

A Model to Predict Survival Following Liver Retransplantation

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In the current era of critical-organ shortage, one of the most controversial questions facing transplantation teams is whether hepatic retransplantation, which has historically been associated with increased resource utilization and diminished survival, should be offered to a patient whose first allograft is failing. Retransplantation effectively denies access to orthotopic liver transplantation (OLT) to another candidate and further depletes an already-limited organ supply. The study group was comprised of 1,356 adults undergoing hepatic retransplantation in the United States between 1990 and 1996 as reported to the United Network for Organ Sharing (UNOS). We analyzed numerous donor and recipient variables and created Cox proportional-hazards models on 900 randomly chosen patients, validating the results on the remaining cohort. Five variables consistently provided significant predictive power and made up the final model: age, bilirubin, creatinine, UNOS status, and cause of graft failure. Although both hepatitis C seropositivity and donor age were significant by univariate and multivariate analyses, neither contributed independently to the estimation of prognosis when added to the final model. The final model was highly predictive of survival (whole model $\chi^2 = 139.63$). The risk scores for individual patients were calculated, and patients were assigned into low-, medium-, and high-risk groups ($P < .00001$). The low degree of uncertainty in the probability estimates as reflected by confidence intervals, even in our high-risk patients, underscores the applicability of our model as an adjunct to clinical judgment. We have developed and validated a model that uses five readily accessible "bedside" variables to accurately predict survival in patients undergoing liver retransplantation. (HEPATOLOGY 1999;29:365-370.)

Since 1987, the rate at which new registrants for liver transplantation have been added to the United Network for

Organ Sharing (UNOS) waiting list has exceeded the growth in the annual number of liver donors by a factor of 1.8.¹ As a direct consequence of this supply-and-demand disparity, there has been a linear increase in the annual number of waiting-list deaths and an exponential increase in median waiting time over the same period. Although UNOS dictates urgency as the single most important selection factor, many experts think that outcome, in particular, the quality of life after liver transplantation, the incidence and severity of recurrence of the underlying disease, and survival, are equally important factors of patient selection.² In the current era of critical-organ shortage, one of the most controversial questions facing transplantation teams is whether retransplantation, which has historically been associated with increased resource utilization and diminished survival,³ should be offered to a patient whose first allograft is failing. Transplantation teams feel committed to offering retransplantation to their patients with failing allografts, and the UNOS system accords retransplantation candidates the same access to available organs as those awaiting first transplants.⁴

However, a broader societal view might be beneficial, because retransplantation effectively denies access to orthotopic liver transplantation (OLT) to another candidate and further depletes an already-limited organ supply. On the basis of these considerations, the objective of this analysis was to develop a model to predict survival following hepatic retransplantation. Moreover, we considered that model-building based on readily available data from a large, heterogeneous patient population from multiple sites would lead to a useful, generalizable aid to clinical decision-making.

PATIENTS AND METHODS

Patient Population, Data Collection

Since 1986, the UNOS, a nonprofit organization based in Richmond, VA, has had a federal contract to operate the national Organ Procurement and Transplantation Network.⁵ With regard to completeness of liver transplantation outcome follow-up, UNOS has recently estimated that the percentages of follow-up range from a low of 98.3% for patient survival at the 3-year time point to a high of 99.9% at the 3-month time point.⁶ The data from the UNOS Scientific Registry for Liver Transplantation were collected (December 15, 1996) for all adults (>18 years of age) who underwent hepatic retransplantation from January 1990 to February 1996 ($n = 1,601$). The number of patients undergoing a third and fourth transplantation were 157 (9.8%) and 16 (1%), respectively. Patients whose indication for initial transplantation was primary or secondary hepatic malignancy ($n = 44$ [2.7%]) were excluded from analysis. In addition, 201 patients with incomplete data sets were excluded. An alternative approach would have been to substitute for each missing value the mean or median value of that variable, but the final model would then have to be fit only to those patients having complete data for all of the variables included in the model.

Biochemical and clinical data had been collected immediately

Abbreviations: UNOS, United Network for Organ Sharing; PNF, primary nonfunction.

