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Updating Prognosis and Therapeutic Effect Evaluation in Cirrhosis with Cox's Multiple Regression Model for Time-Dependent Variables

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A multivariate Cox regression analysis with time-dependent variables has been performed on the data of 415 patients with cirrhosis included in a controlled clinical trial of 10–15 mg prednisone daily versus placebo. The analysis showed that a poor prognosis was associated with a low prothrombin index, marked ascites, GI bleeding, high age, high daily alcohol consumption, high bilirubin and alkaline phosphatase and low albumin values, little liver connective tissue inflammation, and poor nutritional status. Prothrombin index and ascites showed significant interaction with the treatment in such a manner that high prothrombin index and absence of ascites were associated with a beneficial effect of prednisone, whereas low prothrombin index and presence of ascites were associated with a harmful effect of prednisone treatment. The final model was validated in independent patients by comparing their actual survival with that predicted from the model, using a split-sample testing technique. The prognostic factors were combined with an index that can be used to update prognosis whenever changes occur in the clinical status of a patient during the course of the disease. The probability of surviving the next 3 or 6 months can be estimated from the prognostic index at any time during the course. The index may be of value for the correct timing of special therapeutic procedures such as liver transplantation.

Key words: Albumin; alkaline phosphatase; ascites; bilirubin; biometry; liver cirrhosis; multivariate regression analysis; prednisone; prothrombin index

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Prognosis in cirrhosis varies widely, being dependent on patient characteristics. We have previously established the prognostic value of the Child-Turcotte criteria in medically treated patients with cirrhosis (1). Better prognostic

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information was obtained by a prognostic index developed by multivariate analysis (2). Furthermore, that analysis provided the basis for development of an index for prediction of the therapeutic effect in individual patients (3). Those prognostic and therapeutic indices are, however, based on patient data at the time of entry into the trial and do not utilize follow-up information (2). During the course of disease, estimates of prognosis for a given patient may be improved if his/her most recent recordings of prognostic variables can be taken into account.

In this report we develop indices that for a given patient can be estimated repeatedly during the course of disease. With these indices the therapy-dependent prognosis can be updated whenever changes occur in the status of the patient.

PATIENTS AND METHODS

The data of patients included in a controlled clinical trial evaluating the effect of prednisone versus placebo on survival (4) are analyzed. Of 488 patients whose initial biopsy specimens permitted histologic reevaluation by means of updated, more restrictive histologic criteria (5), we included in this analysis only 415 who at the entry into the trial had complete information on the variables studied. The allocation of treatment was based on date of birth, 211 receiving prednisone and 204 placebo. The dosage of prednisone was initially 40 mg/day, being reduced during 1–2 months to a dose of 10–15 mg/day. At the time of entry into the trial, after 3, 6, and 12 months, and thereafter once a year, each patient underwent a detailed assessment, including clinical and laboratory findings. Liver biopsies and radiologic examinations were planned to take place at yearly intervals but were performed less regularly in some patients. During the follow-up period (up to 12 years) 248 died, 118 in the prednisone group (hepatic cause (hepatic failure, GI bleeding, and hepatoma) in 79 and non-hepatic cause (such as cardiovascular disease, extrahepatic neoplasms, and infections) in 39) and 130 in the placebo group (hepatic cause in 78 and non-hepatic in 52) (6). Data on admission to the trial in the 415 patients studied are shown in Table I.

Statistical analysis

The association of admission and follow-up data with survival was analyzed by using the version of the multivariate regression model proposed by Cox (7) for time-dependent variables in the form corresponding to that developed for time-fixed variables described in detail previously (2, 3):

$$PI(t)_T = \log(\lambda(t)/\lambda_0(t)) = b_{tr}z_{tr} + b_1^T z_1(t) + \ldots + b_k^T z_k(t) + b_{k+1}z_{k+1}(t) + \ldots + b_{k+r}z_{k+r}(t).$$

Thus at time t the prognostic index $PI(t)_T$ (during treatment T) of a given patient with the variables $z_1(t)$ to $z_{k+r}(t)$ at that time is a function of these variables weighted with the corresponding coefficients b_1 to b_{k+r}. b_{tr} is an overall treatment effect coefficient, z_{tr} is a treatment indicator (prednisone, 0; placebo, 1), b_1^T to b_k^T are regression coefficients for the k 'therapeutic variables' $z_1(t)$ to $z_k(t)$, having significantly different coefficients for each treatment T (T stands for prednisone or placebo), and b_{k+1} to b_{k+r} are regression coefficients for the r 'prognostic' variables $z_{k+1}(t)$ to $z_{k+r}(t)$, having coefficients common to the two treatments as explained in detail previously (2, 3). ($\lambda(t)$ is the patient's death risk or hazard, and $\lambda_0(t)$ is the so-called basal or underlying hazard (2, 3, 7).) Higher values (scores) of a given variable $z_i(t)$ indicate higher risk if the corresponding regression coefficient b_i is positive, and vice versa if b_i is negative. If $b_i = 0$, then $z_i(t)$ has no influence on the risk. Thus higher values of $PI(t)_T$ mean higher risk (poorer prognosis), and lower values mean lower risk (better prognosis).

