presence of ascites, encephalopathy, renal failure (serum creatinine > 2 mg/dL), and edema refractory to diuretics. Using these predictors, we developed a four variable mathematical prognostic model to help the liver transplant physician predict the following: 1) the amount of intraoperative blood loss; 2) the number of days in the intensive care unit (ICU); and 3) severe complications after surgery. The model uses age, renal failure, Child's class, and United Network for Organ Sharing status. This study is the first to model the outcome of liver transplant in patients with a specific etiology of chronic liver disease (PBC or PSC). The model may be used to help select patients for OLT and to plan the timing of their transplantation. (HEPATOLOGY 1997;25:672-677.)

In the early 1980s, orthotopic liver transplant (OLT) was recognized to prolong survival in patients with chronic liver disease; today it is accepted therapy for end-stage liver disease due to a variety of etiologies.¹ However, as the number of accepted indications for liver transplantation has increased, there has not been a corresponding increase in the number of suitable organ donors. This has resulted in a disparity between donor organ demand and supply that has grown dramatically over the past few years. In 1993, 560 patients died on the liver transplantation waiting list in the U.S.² Transplantation physicians, who deal with progressively longer waiting lists, need to decide which patients to select for liver transplantation and when to enter those patients onto a waiting list. These decisions need to coincide for a transplantation to occur at a timely point in the patient's disease course.

The present allocation system assigns donor livers to the

patients with most advanced disease, resulting in a longer waiting time for less advanced patients. The clinical status of these patients inevitably deteriorates as their waiting time lengthens.³ Since the postoperative course of patients who are end-stage at the time of transplantation is characterized by higher mortality, morbidity, and cost³⁻⁶; this deferral of all patients until their status is terminal has a negative impact upon liver transplantation outcome. Recognizing that not every patient can be transplanted, there is a need for methods which will allow transplantation physicians to predict which patients will most benefit from transplantation. For the referring physicians, the knowledge of factors that lead to poor OLT outcome may enable them to better plan their referrals.

This paper reports the predictors of post-OLT morbidity, as the survival of transplanted patients has improved and become medically acceptable.² Indeed, the risk factors for patient and graft survival could not be assessed as there were not enough events for adequate modeling. We studied the outcome of 436 patients who received a liver transplant for primary biliary cirrhosis (PBC) or primary sclerosing cholangitis (PSC). First, we examined the relationship between selected preoperative variables and intraoperative blood loss, and postoperative morbidity (intensive care unit [ICU] stay and major complications after OLT). Second, we developed a mathematical prognostic model, containing four inexpensive and easily obtained variables, that the liver transplant physician can use to calculate a score for predicting the patient's intraoperative blood loss and postoperative morbidity.

PATIENTS AND METHODS

Methods. We followed 436 patients with established PBC (n = 228) or PSC (n = 208) who underwent OLT between 1985 and 1994 at either the Baylor University Medical Center (BUMC, Dallas, TX), the University of Pittsburgh (Pittsburgh, PA), or the Mayo Clinic (Rochester, MN). The National Institutes of Health Liver Transplant Database forms were the source of the data. These forms were in use at the University of Pittsburgh and Mayo Clinic from 1990 until present. Similar forms were in use at Baylor University Medical Center since 1985.

Follow-up data are shown in Table 1. The median follow-up time was 2 years post-OLT. The higher absolute number of retransplants and deaths at Baylor University Medical Center reflects their longer patient series extending over a 10-year period. Table 2 reports patient demographic, clinical, and biochemical characteristics along with OLT outcome variables. It includes the following 13 preoperative variables that were studied: age, Child's class, Karnofsky score, Mayo risk score, United Network for Organ Sharing (UNOS) status, nutritional status, serum albumin, serum bilirubin, international normalized ratio and the presence of ascites, encephalopathy, renal failure (serum creatinine > 2 mg/dL), and edema refractory to diuretics. Table 2 reports the following: patient mean age was 51 years; 68% were female; 52% had PBC; 83% belonged to Child class B or C; 68% had ascites; 28% had edema refractory to diuretics; 48% had encephalopathy; and 9% had renal failure defined as serum creatinine > 2 mg/dL. The UNOS status shows that 27% of patients were at home; 52% received continuous medical care; 16% were hospital-

Abbreviations: OLT, orthotopic liver transplantation; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; ICU, intensive care unit; UNOS, United Network for Organ Sharing.

