0270-9139/83/0306-0889$02.00/0
HEPATOLOGY

Vol. 3, No. 6, pp. 889–895, 1983
Printed in U.S.A.

Original Articles

Prognostic Factors in Cirrhosis Identified by Cox's Regression Model

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In a controlled clinical trial in 488 patients with chronic liver disese treated with prednisone or placebo, survival data were analyzed using Cox's proportional hazards model. A total of 162 variables were screened separately for prognostic and/or therapeutic effect by log-rank analyses, whereby 46 clinical, biochemical, serological, and histological variables were isolated. Another five variables traditionally found to be important in patients with liver disease were included. After extensively checking the assumptions of the model, the 51 variables were, by a step-wise procedure, reduced to a final model. It comprised, besides a treatment indicator, 12 variables with significant ($p < 0.05$) prognostic or therapeutic effect. The following eight variables had a significant prognostic effect: sex, age, prothrombin, acetylcholinesterase, eosinophil leucocytes in liver parenchyma, liver cell necrosis, inflammation in liver connective tissue, and efferent veins in parenchymal nodules. A prognostic index based on the final model is formed allowing calculation of 5 years survival probability. The usefulness of the prognostic index was tested by a cross-validation method, and no statistical significant difference was found between the estimated and observed survivorship functions.

Numerous factors influence the survival of patients with cirrhosis of the liver. Clinical (1), biochemical (2), and morphological (3) factors have previously been described. The statistical tests used to identify these prognostic variables were all relatively simple allowing only comprison between predefined *groups* of patients. In 1972, a proportional hazard model was proposed by Cox (4) for the analysis of clinical data. This model makes it possible to identify prognostic factors using *all* available data and in this way simulate clinical practice.

In this study, survival data from patients with cirrhosis included in a controlled clinical trial conducted by the Copenhagen Study Group for Liver Diseases are analyzed using the proportional hazards model of Cox (4). The purpose is to identify variables of prognostic significance in patients with cirrhosis, to calculate an index for predicting the prognosis, to suggest ways of evaluating the validity of the index, and to give examples of its application.

PATIENTS AND METHODS

During the period 1962 to 1969, 532 patients with histologically verified liver cirrhosis were included in a randomized clinical trial evaluating the effect of prednisone vs. placebo on survival (1). In 488 patients included in the present study, the intitial biopsy was available for a histological reevaluation, using updated, more restrictive criteria (3), and with these the diagnosis of cirrhosis

Received December 20, 1983; accepted April 26, 1983.

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This work was supported by Grants 12-0344 and 12-1678 from the Danish Medical Research Council.

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was certain in 287 (59%) probable in 101 (21%), compatible in 89 (18%), and unlikely in 11 (2%). The allocation was based on date of birth, 251 receiving prednisone and 237 placebo. The dosage of prednisone was initially 40 mg per day, being reduced after 1 to 2 months, to a maintenance dose of 10 to 15 mg per day. During the trial period (up to September, 1974), 292 of the 488 patients died.

A total of 162 variables were screened separately by log-rank analyses (5) for a prognostic effect, i.e., correlated with survival with or without prednisone treatment. Forty-six variables which showed a tendency to a therapeutic and/or prognostic effect (Tables 1 and 2) were considered for further multivariate analysis. Five additional variables were also included in the analysis because traditionally they are considered important in patients with chronic liver diseases (alcoholism, hematemesis, SGOT, alkaline phosphatase, and leucocytes count).

