DISP.

INDIVIDUAL THERAPY-DEPENDENT PROGNOSIS BASED ON DATA FROM CONTROLLED CLINICAL TRIALS IN CHRONIC LIVER DISEASE

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I. Christensen E, Crowe J, Doniach D, Popper H, Ranek L, Rodés J, Tygstrup N, Williams R. Clinical pattern and course of disease in primary biliary cirrhosis based on an analysis of 236 patients. Gastroenterology 1980; 78: 236-46.

II. Schlichting P, Christensen E, Andersen PK, Fauerholdt L, Juhl E, Poulsen H, Tygstrup N, CSL. Prognostic factors in cirrhosis identified by Cox's regression model. Hepatology 1983; 3: 889-95.

III. Christensen E, Schlichting P, Fauerholdt L, Gluud C, Andersen PK, Juhl E, Poulsen H, Tygstrup N, CSL. Prognostic value of Child-Turcotte criteria in medically treated cirrhosis. Hepatology 1984; 4: 430-5.

IV. Christensen E, Schlichting P, Andersen PK, Fauerholdt L, Juhl E, Poulsen H, Tygstrup N, CSL. A therapeutic index that predicts the indidual effects of prednisone in patients with cirrhosis. Gastroenterology 1985; 88: 156-65.

V. Christensen E, Neuberger J, Crowe J, Altman DG, Popper H, Portmann B, Doniach D, Ranek L, Tygstrup N, Williams R. Beneficial effect of azathioprine and prediction of prognosis in primary biliary cirrhosis: Final results of an international trial. Gastroenterology 1985; 89: 1084-91.

VI. Christensen E, Schlichting P, Fauerholdt L, Juhl E, Poulsen H, Tygstrup N, CSL. Changes of laboratory variables with time in cirrhosis. Prognostic and therapeutic significance. Hepatology 1985; 5: 843-53.

VII. Christensen E, Schlichting P, Andersen PK, Fauerholdt L, Schou G, Pedersen BV, Juhl E, Poulsen H, Tygstrup N, CSL. Updating prognosis and therapeutic effect evaluation in cirrhosis using Cox's multiple regression model for time dependent variables. Scand J Gastroenterol 1986; 21: 163-74.

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CONTENTS

INTRODUCTION

A fundamental characteristic of mammals including homo sapiens is the diversity between individuals adding strength to the species. Thus humans differ in their disposition or susceptibility to contract a given disease. In patients suffering from a given disease, defined according to the state of the art, the manifestations differ showing a "spectrum" of variation between the patients (*Wulff HR,* 1976). Similarly the effect of a given therapy differs between patients with the disease. Hence the concept of responders and non-responders (*Blum AL,* 1982).

This variation makes description difficult and simplifications have been found necessary. Thus the charcteristics of a group of patients with a disease are generally summarized statistically by the average and the variance of each characteristic, disregarding the pattern of covariation with the other characteristics. This also applies to the effect of therapy even if evaluated in controlled clinical trials because generally the results only give the average effect of the tested therapies in the included patients.

This tradition of univariate summarization of observations by their average and a measure of variation (e.g. the variance) has made utilization of the results in the management of new patients difficult. Medical practice deals with the treatment of individual patients, not groups of patients. However, the doctor has generally few or no rational means of exerting an individual approach in the management of a patient because he has to extrapolate average findings from groups of patients to the individual. But in the same way as individual age if unknown cannot be predicted from the average age in a group, the effect of therapy or therapy-dependent prognosis in a patient cannot be predicted from the average therapeutic effect in a group of patients included in a controlled clinical trial. The individual therapeutic effect may, like the age, differ markedly from the average, being greater in some and less in others (*Byar DP et al,* 1976). In some patients the therapeutic effect may be harmful even if the average effect is beneficial.

However, in the same way as individual age (if unknown) to some extent may be predicted from the information given by certain features or indicators covarying with age (elasticity of the skin, amount and color of the hair etc.), the therapy-dependent prognosis for a given patient may to some extent be predicted from the information given by the patient's "therapeutic" and "prognostic" indicators (which covary with therapeutic effect and prognosis, respectively) (*Byar DP* and *Corle DK,* 1977).

