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Optimal timing of liver transplantation for patients with primary biliary cirrhosis: use of prognostic modelling

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Background/Aims: **Liver transplantation remains the only definitive treatment for patients with end-stage primary biliary cirrhosis, although the optimal timing of the procedure remains uncertain. The aim of the study was to use prognostic modelling to determine the optimal timing of transplantation for patients with primary biliary cirrhosis.**

Methods: **A prognostic model for predicting the survival of patients after transplantation was generated using the Cox regression model with data from 312 patients transplanted for primary biliary cirrhosis at the Queen Elizabeth Hospital, Birmingham. The prognosis after transplantation was compared to that without transplantation (using a previously published prognostic index for non-transplantation) both in these patients and in 98 non-transplanted primary biliary cirrhosis patients dying from the liver disease, in order to establish at what stage the prognosis with transplantation was better than without transplantation.**

Results: **The prognostic index for transplantation included the following significant prognostic variables: serum bilirubin, serum albumin, age, year of transplantation, and the presence of ascites or treatment with diuretics. Comparison of prognosis with and without transplantation showed that the predicted gain in survival after transplantation becomes increasingly positive when the 6-month survival probability in the absence of transplantation falls below 0.85. In the non-transplanted patients this occurs on average about 8 months before death.**

Conclusions: **Comparison of the prognosis with and without transplantation provides a rational method for determining the optimum timing of the procedure which occurs approximately when the predicted 6-month survival probability without transplantation falls below 0.85.**

Key words: **Cox regression model; Primary biliary cirrhosis; Prognostic factors; Survival analysis; Transplantation.**

PRIMARY biliary cirrhosis (PBC) is an intrahepatic, chronic, nonsuppurative, destructive cholangitis. The disease tends to progress with time but the rate of progression is highly variable (1). Some treatments such as azathioprine (2), colchicine (3), cyclosporin A (4), methotrexate (5), prednisolone (6) and ursodeoxycholic acid (7) may have some therapeutic benefit. However, none of the medical treatments has been demonstrated effectively to stop progression. Therefore, in advanced cases liver transplantation is the only effective therapeutic measure.

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An important issue in the management of patients with PBC is the optimal timing of transplantation: neither too early (prognosis with transplantation poorer than without), nor too late (patient may die before the procedure can be performed or may be so ill that the chances of tolerating and surviving the procedure may be considerably reduced). To determine the optimal timing of transplantation, it is necessary to estimate the prognosis with and without transplantation for a patient at any given time. This may also help in deciding if and when to refer for transplantation (8).

For non-transplanted patients with PBC, several prognostic models have been developed (2,9–16). In the absence of any controlled clinical trials of transplantation, these models have been used as replacement tools to illustrate the effect of liver transplantation by comparing the observed survival after transplantation

with the survival predicted by prognostic models for non-transplantation (17–19). A few of the prognostic models are time-dependent (14–16), allowing estimates of the prognosis to be updated during the course of the disease. Such models are well suited for monitoring progression since they provide current short-term prognostic estimates.

For patients transplanted for PBC, one prognostic model has been published (20); this was based on a smaller sample of patients in the early days of transplantation.

No systematic comparison of prognosis with and without transplantation in the same patients has been performed. The purpose of this paper is firstly to provide an updated model for prognosis after transplantation for PBC based on a larger sample of patients, most of whom were transplanted after 1985, with improved survival following the procedure, and secondly to compare estimates of prognosis with and without transplantation in patients with PBC and so determine the optimal time of transplantation when the risks of the procedure are outweighed by the risks of dying in the absence of grafting.

Patients and Methods

(I) Prognostic model for transplantation (using the pre-transplant data)

A series of 312 consecutive PBC patients transplanted at the Liver and Hepatobiliary Unit, the Queen Elizabeth Hospital in Birmingham and followed for up to 13.6 years were studied. Summarised pre-transplant data of the patients are presented in Table 1.