In this time-dependent model each variable $z_i(t)$ of a patient is allowed to vary with time t, and correspondingly the risk of the patient can vary in accordance with the value of the variables. If, for example, a patient develops GI bleeding the risk is likely to increase; if the bleeding can be effectively treated, the risk is likely to decrease again. Since the analysis requires that values of the variables are defined for the intervals between the observations, the variables of a patient are considered unchanged until the next information. This corresponds to the clinical situation.

The Cox model in this study is a further deve

Table I. Basal data of the 415 patients studied

Variable	Prednisone, $n = 211$	Placebo, $n = 204$
Median age (years)	60	60
Males (%)	61	56
Daily alcohol consumption >50 g (%)	45	39
Ascites (%)	23	16
GI bleeding (%)	6	9
Poor nutritional status (%)	18	20
Median prothrombin index (>70% of normal)*	66.0	67.5
Median bilirubin (4–22 μmol/l)*	20	19
Median albumin (>44 g/l)*	36.0	37.0
Median alkaline phosphatase (<10 KA units)*	13.0	14.3
Revised histologic diagnosis of cirrhosis†		
Certain (%)	64	54
Probable (%)	19	26
Compatible (%)	15	19
Unlikely (%)	2	1
Chronic aggressive hepatitis (%)	19	21
Moderate or marked liver connective tissue inflammation (%)	63	60

* Lower or upper limit of normal range in parentheses.
† Described in Ref. 5.

opment of our previous model for time-fixed variables (2, 3). The variables in that model were the first to be included as time-dependent variables except for sex and age at randomization. Before stepwise inclusion of new variables in groups in order of decreasing prognostic or therapeutic importance on the basis of our previous analyses (2), only significant variables were retained in the model at each step. A total of 28 variables were analyzed.

Checking of model assumptions and classification of variables as 'therapeutic' or 'prognostic' was performed as in the time-fixed model, as described in detail previously (2, 8, 9). We found that logarithmic scoring of prothrombin index and of albumin and alkaline phosphatase values, and dichotomous scoring of bilirubin ($\geq$ or <70 μmol/l) gave the best fit in the model. Occurrence of hepatic coma preceded death so closely that we did not find it reasonable to include this variable because the clinical value of such late prognostic information would be small.

The difference in prognosis during placebo and prednisone treatment, $PI(t)_{placebo}$-$PI(t)_{prednisone}$, is an estimate of the therapeutic effect of prednisone at time t. This difference reduces to the following simple therapeutic index based on therapeutic variables only (variables 1 to k):

$$TI(t) = b_{tr} + d_1 z_1(t) + \ldots + d_k z_k(t),$$

where $d_i = b_i^{placebo} - b_i^{prednisone}$

The statistical significance of TI(t) is obtained by comparing TI(t)/SE(TI(t))—that is, the normalized therapeutic index NTI(t)—with the standardized normal distribution. $NTI(t) > 1.96$ or $NTI(t) < -1.96$ is considered significant.

Probability of surviving the next 3 or 6 months

For the final model the estimated cumulative underlying hazard function $\hat{\Lambda}_0(t)$ (Fig. 1) was linear apart from the last 1.5–2 years, when the confidence of the curve was small because of the few patients at risk at that time. Thus the underlying hazard may be considered constant (independent of time t): $\lambda_0(t) = \lambda_0 = 0.95$ years^{-1} (estimated by the slope of $\hat{\Lambda}_0(t)$). This means that for a given value of $PI(t)_T$ the prognostic information for the subsequent time period is the same whether early or late in the course of the disease. Thus the various risks of the patients could be satisfactorily described alone by the various levels of the variables in the model.