Controlled clinical trials allow prospective, regular and uniform collection of patient data. For this reason controlled clinical trials in addition to their treatment comparative function also provide ideal settings for study of the course of disease in the included patients (*Starmer CF et al,* 1980; *Byar DP,* 1980). Minimally restrictive selection criteria will imply maximum validity of the results for the total population of patients with the disease.

The purpose of this work is to investigate how to utilize the pattern of covariation of data from controlled clinical trials to describe the course of disease and the therapy-dependent prognosis in specified subgroups and individual patients, because this may lead to a differentiated administration of therapies according to the characteristics and needs of the individual patient.

This report will present recent methods for identification of prognostic and therapeutic variables and the results obtained by these methods in patients with chronic liver disease. Because of the descriptive nature of such analyses the important issue of validation of results will also be dealt with.

Even if most of the referenced investigations of the author and coworkers and of others have been performed using data from patients with chronic liver disease, the general principles will be valid for similar analyses dealing with other diseases.

PREDICTING COURSE OF CHRONIC LIVER DISEASE

Ideally good medical practice would imply that doctors could estimate the prospect of any patient with various treatment alternatives in order to be able to select the best treatment at any time. Since a disease like anything else evolves in time, the time to occurrence of a defined event (disappearance of a symptom, occurrence of a complication etc.) is of particular interest. In many chronic diseases one of the most important variables is duration of survival or time to death. For groups of patients results may be summarized as the cumulative survival probability as a function of time (*Kaplan E* and *Meier P,* 1958). The cumulative survival curve represents the joint survival probability of the studied patients. As recognized by any doctor, survival of individual patients shows wide variation. However, from a cumulative survival curve no information can be obtained about the survival probability of individual patients. That is only possible if covariations between the survival time and other variables can be found and utilized.

It is therefore of interest to identify variables which covary with prognosis and therapeutic effect (*Armitage P* and *Gehan EA,* 1974; *Byar DP* and *Corle DK,* 1977; *Lachin JM,* 1982). For descriptive purposes variables being associated with prognosis may be divided into those not interacting with therapy ("purely" *prognostic* variables), the prognostic value not being associated with the therapy given, and those interacting with therapy (*therapeutic* variables), the prognostic value being associated with the therapy given (*Christensen E et al,* 1985 (IV); *Schlichting P, Christensen E et al,* 1983 (II)).

For example the age will often influence the prognosis markedly and special characteristics of the disease may imply a therapeutic effect greater or less than the average.

PREDICTION OF SURVIVAL FROM BASE-LINE DATA

THERAPY-DEPENDENT PROGNOSIS FOR SUBGROUPS

By subdividing the patients according to different values of one or few variables (stratification), subgroups may be found to have different survival (*Peto R et al,* 1977). If this is so, the variable defining the subgroups covary with survival. If the differences in survival between the subgroups are the same in each treatment group (independent of the treatment) the covarying variable is considered "prognostic". If, however, in corresponding subgroups the survival differ between the treatment groups (covary with the treatment), the variable defining the subgroups is considered "therapeutic".

Prognostic variables

In a large group of patients with Laennec's cirrhosis *Ratnoff* and *Patek* found a very short survival after the occurrence of jaundice, ascites and hematemesis, but the survival was not compared with those not having these features (*Ratnoff OD* and *Patek AJ Jr,* 1942). The prognostic influence of these variables was also described by *Powell* and *Klatskin,* who in addition found continued alcohol consumption to be associated with a poor prognosis (*Powell WJ Jr* and *Klatskin G,* 1968). This has later been confirmed by others (*Tygstrup N et al,* 1971; *Alexander JF et al,* 1971; *Brunt PW et al,* 1974; *Borowsky SA et al,* 1981) as reviewed recently (*Schenker S,* 1984).

In 1964 *Child* and *Turcotte* proposed their criteria for assessment of hepatocellular functional reserve in patients considered for portosystemic shunting (*Child CG* and *Turcotte JG,* 1964). The Child-Turcotte criteria (CTC) comprising serum bilirubin, serum albumin, ascites, neurological disorder and nutrition have been established as prognostic variables in patients with cirrhosis having portacaval shunt surgery (*Conn HO,* 1981), but their value in medically treated cirrhosis had not been studied.