The survival data were analyzed by a multivariate semiparametric regression model proposed by Cox, where the hazard or instantaneous risk of death $\lambda(t)$ at time t after randomization for a patient with variables $z_1, \ldots, z_p$, has the form

$$\lambda(t) = \lambda_0(t)e^{b_1z_1} + \cdots + b_pz_p.t > 0.$$

Here $\lambda_0(t)$, the so-called underlying hazard, is an unknown, unspecified function of time and $b_1, \ldots, b_p$ are unknown regression coefficients. The model implies that the hazards of any two patients are proportional, i.e., the ratio between the hazards is not depending on the time t. If a variable z_i has the value (score) 5 in one patient and 3 in another patient, b_i being 0.2 and all other variables in the model being equal, then the model assumes that the ratio between the hazards of the two patients is

$$e^{0.2\times5}/e^{0.2\times3} = e^{0.4} = 1.49.$$

If b_i had been -0.2, the ratio had been

$$e^{-0.2\times5}/e^{-0.2\times3} = e^{-0.4} = 0.67.$$

Thus, higher values (scores) indicate higher hazard (worse prognosis) if b_i is positive and vice versa if b_i is negative. If $b_i = 0$, then z_i has no influence on survival.

Proportionality was checked by observing a constant vertical difference (independent of t) between plots of estimates of $\log \int_0^t \lambda_0(s)\,ds$ against t for various levels of each variable (6, 7). Scoring of variables with more than two levels had, in several cases, to be altered in order to obtain proportionality and to make these vertical differences roughly proportional to the differences in the corresponding scores (i.e., to obtain linearity). Thus, for some variables, a logarithmic transformation was necessary.

The analysis requires that all patients are represented by a complete set of variables. In order not to reduce the number of patients and variables to be analyzed, missing data were replaced by neutral estimates (8). For each variable, the coefficient was calculated with and without

TABLE 1. A TOTAL OF 116 VARIABLES SHOWING NO SIGNIFICANT PROGNOSTIC OR THERAPEUTIC EFFECT BY THE LOG-RANK TEST IN 488 PATIENTS WITH LIVER DISEASE

Anamnestic variables	Splenomegali
First symptom	Dilated abdominal veins
Previous blood transfusion and when	Testicular atrophia
Previous gallstones and when	Skin striae
Alcohol consumption and duration	Skin bleedings
Medical drugs	Blood pressure
Lung disease and duration	Laboratory variables
Allergic disease and duration	Weight
Rheumatic disease and duration	Blood type
Diabetes and duration	Sedimentation rate
Syphilis and duration	Leucocyte count
Neurologic disease and duration	Wassermann reaction
Cardiac disease and duration	Thymol turbidity
Peptic ulcer and duration	Alkaline phosphatases
Other GI diseases and duration	SGOT
Dyspepsia and duration	Cholesterol
Jaundice and duration	Antiglobulin consumption test
Pale stool and duration	LE cell
Skin itching and duration	Coomb's test
Abdominal pain and duration	Urine glucose
Back pain and duration	X-ray of chest
Previous melaena and duration	X-ray of esophagus
Previous hematemesis and duration	X-ray of stomach
Previous ascites and duration	X-ray of biliary system
Previous edema and duration	X-ray of spine
Previous hepatic coma	Histological variables
Menstruation disturbances	Fragmentation of biopsy
Impotence	Configuration of connective tissue
Clinical variables	Nonseptal fibrosis (qualitative and quantitative)
Palmar erythema	Types of cells in connective tissue (lymphocytes, plasma, eosinophils, and macrophages)
White nails	Granulomas in connective tissue (qualitative and quantitative)
Gynecomastia	Bile duct proliferation (quantitative and qualitative)
Liver tenderness	Abnormal bile ducts (type)
Liver surface	Inflammation in bile ducts (qualitative and quantitative)
Liver consistency	Bile stasis
	Acidophilic bodies
	Liver cell necroses (small and large)
	Marginal liver cell necroses
	Confluent liver cell necroses
	Fat in liver cell
	Bile in liver cells
	Iron in liver cells
	Periodic acid-Schiff positive globules
	Ground-glass appearance
	Types of cells in parenchyma (lymphocytes, plasma, eosinophils, and macrophages)
	Ceroid in liver cells
	Granulomas in parenchyma (quantitative and qualitative)
	Dilated sinusoids
	Connective tissue in sinusoidal wall
	Total histological activity

