Pretransplant Prediction of Prognosis After Liver Transplantation in Primary Sclerosing Cholangitis Using a Cox Regression Model

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Liver transplantation remains the only treatment for patients with end-stage primary sclerosing cholangitis (PSC); however, selection criteria for the procedure and its timing remains uncertain. The aim of this study was to identify pretransplant variables associated with survival after transplantation and to devise a Cox regression model for prediction of post-transplant survival. We studied 118 patients transplanted for PSC at the Queen Elizabeth Hospital, Birmingham, UK, being followed for up to 9¼ years after the procedure. The association between pretransplant data and the post-transplant survival up to 1 year was studied using the logrank test (univariate analyses) and Cox multiple regression analysis. Univariate analyses showed the following variables to be associated with a decreased post-transplant survival: high serum creatinine, high serum bilirubin, biliary tree malignancy, previous upper abdominal surgery, hepatic encephalopathy, ascites, and Crohn's disease, whereas ulcerative colitis was associated with increased post-transplant survival (all $P \leq .05$). The final multiple Cox regression model included the following significant variables: inflammatory bowel disease, ascites, previous upper abdominal surgery, serum creatinine, and biliary tree malignancy (all $P < .03$). Biliary tree malignancy could be omitted from the Cox model with only slight loss of information. The results were validated using the data of 30 independent PSC patients from another center. These results can improve selection of patients with PSC for liver transplantation. The developed prognostic model for transplantation can be used in parallel with previously published prognostic models for nontransplantation. The obtained prognostic estimates will provide additional information that is useful for optimal timing of liver transplantation in the individual patient. (HEPATOLOGY 1999;29:1375-1379.)

Primary sclerosing cholangitis (PSC) is a chronic progressive destructive biliary disorder of unknown etiology with a variable and fluctuating course.[1,2] However, in the majority of the patients the disease in the end progresses to liver failure. About 15% of the patients will develop cholangiocarcinoma.[3] The majority of the patients have associated inflammatory bowel disease, mostly ulcerative colitis, only few have Crohn's disease.[4]

Until now no medical or surgical therapy has been shown effectively to stop the progression of the disease. Therefore, liver transplantation remains the only effective therapy. Because of the variable and fluctuating course of the disease it has been important to identify variables associated with the prognosis. Four prognostic models for prediction of survival have been published.[5-8] They are useful in deciding when the prognosis is likely to be less than 1 year.[9,10] However, optimal timing for a transplantation requires modelling of the risk factors predicting outcome after surgery.

The purpose of this report was to analyze in greater detail which pretransplant variables hold prognostic information about the post-transplant survival and to combine these variables to a prognostic index as a further aid in deciding if and when to perform a liver transplantation in these patients. We have also validated the model in another group of patients transplanted in a different center in the United Kingdom.

PATIENTS AND METHODS

One hundred eighteen consecutive adult patients with PSC transplanted at the Liver and Hepatobiliary Unit, the Queen Elizabeth Hospital, Birmingham, UK, followed for up to 9.26 years, were studied. Summarized pretransplant data of the patients are presented in Table 1.

The association of each variable with survival was studied using the logrank test[11] for comparison of survival curves calculated according to Kaplan and Meier.[12] For quantitative variables the logrank test for trend[12] was used after stratification according to the level of the variable into four strata of approximately equal size (equal numbers of patients). This number of strata enabled a reasonable number (about 30) to be included in each stratum and was detailed enough to provide a guidance to the scoring to be used in the Cox model. The analyses were performed both for the full observation period and for the first year by censoring at this time all observation times greater than 1 year. The latter was done because pretransplant variables can only be expected to predict prognosis after transplantation for a limited period of time ahead. To obtain a model to be used for pretransplant prediction of the prognosis after transplantation, the data were analyzed using time-fixed Cox regression analysis[13,14] including variables with $P < .20$ in univariate analysis. The final Cox model was obtained using backward elimination of insignificant variables ($P > .05$) as previously described.[14] The scoring of the variables was adapted to fulfil model assumptions.[14] The scoring used for inflammatory bowel disease was based on the relative risks in the three groups found in univariate analysis. The cut-off point of 100 μmol/L used for serum creatinine was based on the results of the univariate analysis, which showed that high risk was only present in patients with creatinine

Abbreviations: PSC, primary sclerosing cholangitis; PI, prognostic index; PBC, primary biliary cirrhosis.