From the ¹ Baylor University Medical Center, Dallas, TX; the ² University of Pittsburgh, Pittsburgh, PA; and the ³ Mayo Clinic, Rochester, MN.

Received March 12, 1996; accepted October 22, 1996.

Supported in part by Research Grant DK 34238 from the National Institutes of Health, Public Health Service, Bethesda, MD.

Address reprint requests to: E. Rolland Dickson, M.D., Division of Gastroenterology and Hepatology, Mayo Clinic and Mayo Foundation, 200 First St., SW, Rochester, MN 55905.

Copyright © 1997 by the American Association for the Study of Liver Diseases.
0270-9139/97/2503-0030\$3.00/0

TABLE 1. Follow-Up Data for Patients Who Underwent Liver Transplantation for PBC or PSC

	BUMC (n = 194)	University of Pittsburgh (n = 136)	Mayo Clinic (n = 106)	All Patients (n = 436)
Transplantation dates				
First	4/22/85	8/1/90	4/21/90	
Last	9/2/94	1/11/95	4/25/94	
Retransplants (n)*	25	8	10	43
Deaths (n)	30	12	5	47
Last follow-up date	11/9/94	2/25/95	4/12/95	
Median follow-up (y)	3.1	1.0	2.1	2.0

Abbreviation: BUMC, Baylor University Medical Center.

* Number of patients who underwent one or more retransplants after failure of the initial OLT.

ized; and 5% were in ICU at the time of liver transplant. Median Mayo PBC risk score was 7.3 (range, 4.2-10.3) and for PSC the median risk score was 5.4 (range, 2.9-7.1).

Table 2 also reports the four transplant outcomes as follows: intraoperative blood use (amount of transfused fresh frozen plasma, packed red blood cells, and cell saver), number of days in an ICU, severe complications within 30 days of OLT, and severe complications that occur after 30 days from OLT. Severe complications in-

cluded retransplantation, patient death, and any medical event prompting the patient management team to respond with diagnostic or therapeutic action. For example, an infection was treated with a course of antibiotics or a biliary leak was corrected with a percutaneous, endoscopic, or surgical procedure. Medical problems requiring therapeutic intervention, but unrelated to the transplant surgery itself or to the side effects of immunosuppressive drugs, were not considered as complications and were not included in the outcomes. The differences in mean and median outcomes among the three institutions shown in Table 2 may reflect differences in data collection and coding practices. Table 3 reports the types of complications that occurred after OLT. As reported, infections have the highest frequency.

Statistical Analysis. All statistical analyses were performed using the SAS⁷ and S-PLUS⁸ packages. Inter-center differences in demographic variables were compared using the rank sum and binomial tests. Overall patient and graft survival were computed by the Kaplan-Meier method. Each outcome (blood loss, ICU days, early and late complications) was analyzed separately. Univariate and multivariate examinations of blood loss and ICU days were based on linear regression with a logarithmic transformation of the dependent variable. Complications were examined using Poisson regression, accounting for both the differential amount of follow-up for each patient and the decreasing overall rate of events during the months following OLT. Because of possible differences among the transplant centers in coding and recording these variables, particularly in the local interpretation of what constitutes a "severe" complication, all models were adjusted for both institution and diagnosis (PBC or PSC). The

TABLE 2. Demographic, Clinical, Biochemical Features, and Outcomes in Patients Who Underwent Liver Transplantation for PBC or PSC

	BUMC (n = 194)	University of Pittsburgh (n = 136)	Mayo Clinic (n = 106)	All Patients (n = 436)
Demographic				
Age (y) (mean ± SD)	49 ± 10	53 ± 12	50 ± 10	51 ± 11
Sex (% female)	72	66	64	68
Liver disease (% PBC)	56	57	40	52
Clinical				
Ascites, (%)	69	63	74	68
Child's-Pugh class, (%)				
A	17	20	13	17
B	53	58	44	52
C	30	21	42	31
Edema (%)*	31	19	35	28
Encephalopathy, (%)	58	45	36	48
Karnofsky score (median)†	70	50	70	60
Mayo risk score (median)				
PBC	7.2	7.2	7.9	7.3
PSC	5.4	—	5.5	5.4
Nutritional status (%)				
Excellent	20	50	16	28
Fair	66	41	67	59
Poor	14	9	16	13
Renal failure (%)‡	8	11	9	9
UNOS status (%)				
ICU/liver failure (1)	9	4	0	5
Hospitalized (2)	13	26	4	16
Continuous medical care (3)	48	62	42	52
At home (4)	30	8	54	27
Biochemical (median)				
Albumin (g/L)	3.3	3.3	2.9	3.2
Bilirubin (mg/dL)	6.6	4.6	7.9	6.3
INR	1.2	1.3	1.3	1.3
OLT outcomes				
Operative blood loss, liters (median)	1.1	3.3	4.0	2.2
ICU, days (median)	3	6	3	3
Severe complications (× ± SD)§	0.9 ± 1.5	1.2 ± 2.1	1.8 ± 2.0	1.2 ± 1.9
Severe complications (× ± SD)¶	1.4 ± 2.1	1.2 ± 2.2	3.3 ± 3.7	1.8 ± 2.7