TABLE 2. A TOTAL OF 46 VARIABLES SHOWING EITHER PROGNOSTIC OR THERAPEUTIC EFFECT BY THE LOG-RANK TEST IN 488 PATIENTS WITH LIVER DISEASE

Age	Length of biopsy
Sex	Destruction of liver lobular architecture
Duration of history	Size of parenchymal nodules
History of previous clinical hepatitis	Amount of liver connective tissue
Incapacitation	Thickness of connective tissue septa
Clinical ascites	Degree of periportal fibrosis (less than 500 μm)
Peripheral edema	Degree of inflammation in connective tissue
Nutritional status	Degree of inflammation in parenchyma
Spider nevi	Lymphocytes in connective tissue
Arthralgia	Lymphocytes in parenchyma
Psychiatric disturbances	Eosinophil leukocytes in parenchyma
Muscular wasting	Small (less than five hepatocytes) diffuse focal liver cell necrosis
Liver size (clinical)	Small (less than five hepatocytes) piecemeal necrosis
Esophageal varices on X-ray	Large (more than five hepatocytes) piecemeal necrosis
Hemoglobin	Mallory bodies
Thrombocytes	Pericellular fibrosis
Bilirubin	Kupffer cell proliferation
Prothrombin	Efferent veins in parenchymal nodules
Acetylcholinesterase	Sinusoid dilatation
Albumin	Histological overall activity (parenchyma + connective tissue)
γ-globulin	
Sulfobromophthalin retention test	Histological main groups
Antinuclear factor	Chronic aggressive hepatitis
Rheumatoid arthritis test	

inclusion of neutral estimates, and in no case a significant difference was found (Table 3).

At the first stage, analyses were performed separately for the prednisone- and placebo-treated patients. Plots of estimates of log $\int_0^t \lambda_{0,\text{pred}}(s)ds$ and log $\int_0^t \lambda_{0,\text{plac}}(s)ds$ against t shows a constant vertical difference between the curves (Figure 1) which is compatible with the claim that the underlying hazards ($\lambda_{0,\text{pred}}$ and $\lambda_{0,\text{plac}}$) are proportional (6, 7). The same conclusion was reached by the goodness-of-fit test of Andersen (9) ($\chi^2 = 7.16$, df = 5, p = 0.21).

Therefore, the model could be reduced to one with a common underlying hazard $\lambda_0(t)$ and an overall treatment effect, $b_{\text{treatment}}$. The latter model specifies that the hazard for a placebo-treated patient with variables $z_1, \ldots, z_p$ is

$$\lambda_0(t) \cdot \exp(z_1 b_1^{\text{plac}} + \cdots + z_p b_p^{\text{plac}} + b_{\text{treatment}}),$$

and for a prednisone-treated patient with the same set of variables the hazard is

$$\lambda_0(t) \cdot \exp(z_1 b_1^{\text{pred}} + \cdots + z_p b_p^{\text{pred}}).$$

The regression coefficients for each variable tested were calculated for the prednisone and the placebo group separately. In cases where the coefficients could be replaced by one common coefficient, the significance was tested by the likelihood ratio test (10), and if the coefficient was significantly different from zero, the variable was considered to be "prognostic". In cases without a common coefficient, the difference $b_{\text{pred}} - b_{\text{plac}}$ was calculated, the significance was tested by comparing the difference with its estimated standard error, and if the difference was significant the variable was considered to be "therapeutic".