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preceding retransplantation (within 24 hours), and included serum total bilirubin, creatinine, albumin level, and prothrombin time. Other potential covariates were examined: donor and recipient age, gender, and race; initial underlying liver disease leading to primary liver transplantation; time to retransplantation; etiology of graft failure; immunosuppression (cyclosporine- vs. tacrolimus-based); and UNOS status at the time of retransplantation. Missing data for specific variables resulted in their exclusion. For example, data regarding basal immunosuppression and mechanical ventilation were available for only 668 and 553 patients, respectively, and, therefore, these variables were not included for analysis. Primary nonfunction (PNF) as a cause of graft failure was defined as a graft with such poor initial function that retransplantation occurred within 2 weeks following the primary procedure, without identifiable technical (i.e., vascular thrombosis; $n = 51$) or immunological (i.e., hyperacute rejection; $n = 27$) causes of failure.^{7,8} The UNOS database identified the specific causes of non-PNF graft failure in only one third of the patients; therefore, in a significant proportion of patients, the specific etiology of graft failure was not available. UNOS status had been designated as follows: 1 (intensive care unit-bound), 2 (continuously hospitalized), 3 (continuous medical care), 4 (stable at home).¹

The current study group was comprised of the 1,356 patients with complete data sets who met the inclusion criteria as outlined above. The mean (\pm SEM) follow-up to date of death (in 558 patients) or last follow-up was 843.9 ± 20.9 days. Table 1 presents the descriptive statistics of the patients. The patients ranged in age from 18 to 71 years (mean age, 46 years). There were 808 men and 548 women; 1,192 were white, 89 were black, and 46 were Asian.

Statistical Methodology

Survival Analysis. The starting time for all survival analyses was the date of hepatic retransplantation, and death from any cause was treated as a failure for survival analyses. The survival curve for each

risk group was estimated using the Kaplan-Meier method and compared by the log rank and Wilcoxon rank tests. Cox proportional-hazards regression modeling^{9,10} was used, in which each patient is given a risk score:

$$R = \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \dots + \beta_k X_k,$$

where $X_1, X_2, X_3, \dots, X_k$ are the levels of k prognostic variables (risk factors), and $\beta_1, \beta_2, \beta_3, \dots, \beta_k$ are regression coefficients. The regression coefficients are estimated by the method of maximum likelihood estimation applied to the Cox partial likelihood. Each coefficient β_i has the simple interpretation that every unit increase in the i th covariate, X_i , increases the risk of dying by the multiplicative factor $\exp(\beta_i)$. High risk scores correspond to poor prognosis, and smaller values (including negative ones) correspond to better prognosis. For example, suppose 2 patients differ in the R score by an amount d . Then, by the Cox proportional-hazards assumption, at every point in time, the patient with the higher R has $\exp(d)$ times as much risk of dying as the patient with the lower R .¹¹

Moreover, if $S(t, X)$ denotes the probability that a patient with risk-factor values $x = \{X_1, X_2, X_3, \dots, X_k\}$ and risk score R will be alive t years later, and $S_0(t)$ is the survival function for a hypothetical individual having risk score R_0 (corresponding to the average values of the covariates X), then it follows from the proportional-hazards assumption¹² that:

$$S(t, X) = [S_0(t)]^{\exp(R-R_0)}.$$

Model estimation and assessment were performed by computer, using the SPSS (version 7.5; SPSS Inc., Chicago, IL) advanced statistics module. To pick a small subset of variables that adequately predicted survival, we used both forward-stepwise and backward-elimination subset-selection methods. Briefly, with the forward-selection method, the model was built up by including at each step the variable giving the largest reduction in the likelihood ratio or, equivalently, the largest increase in the χ^2 model. In contrast, the backward-elimination method started with a model that included all variables, and then insignificant variables were removed stepwise by excluding the most insignificant variable at each step until each remaining variable contributed significantly to the model.^{13,14} The candidate variables were groupings of the clinical, biochemical, and histological variables recorded at the time of retransplantation. Binary variables (e.g., the presence or absence of PNF as a cause of graft failure or hepatitis C virus serostatus) were coded as 0 or 1. For quantitative variables, we included standard transformations such as square, natural logarithm, and square root. The independence, normality, linearity, and constant variance assumptions required for regression hypothesis tests were studied in terms of the partial residuals from the sample regression equation.