Interpretation of $PI(t)_T$ can be facilitated by transformation to the conditional probability

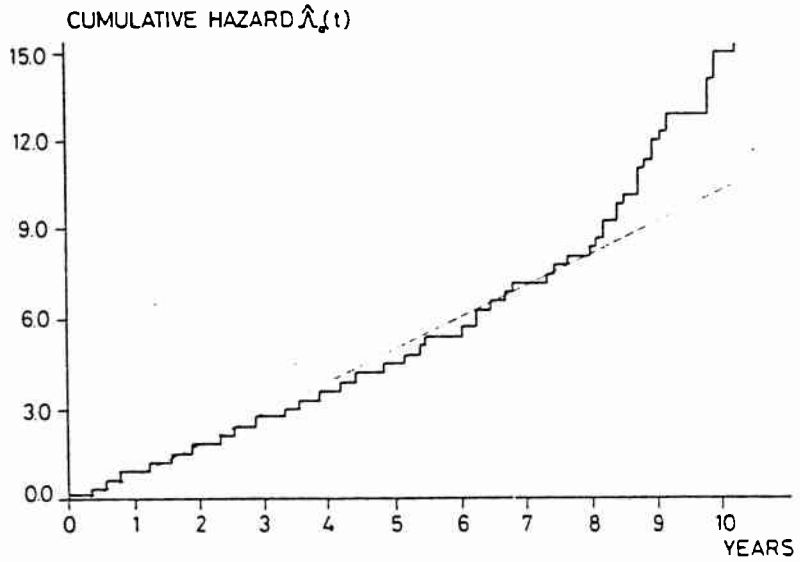

Fig. 1. Estimated integrated (cumulative) underlying hazard $\hat{\Lambda}_0(t)$ in the final time-dependent Cox regression model.

P(t,h) of surviving a short time interval h (say 3 or 6 months) after time t given survival to that time, estimated approximately as $\hat{P}(t,h) = \exp(-0.95 \cdot h \cdot \exp(PI(t)_T))$ (10).

The final model was validated as described in the Appendix by comparing actual survival in independent patients with survival predicted from the model by means of a split-sample testing technique. For comparison the previously developed prognostic index PI_T for time-fixed variables (2) was validated similarly.

Examples of estimation of the indices and their interpretation are given in Results.

RESULTS

Prognostic and therapeutic variables

Table II shows variables with significant association with prognosis or therapeutic effect together with their scoring in the final model. Two variables, prothrombin index and ascites, were therapeutic—that is, low prothrombin index and presence of ascites were associated with higher risk, and high prothrombin index and no ascites with lower risk during prednisone than during placebo treatment.

Seven variables had highly significant prognostic but no significant therapeutic influence (Table II). Thus marked GI bleeding (necessitating blood transfusion), high age, high daily alcohol consumption (but not the duration of alcoholism or the cumulative alcohol consumption), bilirubin value $\geq 70\,\mu mol/l$, low serum albumin concentration, no or slight inflammation in liver connective tissue, poor nutritional status, and high alkaline phosphatase value were associated with higher risk.

Age at randomization has been used in our analysis. The same regression coefficient would have been obtained if age had been included as a time-dependent variable, but λ_0 would have been slightly less. High alkaline phosphatase value and nutritional status (obesity) tended to be associated with higher risk during prednisone than during placebo treatment, but these tendencies were not statistically significant. Acetylcholinesterase, spider nevi, hepatomegaly, esophageal varices, aspartate aminotransferase, and gamma globulin could not add significant information to the final model.

Prognostic and therapeutic indices and their interpretation

The information in Table II can be used to update prognosis in any patient from his/her data by calculating the prognostic index $PI(t)_T$. This can be done easily by using Table III, in which the regression terms have been replaced by simple numbers to be added (only one number for each variable if applicable). If a patient has values between those in the table, interpolation should be used.

If, for example, a patient receiving prednisone has the following variables: prothrombin index, 59%; no ascites; no GI bleeding; age, 61 years; a daily alcohol consumption of >50 g; bilirubin, 17 μmol/l; albumin, 42.6 g/l; moderate liver connective tissue inflammation; normal nutritional status; and alkaline phosphatase, 7.8 KA units, then A = 1 (for age) + 13 (for alcohol consumption) + 1 (for alkaline phosphatase) = 15, and S = 1 (for prothrombin index) + 25 (for albumin) + 6 (for connective tissue inflammation) = 32. (The other variables did not apply (and thus scored 0) for this patient.) Then $PI(t)_{prednisone} = (A - S)/10 = (15–32)/10 = -1.7$.

Using Fig. 2, it is possible to derive from the value of $PI(t)_T$ the estimated probability of surviving the next 3 or 6 months. For the example presented above the prognosis is relatively good, the estimated probabilities of surviving the next 3 and 6 months being 0.96 and 0.92, respectively (Fig. 2).