Thus, the model could be reduced to one with r prognostic coefficients common for the two types of treatment and with k pairs of therapeutic coefficients significantly different in the prednisone and placebo treated group:

$$\lambda(t) = \lambda_0(t) \cdot \exp\,(z_{\text{treatment}}\, b_{\text{treatment}} + z_1 b_1^{\text{T}} + \cdots + z_k b_k^{\text{T}} + z_{k+1}\, b_{k+1} + \cdots + z_{k+r}\, b_{k+r})$$

TABLE 3. ESTIMATES BASED ON 288 PATIENTS WITH COMPLETE COVARIATES RECORDS

Variable	Scoring	Regression coefficient b	Standard error S.E. (b)
Treatment		−0.15	0.23
Sex		0.34	0.19
Age		0.04	0.01
Prothrombin (% of normal)		−0.35	0.31
Acetylcholinesterase (μmoles/min/ml)		−0.62	0.19
Eosinophil leucocytes		0.10	0.19
Small focal liver cell necrosis		0.49	0.18
Inflammation in liver connective tissue		−0.53	0.14
Efferent veins in parenchymal nodules		0.38	0.12
Ascites	Prednisone	0.71	0.20
	Placebo	0.20	0.19
Antinuclear factor	Prednisone	−0.18	0.20
	Placebo	0.42	0.14
Large piecemeal necrosis	Prednisone	−0.91	1.08
	Placebo	1.16	0.48
Parenchymal nodules	Prednisone	0.98	0.38
	Placebo	−0.61	0.47

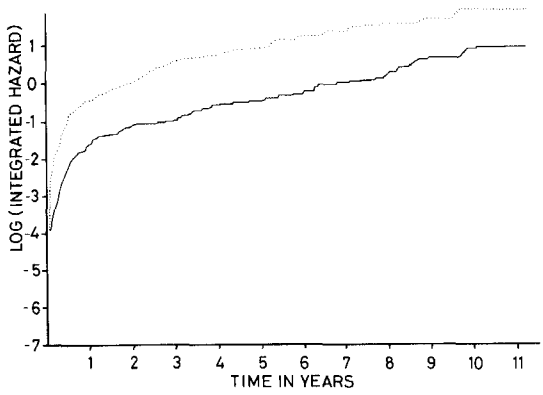

FIG. 1. Logarithmic values of estimated integrated underlying hazard functions for placebo (. . . .) and prednisone (——) treated patients.

where T = prednisone or placebo, and $z_{treatment}$ is the indicator for placebo treatment (0 = prednisone, 1 = placebo).

The large number of variables could not all be included in a single analysis, and therefore the procedure described had to be repeated by introducing new variables once the model had been reduced.

We were thus using a modification of the standard backward elimination procedure. Our procedure was chosen to provide an opportunity of selecting the order in which we try to eliminate the covariates on the basis of prior opinion of their relative importance.

On the basis of the final model, a prognostic index (PI) for a given patient can be calculated for each treatment T:

$$PI = \log(\lambda(t)/\lambda_0(t)) = z_{treatment}\, b_{treatment} + z_1 b_1{}^T + \cdots + z_k b_k{}^T + z_{k+1}\, b_{k+1} + \cdots + z_{k+r}\, b_{k+r},$$

where $z_{treatment} = 0$ for prednisone or 1 for placebo treatment. Higher values for PI mean higher risk, i.e., worse prognosis (shorter survival), and lower (including negative) values mean better prognosis. It should be noted that being dependent on the scoring of the variables the absolute value of PI can only be interpreted in connection with the values of the estimated integrated underlying hazard function $\hat{\Lambda}_0(t)$ (11).

Thus, PI and $\hat{\Lambda}_0(t)$ can be combined to an estimate of the survivorship function $S(t, z_0)$ for patients with covariates $z_0 = (z_{01}, \ldots, z_{0p})$, namely the estimate: $\hat{S}(t, z_0) = \exp[-e^{PI}\hat{\Lambda}_0(t)]$, and a graph giving the estimated probability of surviving a given time t, e.g., the 5 years survival probability, as a function of the index PI can be constructed. Another measure for the prognosis calculated from PI is the median survival time (MST) indicating the span of time that the patient will survive with 50% probability. The relation between MST and PI can then be given as a plot with MST as a function of PI.