We performed model-building on 900 random patients using a split-sample testing technique, with the validation cohort comprised of the remaining 456 patients. Patients undergoing third and fourth liver transplantations were controlled for with a dummy variable for the number of transplants. Two graphical approaches were used to check the Cox proportional-hazards assumption, i.e., log-log survival curves and observed-versus-expected overlay survival curves.¹³ In addition, since the statistical comparison between the observed and predicted survival curves using the one-sample log rank test is limited because the predicted survival curves are random and not fixed as assumed by the test,¹⁴ the goodness-of-fit testing approach, which uses a one-degree-of-freedom χ^2 statistic based on observed and expected survival probabilities, was used. Covariation was adjusted for in the Cox regression model, so that only the independent association of each variable with the hazard was presented in the estimated model.

RESULTS

Univariate Analyses. Table 2 shows the results of entering the potential prognostic variables one at a time into Cox regression models. The probability value expresses the statis-

TABLE 1. Baseline Demographic, Clinical, and Biochemical Characteristics in Patients Undergoing Hepatic Retransplantation ($n = 1,356$)

Characteristic	
Demographic	
age (yr, mean \pm SEM)	46.3 \pm .30
male sex (%)	808 (59.6)
race (% white)	1,192 (87.9)
Clinical	
interval to retransplantation (n, %)	
<1 wk	398 (29.3)
8-14 d	185 (13.7)
15-31 d	138 (10.2%)
1-6 mo	283 (20.8%)
6-12 mo	139 (10.3%)
1-2 yr	83 (6.1%)
>2 yr	130 (9.6%)
PNF (%)	505 (37.2)
Hepatitis C seropositivity	323 (23.8)
UNOS	
status 1	815 (60.1)
status 2	332 (24.5)
status 3	151 (11.2)
status 4	57 (4.2)
Donor age (yr, mean \pm SEM)	34.0 \pm .42
Donor male sex (n, %)	815 (60.1%)
Biochemical (median)	
Total bilirubin (mg/dL)	15
Serum creatinine (mg/dL)	1.9
Albumin (g/L)	2.9
Prothrombin time (s)	15.3
Risk score (mean)	0.869

TABLE 2. Potential Prognostic Variables Entered in Univariate Cox Regression Model

Variable	Relative Risk	P
Age	1.02	<.0001
Cr	1.14	<.0001
Cr (square root value)	1.68	<.0001
Cr (log value)	1.86	<.0001
TB	1.01	<.0001
TB (square root value)	1.15	<.0001
TB (log value)	1.27	<.0001
UNOS status	1.28	<.0001
PNF	0.68	.0007
Hepatitis C status	1.236	.032
Donor age	1.005	.041
Donor gender	0.99	.936
Gender match*	0.99	.94
Albumin	0.98	.65
Prothrombin time	1.01	.1
Interval (days) to retransplantation	1.02	.15

Abbreviations: Cr, creatinine; TB, total bilirubin.
 *Four groups analyzed based on donor/recipient gender match.

tical significance of a variable's association with survival, and the relative risk summarizes the multiplicative increase in the risk of death for each unit increase in the variable, independent of the mean, all other variables being unchanged. For example, for every year increment in age, the instantaneous risk of death is multiplied by 1.02 (over 10 years, the factor by which risk is multiplied is $1.02^{10} = 1.19$). Standard transformations such as square, natural logarithm, and square root were used to decrease the unexplained variation (i.e., nonconstant variance and outliers) and make the distribution of covariates more similar to a normal distribution.