The association of each variable with survival was studied using the logrank test (21) for comparison of survival curves calculated according to Kaplan & Meier (22). For quantitative variables the logrank test for trend (21) was used after stratification according to the level of the variable into four strata of approximately equal size. These analyses were performed both for the full observation period after transplantation and for the first 6 months after transplantation by censoring at this time all observation times greater than 6 months. The latter was done because pre-transplant variables are likely to have only a short-term effect on the prognosis after transplantation. To obtain a model to be used for pre-transplant prediction of the prognosis after transplantation, the 6-month survival data were also used in multivariate time-fixed Cox regression analysis (23,24) including variables with $p<0.20$ in univariate analysis. The final Cox model was obtained using backward elimination of insignificant variables ($p>0.05$) as previously described (24). The scoring of the variables was adapted to fulfil model assumptions (2,24). In the analysis the few missing variables were replaced by the mean value of the variable in question. The Cox regression model allows the calculation of a prognostic index (PI) in any given patient:

$$PI = b_1 z_1 + \ldots + b_q z_q, \qquad \text{(Equation 1)}$$

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 ahead. Since pretransplant variables can be expected to predict only a limited period ahead after the transplantation, we only use the model to predict 6-month ahead. The predicted 6-month survival probability is estimated as follows:

$$S_{6mo\text{-}trans} = \exp[-\Lambda_0(6mo) \times \exp(PI_{trans})], \qquad \text{(Equation 2)}$$

where $\Lambda_0(6mo)$ is the estimated cumulative underlying hazard function at 6 months (2,24).

(II) Prognostic model for non-transplanted patients

To estimate the current prognosis during the course without transplantation, we used our previously published time-dependent Cox model, considering only hepatic deaths as end-points (Model A-II) (13) because liver transplantation can only be expected to prevent death due to the liver disease ("hepatic deaths", i.e. deaths from liver failure, gastrointestinal bleeding, or both). This model is used in the formula below to give the current time-dependent prognostic index:

$$\begin{aligned} PI_{non\text{-}trans} = {} & 3.02 \times (\log_{10}[\text{serum bilirubin } \mu\text{mol/l}] \\ & - 1.53) + 1.43 \text{ (if ascites present)} \\ & - 0.077 \times (\text{serum albumin g/l} - 34.3) \\ & + 0.043 \times (\text{age years} - 55) \\ & + 0.74 \text{ (if gastro-intestinal bleeding present).} \end{aligned} \qquad \text{(Equation 3)}$$

($PI_{non\text{-}trans}$ can be obtained in a simpler way using the previously published pocket chart (Table 5 in reference 14).)

With this prognostic index one can, during the course of the disease, estimate the probability of surviving the following 6 months using this relation:

$$S_{6mo\text{-}non\text{-}trans} = \exp[-0.0105 \times \exp(PI_{non\text{-}trans})], \qquad \text{(Equation 4)}$$

where -0.0105 is the underlying hazard λ_0 (being 0.021 years^{-1} (14)) times the time period (0.5 years).

(III) Comparison of estimates of prognosis with and without transplantation

The prognosis *with* as well as *without* transplantation was estimated both in the transplanted patients described above and, for illustrative purposes, also in 98 non-transplanted patients (not any kind of a control group) with complete data at 12–0.5 months (on average 6 months) prior to death from a hepatic cause (as defined above). These patients were included in two placebo-controlled, prospective randomised clinical trials evaluating the effect of azathioprine (2) and d-penicillamine (25). These trials were performed at a time when liver transplantation was not yet regularly performed in the participating

TABLE 1

Summarised pre-transplant data of 312 consecutively transplanted patients with PBC used for development of a pre-transplant prognostic model for transplantation