The predictive power of the model was tested as follows: a random sample comprising approximately 75% of the patients was drawn, and the regression coefficients corresponding to the variables in the final model and the underlying hazard function were estimated. From these estimates, the individual survivorship functions for the rest of the patients (~25%) were estimated as described previously. The average estimated survivorship functions in three groups obtained by dividing the patients according to their PI values were compared with the Kaplan-Meier plots. In each group, the difference between observed and estimated survivorship functions was tested using the one sample log-rank test (12).

RESULTS

Tables 4 and 5 show the scoring and the estimated regression coefficients for the 13 variables comprising the final Cox multiple regression model together with their estimated standard errors. Variables are classified according to their effect in the model either as prognostic (Table 4) or therapeutic (Table 5) variables. From Table 4, it is seen that two clinical, two biochemical, and four morphological variables each provided significant prognostic but not therapeutic information. As indicated by the coefficients, the following set of variables results in a poor prognosis: male, high age, low prothrombin and low acetylcholinesterase activity, many parenchymal eosinophil leucocytes in liver biopsy, presence of small focal liver cell necrosis, no or slight inflammatory activity in the liver connective tissue, and many efferent veins in regeneration nodules.

The four variables in Table 5 were all found to be "therapeutic" according to the definition given previ-

TABLE 4. "PROGNOSTIC" VARIABLES IN THE FINAL MODEL

Variable	Scoring	Regression coefficient b	Standard error S.E. (b)	p value
Treatment	Placebo: 1 Prednisone: 0	0.150	0.173	0.39
Sex	Female: 0 Male: 1	0.317	0.143	0.03
Age (yr)	Age: 60	0.049	0.007	3×10^{-12}
Prothrombin (% of normal)	Log (value) −4	−0.495	0.211	0.02
Acetylcholinesterase (μmoles/min/ml)	Log (value × 100) −4	−0.612	0.136	6×10^{-6}
Eosinophil leukocytes in liver parenchyma	None: 0 Few: 1 Moderate: 2 Many: 3	0.299	0.142	0.04
Small focal liver cell necrosis	None: 0 Present: 1	0.310	0.124	0.01
Inflammation in liver connective tissue	None: 0 Slight: 1 Moderate: 2 Severe: 3	−0.390	0.096	2×10^{-5}
Efferent veins in parenchymal nodules	None: 0 Few: 1 Many: 2	0.258	0.093	0.006

TABLE 5. "THERAPEUTIC" VARIABLES IN THE FINAL MODEL

Variable	Scoring	Regression coefficient b	Standard error S.E. (b)	p value
Ascites	None: 0	Prednisone: 0.719	0.125	$8 \cdot 10^{-9}$
	Slight: 1	Placebo 0.105	0.131	0.42
	Moderate or marked: 2			
Antinuclear factor	Not present: 0	Prednisone: −0.124	0.160	0.44
	+: 1, ++ or +++: 2	Placebo: 0.311	0.120	0.01
Large piecemeal necrosis (>5 hepatocytes)	None or few: 0	Prednisone: −0.739	0.490	0.13
	Moderate or severe: 1	Placebo: −0.726	0.402	0.07
Parenchymal nodules	None or all Nodules < normal lobules: 0	Prednisone: 0.729	0.274	0.008
	All nodules > normal lobules	Placebo: −0.607	0.285	0.03

ously, but this also implies prognostic information. The meaning of these four variables is discussed in detail elsewhere (Christensen E. et al., unpublished observations).

Some variables indicate a poor prognosis at a lower level of significance ($0.05 < p < 0.2$) in the model including the variables given in Tables 4 and 5. These are psychic disturbances, presence of highly positive rheumatoid arthritis test, presence of esophageal varices on X-ray, alcoholism, and a long history of liver disease. Similarly, a good prognosis is indicated by high histological activity, many lymphocytes in connective tissue or parenchyma, and a high degree of pericellular fibrosis.