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TABLE 1. Summarized Pretransplant Data of 118 Consecutively Transplanted Patients With PSC Used for Development of a Pretransplant Prognostic Model for Transplantation

Variable	Median (Range) or Percent (Fraction)
Age (yrs)	45.9 (17, 66)
Males (%)	69% (81/117)
Year of transplantation	1993 (1986, 1997)
Malignancy (%)	7% (8/118)
Ulcerative colitis (%)	58% (69/118)
Crohn's disease (%)	6% (7/118)
Previous upper abdominal surgery (%)	31% (37/118)
Encephalopathy (%)	19% (22/118)
Variceal hemorrhage (%)	26% (31/118)
Ascites (%)	42% (50/118)
Diuretic treatment (%)	41% (49/118)
Plasma albumin (g/L)	30 (14, 44)
Plasma prothrombin (INR)	1.2 (0.8, 6.0)
Plasma bilirubin (μmol/L)	171 (9, 997)
Plasma aspartate transaminase (U/L)	133 (27, 8,580)
Plasma alkaline phosphatase (U/L)	1,040 (113, 3,456)
Plasma creatinine (μmol/L)	88 (41, 933)
Blood group A gene (%)	39% (46/118)
Blood group B gene (%)	18% (21/118)
Rhesus blood group gene (%)	84% (99/118)

Abbreviation: INR, International Normalized Ratio.

≥100 μmol/L corresponding to about one quarter of the patients. The strata with serum creatinine less than 100 μmol/L had similar low risks. Logarithmic scoring (to improve normality and decrease nonconstant variance) was markedly inferior to the chosen scoring. In the Cox analysis, the one missing serum creatinine value was replaced by the mean scoring of the variable. The fit of the model to the data was tested using an overall goodness-of-fit test.[15] Confidence intervals of estimated survival probabilities were calculated according to standard methodology.[16]

The Cox regression model allows the calculation of a prognostic index (PI) in any given patient:

$$PI = b_1z_1 + \cdots + b_qz_q, \quad (1)$$

where z_1 to z_q are the patient's values of the variables in the model and b_1 to b_q are the corresponding regression coefficients. A given PI_{trans} (for transplantation) can be transformed to an estimate of surviving a given time, *e.g.*, 1 year ($S_{1\ yr}$):

$$S_{1\ yr\text{-}trans} = \exp\,[-\Lambda_0(1\ yr) \times \exp\,(PI_{trans})], \quad (2)$$

where $\Lambda_0(1\ yr)$ is the estimated cumulative underlying hazard function at one year.[14]

The prognostic model was validated in an independent smaller group of 30 transplanted PSC patients from Leeds followed for up to 6 years. Four of the patients died after the transplantation. Data for these patients are shown in Table 2. The PI were calculated for all these patients, which were then divided into two groups according to their PI values. The average estimated survival functions in these two groups of patients were compared with Kaplan-Meier plots of the observed survival, and in each group the difference was tested using the one sample logrank test.[17,18]

RESULTS

Pretransplant Prognostic Model for Transplantation. The 1-year cumulative survival of the 118 patients was 79% and at 9.26 years 51%. The total number of deaths in the full observation period was 36. Twenty four deaths occurred within the first year after transplantation. Eight patients had cholangiocarcinoma. Six of these died, all within the first year of transplantation. In the 110 patients without cholangiocarcinoma the cumulative survival was 84% after 1 year and 54% after 9.26 years.

TABLE 2. Summarized Pretransplant Data of 30 Independent Consecutively Transplanted Patients With PSC Used for Validation of the Prognostic Model for Transplantation

Variable	Median (Range) or Percent (Fraction)
Age (yrs)	44.9 (22, 65)
Males (%)	80% (24/30)
Year of transplantation	1995 (1990, 1997)
Malignancy (%)	0% (0/30)
Ulcerative colitis (%)	63% (19/30)
Crohn's disease (%)	7% (2/30)
Previous upper abdominal surgery (%)	17% (5/30)
Ascites (%)	17% (5/30)
Plasma creatinine (μmol/L)	75 (61, 204)

The findings of the univariate prognostic analyses using the logrank test are shown in Table 3. The findings for the full observation period are similar to those for the first year. The survival in patients with ulcerative colitis, Crohn's disease, and without these diseases is shown in Fig. 1.