Multivariate Analyses, Survival Modeling, and Validation of Model. In selecting variables for the model, we used both forward-stepwise and backward-elimination methodologies on 900 randomly assigned patients to the model-building data set. Analysis of the interval to retransplantation as a potential confounding variable revealed no significant corre-

lation between time to retransplantation and outcome. Variables had to have a $P \leq .05$ to be retained in the model. Five variables consistently provided significant predictive power: age, bilirubin, creatinine, UNOS status, and cause of graft failure. Two models identified hepatitis C virus seropositivity (regression coefficients: 0.240 and 0.252) as significant, and two models identified donor age (regression coefficient: .0073 in both), but neither variable contributed significantly and independently to the estimation of prognosis when added to the final model. The models were validated on the remaining cohort of 456 patients, and the final multivariate model chosen (created by forward-stepwise regression) had the lowest likelihood ratio and the highest χ^2 , demonstrating that this model actually best explains or fits the observed data (whole model $\chi^2 = 139.63$). Moreover, graphical analysis demonstrated no significant differences between survival predicted from the model based on the building data set and the observed survival among the patients making up the randomly chosen validation set (Fig. 1). The final model was fit only to those patients having complete data for all of the variables included in the model (Table 3).

Derivation of Risk Scores. Risk scores for individual patients were calculated by combining the values of the five prognostic variables as follows:

$$R = .024 (\text{recipient age in years}) + .112 (\sqrt{\text{bilirubin in mg/dL}}) + .230 (\log_e \text{ creatinine mg/dL}) - .974 (\text{cause of graft failure}) + \text{UNOS coefficient}$$

with the cause of graft failure coded as 1 for PNF and 0 for non-PNF; for UNOS status 1, the coefficient is equal to $-.261$; for status 2, $-.463$; for status 3, -1.07 . The risk scores were normally distributed. The risk-score cutoff values dividing the three risk groups (0.75 and 1.47) were chosen so that the three groups had roughly an equal number of deaths in the first 3 months following hepatic retransplantation. Low-, medium-, and high-risk groups were comprised of 593

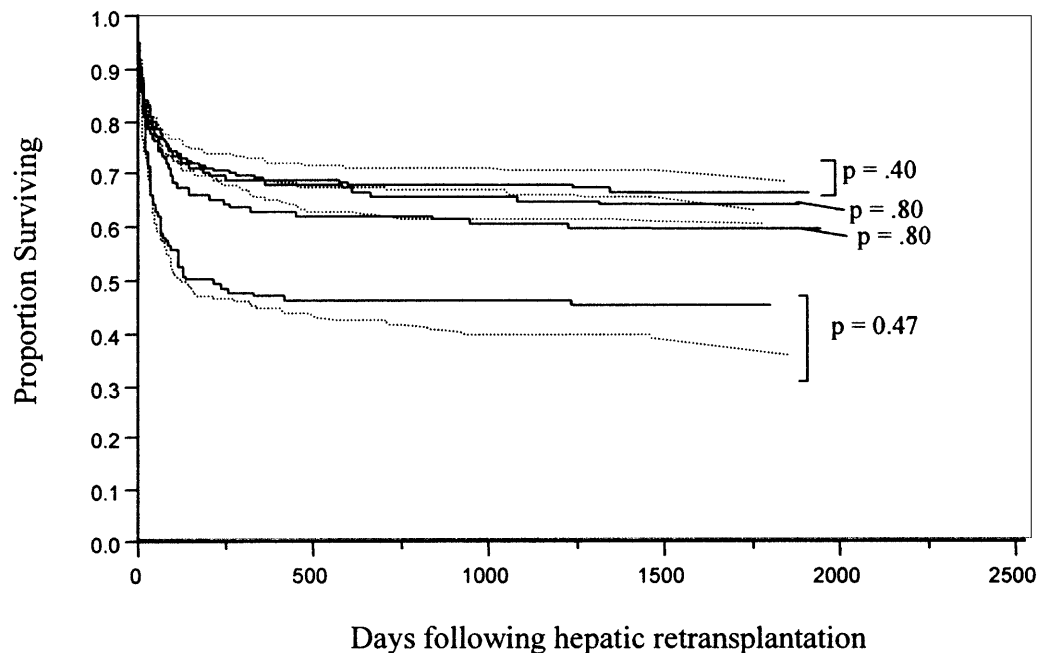


FIG. 1. Actual Kaplan-Meier and predicted (broken lines) survival curves for risk quartiles for the 1,356 patients undergoing hepatic retransplantation. Comparing observed and expected survival by the log rank tests reveals no statistically significant difference.