The value of $PI(t)_{placebo}$ would be −1.8 (S = 33 in this case (1 added for placebo treatment, the number for prothrombin index being virtually unchanged (Table III))), or nearly the same as for prednisone treatment. Thus in this patient nothing seems to be gained by giving prednisone. This can also be seen from the therapeutic index NTI(t). Because of the few therapeutic variables

Table II. Significant prognostic or therapeutic variables in time-dependent Cox regression analysis

Variable	Scoring	Treatment group(s)	Regression coefficient b	Standard error SE(b)	*p* Value
Treatment	Prednisone = 0 Placebo = 1	Both	−0.13	0.19	0.5
Prothrombin index (% of normal)	Log_e(value) −4	Pred. Plac.	−1.58 −0.83	0.22 0.19	$<10^{-4}$ $<10^{-4}$
Ascites, slight	Present = 1 Otherwise = 0	Pred. Plac.	0.96 0.34	0.25 0.27	10^{-4} 0.21
Ascites, moderate or marked	Present = 1 Otherwise = 0	Pred. Plac.	1.66 1.17	0.25 0.23	$<10^{-4}$ $<10^{-4}$
GI bleeding, marked	Present = 1 Otherwise = 0	Both	1.41	0.18	$<10^{-4}$
Age (years)	Value −60	Both	0.052	0.0085	$<10^{-4}$
Alcohol consumption, daily	None = 0, 10–50 g = 3, >50 g = 9	Both	0.14	0.024	$<10^{-4}$
Bilirubin (μmol/l)	<70 = 0, ≥70 = 1	Both	0.94	0.18	$<10^{-4}$
Albumin (g/l)	Log_e(value × 10) − 4	Both	−1.20	0.27	$<10^{-4}$
Liver connective tissue inflammation	None or slight = 0, moderate or marked = 1	Both	−0.56	0.14	$<10^{-4}$
Nutritional status	Meager or cachectic = 1, otherwise = 0	Both	0.56	0.16	$<10^{-3}$
Alkaline phosphatase (KA units)	Log_e(value × 10) − 4	Both	0.36	0.11	$<10^{-3}$

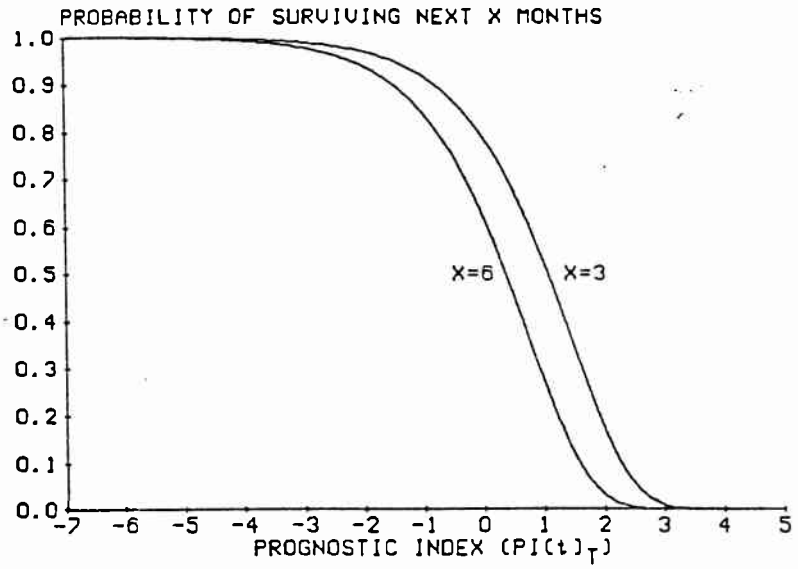

Fig. 2. Estimated probability of surviving the next 3 or 6 months as a function of $PI(t)_T$.

it was possible to present NTI(t) graphically simply as a function of prothrombin index and the degree of ascites, as shown in Fig. 3. From this figure one can obtain NTI(t) for any given patient by reading NTI(t) against the level of the two therapeutic variables in the patient. Calculation of NTI(t) is therefore unnecessary. As can be seen in Fig. 3, a significant beneficial effect of prednisone ($NTI(t) > 1.96$) is only seen for a prothrombin index greater than 125 in the absence of ascites. In such cases prednisone should be given. Significantly harmful effects of prednisone ($NTI(t) < -1.96$) are seen if the prothrombin index is less than 33 in the absence of ascites or less than 60 if ascites is present. In these situations prednisone should not be given. For the patient presented above NTI(t) is −0.4, indicating that the small tendency towards harmful effect of prednisone is far from statistically significant in this patient.