Variable	Median or %	(Range) (or fraction)
Age (years)	53	(33, 73)
Females (%)	89%	(277/312)
Year of transplantation (calendar year)	1990	(1981, 1994)
Laparotomy (%)	37%	(116/312)
Encephalopathy (%)	27%	(83/312)
Variceal haemorrhage (%)	41%	(125/305)
Ascites (%)	56%	(172/308)
Diuretic treatment (%)	56%	(172/307)
Plasma albumin (g/l)	30	(13, 49)
Plasma prothrombin time prolongation (s)	1.2	(0.79, 3.3)
Plasma bilirubin (μmol/l)	193	(9, 1300)
Plasma creatinine (μmol/l)	81	(36, 582)
Plasma urea (μmol/l)	5.5	(2.0, 60)
Plasma sodium (mmol/l)	135	(110, 155)
Plasma potassium (mmol/l)	4.2	(2.4, 6.8)
Blood group A gene (%)	47%	(147/312)
Blood group B gene (%)	11%	(34/312)
Rhesus blood group gene (%)	83%	(258/312)

TABLE 2

Pre-transplant variables associated with prognosis after transplantation in 312 transplanted patients with PBC. Results of univariate analyses using the logrank test

Variable	Direction of association[1]	*p*-value	
		Total observation period	First 6 months
Age (years)	↑	0.29	0.69
Females (%)	–	0.81	0.74
Year of transplantation (calendar year)	↓	0.01	0.002
Laparotomy (%)	–	0.66	0.96
Encephalopathy (%)	↑	0.12	0.12
Variceal haemorrhage (%)	↑	0.14	0.33
Ascites (%)	↑	0.002	0.008
Diuretic treatment (%)	↑	0.16	0.16
Ascites or diuretic treatment or both (%)	↑	0.003	0.002
Plasma albumin (g/l)	↓	0.003	0.002
Plasma prothrombin time prolong. (s)	↑	0.11	0.14
Plasma bilirubin (μmol/l)	↑	0.03	0.002
Plasma creatinine (μmol/l)	↑	0.007	0.04
Plasma urea (μmol/l)	↑	0.03	0.12
Plasma sodium (mmol/l)	↓	0.02	0.07
Plasma potassium (mmol/l)	–	0.87	0.39
Blood group A gene (%)	–	0.49	0.50
Blood group B gene (%)	–	0.24	0.23
Rhesus blood group gene (%)	↓	0.0007	0.02

[1] 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 (–).

centres. Therefore, these unselected "historic" patients can illustrate the natural history of the disease without transplantation. The rate of development of the prognostic indices prior to (hepatic) death was also examined to determine when the prognosis (i.e. the 6-month survival probability) with transplantation would be better than without. This was done in 31 of the non-transplanted patients who had complete data 6 months apart before death from a hepatic cause. Medians with non-parametric 95% confidence intervals of quantitative variables were estimated as described by Brown & Hollander (26).

Results

Prognostic model predicting survival after transplantation

The 6-month overall survival of the 312 patients was 83.7%. At 13.6 years it was 68%. The total number of deaths in the survival period was 71. Fifty-one deaths occurred within the first 6 months after transplantation.

The results of the univariate prognostic analyses using the logrank test are shown in Table 2. The results for the full observation period are similar to those for the first 6 months.

The final Cox regression model for 6-month survival is shown in Table 3. The model included as significant variables: the year of transplantation, the albumin/age ratio, the plasma bilirubin, and whether ascites was present or diuretics were given, or both. The scorings shown in Table 3 gave the best fit in the model. Albumin and age had borderline statistical significance ($p=0.081$ and $p=0.063$, respectively) when either was included separately in the model, but since serum albumin decreases physiologically with age (27), the albumin/age ratio was used as an appropriate interaction variable which gave a satisfactory fit in the model. The survival in patients grafted after 1990 tended to be slightly better than in the previous 5-year period, but the difference did not reach statistical significance. Λ_0(6mo) for the

TABLE 3

Final Cox regression model for pre-transplant prediction of short-term survival (up to 6 months) after transplantation[1]

Variable	Scoring	b	SE(b)	*p*-value
Year of transplantation	1981–85: 1 After 1985: 0	0.962	0.361	0.008
Albumin/age ratio	(g/l)/years	−2.402	0.988	0.015
Plasma bilirubin	μmol/l	0.00143	0.00063	0.025
Ascites or diuretic treatment	yes: 1 no: 0	0.791	0.380	0.037