Abbreviations: INR, international normalized ratio; BUMC, Baylor University Medical Center.

* Edema despite diuretic therapy.

† High Karnofsky indicated healthier patient.

‡ Creatinine >2 mg/dL and/or urine output <10 mL/kg/24 hours.

§ Medical event requiring intervention within 30 days of OLT surgery.

¶ Medical event requiring intervention more than 30 days after OLT surgery.

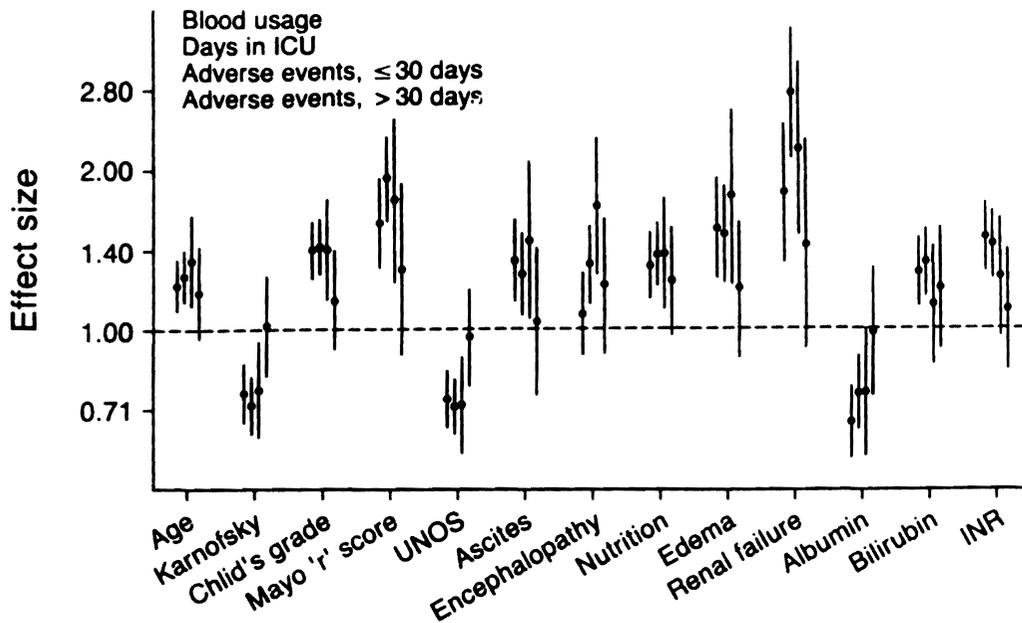


FIG. 1. Univariate analysis: predictors of operative and postoperative outcome.

net effect of these procedures is that the final models are multiplicative. That is, a coefficient of 1.25 for ascites means that a patient with ascites is expected to have 25% more complications than a patient without ascites. The final models were verified using the robust regression methods of Chambers and Hastie⁹ to ensure that no single case (outlier) had an undue effect on the estimates.

Univariate Analysis. Figure 1 reports the univariate effect of a risk factor on a particular outcome. For the continuous variables of age, Karnofsky, Mayo *r* score, albumin, bilirubin, and international normalized ratio Fig. 3 reports the effect on two patients: one at the 25th percentile and the other at the 75th percentile.