The final Cox regression model for survival up to 1 year after transplantation is shown in Table 4. The model included the following as significant variables: inflammatory bowel disease (Crohn's disease harmful; ulcerative colitis beneficial), ascites, previous upper abdominal surgery, malignancy (cholangiocarcinoma), and serum creatinine. The scorings shown in Table 4 gave the best fit in the model. The

TABLE 3. Pretransplant Variables Associated With Prognosis After Transplantation in 118 Transplanted Patients With PSC

Variable	Direction of Association*	*P* Value: Total Observation Period	*P* Value: First Year
Age (yrs)	—	.72	.94
Males (%)	—	.97	.72
Year of transplantation	↓	.11	.051
Malignancy (%)	↑	.0007	.0002
Ulcerative colitis (%)	↓	.06	.004
Crohn's disease (%)	↑	.005	.003
Previous upper abdominal surgery (%)	↑	.01	.02
Encephalopathy (%)	↑	.06	.007
Variceal hemorrhage (%)	↑	.32	.18
Ascites (%)	↑	.006	.005
Diuretic treatment (%)	—	.49	.55
Plasma albumin (g/L)	↓	.06	.40
Plasma prothrombin (INR))	↑	.17	.06
Plasma bilirubin (μmol/L)	↑	.02	.02
Plasma aspartate transaminase (U/L)	—	.88	.71
Plasma alkaline phosphatase (U/L)	—	.51	.22
Plasma creatinine (μmol/L)	↑	.02	.04
Blood group A gene (%)	—	.30	.47
Blood group B gene (%)	↑	.07	.21
Rhesus blood group gene (%)	↑	.20	.26

NOTE. Results of univariate analyses using the logrank test.

Abbreviation: INR, International Normalized Ratio.

*Presence of the characteristic (qualitative variables) or of higher values of the variable (quantitative variables) are associated with a higher risk (↑) (poorer prognosis), a lower risk (↓), or not associated with the prognosis (—).