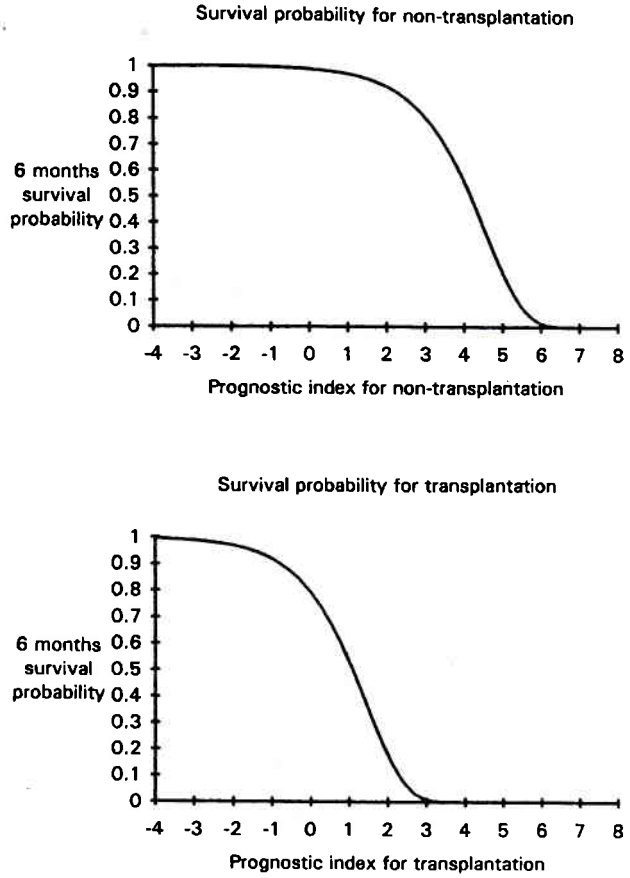

Fig. 1. The predicted 6-month survival probability as a function of the prognostic index for non-transplantation (upper panel) and for transplantation (lower panel). PI_{trans}-values being 3.1 less than $PI_{non\text{-}trans}$-values correspond to similar 6-month survival probabilities.

model was 0.2326. Inserting this value in formula 2, the 6-month survival probability can be calculated from that formula, given the prognostic index (PI_{trans}) of the patient. (For t=1, 2, 3, 4 and 5 months after the transplantation, $\Lambda_0(t)$ was 0.1323, 0.1805, 0.1854, 0.2109, 0.2217, respectively.)

Using Fig. 1, the 6-month survival probability corresponding to a given prognostic index PI can be read directly both for non-transplantation ($PI_{non\text{-}trans}$) (12) (Fig. 1 upper panel) and transplantation (PI_{trans}) (Fig. 1 lower panel). Using simple algebra, it can be shown that PI_{trans}-values 3.1 less than $PI_{non\text{-}trans}$-values predict similar 6-month survival probabilities.

Comparison of prognosis with and without liver transplantation

Fig. 2 shows the relation between the prognostic index values for survival with and without transplantation in the 303 transplanted patients with complete data (upper panel) and in 98 non-transplanted patients with complete data available between 12–0.5 months (on average 6 months) prior to death from a hepatic cause (lower panel).

The findings are similar in both groups, showing a small variation in the prognostic index for transplantation (PI_{trans}). Furthermore, only for non-transplantation prognostic index ($PI_{non\text{-}trans}$) values above ~2.5 is the predicted 6-month survival probability for trans-