Multivariate Analysis. Our goal was to select a simple model that would be applicable to each outcome. That is, we preferred not to have one set of variables for predicting blood loss, another to predict ICU days, and yet a third to predict complications; however, the relative weight of each variable within the model might vary among outcomes. Because the variables shown in Fig. 1 are highly interdependent, stepwise regression methods can be very misleading, ie, the deletion of only a few patients can lead to selection of a completely different set of variables.¹⁰ First, stepwise regression was used to determine that a four-variable multivariate model would provide the best prediction (a five-variable model was not significantly better

than a four-variable model). Second, the bootstrap method was used to assess which three- or four-variable models were similar, in predictive accuracy, to the "best" model chosen by the stepwise procedure. For blood usage, for example, it selected 38 of the 715 possible four-variable combinations and 2 of the 286 possible three variable combinations. Models were considered equivalent if their *r* statistics were within .5 standard error of each other. This was repeated for each outcome. The final model was one which was closest to the "best" model in all three categories of outcome.

RESULTS

Survival. Overall 2-year patient survival was 90% (Fig. 2A). Overall 2-year graft survival was 82% (Fig. 3A). There was no statistically significant difference between PBC and PSC in the surviving proportion of patients (*P* = .71) and grafts (*P* = .66), as shown in Figs. 2B and 3B.

Univariate Analysis. The univariate analyses are shown in Fig. 1. The variables studied are represented on the x axis and their estimated multiplicative effect (with 95% confidence intervals) for the four outcomes is displayed on the y

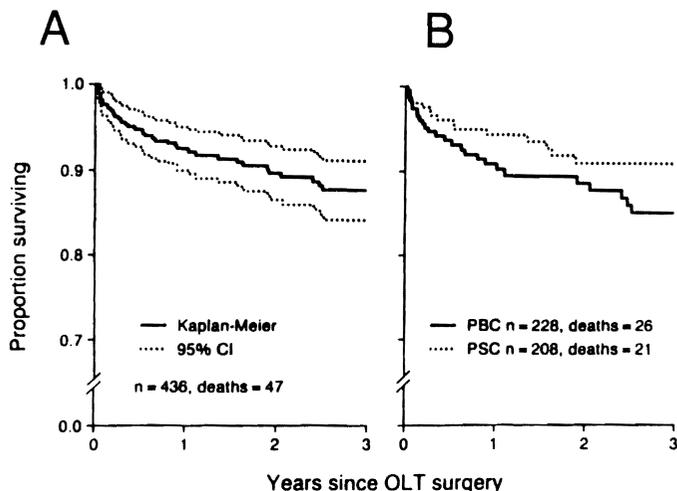


FIG. 2. Patient survival after OLT. (A) Total patients and (B) PBC and PSC (*P* = .71).

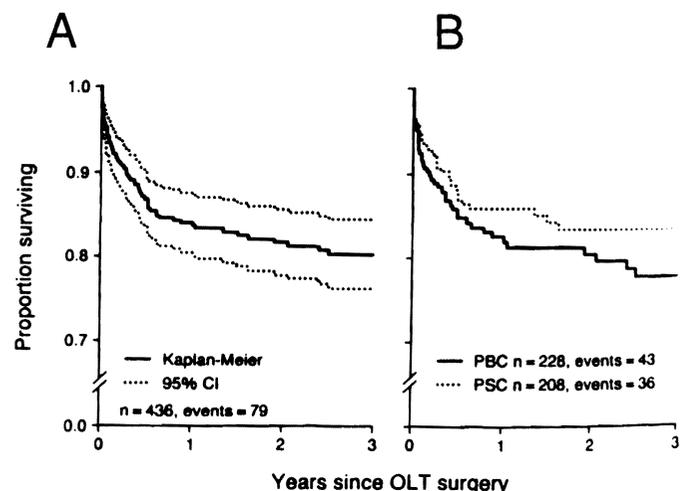


FIG. 3. Graft survival after OLT. (A) Total patients and (B) PBC and PSC (*P* = .72).

TABLE 3. Types of Severe Complications Among Patients Who Underwent Liver Transplantation for PBC or PSC

Complication Type*	≤30 Days After OLT (n = 521)	>30 Days After OLT (n = 775)
	(%)	(%)
Infectious	23	38
Abdominal	13	8
Biliary	10	9
Cardiac	8	2
Renal	8	6
Graft Failure	6	<1
Vascular	6	4
GI	5	3
Neuro/Psych	5	2
Pulmonary	5	2
Circulatory	4	<1
Retransplant	4	4
Surgical	2	1
Death	2	5
Other	1	15
Metabolic/Endo	0	<1
Neoplasm	0	<1

Abbreviation: GI, gastrointestinal.