TABLE 3. Final Survival Model for Patients Undergoing Retransplantation

Variable	Regression Coefficient (β)	SE	Wald χ^2	P	exp (β)
Age	0.024	0.004	30.59	<.00001	1.02
Bilirubin (Square Root)	0.112	0.027	17.07	<.00001	1.11
Creatinine (\log_e value)	0.230	0.085	7.37	.006	1.26
PNF	-0.974	0.143	46.10	<.00001	0.37
UNOS status			19.53	<.00001	
Status 1	-0.261	0.415	.394	.530	0.77
Status 2	-0.462	0.420	1.21	.270	0.63
Status 3	-1.079	0.446	5.85	.015	0.34

NOTE. The model was based on the outcome of 1,356 patients.

patients (146 deaths in the first 3 postoperative months), 498 patients (144 deaths), and 265 patients (137 deaths), respectively. Figure 2 demonstrates the Kaplan-Meier (actual) survival curves of the risk groups for the entire cohort.

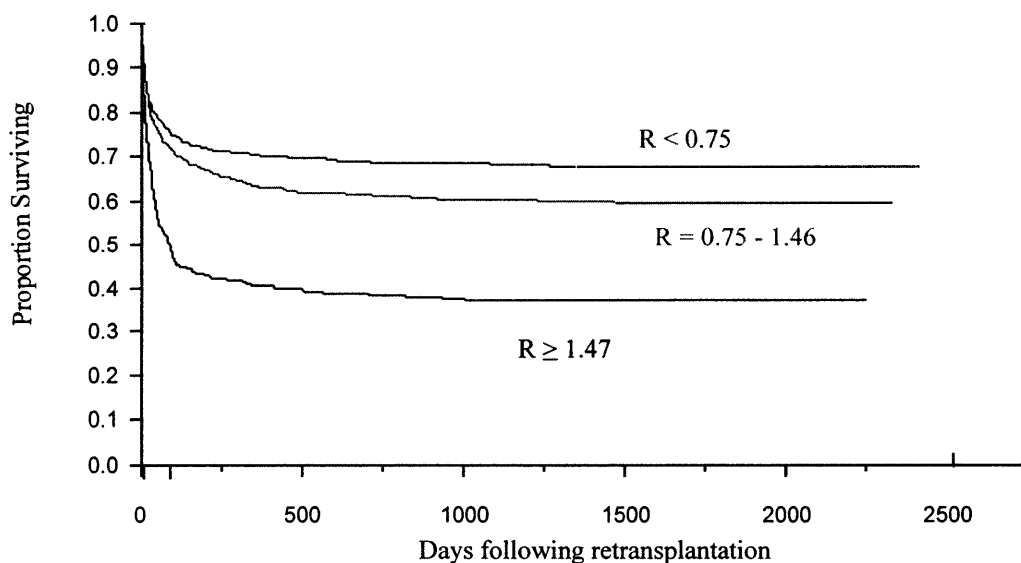
Survival Probabilities, Accuracy of Point Estimates. Following retransplantation, mortality is concentrated in the first few postoperative months and years. To obtain the probability of survival for a given patient for a specific time t , the R is calculated and entered into the equation that computes $S(t)$ as in Table 4. Estimates of uncertainty for the approximated survival probabilities were determined with confidence intervals, as previously described.^{14,15}

Table 5 shows covariate values, risk scores, and predicted survival probabilities of 9 representative patients at the three levels of risk. The confidence intervals, even in the high-risk group, which has the fewest number of patients, and therefore the largest standard error, are reasonably narrow and suggest that the predicted probabilities are clinically useful because the uncertainty is low.