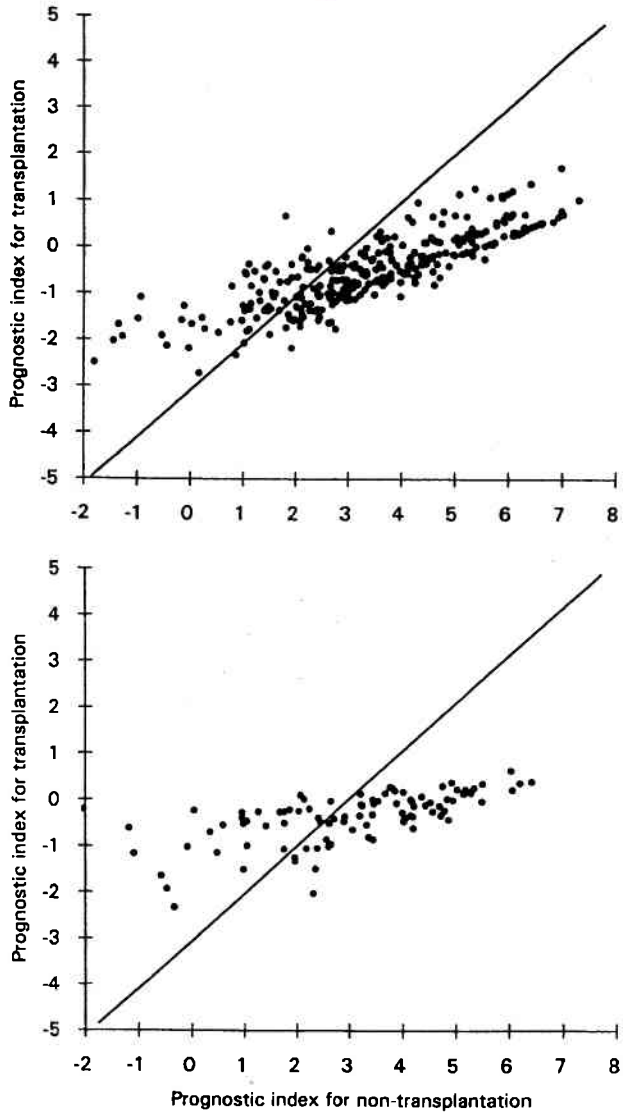

Fig. 2. The relation between the prognostic index values for transplantation and non-transplantation in 303 transplanted patients with complete data (upper panel) and in 98 non-transplanted patients with complete data at 12–0.5 months (on average 6-month) prior to death from a hepatic cause (lower panel). The line of identical predicted 6-month survival probability for the two indices is shown. PI-combinations below this line indicate a comparatively higher predicted 6-month survival for transplantation, which should therefore be considered.

plantation better than for non-transplantation (the points lie below the indicated line of equal predicted 6-month survival probabilities).

Fig. 3 shows the relation between the prognostic index for non-transplantation ($PI_{non\text{-}trans}$) and the predicted gain in 6-month survival probability from transplantation in transplanted patients (upper panel) and non-transplanted patients on average 6 months prior to death from a hepatic cause (lower panel). In both groups of patients the gain in predicted 6-month survival probability starts to increase at prognostic index values of about 2.5.

Fig. 4 shows the observed development of the prognostic index for non-transplantation ($PI_{non\text{-}trans}$) and its associated predicted 6-month survival probability in 31 non-transplanted patients with complete sets of data at 6-month interval before death from a hepatic cause. In this period the median prognostic index for non-transplantation ($PI_{non\text{-}trans}$) increases from 2.4 to 3.8 (with a corresponding decrease in the median predicted 6-month survival probability of 0.86 to 0.53), whereas the median prognostic index for transplantation (PI_{trans}) (and the corresponding predicted 6-month survival probability) change only slightly in the same period of time. Thus the gain from transplantation starts to become positive around 8 months prior to death from a hepatic cause, corresponding to a prognostic index for non-transplantation ($PI_{non\text{-}trans}$) of about 2.5.