* Medical events requiring some intervention.

axis. The dashed line at 1.00 represents the outcome of liver transplantation for an "average" PBC or PSC patient at the respective medical center. Increasing Karnofsky score, UNOS status, and albumin have a positive effect on outcome (a rate < 1); increasing values of all the other variables cause an increase in the amount of blood, days in ICU, or number of complications. For example, the presence of pretransplant ascites is associated with a 35% increase in the blood usage during surgery, a 27% increase in the number of ICU days, and a 46% increase in the number of major complications within 30 days of transplantation. The change in longer term complication rate (>30 days after OLT) was not statistically significant, as shown by a confidence interval that straddles 1.0. The effect of each predictor on the first three outcomes is remarkably consistent, ie, the estimated effect on ICU days, for example, is almost always within the confidence limit for blood usage and complications effects. The confidence intervals for complications are somewhat wider, reflecting the more uncertain nature of that measurement.

TABLE 5. Coefficients for Calculations of Blood Usage Score, ICU Score and Complications Score, and Examples of Calculating These Scores and Their Effects

	Blood Usage Score	ICU Score	Complications ≤30 Days Score
Constant	-45.0	-48.0	-57.0
Age (y)	1.0	1.1	1.8
Renal failure*	19.0	63.0	53.0
Child's Class†	29.0	25.0	12.0
UNOS status‡	-21.0	-19.0	-19.0

NOTE. **Example 1.** 60-year-old with normal renal functioning, a modified Child's score of 8, and hospitalized.

Blood usage score = $-45.0 + 1.0 \times 60 + 19.0 \times 0 + 29.0 \times 2 - 21.0 \times 2 = 31.0$

Blood use effect = $\exp(31.0/100) = 1.36$

ICU score = $-48.0 + 1.1 \times 60 + 63.0 \times 0 + 25.0 \times 2 - 19.0 \times 2 = 30.0$

ICU effect = $\exp(30.0/100) = 1.35$

Complications score = $-57.0 + 1.8 \times 60 + 53.0 \times 0 + 12.0 \times 2 - 19.0 \times 2 = 37.0$

Complications effect = $\exp(37.0/100) = 1.45$.

Example 2. 45-year-old, with creatinine mg/dL = 2.1, Child's C and in the ICU.

Blood usage score = $-45.0 + 1.0 \times 45 + 19.0 \times 1 + 29.0 \times 3 - 21.0 \times 1 = 85.0$

Blood use effect = $\exp(85.0/100) = 2.34$

ICU score = $-48.0 + 1.1 \times 45 + 63.0 \times 1 + 25.0 \times 3 - 19.0 \times 1 = 20.5$

ICU effect = $\exp(20.5/100) = 3.34$

Complications score = $-57.0 + 1.8 \times 45 + 53.0 \times 1 + 12.0 \times 3 - 19.0 \times 1 = 94.0$

Complications effect = $\exp(94.0/100) = 2.56$.

* Coded: 0 for normal renal function and 1 for renal failure (creatinine mg/dL >2.0 and/or urine output <10 mL/kg/24 hrs).

† Coded: 1 for Child's A or Modified Child's ≤7; 2 for Child's B or modified Child's >7 and <11; and 3 for Child's C or modified Child's ≥11. Modified Child's Classification: Mayo Clinic Proceedings, March 85, Vol. 60.

‡ Coded: 1) ICU/liver failure; 2) hospitalized; 3) continuous care; and 4) at home (coding is consistent with the May '95 change in UNOS status classification).

All of the variables, except encephalopathy, are significant univariate predictors for blood loss; all 13 variables are significant for ICU days, and all but albumin, bilirubin, and international normalized ratio, are significant predictors of early complications. No variable was significantly predictive of complications occurring >30 days after OLT. However, nutritional status was the preoperative factor closest to statistical significance ($P = .075$) for prediction of complications >30 days after OLT.

Multivariate Analysis. The multivariate analysis is pre-

TABLE 4. Regression Coefficients for Blood Usage, ICU Days, and Complications Within 30 Days of OLT Surgery for Patients Who Underwent Liver Transplantation for PBC or PSC

	Blood Usage*			ICU Days*			Complications ≤30 days*		
	Regression Coefficient	SE	P§	Regression Coefficient	SE	P§	Regression Coefficient	SE	P§
Intercept	0.98	—	—	0.79	—	—	0.60	—	—
Age (y)	0.01	0.00	.017	0.01	0.00	.004	0.02	0.01	.020
Renal failure**	0.19	0.17	.255	0.63	0.16	<.001	0.53	0.23	.021
Child's Class†	0.29	0.07	<.001	0.25	0.07	<.001	0.12	0.13	.354
UNOS status‡	-0.21	0.06	<.001	-0.19	0.06	.001	-0.19	0.11	.084
BUMC vs. Mayo#	-1.34	0.13	<.001	-0.10	0.12	.380	-0.05	0.21	.796
Univ. Pitt. vs. Mayo##	-0.38	0.14	.006	0.45	0.13	<.001	-0.30	0.23	.196
PBC vs. PSC@	0.04	0.09	.608	0.08	0.09	.373	-0.11	0.17	.522

* Dependent variable in regression models, log transformation used for blood usage and ICU days.