Using data from the control group of the first controlled

clinical trial performed by the Copenhagen Study Group for Liver Diseases (the CSL-1 trial) *(Copenhagen Study Group for Liver Diseases,* 1974) we have been able to confirm the prognostic value of CTC in medically treated cirrhosis (*Christensen E et al,* 1984 (III)). Using stratification we found that survival decreased significantly with increasing degree of abnormality of albumin, ascites, bilirubin and nutrition. Survival only tended to be associated with neurological status ($p = 0.11$) probably because no patient had hepatic coma at the entry into the trial.

In the CSL-1 trial each of a number of other variables were found to have an association with prognosis when analyzed using stratification (*Schlichting P, Christensen E et al,* (1983 (II) and unpublished observations). Of these the most important variables being associated with a poor prognosis were: high age, low hemoglobin, low acetylcholinesterase activity, low prothrombin index (long prothrombin time), high gamma globulin, high sulfobromophthalein retention, many spider naevi, hepatomegaly, peripheral edema, incapacitation.

Thus a number of single prognostic variables have been identified using univariate analyses. The prognostic information obtained by using combinations of variables may be greater, but the amount of extra information provided cannot be predicted from univariate analyses alone, because the correlations between the variables play an inportant role.

Many have attempted to combine the 5 variables in the Child-Turcotte criteria (*Conn HO,* 1981). Thus it has been suggested to score each of the 5 variables as 1, 2 and 3 for grade A, B and C, respectively, and to add the numbers to a total score between 5 and 15 (*Conn HO,* 1981). Even though this simple score may be of some value (*Christensen E et al,* 1984 (III)) it is not optimal because it assumes equal weighing of the 5 variables, which is probably incorrect, and because important prognostic variables such as age and prothrombin index are not included.

Orrego et al, has proposed a combined clinical and laboratory index (CCLI) for global assessment of the severity of alcoholic liver disease (*Orrego H et al,* 1983). The index was based on 12 variables which in univariate analyses showed significant association with survival. The correlations between the variables were not taken into account. Thus many of the variables were probably redundant. This was indicated by multivariate analyses which identified only 4 independent prognostic variables in the same set of data (*Orrego H et al,* 1983).

In primary biliary cirrhosis (PBC) *Shapiro* found serum bilirubin to be an important prognostic variable (*Shapiro JM et al,* 1979). We have confirmed this by stratified analysis of the data from an international controlled clinical trial of azathioprine versus placebo in PBC (the PBC-1 trial (*Crowe J et al,* 1980)), where we found that high bilirubin level at the entry into the trial was associated with a poor prognosis *(Christensen E et al,* 1980 (I)). In addition we found that high age and histologic stage 4 (cirrhosis) to be associated with a poor prognosis (*Christensen E et al,* 1980 (I)). Except for minor differences these results agree rather well with later published results (*Roll J et al,* 1983).

Therapeutic variables

In alcoholic hepatitis stratified analyses of controlled clinical trials seem to indicate that corticosteroid hormones may have a beneficial effect in patients with hepatic encephalopathy (*Conn HO,* 1978; *Maddrey WC et al,* 1978; *Juhl E* and *Christensen E,* 1985).

In unselected patients with cirrhosis prednisone has not been found to have a significant effect on survival (*Wells R,* 1960; *Copenhagen Study Group for Liver Diseases,* 1974). However, by stratification of the patients in the CSL-1 trial it was found that non-alcoholic women without ascites had a significantly beneficial effect of prednisone (*Copenhagen Study Group for Liver Diseases,* 1974). The beneficial effect of prednisone on survival in this subgroup may be related to the significant effect of the treatment in reducing the risk of development of esophageal varices, of bleeding from esophageal varices and of dying from such bleeding as demonstrated by stratified analyses of the data (*Christensen E et al,* 1981).