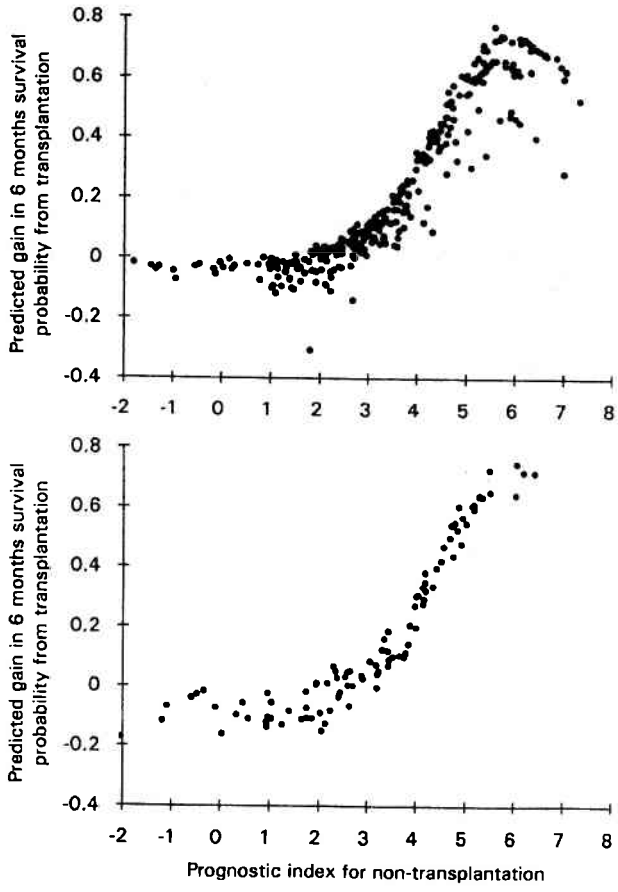

Fig. 3. The relation between the prognostic index for non-transplantation and the predicted gain in 6-month survival probability from transplantation in 303 transplanted patients (upper panel) and 98 non-transplanted patients on average 6 months prior to death from a hepatic cause (lower panel).

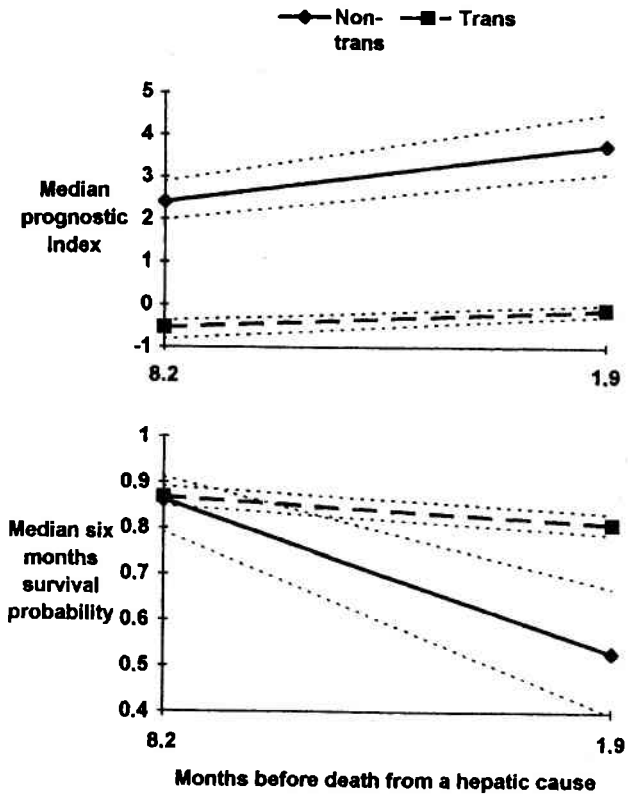

Fig. 4. Development of the median prognostic index for non-transplantation and its associated predicted 6-month survival probability (with 95% confidence intervals indicated by light dotted lines) in 31 non-transplanted patients with complete data 6 months apart before death from a hepatic cause.

Practical application of the prognostic indices in individual patients

The following examples illustrate the calculation of the prognostic indices and the interpretation of the resulting values. The calculation of the prognostic index for transplantation is facilitated by the pocket chart presented in Table 4, according to the principles previously described (14,24).