In Table IV a detailed example with calculation of the indices at various times after entry into the trial is presented for a given patient. After a slight improvement at 6 months there is a gradual accelerative deterioration with increase in $PI(t)_{prednisone}$ and decrease in probability of surviving the next 6 months (Fig. 2). For comparison, $PI(t)_{placebo}$ and NTI(t) are also calculated in Table IV. Only at 23.5 months after entry into the trial is NTI(t) significantly different from zero; the negative value indicates that prednisone would have a harmful effect in this phase of the patient's disease owing to the low value of the prothrombin index in the presence of ascites (Fig. 3).

Validation of the model

As described in detail in the Appendix, we found that $PI(t)_T$ predicted survival in independent patients more precisely than our previously developed time-fixed prognostic index PI_T (2). Nevertheless, for higher values of $PI(t)_T$ (high risk), risk tends to be overestimated, especially during the first 6 months after entry into the trial. For low $PI(t)_T$ values (low risk), risk tends to be underestimated. This is in contrast to the time-fixed index PI_T, which for high risk (high $PI(t)_T$) underestimates the risk and for low risk (low $PI(t)_T$) overestimates the risk.

DISCUSSION

In cirrhosis the course may be irregular with phases of improvement or deterioration (11).

Table III. Pocket chart for estimation of 'actual' prognostic index $PI(t)_T$ by addition of points

Variable		Points to add (A)			Points to subtract (S)		
		Pred.	Plac.	Both	Pred.	Plac.	Both
Treatment							1
Prothrombin index (% of normal)	10	27		14			
	15	20		11			
	20	16		8			
	30	10		5			
	40	5		3			
	55	0		0	0		0
	70				4		2
	105				10		5
	150				16		8
Ascites							
Slight		10		3			
Moderate or marked		17		12			
GI bleeding, marked				14			
Age at randomization (or at diagnosis) (years)	20				21		
	30				16		
	40				10		
	50				5		
	60			0	0		
	70			5			
	80			10			
Alcohol consumption							
10–50 g/day				4			
>50 g/day				13			
Serum bilirubin > 70 µmol/l or > 4 mg%				9			
Serum albumin (g/l)	15				12		
	20				16		
	30				20		
	40				24		
	50				27		
	60				29		
Liver connective tissue inflammation							
None or slight					0		
Moderate or marked					6		
Unknown					4		
Nutritional status, meager or cachectic				6			
Alkaline phosphatase (KA units)	5			0			
	10			2			
	17			4			
	30			6			
	50			8			
	70			10			

Sum of points to be added (A) =
Sum of points to be subtracted (S) =
A − S =
$PI(t)_T = (A - S)/10 =$

After the situation at the time of diagnosis, which is often made during an exacerbation requiring hospitalization, signs of improvement occur in many patients within the first 3 months (11). Estimates of prognosis based on the initial situation may accordingly be less precise in some patients. A more precise estimation of prognosis may be expected if the most recent recordings of prognostic variables in a given patient can be taken into account. The Cox regression model

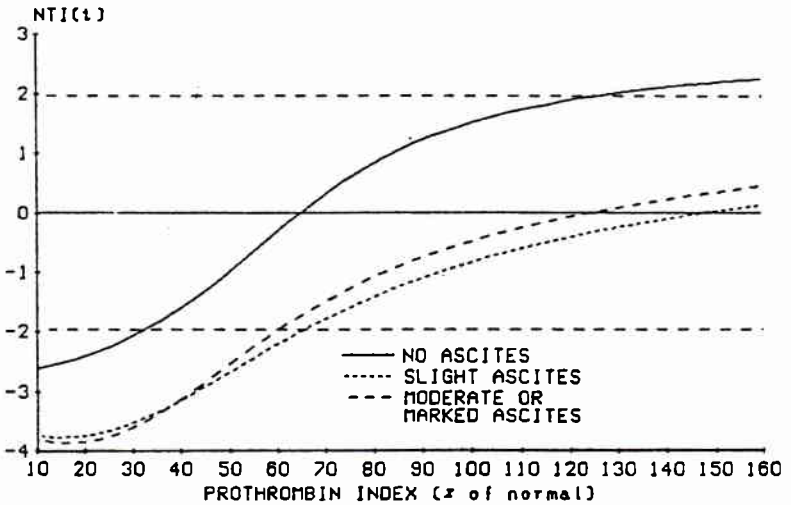

Fig. 3. Normalized therapeutic index NTI(t) as a function of prothrombin index and the degree of ascites.

for time-dependent variables (7), which has been used in this paper, requires that the value of each variable in each patient is defined for the intervals between the observations. In the analysis the value of a variable was considered unchanged from a given recording until the next, because this corresponds to the clinical situation. Actually, the values may increase or decrease before the next follow-up study. Thus, recording of change may be delayed. If a variable for some reason is recorded less frequently, the delay in recording of change may be longer and its prognostic importance less, perhaps insignificant. Since the frequency of investigations to some extent