DISCUSSION

At present, more than 4,000 liver transplantations in over 100 centers are performed each year in the United States.

However, it is estimated that between 8,000 and 10,000 potential liver transplantation candidates could be identified each year, and the disparity between the number of cadaveric donors versus candidates requiring a liver transplantation continues to grow.¹⁶ These evolving dynamics have led some centers to pursue a more liberal policy of donor-organ acceptance, *i.e.*, use of marginal donors, and this may be associated with a greater incidence of severe ischemic/preservation injury, as reflected by the development of PNF. A clinical conundrum results with increased graft loss as a result of an approach developed in response to the limited availability of organs. However, a recent study from the University of California at Los Angeles demonstrated that patients with PNF who undergo prompt retransplantation have survival rates comparable with patients undergoing primary liver transplantation.¹⁷ Our current analysis also demonstrates that etiology of graft failure is an important determinant of the ultimate outcome of retransplantation, and that PNF carries a more favorable prognosis. Because of the subjective nature of histological interpretation, as well as the potential coexistence of two processes, *i.e.*, recurrent hepatitis C and chronic rejection,¹⁸ we dichotomized graft failure, *i.e.*, PNF versus non-PNF. The latter category includes



Patients at Risk

593	487	439	415	403	403
498	396	357	317	300	299
265	178	128	105	96	96

FIG. 2. Kaplan-Meier analysis of survival for patients undergoing hepatic retransplantation stratified into low- ($n = 593$), medium- ($n = 498$), and high-risk groups ($n = 265$) ($P < .00001$ by Wilcoxon rank sum). The number of patients in each group at various time points is also indicated.

TABLE 4. Underlying Survival Function for Final Model of Patients Undergoing Hepatic Replantation

Time	1 mo	3 mo	1 yr	2 yr	3 yr
$S_0(t)^*$	0.816	0.697	0.626	0.605	0.596

* $S_0(t)$ gives the estimated survival probabilities for a patient with risk score 0.869, the corresponding risk score of the average patient in the data set. To calculate the survival of a given patient with a risk score of R, the following equation is used: $S(t) = S_0(t)^{exp(R - 0.869)}$.

chronic rejection, recurrent underlying liver disease, hepatic artery thrombosis, and biliary complications. Of note, specific causes of non-PNF graft failure were not listed for two thirds of the patients in the UNOS database; more distinct, objective classification of the subgroups comprising the non-PNF group could potentially further refine our model.

Survival rates following primary liver transplantation have been shown to decrease with increasing levels of urgency, resulting in a conflict between equity and efficacy in organ allocation.¹⁹ A logistic regression analysis of 418 patients undergoing retransplantation at the University of Pittsburgh showed that recipient age, mechanical ventilatory status, serum creatinine, and serum bilirubin were important in predicting survival.²⁰ Our model, based on more than three times the number of patients of that study, further confirms the principle that preoperative recipient physiology, whether assessed directly (i.e., serum bilirubin and creatinine) or via surrogate parameters (i.e., UNOS status), is of paramount importance in predicting survival following retransplantation. The advantage of Cox proportional-hazards modeling is in providing a quantifiable assessment of risk at different time points. Further analysis may determine the specific contribution of donor variables to outcome; both the former study and the current analysis identified donor age as a prognostically significant variable, but adding it to our final model did not strengthen its predictive value. Moreover, it has previously

been demonstrated that the recipient's underlying condition has a significant impact on the morbidity and total charges related to primary transplantation.^{21,22} It will be of considerable interest to determine if prospective cost analyses of patients undergoing hepatic retransplantation demonstrate a correlation between costs and risk score that could ultimately impact on reimbursement by third-party payers. Our five-variable model shows that when retransplantation is applied to low-risk patients, i.e., risk scores < .75, the survival is comparable with primary liver transplantation. Knowing which variables at the time of retransplantation predict a poor outcome is obviously of clinical relevance, but it might be expected that incorporation of longitudinal data about the course of these variables into a modified Cox regression model (with time-dependent variables¹²) would improve the model's predictive power and provide useful insight regarding the optimal timing of retransplantation. Ideally, patients should be identified and considered for regrafting when survival without repeat transplantation is unlikely to be longer than 2 to 3 years, but before the development of progressive deterioration that increases the risks, and likely the expense, of hepatic retransplantation.