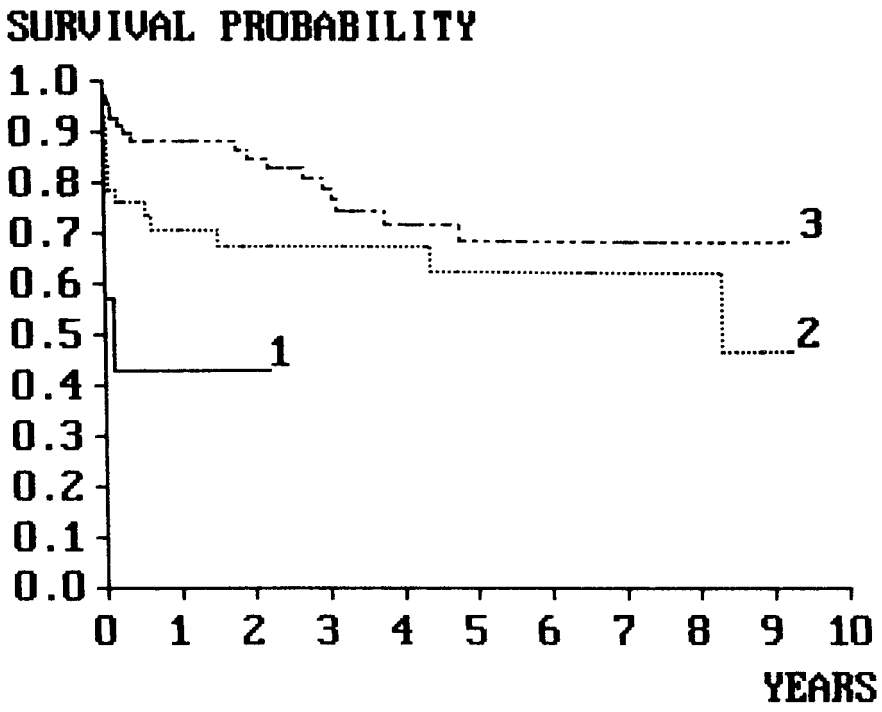

FIG. 1. Observed survival in 118 transplanted patients with PSC with Crohn's disease (1) (N = 7), no inflammatory bowel disease (2) (N = 42), and ulcerative colitis (3) (N = 69). Comparison of survival up to 1 year: P_{trend} = .0004; 1 versus 2, P = .08; 1 versus 3, P = .0003; 2 versus 3, P = .02. Comparison of survival up to 9¼ years: P_{trend} = .01; 1 versus 2, P = .10; 1 versus 3, P = .0008; 2 versus 3, P = .17.

remaining variables including year of transplantation, bilirubin, and albumin could not add significantly to the model.

Cox regression analysis omitting malignancy from the model gave coefficients (and standard errors) similar to those seen in the model for all the patients: inflammatory bowel disease, 0.520 (0.126); previous upper abdominal surgery, 1.595 (0.450); ascites, 1.453 (0.458); serum creatinine, 1.480 (0.442); model-χ^2 = 36.08, degrees of freedom = 4, P = .0000003. Repeating the analysis using only the data of the 110 patients without malignancy produced these rather similar coefficients (and standard errors): inflammatory bowel disease, 0.571 (0.135); previous upper abdominal surgery, 1.699 (0.527); ascites, 1.788 (0.564); serum creatinine, 1.377 (0.526); model-χ^2 = 32.11, d.f. = 4, P = .000002. For all the Cox models, the goodness-of-fit test[15] indicated a satisfactory fit ($P > .45$).

For the final model presented in Table 4, the cumulative underlying hazard rate $\Lambda_0(t)$ is for 3 months, 0.0295; for 6 months, 0.0340; and for 1 year, 0.0390. Using the latter value, the 1-year survival probability can be calculated using equation 2 given the prognostic index (PI_{trans}) of the patient.

However, using Fig. 2, the 1-year survival probability corresponding to a given prognostic index PI_{trans} can be read directly.

The result of the validation using data from 30 independent transplanted PSC patients is shown in Fig. 3. There is no significant difference between the observed and expected survival functions.

Practical Application of the PI in Individual Patients. The following example illustrates the calculation of the prognostic index and the interpretation of the resulting value:

At a given time, a PSC patient has the following variables: no inflammatory bowel disease, previous upper abdominal surgery, ascites, serum creatinine <100 μmol/L and no cholangiocarcinoma. PI_{trans} = 0 × 0.534 (for no inflammatory bowel disease) + 1 × 1.393 (for previous upper

TABLE 4. Final Cox Regression Model for Pretransplant Prediction of Short-Term Survival (up to 1 year) After Transplantation for PSC

Variable (*P* Value)	Scoring	b	SE(b)
Inflammatory bowel disease (0.00004)	No: 0 Ulcerative colitis: −1 Crohn's disease: 4	0.534	0.130
Previous upper abdominal surgery (0.002)	Yes:1 No: 0	1.393	0.455
Ascites (0.002)	Present: 1 Absent: 0	1.431	0.453
Serum creatinine (0.02)	<100 μmol/L: 0 ≥100 μmol/L: 1	1.111	0.479
Malignancy (0.03)	Present: 1 Absent: 0	1.191	0.547

NOTE. Total significance of model: χ^2 = 40.27, d.f. = 5, P = .0000001.

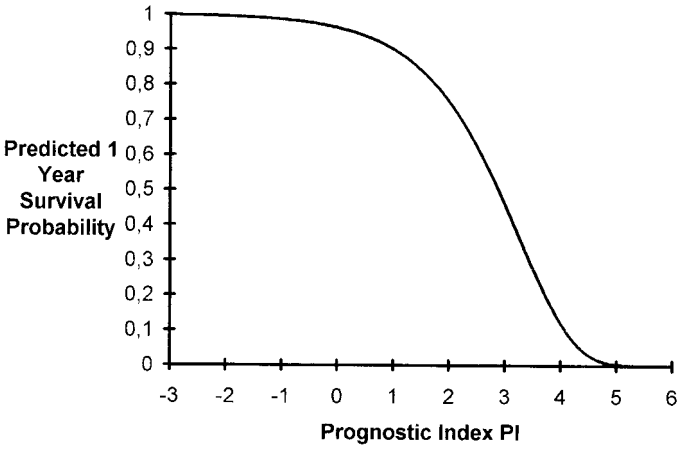

FIG. 2. Estimated probability of surviving 1 year after transplantation as a function of the prognostic index (PI).