The PI for patients is calculated by adding all the products of each of the variable scores with the corresponding coefficient. As noted previously, the absolute value of PI can only be interpreted in connection with $\hat{\Lambda}_0(t)$. In Figure 2, the distribution of the PI for the total material is shown.

Useful transformations are given in Figures 3 and 4, where the estimated probability of 5 years survival and MST are shown as functions of PI. For values of PI less than −2.0, the median survival time can only be estimated to be more than 3,700 days.

A PI of −1 gives an estimated 5 years survival probability of approximately 50% and an MST of 2,000 days. An example, if a placebo-treated (z = 1), female (z = 0) patient, age 70 (z = 10) presents the following variables: prothrombin 75% of normal (z = 0.32), cholinesterase activity of 2.7 mmoles per min^{-1} (z = 1.60), no eosinophilic leucocytes in liver parenchyma (z = 0), no small focal liver cell necrosis (z = 0), severe inflammation in liver connective tissue (z = 3), few efferent veins (z = 1), slight ascites (z = 1), high positive antinuclear factor (z = 2), moderate number of large piecemeal necrosis (z = 1), and all parenchymal nodules larger than normal nodules (z = 1), then $PI = 1 \cdot (0.150) + 0 \cdot (0.317) + 10 \cdot (0.049) + 0.32 \cdot (-0.495) + 1.60 \cdot (-0.612) + 0 \cdot (0.299) + 0 \cdot (0.310) + 3 \cdot (-0.390) + 1 \cdot (0.258) + 1 \cdot (0.105) + 2 \cdot (0.311) + 1 \cdot (0.726) + 1 \cdot (-0.607) = -0.6$.

From Figures 3 and 4, the 5-year survival probability during placebo treatment and the MST are estimated to 40% and 1,350 days, respectively.

To validate the final model, 366 patients were randomly drawn from the total material, and the regression coefficients comprising the final model were estimated. The remaining 122 patients were divided into three groups according to the value of their PI, and the average estimated survivorship function in each group was compared with the empirical survivorship function (Figure 5). No statistical significant difference was found between the estimated and observed functions ($\chi^2 = 1.14$, df = 3, p = 0.77).

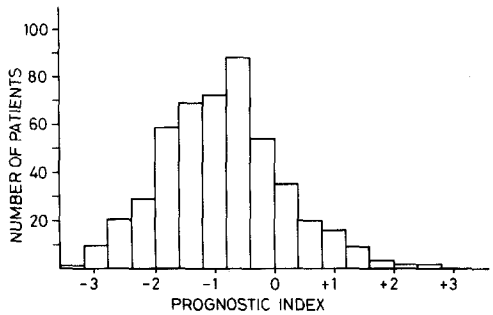

FIG. 2. Distribution of PI in 488 patients.

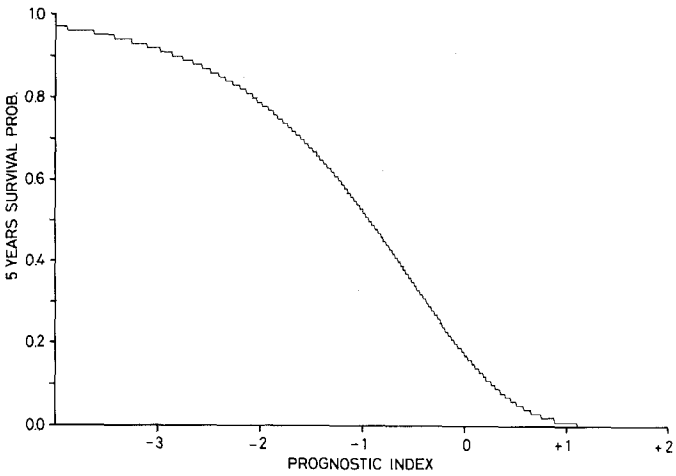

FIG. 3. Estimated probability of 5 years survival as a function of PI.