A histologic reevaluation of the admission biopsies (*Schlichting P et al,* 1981) identified 98 patients fulfilling the histologic criteria of chronic aggressive hepatitis (*Schlichting et al,* 1982a) in whom prednisone has a significantly beneficial effect (*Schlichting P et al,* 1982a; *Wright EC et al,* 1977). Nevertheless, among the non-alcoholic women without ascites several patients not fulfilling the histologic criteria of chronic aggressive hepatitis seemed to have a beneficial effect of prednisone treatment (*Schlichting P, Christensen E et al,* 1982b).

In the CSL-1 trial it was also found that patients with ascites seemed to have a harmful effect of prednisone treatment (*Copenhagen Study Group for Liver Diseases,* 1974). This may be related to the finding that in patients with ascites, prednisone significantly increases the risk of developing esophageal varices (*Christensen E et al,* 1981). Other important variables shown by stratified analyses to be associated with a beneficial effect of prednisone are: no large regenerative nodules, many small focal liver cell necroses, piecemeal necroses, moderate or marked pericellular fibrosis, chronic aggressive hepatitis, antinuclear antibody, arthralgia (*Schlichting P, Christensen E et al,* 1983 (II) and unpublished observations).

In primary biliary cirrhosis stratified analyses have not revealed any variable having a significant interaction with azathioprine treatment (*Christensen E et al,* 1985 (V)). Preliminary results seemed to show that d-penicillamine was effective in patients in histologic stage 3 and 4 (*Epstein O et al,* 1981), but this has not been confirmed by later results (*Matloff DS et al,* 1982; *Neuberger J, Christensen E, et al,* 1985; *Dickson RE et al,* 1985).

THERAPY-DEPENDENT PROGNOSIS FOR INDIVIDUAL PATIENTS

The method of stratification has limitations. It allows only few variables to be analyzed simultaneously because the number of patients in each subgroup and hence the power of appropriate statistical tests (e.g. the logrank test) rapidly decreases with increasing number of subgroups (*Byar DP* and *Green SB,* 1980; *Lachin JM,* 1982; *Simon R,* 1984). Therefore the possibilities of combining information from more prognostic and therapeutic variables are limited. The results obtained by stratification are not optimal and may be difficult to utilize in certain situations. For example on the basis of the previous results it may be difficult to decide if a patient with histologic chronic aggressive hepatitis (which considered as a group has a beneficial effect of prednisone) and ascites (indicating a harmful effect of prednisone) should be treated with prednisone or not.

Multivariate statistical methods

Using multivariate statistical methods one can analyze the pattern of covariation of many variables with the "end-point" variable of interest e.g. survival (*Armitage P* and *Gehan EA,* 1974; *Lachin JM,* 1982; *Simon R,* 1984). The simplest multivariate models have this linear form:

$$Y = z_1 b_1 + \ldots + z_p b_p .$$

Y is the dependent "end-point" variable which "depends on" or is "explained" or "predicted" by the independent (predictor-) variables z_1 to z_p each of which is multiplied by a corresponding regression coefficient b_1 to b_p. The amount by which each predictor variable z_i contributes to the prediction of Y depends on the magnitude of the corresponding term $z_i b_i$; if the term is big (numerically), the contribution is big; if the term is small (numerically) i.e. rather close to zero, the contribution

is small. Higher values (scores) of a given variable z_i indicate higher value of Y if the corresponding regression coefficient b_i is positive and vice versa if b_i is negative. If $b_i = 0$ then z_i has no influence on Y.

(Since the variable Y is the "end-point" or outcome variable which expresses "prognosis" we have often in our studies used the term PI for prognostic index instead of Y.)

Y varies with the specific type of multiple regression analysis. If a simple quantitative variable (e.g. the loss of weight in kg after 4 weeks treatment of ascites with diuretics) is the "end-point" variable to be predicted it may be used directly as Y (standing for E(Y), the expectation of Y) in simple multiple regression analysis (*Draper NR* and *Smith H,* 1981).

If the "end-point" variable of interest is a binary, e.g. the proportion P of patients who have died within a specified time interval irrespective of the exact time of death, then multiple logistic regression analysis (*Cox DR,* 1970; *Lachin JM,* 1982; *Simon R,* 1984) may be used. In that case $Y = \log_e (P/(1-P))$.