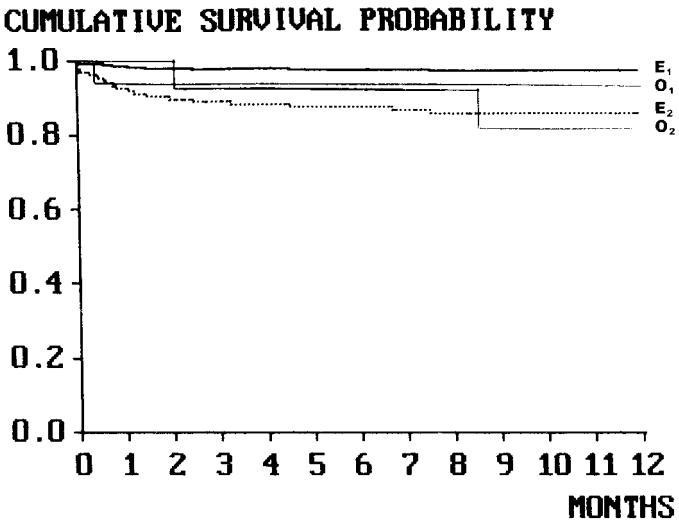

FIG. 3. Observed (O) and estimated (E) 1-year survival functions of independent transplanted PSC patients divided into two groups according to their PI: Group 1, PI $\leq$ 0, N = 16; group 2, PI $>$ 0, N = 14. Group 1, $O_1 = 1$, $E_1 = 0.42$; group 2, $O_2 = 2$, $E_2 = 2.02$; $\chi^2 = 0.80$, d.f. = 2, $P = .67$, where O and E are the observed and expected numbers dying in each group.

abdominal surgery) + 1 $\times$ 1.431 (for ascites) + 0 $\times$ 1.111 (for serum creatinine) + 0 $\times$ 1.191 (for no cholangiocarcinoma) = 2.824.

Using Fig. 2, the estimated probability of surviving 1 year $S_{1\ yr\text{-}trans}$ can be read to 0.52 or 52%. (Calculation using equation 2 gives the same result.). Calculation of the 95% confidence interval is complex[16] and depends (besides on PI) also on the particular data of the patient. For this patient the 95% confidence interval is relatively large: 23% to 74%. In general the confidence interval is largest for survival probabilities around 0.5 and becomes increasingly narrow as the survival probability approaches 1 or 0. Thus, for another patient having ulcerative colitis and ascites, but no previous upper abdominal surgery, normal serum creatinine and no malignancy PI_{trans} = 0.897. The estimated 1-year survival probability becomes 0.91 (95% confidence interval 0.80-0.96). Thus, for individual patients the prognostic estimates are not precise but are only guidelines to be used in the context of other relevant clinical information.

DISCUSSION

For patients with chronic liver diseases, indications for transplantation are relatively clearly defined; however, the timing of the procedure remains less certain. Because of the inevitable risks of major surgery, transplantation too early may put the patient at increased risk of premature death; conversely, if the procedure is done too late, then the patient's chances of surviving the procedure are reduced. Thus, the optimal timing of surgery is dependent on the clinician balancing the risks and benefits of surgery with the risks and benefits of postponing surgery. For patients with primary biliary cirrhosis (PBC) it has been shown that the factors predicting survival in the absence of transplantation differ from those predicting survival after surgery.[19]

During the last decade, several prognostic models have been developed to assess the natural history of patients with PSC.[5-8] These models have identified serum bilirubin, histological stage, age, hemoglobin, alkaline phosphatase, and the presence of hepatomegaly and splenomegaly as important prognostic indicators. The presence of cholangiocarcinoma is also clearly an important prognostic marker both in the grafted and nongrafted group.[3] Because of the poor survival after transplantation, most centers exclude patients with known cholangiocarcinomas from transplantation. However, some patients are found to have a cholangiocarcinoma only after examination of the resected liver and biliary tree.[20]