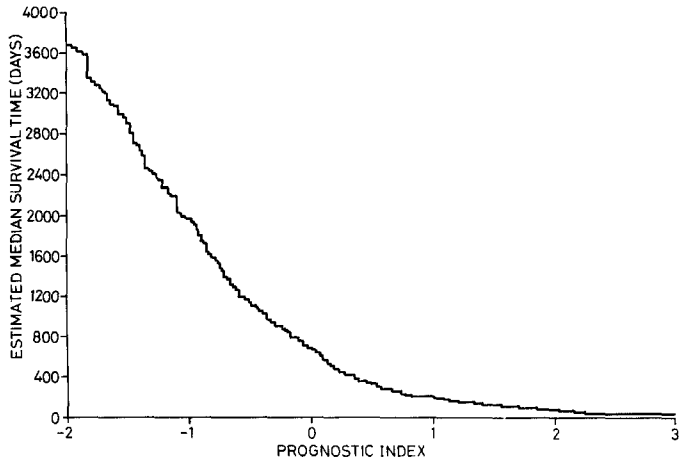

FIG. 4. Estimated MST in days as a function of PI.

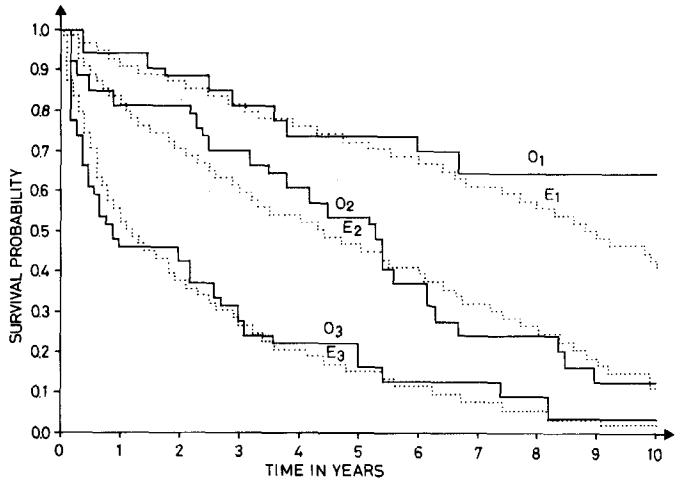

FIG. 5. Observed (——) and estimated (. . . .) survival functions for three groups of patients divided according to values of PI [Group I: PI ≤ −0.90; number of patients (N_1) = 41; observed number dying (0_1) = 10, expected number to die (E_1) = 14.0. Group II: −0.90 < PI < −0.22; N_2 = 40; O_2 = 28, E_2 = 28.0. Group III: PI ≥ −0.22; N_3 = 41; O_3 = 34, E_3 = 34.0].

DISCUSSION

Since the formulation of the proportional hazards model it has been used in analyzing various sets of clinical data (13–16). The model is very useful in controlled clinical trials for comparing the effect of treatments on the time to some event, in casu death, irrespective of cause, being able to adjust simultaneously for the influence of several concomitant variables. This property of the model makes it superior to the previously used methods where the survival in subgroups of patients were compared by, e.g., log-rank tests. The Cox model has somewhat stronger assumptions of the covariates having simultaneously a proportional effect on the hazard function, but one should notice also that the power of the log-rank test is low against differences which cannot be described by proportionality factors.

These stronger assumptions make the methods for checking the model very important, but in the existing literature such methods have been employed only rarely. In this study, however, the models' assumptions have been checked, and in several cases preliminary scorings of the covariates have been altered to obtain proportionality and linearity and hence make the results more reliable.

As described, the large number of variables could not be included in a single analysis. We therefore started with a subsample of 18 variables and after reducing this model, new variables were introduced. When doing multiple regression analysis, the final model is not unique. If the variables had been omitted or included in another sequence, the resulting model might have looked slightly different. Our procedure will catch the most significant variables, but some of the less significant ones might have been replaced by others.