In summary, we have developed and validated a model that uses five readily accessible "bedside" variables to accurately predict survival in patients undergoing hepatic retransplantation. It is possible that other potentially important factors for which our data were not complete, particularly immunosuppression and donor variables, may provide additional prognostic information. The model was derived from liver patients retransplanted at numerous institutions in the United States, which improves its generalizability, but further corroboration using an independent cohort of ethnically diverse patients (e.g., European Liver Transplant Registry), as well as prospective analysis of patients undergoing hepatic retransplantation, is an important step in evaluating the model's validity and usefulness. The physician caring for a liver transplant recipi-

TABLE 5. Covariate Values, Risk Scores, and Predicted Survival Probabilities with 95% Confidence Intervals for Representative Patients in Study Cohort

Risk Group	Covariate Values for Model Variables					Risk Score	Survival Probability (95% Confidence Intervals)				
	Age (yr)	Bilirubin (mg/dL)	Creatinine (mg/dL)	UNOS Status	Cause of Graft Failure		1 mo	3 mo	1 yr	2 yr	3 yr
Low-risk											
A	43	10	1.1	3	non-PNF	0.33	0.89 (.86-.91)	0.81 (.78-.83)	0.76 (.73-.78)	0.75 (.72-.77)	0.74 (.72-.76)
B	40	17	2	1	PNF	0.35	0.89 (.86-.91)	0.81 (.78-.83)	0.76 (.73-.78)	0.74 (.71-.77)	0.74 (.70-.76)
C	62	3	2	1	PNF	0.61	0.86 (.83-.88)	0.76 (.73-.78)	0.70 (.67-.72)	0.68 (.65-.70)	0.67 (.65-.70)
Moderate-risk											
A	20	30	5	2	non-PNF	1.00	0.79 (.76-.82)	0.66 (.63-.69)	0.59 (.55-.61)	0.56 (.53-.59)	0.55 (.53-.58)
B	54	2	1.3	2	non-PNF	1.05	0.78 (.76-.81)	0.65 (.62-.68)	0.57 (.54-.60)	0.55 (.52-.57)	0.54 (.51-.56)
C	56	47	6.4	1	PNF	1.3	0.73 (.70-.76)	0.57 (.54-.60)	0.49 (.46-.51)	0.46 (.43-.49)	0.45 (.42-.48)
High-risk											
A	50	38	0.7	1	non-PNF	1.55	0.67 (.63-.71)	0.49 (.45-.53)	0.40 (.36-.43)	0.37 (.33-.41)	0.36 (.32-.40)
B	52	40	3.2	2	non-PNF	1.76	0.61 (.57-.65)	0.42 (.38-.45)	0.32 (.28-.36)	0.29 (.26-.33)	0.28 (.24-.32)
C	63	8	3.6	1	non-PNF	1.86	0.58 (.54-.61)	0.38 (.34-.41)	0.28 (.24-.32)	0.26 (.22-.29)	0.25 (.21-.28)

ent with a failing allograft is faced with the challenge of determining when the prognosis is better with retransplantation than without. Although our model does not answer this question, which would require a "simulated" control group²³ not undergoing retransplantation, it should enhance a clinician's decision-making process with respect to determining short- and long-term prognosis following retransplantation. The limitations of applying any mathematical model to predict outcome in an individual patient always must be considered,^{24,25} and, in general, the precision of diagnostic models in predicting outcome is greatest in the average patient.²⁶ However, in the current analysis, the low degree of uncertainty in the probability estimates as reflected by confidence intervals, even in the high-risk patients, underscores the applicability of our model as an adjunct to clinical judgment. In the current era of extreme organ shortage, whether retransplantation is justified in patients with high risk scores must be carefully evaluated.

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