** Coded: 0 for normal renal function and 1 for renal failure (creatinine mg/dL >2.0 and/or urine output <10 mL/kg/24 hrs).

† Coded: 1 for Child's A or modified Child's ≤7; 2 for Child's B or modified Child's >7 and <11; and 3 for Child's C or modified Child's ≥11.

‡ Coded: 1) ICU/liver failure; 2) hospitalized; 3) continuous care; and 4) at home.

§ Two-tailed P value test if regression coefficient = 0.

Mayo coded as 0 and BUMC coded as 1.

Mayo coded as 0 and Univ. Pitt coded as 1.

@ PSC coded as 0 and PBC coded as 1.

sented in Tables 4 and 5. As no variable was predictive of late-term (>30 days) severe complications, we did not analyze further that outcome. Because the predictor variables are correlated, multiple combinations of different independent variables can be incorporated into models that carry essentially the same predictive accuracy. In order to develop a final model that was simple to use, we examined models containing only four or fewer variables. Using the bootstrap method described earlier, 11 three-variable and 89 four-variable models were indistinguishable from the "best" four-variable multivariate model for ICU days, found by stepwise regression. For prediction of the other two outcomes, we obtained the following: 2 three-variable and 38 four-variable models (blood loss) and 2 three-variable and 25 four-variable models (complications in the first 30 days of transplant). Only four of all four-variable models predicted all three outcomes within 0.5 SE of the regression coefficient. The highest ranking model among these included age, renal failure, Child's class, and UNOS status. Table 4 shows the regression coefficients, the standard errors, and the *P* values for this model. Statistically significant differences in outcomes among institutions are believed to be secondary to different practices for data collection and coding.

Calculation of Outcome Score and Effect. A score can be calculated from the four-variable model to predict the effect on outcome for any particular combination of preoperative factors. The patient's age is in years; the presence of renal failure is coded as 1, while its absence is zero; numerical values of 1, 2, 3 are attributed to Child's class A, B, and C, respectively; UNOS is coded as the following: 1) ICU/liver failure, 2) hospitalized, 3) continuous care, and 4) at home. The following formulas are used to calculate the score for each outcome:

Blood Usage Score: $-45 + (1 \times \text{age}) + (19 \times \text{renal failure}) + (29 \times \text{Child's class}) - (21 \times \text{UNOS status})$.

ICU Score: $-48 + (1.1 \times \text{age}) + (63 \times \text{renal failure}) + (25 \times \text{Child's class}) - (19 \times \text{UNOS status})$.

Complications Score: $-57 + (1.8 \times \text{age}) + (53 \times \text{renal failure}) + (12 \times \text{Child's class}) - (19 \times \text{UNOS status})$.

The size of the multiplicative effect is calculated as:

$$\exp(\text{score}/100).$$

Table 5 shows the calculation for two hypothetical subjects. For the first patient, we expect that the use of intraoperative blood products will increase by 36%, the number of ICU days will increase by 35%, and the number of major complications in the first 30 days after OLT will increase by 45%. These changes pertain to the "average" patient who has been defined by the authors to be the following: 50 years old, Child B, not hospitalized but having continuous medical care (UNOS status 3), and with normal renal function. A patient with more advanced liver disease (Child class C, instead of B), worse UNOS status, and the presence of renal failure is expected to have a more negative outcome as shown in Example 2.

DISCUSSION

The survival of patients transplanted for PBC and PSC has improved to such an extent (2-year patient survival 90% and graft survival 82%) that it is no longer a concern for medical research. Thus, the focus of this study is the morbidity of the patient in the post-liver transplant period. Several authors have reported on pretransplantation factors that might predict less favorable outcomes after liver transplant.¹¹⁻¹³ These reports have referred most often to series of patients who had mixed etiologies of end-stage liver disease. We chose to study 13 easily obtainable variables in a homogeneous group of patients (with cholestatic liver diseases) undergoing OLT. We chose these variables because the existing literature supports their association with the outcome of liver trans-

plantation. We studied intraoperative blood loss, number of days in ICU, and severe complications occurring within and after 30 days from transplantation. We agree with a recent report by Clavien et al.,¹⁴ that there is a need to accurately define and standardize the complications occurring post-OLT to compare outcome studies from different transplant centers. To accomplish this, we chose a simple definition of severe complication that is easily applicable at different transplant centers.