Example 1. At a given time, a PBC patient shows the following variables: albumin 26 g/l, age 61 years, biliru-

TABLE 4

Pocket chart for easy calculation of prognostic index for transplantation

Variable								Points to add
Albumin (g/l):	20	25	30	35	40	45	50	
		Points for albumin-age *combination*:						
Age (years): 30	−16	−20	−24	−28	−32	−36	−40	
35	−14	−17	−21	−24	−27	−31	−34	
40	−12	−15	−18	−21	−24	−27	−30	
45	−11	−13	−16	−19	−21	−24	−27	
50	−10	−12	−14	−17	−19	−22	−24	
55	−9	−11	−13	−15	−17	−20	−22	
60	−8	−10	−12	−14	−16	−18	−20	
65	−7	−9	−11	−13	−15	−17	−18	
70	−7	−9	−10	−12	−14	−15	−17	
Bilirubin (μmol/l):		Points for bilirubin:						
	10	0						
	100	1						
	200	3						
	300	4						
	400	6						
	500	7						
Ascites or diuretic:		Points for ascites or diuretic:						
	Yes	8						
	No	0						
Sum of added points (S)= PI_{trans}=S/10=								

Note: Only one value of each variable or variable combination should be used in the calculation. If a patient has values between those in the table, interpolation should be used.

bin 29 μmol/l, ascites present (scored as 1) and no GI bleeding (scored as 0).

A. Current prognosis for non-transplantation:
Using equation 3, $PI_{non\text{-}trans} = 3.02\times(\log_{10}[29] - 1.53)$ (for bilirubin) + 1.43 × 1 (for ascites) −0.077 × (26−34.3) (for albumin) + 0.043 × (61−55) (for age) + 0.74 × 0 (for gastro-intestinal bleeding) = 2.12. However, $PI_{non\text{-}trans}$ can be obtained in a simpler way using the previously published pocket chart (Table 5 (model A-II) in reference 14). With that pocket chart the calculation is as follows:

$PI_{non\text{-}trans} = (5+14-11+13+0)/10 = 2.1.$

Using Fig. 1 (upper panel) $S_{6mo\text{-}non\text{-}trans}$ can be read as 0.92 or 92%. (Calculation using equation 4 gives the same result.)

B. Prognosis for transplantation:
Using the model presented in Table 3, PI_{trans} = −2.402×(26/61) (for albumin/age ratio)+0.00143×29 (for bilirubin)+0.791×1 (for ascites) = −0.19. (For present day transplantation, the term for year of transplantation vanishes.) Using the pocket chart for this model presented in Table 4, the calculation simplifies to: $PI_{trans} = (-10+0+8)/10 = -0.2.$

Using Fig. 1 (lower panel) $S_{6mo\text{-}trans}$ can be read as 0.83 or 83%. (Calculation using equation 2 gives the same result.)

C. Gain of transplantation:
The predicted gain in 6-month survival probability to be obtained with transplantation is 0.83−0.92 = −0.09 or −9%, i.e. the predicted gain is negative and transplantation should not be performed at this time.

Example 2. At a given time, a PBC patient shows the following variables: albumin 29 g/l, age 47 years, bilirubin 79 μmol/l, ascites present (scored as 1) and GI bleeding present (scored as 1).

A. Current prognosis for non-transplantation:
Using equation 3, $PI_{non\text{-}trans} = 3.02\times(\log_{10}[79]-1.53)$ (for bilirubin)+1.43×1 (for ascites) −0.077×(29−34.3) (for albumin)+0.043×(47−55) (for age)+0.74×1 (for gastro-intestinal bleeding) = 3.35. Using the previously published pocket chart (Table 5 (model A-II) in reference 14), $PI_{non\text{-}trans}$ can be obtained in a simpler way. With the pocket chart, the calculation is as follows:

$PI_{non\text{-}trans} = (18+14-14+8+7)/10 = 3.3.$

Using Fig. 1 (upper panel) $S_{6mo\text{-}non\text{-}trans}$ can be read as 0.74 or 74%. (Calculation using equation 4 gives the same result.)