Table IV. Example with $PI(t)_T$ calculated at various times in a prednisone-treated male patient who died of hepatic failure 25 months after entry into the trial

Variable	Entry	6 months	12 months	18 months	23.5 months
Prothrombin index (% of normal)	59	77	88	72	50
Ascites, slight	No	No	No	Yes	No
Ascites, moderate or marked	No	No	No	No	Yes
GI bleeding, marked	No	No	No	No	No
Age at randomization (years)	61	61	61	61	61
Alcohol consumption, daily (g)	>50	10–50	10–50	10–50	10–50
Bilirubin (μmol/l)	17	22	24	34	120
Albumin (g/l)	42.6	44.8	33.1	39.0	26.0
Liver connective tissue inflammation, moderate or marked	Yes	Yes	Yes	Yes	Yes
Nutritional status, meager or cachectic	No	No	No	No	No
Alkaline phosphatase (KA units)	7.8	18.0	21.1	27.2	39.8
$PI(t)_{prednisone}$	−1.71	−2.73	−2.52	−1.35	1.49
Prob. of surv. next 6 months	0.92	0.97	0.96	0.88	0.12
$PI(t)_{placebo}$	−1.78	−2.60	−2.29	−1.89	0.81
Prob. of surv. next 6 months	0.92	0.96	0.95	0.93	0.34
NTI(t)	−0.38	0.68	1.15	−1.71	−2.54

depends on the ease with which they can be performed, the clinical and simple laboratory tests are favored in a time-dependent analysis at the expense of more special tests, including liver biopsies.

It is important to keep in mind that the time-dependent Cox model only analyzes the association of the risk of death with the 'actual' level of time-dependent variables. The course in time of the variables themselves is not modeled. Furthermore, after entry into the trial the effect of the therapy being significant in selected patients (3) may influence the comparability of the two treatment groups after randomization. However, the multivariate model was designed to adjust for differences between the two treatment groups. Nevertheless, the therapeutic differences should be interpreted and used with some caution. Consequently, we did not attempt to estimate the probability of surviving a period longer than 6 months.

It is well known that hepatic coma is associated with very poor prognosis. In our data hepatic coma preceded death so closely that we did not find it justified to include this variable. Therefore our model is best suited to estimate prognosis before hepatic coma occurs.

For the final model we found that the underlying hazard could be considered constant. This means that the prognostic information provided by the model means the same whether early or late in the course of disease. Thus the various risks in the various patients at various times is described satisfactorily only by the various levels of the variables in the final model.

The analysis showed that two variables, ascites and prothrombin index, had a more marked prognostic influence during prednisone than during placebo treatment. These findings support previous results based on data at admission to the trial, showing that the beneficial effect of prednisone is seen among compensated patients, whereas in uncompensated patients the side effects seem to exceed any beneficial effects of the treatment (3, 4). Corticosteroid hormones significantly increase the prothrombin index, possibly by stimulating synthesis in the liver (12, 13). Our results confirm this effect of prednisone on the prothrombin index. A lack of response may suggest severe liver damage, and this may explain why the unfavorable prognostic influence of low values is greater during prednisone than during placebo treatment.

The remaining variables in the final model showed no significant interaction with the therapy. The harmful influence on prognosis of GI bleeding necessitating blood transfusion, low serum albumin values, high bilirubin values, poor nutritional status, and high alkaline phosphatase values, being indicators of advanced cirrhosis, is in accordance with clinical experience. Furthermore, the risk increases with age, as one would expect. The analysis confirms that the present alcohol consumption has a significant influence on prognosis (14). It improves during abstention and becomes worse during abuse. We found no significant influence of the duration of alcoholism or the cumulative alcohol consumption. Of histologic variables only no or slight inflammation of the liver connective tissue had a significant association with a poor prognosis. This finding may indicate decreased capability to react adequately to liver injury.