In our study, we found that several preoperative factors predict intraoperative blood loss, ICU stay, and severe complications occurring in the first month following liver transplantation. These factors lose their predictive value for complications that occur >30 days after OLT. However, pretransplantation nutritional status almost reached statistical significance in predicting late-term severe complications. A more definite evidence of a relationship between preoperative malnutrition and post-OLT outcome has been shown by Pikul et al.¹⁵

Our prognostic model includes age, renal failure, Child's class, and UNOS status. Other four-variable models were formulated during the multivariate analysis that were equally accurate from the statistical point of view for the purpose of predicting outcome. However, this model contains variables that are readily obtainable from the medical record and is easy to use by the liver transplant physician.

It is evident that the heaviest weight is given to the presence or absence of renal failure (creatinine > 2 mg/dL), as shown by its higher regression coefficient, and this is in agreement with the literature. Cuervas-Mons et al.¹¹ found that preoperative serum creatinine level greater than 1.7 mg/dL could predict survival or death in 79% of the cases. Baliga et al.¹² reported that serum creatinine level at the time of placement on the transplant waiting list, and the hospitalization status immediately pretransplant were related to early postoperative sepsis and hospital death. Those findings have been confirmed more recently by Doyle et al.¹³ in a prospective study. They reported that preoperative serum creatinine levels and the need for retransplantation were important predictors of graft failure. Mor et al.¹⁶ found that elevated serum creatinine, decreased platelets, and a prolonged partial thromboplastin time were risk factors for increased intraoperative blood loss. A recent and refined analysis of the effect of pretransplantation renal function on outcome has been published by Gonwa et al.¹⁷ In a very large series, patients with renal failure secondary to hepatorenal syndrome were separated from those with other causes of renal dysfunction. They confirmed their previous finding that hepatorenal syndrome negatively influences survival, but they could not show an effect of preoperative renal function (defined by either glomerular filtration rate or serum creatinine) on outcome, in the group of patients who did not have hepatorenal syndrome. This, as acknowledged by the authors, could be explained by the fact that the only outcome studied was survival. In a previous study, the same group demonstrated that preoperative renal failure was associated with increased rate of infection and intraoperative blood loss.¹⁸ Thus, renal dysfunction may be a risk factor for post-OLT morbidity and could be an indirect risk factor for increased mortality. In our series (436 patients), there were 40 patients (9%) with renal failure, of which only one was known to have hepatorenal syndrome. Given these findings, we think it is important to prevent or treat preoperatively renal dysfunction in the individual patient. There is also a need to define which underlying pathophysiological mechanisms determine a negative outcome in patients with renal dysfunction.

Preoperative recipient physiology, assessed by either the APACHE II or the UNOS scoring system, is not only a primary determinant of survival and cost,¹⁹ but also a predictor of morbidity after liver transplantation.²⁰ Child-Pugh class

has also been associated with post-OLT morbidity in terms of need for dialysis and infections.¹² This study has confirmed that both UNOS status and Child class at the time of transplantation are important predictors of morbidity in patients undergoing OLT for PBC or PSC. Finally, it is interesting to note that regression coefficients for prediction of ICU days and complications in the first 30 days' post-OLT are very close in value. This indirectly supports the validity of the definition of "severe" complications chosen for our study.

Clinicians using these models should recognize that, in general, the precision of prognostic models in predicting outcome is greatest in the average patient. However, in the individual patient, the predicted outcomes may be imprecise, ie, have a wider error. Also, as a risk factor can vary among patients, the corresponding confidence limits for prediction at the individual level can vary as well. Our patient database and post-OLT outcomes are derived from transplant centers performing a large number of transplants each year. Thus our patient series is representative of the general population of patients that undergo OLT for PBC and PSC at established transplantation centers. External validation, as with any new prognostic model, is needed to establish this methodology.