If, however, the "end-point" variable is survival as the exact time to death or censoring (time of last information), then the Cox multiple regression model for censored survival data may be used (*Cox DR,* 1972). Here $Y = \log_e (\lambda(t)/\lambda_0(t))$ or the logarithm of the ratio of the hazard for a given patient at time t ($\lambda(t)$) to the so-called underlying hazard at that time ($\lambda_0(t)$) (*Cox DR,* 1972). In the Cox model the special assumption of proportional hazards, i.e. that Y does not depend on t, (*Cox DR,* 1972; *Elashoff JD,* 1983) should be carefully checked as described previously (*Schlichting P, Christensen E et al,* 1983 (II)).

In multivariate statistical analyses any included patient must be represented by a complete set of variables. In order not to reduce the number of patients and variables to be analyzed, missing data may be replaced by neutral estimates (*Beale EML et al,* 1975).

Strategy for identification of therapeutic and prognostic variables

The goal is to design a model in which the end-point variable of any given patient can be described satisfactorily as a function of the therapy given and the variables (covariates) characterizing the patient. This implies that the model should be based on all patients and allow for the treatment given, the covariates and the treatment-covariate interactions (*Byar DP* and *Corle DK,* 1977; *Byar DP* and *Green SB,* 1980). To achieve this goal the following strategy (illustrated for two treatment groups A and B) can be used (*Schlichting P, Christensen E et al,* 1983 (II); *Christensen E et al,* 1985 (IV); *Christensen E et al,* 1985 (V)); *Byar DP* and *Corle DK,* 1977; *Byar DP* and *Green SB,* 1980):

1. Separate multivariate analysis of each treatment group to see if the difference in Y-values between treatment groups can be considered to be constant. This will present no problem in logistic regression analysis or simple multiple regression analysis except for testing for variance-homogeneity in the latter case. However in the Cox regression model a constant difference in Y-values between the treatments implies that the underlying hazards $\lambda_0(t)$ for the treatments are proportional. Since the underlying hazards may change with time, the proportionality must be checked either by observing a constant vertical difference between plots of the logarithm of the estimated cumulative hazard function against time t for each of the treatments (*Kalbfleisch JD* and *Prentice RL,* 1980; *Schlichting P, Christensen E et al,* 1983 (II)), by the goodness of fit test by *Andersen (Andersen PK,* 1982; *Schlichting P, Christensen E et al,* 1983 (II)) or by other corresponding tests.

2. Inclusion in the statistical model of an overall treatment term ($z_{tr}b_{tr}$, where b_{tr} is an overall treatment effect coefficient and z_{tr} is an indicator of the treatment (e.g. 0 for treatment A and 1 for treatment B) to allow analysis of both treatment groups in the same model. In the Cox regression model this implies the assumption of a common underlying hazard ($\lambda_0 t$)) for the treatment groups (*Schlichting P, Christensen E et al,* 1983 (II)).

3. Estimation of separate regression coefficients b_i^T for each treatment (T stands for either treatment A or treatment B etc.) to allow for possible treatment-covariate interaction.

4. Testing for each included variable if the difference $b_i^{tr.A} - b_i^{tr.B}$ is significant by comparing the difference with its standard error. If the difference is significant, the treatment-covariate interaction is significant and the variable is considered "therapeutic" and retained in the model with one coefficient for each treatment. If the difference is insignificant, one coefficient b_i common for the two treatments should be estimated to replace $b_i^{tr.A}$ and $b_i^{tr.B}$.

5. Testing significance of each coefficient b_i using the likelihood ratio test (*Rao CR,* 1973). If significant the variable is considered "prognostic" and retained in the model, if not, it is excluded.

Therapy-dependent prognostic index

Following the above procedure the model is finally reduced to one with r prognostic coefficients common for the two treatments and with k pairs of therapeutic coefficients significantly different for treatment A and treatment B:

$$Y_T = PI_T = b_{tr}z_{tr} + b_1^T z_1 + \ldots + b_k^T z_k + b_{k+1}z_{k+1} + \ldots + b_{k+r}z_{k+r}.$$

From the model values of Y_T ($= PI_T$ for prognostic index) may be estimated for each of the therapeutic alternatives T in any patient with the variables $z = (z_1 \ldots z_{k+r})$.