Furthermore, when one final model is obtained, we base our prognosis on a combination of the variables in the model and their corresponding regression coefficients with an estimate of the cumulative underlying hazard function. Hence, it is to be expected that differences in the prognosis due to differences between variables included in two such final models, will be small.

As noted previously, we have replaced missing values of covariates by estimated values. Table 3 shows the regression coefficients corresponding to the variables in the final model estimated using solely the 288 patients with complete records. It is seen that the values are very similar to those including also estimated covariate values (Tables 4 and 5). It is more difficult to judge the correctness of the estimated variances. According to Beale and Little (8), the use of estimated covariate values will slightly underestimate the variances in a normal regression situation. This is also likely to be the case in our more complicated regression situation used in the present study, but since only 4.3% of the values of the covariates included in the final model were estimated, the effect is expected to be small.

Our results indicate sex to be a significant prognostic variable. We also identified alcohol consumption as having some prognostic information but this information was not significant in a model including sex. This association between sex and alcoholism may be caused by the fact that in the present material, 60% of the males against 10% of the females admit a large alcohol intake. However, we chose sex to be included in the final model because this variable, in addition to its higher significance, was considered to be more reliable than alcohol consumption. That age is a very strong prognostic variable is not surprising. Knowing that prothrombin and acetylcholinesterase reflect residual liver function, the regression coefficients are in accordance with general experience (17). The explanation of eosinophil leucocytes being a prognostic factor is uncertain, but might be a simple type I error. Parenchymal damage in form of small focal liver cell necroses implies a poor prognosis, whereas inflammation in liver connective tissue has the opposite effect, perhaps because it reflects the capability of the organism to react adequately to liver injury.

Presence of efferent veins is almost exclusively, but not always, seen in macronodular cirrhosis. It is therefore surprising that efferent veins and large nodules (see later) imply opposite prognostic information. This may indicate that finding of efferent veins in patients with macronodular cirrhosis identify a subgroup of patients with a poorer prognosis.

Among the therapeutic variables (Table 5), it is noteworthy that presence of ascites in the placebo-treated patients implies no significant prognostic information ($p = 0.42$). Presence of antinuclear factor is an unspecific serological indicator of self-perpetuated autoimmune processes and may therefore imply a bad prognosis. Piecemeal necrosis is, according to Popper et al. (18), the morphologic expression of a selfperpetuating destruction of liver cells reflecting progression, and our results concerning placebo-treated patients with large piecemeal necrosis is in accordance with this finding.

Macronodular cirrhosis can develop directly after, for example, acute hepatitis with extensive confluent and panlobular necroses (primary macronodular) or a micronodular cirrhosis might convert to macronodular cirrhosis if the patients live long enough (secondary macronodular) (19, 20). Therefore, at least part of the patients with a pure macronodular cirrhosis, e.g., all regeneration nodules larger than normal lobules, have survived the stage of micronodularity and have a good prognosis (regression coefficient for placebo treatment is negative). The therapeutic information of ascites, antinuclear factor, large piecemeal necrosis, and presence of parenchymal nodules are discussed elsewhere (Christensen, E. et al. unpublished observations).

Calculation of the PI can easily be translated to a pocket calculator program, making the index more easy to handle in daily clinical practice.

In addition, the prognostic power of PI was demonstrated by a simple dividing of the patients in three groups according to values of PI. No statistical significant difference was found in the groups between the observed and estimated survivorship functions.

Finally, as the variables in the final model can be interpreted in a meaningful way, we conclude that the clinical relevance of PI has been justified.

Acknowledgments: The authors are very grateful to

Niels Keiding for many constructive comments, to Richard Kay and to J. D. Kalbfleisch for making the computer programs for analyzing the regression model available to us, and to Frank Cederbye and Peter Rytgaard for making most of the calculations. We thank the Department for Data Processing at Rigshospitalet for generous computer access in the early phase of the study.

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