CONCLUSION

In patients with PBC and PSC many preoperative variables predict intraoperative blood loss, ICU stay, and morbidity in the first 30 days' post-OLT. We have presented a new mathematical model that utilizes age, Child class, UNOS status and renal failure to predict which patients undergoing OLT will have a more favorable outcome. This model has been developed on a relatively large number of patients undergoing OLT at three major medical centers.

As with other mathematical models, the intention is to assist the physician in the clinical assessment of patient selection and timing of OLT without replacing clinical judgment. This model has been obtained from patients with cholestatic liver diseases and to date has not been tested in patients with other liver diseases.

REFERENCES

- Maddrey, Sorrell. Selection of patients for liver transplantation. In: Keefe EB, ed. Transplantation of the liver. 2nd Ed. Appleton and Lange, 1995.
- Terasaki PI, Cecka JM. Clinical transplants. UNOS 1994.
- Gordon RD, Hartner CM, Casavilla A, Selby RR, Bronsther O, Miele L, Martin M, et al. The liver transplant waiting list—a single-center analysis. *Transplantation* 1991;51:128-134.
- Shaw BW Jr, Wood RP, Gordon RD, Iwatsuki S, Gillquist WP, Starzl TE. Influence of selected patient variables and operative blood loss on six-month survival following liver transplantation. *Semin Liv Dis* 1985;5:385-393.
- Williams JW, Vera S, Evans LS. Socioeconomic aspects of hepatic transplantation. *Am J Gastroenterol* 1987;82:1115-1119.
- Evans RW, Manninen DL, Dong FB. An economic analysis of liver transplantation: costs, insurance coverage, and reimbursement. *Gastroenterol Clin North Am* 1993;22:451-473.
- SAS Institute, Inc. SAS User's Guide. Volume 1. Cary: SAS Institute, Inc., 1989.
- Statistical Sciences, Inc. S-PLUS Reference Manual. Version 3.2. Seattle: Stat Sci, A Division of Math Soft, Inc., 1993.
- Chambers JM, Hastie TJ. In: Wadsworth S, ed. *Statistical Models*. Pacific Grove: 1992: 229.
- Gong G. Cross-validation, the jackknife, and the bootstrap: Excess error estimation in forward logistic regression. *J Am Stat Assoc* 1986;81:108-113.
- Cuervas-Mons V, Millan I, Gavaler JS, Starzl TE, Van Thiel DH. Prognostic value of preoperatively obtained clinical and laboratory data in predicting survival following orthotopic liver transplantation. *HEPATOLOGY* 1986;6:922-927.
- Baliga P, Merion RM, Turcotte JG, Ham JM, Henley KS, Lucey MR, Schork A. Preoperative risk factor assessment in liver transplantation. *Surgery* 1992;112:704-711.
- Doyle HR, Marino IR, Jabbour N, Zetti G, McMichael J, Mitchell S, Fung J, et al. Early death or retransplantation in adults after orthotopic liver transplantation. *Transplantation* 1994;57:1028-1036.
- Clavien PA, Camargo Jr. CA, Croxford R, Langer B, Levy GA, Greig PD. Definition and classification of negative outcomes in solid organ transplantation. Application in liver transplantation. *Ann Surg* 1994;220:109-120.
- Pikul J, Sharpe MD, Lowndes R, Ghent CN. Degree of preoperative malnutrition is predictive of postoperative morbidity and mortality in liver transplantation recipients. *Transplantation* 1994;57:469-472.
- Mor E, Jennings L, Gonwa TA, Holman MS, Gibbs J, Solomon H, Goldstein RM, et al. The impact of operative bleeding on outcome in transplantation of the liver. *Surg Gyn Obstet* 1993;176:219-227.
- Gonwa TA, Klintmalm GB, Levy M, Jennings LS, Goldstein RM, Husberg BS. Impact of pretransplant renal function on survival after liver transplantation. *Transplantation* 1995;59:361-365.
- Gonwa TA, Morris CA, Goldstein RM, Husberg BS, Klintmalm GB. Long-term survival and renal function following liver transplantation in patients with and without hepatorenal syndrome—experience in 300 patients. *Transplantation* 1991;51:428-430.
- Spanier TB, Klein RD, Nasraway SA, Rand WM, Rohrer RJ, Freeman RB, Schwaitzberg SD. Multiple organ failure after liver transplantation. *Crit Care Med* 1995;23:466-473.
- Ghent CN. Survival following liver transplantation. In: Maddrey, Sorrell. *Transplantation of the liver*. Ed. 2. Appleton and Lange, 1995.