This analysis has shown that, although many of those factors predicting survival in the absence of transplantation are associated with a poor outcome after transplantation, they were not found to be important factors included in the multivariate analysis. Of those factors that are identified as predicting survival after transplantation, it is well recognized that cholangiocarcinoma is associated with a poor outcome because of tumor recurrence.[21-23] For this reason we present prognostic models with and without cholangiocarcinoma being included as an independent variable. However, the final model, which includes cholangiocarcinoma, seems to predict survival reasonably well, which is also true in patients without cholangiocarcinoma as shown in the small sample of 30 independent patients of whom no one had malignancy.

The influence of the calendar year of transplantation although borderline significant in univariate analysis was insignificant in the Cox model. Therefore, the presented prognostic model is also relevant to PSC patients transplanted today. This is supported by the fact that the survival of the 30 independent patients was correctly predicted, although they were transplanted in the slightly later time period.

Ricci et al.[24] did a multivariate analysis assessing prognosis after transplantation for 436 patients transplanted with cholestatic disease in three centers; they found that age, renal dysfunction, Child's classification, and United Network for Organ Sharing status were significant predictors of morbidity. Although a combination of patients with PSC and PBC allows for greater power of analysis, we found that prognostic factors for the two diseases differ. Wiesner et al.[23] have identified general risk factors for a poor prognosis to include UNOS status 1, recipient age over 65 years, poor nutritional status, Child's class C, and renal failure needing dialysis before and/or after transplantation. Risk factors for survival after transplantation for PSC were identified as disease severity, previous biliary or shunt surgery, concurrent bile duct cancer, and the presence of inflammatory bowel disease. However, whether previous upper abdominal surgery affects outcome is controversial: thus, whereas Goss et al.[21] and Narumi et al.[22] found that there was no adverse effect on outcome, lshmail et al.[25] found the opposite.

The inclusion of inflammatory bowel disease as a prognostic factor for survival after transplantation has not been recognized hitherto, although Narumi et al.[22] found that of those patients grafted for PSC, those with inflammatory bowel disease had a greater risk of severe rejection and a greater need for retransplantation. There was no separation between those with Crohn's disease and those with ulcerative colitis. It has been suggested that the association with inflammatory bowel disease may identify a variant of PSC and there is controversy whether the coexistence of inflammatory bowel disease affects the progression of PSC.[4,5,26,27] Furthermore, it was also unexpected that while ulcerative colitis was associated with a better outcome after surgery, Crohn's disease has an adverse impact. This difference cannot be explained by the differences in previous abdominal surgery or

differences in anti-inflammatory therapy before transplantation. It is perhaps more likely that whereas patients with ulcerative colitis have disease limited to the colon, in patients with Crohn's disease there is a more generalized arteritis that may affect healing or immune responses to the graft. Other possible explanations may lie in host factors: patients who are at risk of developing Crohn's disease may differ genetically or in other ways from those who develop ulcerative colitis. It is important that these findings are confirmed by others.

Results after transplantation for PSC appear to be worse than for transplantation for other cholestatic diseases such as PBC.[21-23] In general, PBC tends to run a more predictable course with a gradual progression, whereas PSC tends to fluctuate. The use of prognostic models will be important in helping time the procedure: the Mayo model can be used to identify those patients with a poor prognosis in the absence of transplantation, but if the prognosis after transplantation is known, then the optimal timing for transplantation can be assessed. In this context, proper attention should be paid to the influence of referral practice and the length of waiting lists, because these issues may markedly influence the actual time when transplantation can take place. The same considerations are relevant for patients with PBC in whom a similar approach has been suggested.[19]

It is important that the limitations of prognostic models are recognized: there is a relatively wide confidence interval, so application of prognostic information to the individual must be done with caution. The model is inevitably derived from retrospective data; thus, introduction of new techniques advances in, for example, immunosuppression may require that the model is modified. However, this model appears to be robust in that application of the model to patients grafted in another center shows good predictive powers.

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