The time-dependent Cox regression model included a different set of significant variables than the time-fixed Cox regression model (2), as can be seen in Table V. Variables that were significant in the time-fixed Cox model (acetylcholinesterase, antinuclear factor, and five histologic variables) were not significant in the time-dependent model, probably because these variables have been recorded less frequently than the others. Only liver connective tissue inflammation, being the most significant histologic variable in the time-fixed model (2), has maintained its significance in the time-dependent model. Albumin, which has been recorded more regularly, has replaced acetylcholinesterase, to which it is positively correlated. Present alcohol consumption, which is correlated to (male) sex, has replaced this time-fixed variable. The prothrombin index has become a therapeutic variable, probably mainly because of the effect of corticosteroid hormone on the levels (see above). New prognostic variables include GI bleeding, which varies highly with time (15), alkaline phosphatase, bili-

Table V. Comparison of effect of variables in different prognostic models

Variable	Time-dependent Cox model		Time-fixed Cox model	
	Progn. effect	Ther. effect	Progn. effect	Ther. effect
Clinical				
Age	+	−	+	−
Sex	−	−	+	−
Ascites	+	+	+	+
GI bleeding	+	−	−	−
Actual alcohol consumption	+	−	−	−
Nutritional status	+	−	−	−
Laboratory				
Prothrombin index	+	+	+	−
Bilirubin	+	−	−	−
Albumin	+	−	−	−
Alkaline phosphatase	+	−	−	−
Acetylcholinesterase	−	−	+	−
Antinuclear factor	−	−	+	+
Histologic				
Liver connective tissue inflammation	+	−	+	−
Large piecemeal necroses	−	−	−	+
Macronodular cirrhosis	−	−	+	+
Small focal liver cell necroses	−	−	+	−
Efferent veins in parenchymal nodules	−	−	+	−
Eosinophil leukocytes in liver parenchyma	−	−	+	−

rubin, and nutritional status. The latter two, being included in the Child-Turcotte criteria, had a weak prognostic influence at the entry into the trial (1). Age has a similar effect in the two models, but ascites has a more marked prognostic influence in the time-dependent model. This may be explained by development of more abnormal values (such as marked ascites) before death in patients who had less abnormal or normal values (such as no ascites) at the time of entry into the trial. This demonstrates the value of the follow-up information.

The model was validated for independent patients by means of a split-sample testing technique (see Appendix for details). No significant difference between numbers of deaths observed (O) and expected (E) from the index was found. Nevertheless, for high values of $PI(t)_T$ (high risk) risk tended to be overestimated, particularly in the first 6 months after entry into the trial, whereas for low values of $PI(t)_T$ (low risk) risk tended to be underestimated. The reason is that, in the calculation of the expected numbers of deaths, on the basis of $PI(t)_T$, the influence of possible change during the next 6 months, in particular the possibility of improvement in high-risk patients and of deterioration in low-risk patients (regression toward the mean), is not taken into account. This discrepancy, being most pronounced within the first 6 months, may be explained by the relatively more abnormal values in many laboratory variables at the time of entry into the trial, being followed by a marked regression towards normal within the first months (11). This initial regression indicates that follow-up data (when available) should be used to update prognosis.

The validation also showed that $PI(t)_T$ predicted outcome more accurately than our previously developed prognostic index PI_T for time

fixed variables (2), as one may expect. The latter index may be considered an average over time of the $PI(t)_T$ values.

If the degree of connective tissue inflammation is unknown (liver biopsy not available), $PI(t)_T$ may still be obtained with little loss of precision (Table III) by substituting a number corresponding to the average value of this variable in the patients (Table I). This is a further advantage of $PI(t)_T$.

The model has provided the basis for the time-dependent indices ($PI(t)_T$ and NTI(t)), which can be obtained repeatedly during the course of disease to update prognosis and therapeutic effect evaluation, using the most recent information (see example in Table IV). $PI(t)_T$ can be obtained simply by adding the appropriate numbers in Table III, and NTI(t) can be obtained directly from Fig. 3. The interpretation of $PI(t)_T$ is facilitated by conversion to the probability of surviving the next 3 or 6 months (Fig. 2). This may be of value when close monitoring is important, such as for optimal timing of certain resource-demanding and potentially hazardous therapeutic procedures, including liver transplantation (16).