Thus outcome or prognosis is considered to be dependent on or "explained" by the prognostic and therapeutic variables and the therapy given.

In simple multiple regression analysis the PI_T-value may be used directly as an estimate of the outcome to be expected.

In multiple logistic regression analysis the estimated PI_T-value may be transformed to an estimate of P or the probability of having the outcome being studied using the relation $P = \exp(PI_T)/(1 + \exp(PI_T))$.

In the Cox regression model PI_T for a patient with the variables $z = (z_1 \ldots z_{k+r})$ may be combined with the cumulative underlying hazard function $\hat{\Lambda}_0(t)$ estimated as a step function (*Breslow NE,* 1972), to the estimated survivorship function $\hat{S}(t,z) = \exp((-\exp(P\bar{I}_T))\,\hat{\Lambda}_0(t))$ (*Schlichting P, Christensen E et al,* 1983 (II); *Christensen E et al,* 1985 (V)).

The interpretation of PI_T for the Cox model may be facilitated by construction of a graph showing the estimated probability of surviving a given time, e.g. 5 years as a function of PI_T (*Andersen PK, Christensen E et al,* 1983; *Schlichting P, Christensen E et al,* 1983 (II); *Christensen E et al,* 1985 (V)). The median survival time (MST) is another measure of prognosis which can be estimated for a patient with a given PI_T as the span of time that the patient will survive with 50% probability. This relation can be presented as a plot showing MST as a function of PI_T. (*Andersen PK, Christensen E et al,* 1983; *Schlichting P, Christensen E et al,* 1983 (II); *Christensen E et al,* 1985 (V)).

Therapeutic index

The effect of treatment A compared to that of treatment B can be estimated as $PI_{tr.A} - PI_{tr.B}$ (*Christensen E et al,* 1985 (IV)). Because the prognostic terms for variables k + 1 to k + r are identical in $PI_{tr.A}$ and $PI_{tr.B}$, they vanish and the difference reduces to

the following simple therapeutic index (TI), which is based on therapeutic variables only (variables 1 to k):

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

where $d_i = b_i^{tr.A} - b_i^{tr.B}$ (*Christensen E et al,* 1985 (IV)).

The standard error of the therapeutic index (SE(TI)) can be estimated from the covariance matrix for therapeutic variables and the statistical significance of TI can be evaluated by comparing TI/SE(TI) or the normalized therapeutic index (NTI) with the standardized normal distribution. NTI >1.96 or <-1.96 may be considered significant (*Christensen E et al,* 1985 (IV)). Another somewhat more complex approach has been described (*Shuster J et al,* 1983).

To estimate the treatment effect on survival time using the Cox regression model it is necessary to calculate $PI_{tr.A}$ and $PI_{tr.B}$. Each of these can be transformed to the estimated median survival time (MST_T) and then the effect of therapy can be expressed as the median survival difference ($MSD = MST_{tr.A} - MST_{tr.B}$). This is an estimate of the gain (positive or negative) in terms of (added or subtracted) survival time to be expected from treatment A compared with treatment B (*Christensen E et al,* 1985 (IV)).

Individual therapy-dependent prognosis

We have performed Cox multiple regression analyses using the principles described above (*Andersen PK, Christensen E et al,* 1983; *Schlichting P, Christensen E et al,* 1983 (II); *Christensen E et al,* 1985 (IV)).

For the analysis of the CSL-1 trial (*Schlichting P, Christensen E et al,* 1983 (II); *Christensen E et al,* 1985 (IV)) the results obtained are summarized in Tables 1 and 1A. As seen from Table 1 a number of "purely" prognostic variables were found, i.e. female sex, younger age, high prothrombin index, high acetylcholinesterase activity, marked inflammation in liver connective tissue, no efferent veins in regenerative nodules, no small focal liver cell necroses, and no eosinophil leucocytes in liver parenchyma were associated with a good prognosis (*Schlichting P, Christensen E et al,* 1983 (II)).