B. Prognosis for transplantation:
Using the model presented in Table 3, $PI_{trans} = -2.402\times(29/47)$ (for albumin/age ratio)$+0.00143\times79$ (for bilirubin)$+0.791\times1$ (for ascites) $= -0.58$. (For present day transplantation, the term for year of transplantation vanishes.) Using the pocket chart for this model presented in Table 4, the calculation simplifies to: $PI_{trans} = (-15+1+8)/10 = -0.6$.

Using Fig. 1 (lower panel) $S_{6mo\text{-}trans}$ can be read as 0.88 or 88%. (Calculation using equation 2 gives the same result.)

C. Gain of transplantation:
The predicted gain in 6-month survival probability to be obtained with transplantation is $0.88-0.74 = 0.14$ or 14%, i.e. in this patient the predicted gain is slightly positive and preparation for transplantation should be started.

Discussion

Although liver transplantation is the only effective therapy for patients with end-stage primary biliary cirrhosis, timing of the procedure is difficult. Even though results of transplantation have improved, significant morbidity and mortality are still associated with the procedure. If a patient is transplanted early in the course of disease, there remains the risk that the patient may die prematurely as a consequence of surgery. Conversely, if the patient is transplanted late in the course of the disease, the patient is less likely to survive the surgery.

The presented model for estimating survival after transplantation shares some variables (bilirubin, year of transplantation, diuretics) with the previously published model based on a smaller sample (19). New variables in the present model are albumin and age. Another recently published model for predicting events after transplantation for patients with cholestatic diseases (including PBC) included age, renal failure, Child's class and degree of incapacitation (28). However, that model was designed for prediction of blood loss, days in intensive care unit and severe complications after surgery, but not for prediction of survival and so it does not allow comparison with survival estimates in the absence of transplantation.

Although many of the factors (serum bilirubin, age, serum albumin, presence of ascites) which predict the survival in the absence of transplantation also predict survival after transplantation, their relative importance differs in the two models. This is reflected in the regression coefficients and the scoring of the variables.

Despite slight short-term fluctuation and reversibility, especially in the early stages, the PBC tends to run a progressive course, which may accelerate in the late stages. Even though GI bleeding, which is included in the model for non-transplantation, may be effectively treated, and the risk is thereby reduced, further episodes will occur in many patients. Therefore, $PI_{non\text{-}trans}$-values should be given the same weight irrespective of whether GI bleeding is a contributing variable or not.

Comparison of the two models in individual patients shows that the predicted gain from transplantation starts to become clinically important when $PI_{non\text{-}trans}$ reaches values of about 2.5, corresponding to a predicted 6-month survival of about 0.85. With a further increase in $PI_{non\text{-}trans}$, the predicted gain to be expected following the transplantation increases further. Thus if $PI_{non\text{-}trans} \geq 2.5$, transplantation should ideally be done within the following 6 months. However, consideration of survival probabilities may be less relevant if the patient suffers from severe symptoms such as intractable pruritus. In such cases the transplantation may be indicated even if $PI_{non\text{-}trans}$ has not yet reached 2.5. That such considerations have been made in some of the transplanted patients is apparent in Fig. 3, where some individual points fall below zero.

Although these results do suggest the optimal time for transplantation, they do not and indeed cannot indicate the optimal time for listing of patients. The length of time a patient waits for a liver will depend on a number of factors, including the size and weight of the patient and the blood group. Furthermore, waiting lists and their priority rules vary between centres and between countries. However, by knowing all the factors which influence the waiting time and by judicious use of prognostic models, it should be possible for the clinician to determine more accurately the time not only of transplantation but also of listing. Greater understanding of when to list patients for transplantation will also allow clinicians in non-transplant centres to refer patients for assessment at the appropriate time (20).

Finally, prognostic modelling should not be considered the final truth but rather a supplementary tool, the relevance of which will depend on the clinical situation in each individual case. There are many reasons for referring patients for transplantation, end-stage disease being only one. Nonetheless, comparison of prognosis with and without transplantation provides a

rational method, which allows the clinician to give advice on the timing of transplantation and supports a cost-effective use of a scarce and expensive resource.

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