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REFERENCES

1. Christensen E, Schlichting P, Fauerholdt L, Gluud C, Andersen PK, Juhl E, Poulsen H, Tygstrup N, the Copenhagen Study Group for Liver Diseases. Hepatology 1984, 4, 430–435
2. Schlichting P, Christensen E, Andersen PK, Fauerholdt L, Juhl E, Poulsen H, Tygstrup N, the Copenhagen Study Group for Liver Diseases. Hepatology 1983, 3, 889–895
3. Christensen E, Schlichting P, Andersen PK, Fauerholdt L, Juhl E, Poulsen H, Tygstrup, CSL. Gastroenterology 1985, 88, 156–165
4. Copenhagen Study Group for Liver Diseases. N Engl J Med 1974, 291, 271–273
5. Schlichting P, Fauerholdt L, Christensen E, Poulsen H, Juhl E, Tygstrup N. Liver 1981, 1, 56–61
6. Schlichting P, Christensen E, Fauerholdt L, Poulsen H, Juhl E, Tygstrup N, CSL. Scand J Gastroenterol 1983, 18, 881–888
7. Cox DR. J R Statist Soc [B] 1972, 34, 187–220
8. Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. Wiley, New York, 1980
9. Andersen PK, Christensen E, Fauerholdt L, Schlichting P. Scand J Statist 1983, 10, 49–52
10. Andersen PK. Proceedings from the SIMS Conference on Modern Statistical Methods in Chronic Disease Epidemiology. Wiley, New York, 1985 (in press)
11. Christensen E, Schlichting P, Fauerholdt L, Juhl E, Poulsen H, Tygstrup N. Hepatology 1985, 5, 843–853
12. Ozoylu S, Straus HS, Diamond LK. Nature 1962, 195, 1214–1215
13. David DS, Grieco MH, Cushman P. J Chron Dis 1970, 22, 637–711
14. Tygstrup N, Juhl E, CSL. In Gerok W, Sickinger K, Hennekeuser HH, eds. Alcohol and the liver. Schafttaur, Stuttgart, 1971, 519–526
15. Christensen E, Fauerholdt L, Schlichting P, Juhl E, Poulsen H, Tygstrup N, CSL. Gastroenterology 1981, 81, 944–952
16. Scharschmidt BF. Hepatology 1984, 4, 95s–101s

APPENDIX

Validation of the model

Among the 415 patients 311 (75%) were randomly drawn, and by means of their data the regression coefficients corresponding to the variables in the final model and the (constant) underlying hazard λ_0 were estimated. By means of these regression coefficients $PI(t)_T$ was estimated in the remaining 104 patients at entry into the trial and every half year while being observed up to 9.5 years after randomization. In each of three groups, defined in accordance with the level of $PI(t)_T$, the observed (O) and expected (E) numbers of deaths in each subsequent half-year interval were obtained. The E values were estimated by adding in each group the conditional probabilities of dying in the following half-year interval, the probability for each patient being estimated as $1 - \hat{P}(t,0.5)$ (that is, 1 minus the prob-

Appendix Table I. Evaluation of time-dependent Cox regression model. Comparison in a random sample comprising 104 patients of number of deaths observed (O) and expected from their $PI(t)_T$ values (E) and their PI_1 values (E^0) estimated by means of regression coefficients obtained by analysis of the remaining 311 patients' data

Time interval after entry	$PI(t)_T \leq -4.2$			$-4.2 < PI(t)_T \leq -2.0$			$PI(t)_T > -2.0$		
	O	E	E^0	O	E	E^0	O	E	E^0
0.0–0.5 years	0	0.19	0.56	4	4.73	7.49	8	13.55	6.63
0.5–1.0 years	1	0.31	1.26	4	2.76	5.59	6	5.12	2.54
1.0–4.0 years	3	1.44	4.63	11	12.49	17.89	7	12.38	3.25
4.0–10.0 years	1	1.75	6.93	14	7.13	12.70	3	3.28	0.63
Total in 10 years	5	3.68	13.37	33	27.11	43.67	24	34.32	13.05

Comparison of O and E: chi-square = 4.86, d.f. = 3, $P = 0.18$.
Comparison of O and E^0: chi-square = 17.0, d.f. = 3, $P = 0.0007$.
To save space, the numbers for each half-year interval after the first year have been summarized in fewer intervals.

ability of surviving the following half year). O and E values were added over all 20 intervals, and $\sum_{1}^{3}(O - E)^2/E$ was compared with the chi-square distribution with 3 degrees of freedom.

For comparison the previouly developed prognostic index PI_T for time-fixed variables (2) was validated in a similar manner. The coefficients for the index and the cumulative underlying hazard $\hat{\Lambda}_0(t)$ were estimated from the 75% sample, and PI_T (2) was calculated in the remaining patients. In this case the conditional probabilities of dying in each half-year interval (used for estimation of the E values) were obtained as $1\text{-}\exp(-(\hat{\Lambda}_0(t + 0.5) - \hat{\Lambda}_0(t))\exp(PI_T))$, where $\hat{\Lambda}_0(t + 0.5) - \hat{\Lambda}_0(t)$ is the increase in cumulative hazard over the interval from time t to t + 0.5 years.

As shown in Appendix Table I, the difference between numbers of deaths observed (O) and expected (E) from the time-dependent index $PI(t)_T$ was not significant. In contrast, the results for the time-fixed index PI_T (2) show a highly significant difference between the numbers of deaths observed (O) and expected (E^0) from that index.

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