The effect of therapy (prednisone) was insignificant in the total group of studied patients but 4 variables showed significant interaction with therapy. Thus absence of ascites, presence of antinuclear factor, many large piece-meal necroses and parenchymal nodules undefined or $<$normal lobules were associated with a beneficial effect of prednisone therapy (*Christensen E et al,* 1985 (IV)).

Using the information in Table 1A the therapy-dependent prognostic index for a given patient may be obtained simply by summing the appropriate numbers corresponding to the level of each of the patient's variables (one number for each variable).

PI_T-values can be transformed to more familiar measures of the prognosis i.e. the estimated 5 years survival probability (Figure 1) and the estimated median survival time (Figure 2) (*Schlichting P, Christensen E et al,* 1983 (II); *Christensen E et al,* 1985 (IV)).

The normalized therapeutic index (NTI) was estimated as described above with treatment A = placebo and treatment B = prednisone. From Table 2 NTI can be read directly against the particular combination of the therapeutic variables in a given patient with cirrhosis. Our studies showed NTI to be distributed in 3 rather well separated groups (*Christensen E et al,* 1985 (IV)). Among the 488 patients studied a significantly positive TI (NTI >1.96) was found in 121, 96 had a significantly negative TI (NTI <-1.96) and the remaining patients had insignificant intermediary values. Actual survival curves showed a markedly beneficial effect of prednisone in patients with NTI >1.96 and a markedly harmful effect of the treatment in patients with NTI <-1.96 (*Christensen E, et al,* 1985 (IV)).

For the most favorable combination of therapeutic variables and median prognostic variables the estimated median gain of prednisone treatment was more than 9.1 years of added survival time. For the most unfavorable combination of therapeutic

Table 1. *Significant prognostic or therapeutic variables and their regression coefficients in time-fixed Cox regression model for cirrhosis.*

Variable	Scoring	Treatment group(s)	Regression coeff. (b)	Standard error (SE(b))	p-value
Treatment	prednisone: 0; placebo: 1	both	0.15	0.17	0.39
Antinuclear factor	−: 0; +: 1; + + or + + +: 2	plac pred	0.31 −0.12	0.12 0.16	0.01 0.44
Large piecemeal necroses (>5 hepatocytes)	none or few: 0 moderate or many: 1	plac pred	0.73 −0.74	0.40 0.49	0.07 0.13
Ascites	none: 0; slight: 1; moderate or marked: 2	plac pred	0.11 0.72	0.13 0.12	0.42 <0.0001
Size of largest regenerative nodule in liver biopsy	≤normal lobule or undefined: 0; >normal lobule: 1	plac pred	−0.61 0.73	0.29 0.27	0.03 0.008
Sex	female: 0; male: 1	both	0.32	0.14	0.03
Age (years)	age −60	both	0.049	0.007	<0.0001
Prothrombin index (% of normal)	$\log_e$(value) −4	both	−0.50	0.21	0.02
Acetylcholine esterase (μmoles/min × ml)	$\log_e$(value × 100) − 4	both	−0.61	0.14	<0.0001
Inflammation in liver connective tissue	none: 0; slight: 1; moderate: 2; marked: 3	both	−0.39	0.096	<0.0001
Efferent veins in liver regenerative nodules	none: 0; few: 1; moderate: 2	both	0.26	0.093	0.006
Few diffuse focal small liver cell necroses	present: 1; otherwise: 0	both	0.31	0.12	0.01
Eosinophil leucocytes in liver parenchyma	none: 0; few: 1; moderate: 2; many: 3	both	0.30	0.14	0.04

Plac: placebo. Pred: prednisone.
From: *Schlichting P, Christensen E et al,* 1983 (II) and *Christensen E, et al.,* 1985 (IV).

Table 1A. *Pocket chart for calculation of therapy-dependent prognostic index PI_T in cirrhosis.*

Variable	Points add (A) pred.	Points add (A) plac.	Points subtract (S) pred.	Points subtract (S) plac.
	both		both	
Treatment (placebo)		1.5		
Antinuclear factor,				
+		3	1	
+ + or + + +		6	2	
Large piecemeal necroses (>5 hepatocytes), moderate or many:		7	7	
Ascites,				
slight	7	1		
moderate or marked:	14	2		
Size of largest regenerative nodule in liver biopsy,				
>normal lobule:	7			6
Male sex		3		
Age (years)				
20			20	
30			15	
40			10	
50			5	
60		0	0	
70		5		
80		10		
Prothrombin index (% of normal)				
10		8		
20		5		
35		2		
55		0	0	
80			2	
100			3	
150			5	
Acetylcholine esterase (µmoles/min × ml)				
1.0			4	
1.5			6	
2.0			8	
2.8			10	
3.9			12	
5.4			14	
7.4			16	
Inflammation in liver connective tissue,				
slight			4	
moderate			8	
marked			12	
Efferent veins in liver regenerative nodules,				
few		3		
many		5		
Few diffuse focal small liver cell necroses		3		
Eosinophil leucocytes in liver parenchyma,				
few		3		
moderate		6		
many		9		
Sum of points to be added (A) =				
Sum of points to be subtracted (S) =			←	
A − S =				
PI_T = (A − S)/10 =				

Note: For each variable only one number (if applicable) should be used in the addition. If a patient has values between those in the table, interpolation should be used.

Plac.: for placebo treated patients.
Pred.: for prednisone treated patients.
Both: for both placebo and prednisone treated patients.
Based on: *Schlichting P, Christensen E et al,* 1983 (II) and *Christensen E et al,* 1985 (IV).

variables the estimated median loss in survival time by using prednisone was about 6.8 years (*Christensen E et al, 1985* (IV)).

The gain in survival time obtained by administering prednisone according to TI compared with "random" treatment allocation was found to be 349 years during 10 years of follow-up, the gain mainly being confined to those having a significantly positive or negative therapeutic index (*Christensen E et al,* 1985 (IV)).

Our results confirmed that patients with autoimmune liver disease (ANF, large piecemeal necroses) in early stages (no ascites, no large regenerative nodules) are the most obvious candidates for steroid treatment (*Czaja AJ et al,* 1984). Hepatitis B surface antigen was not available at the time of the study, but probably less than half of those fulfilling the histologic criteria of chronic aggressive hepatitis had the HB_sAg-positive type of the disease (*Dietrichson O et al,* 1973). It is interesting to note that of the 98 patients with histologic chronic aggressive hepatitis, 57 had a significantly positive TI (virtually all of whom had positive ANF), 8 had a significantly negative TI and 33 had an insignificant TI. It is conceivable that the HB_sAg-positive patients, in whom prednisone may have no or harmful effects (*European CAPO-group,* 1984; *EASL trial group,* 1985), would be in the latter two groups. Therefore, if HB_sAg had been available, it would probably not have improved the therapeutic classification significantly.

In patients with primary biliary cirrhosis included in the PBC-1 trial a similar Cox regression analysis revealed that 6 variables including the treatment (azathioprine or placebo) had a significant independent prognostic influence (*Christensen E et al,* 1985 (V)). The results are summarized in Table 3 and 3A.

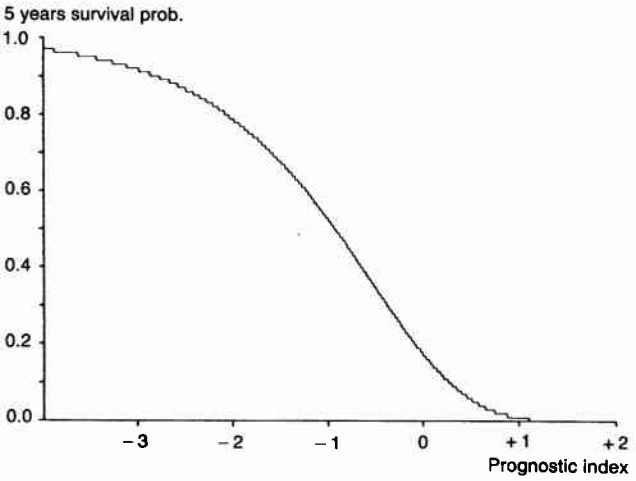

Fig. 1. *Estimated probability of surviving 5 years by prognostic index PI_T in cirrhosis (From:* Schlichting P, Christensen E et al, *1983 (II)).*

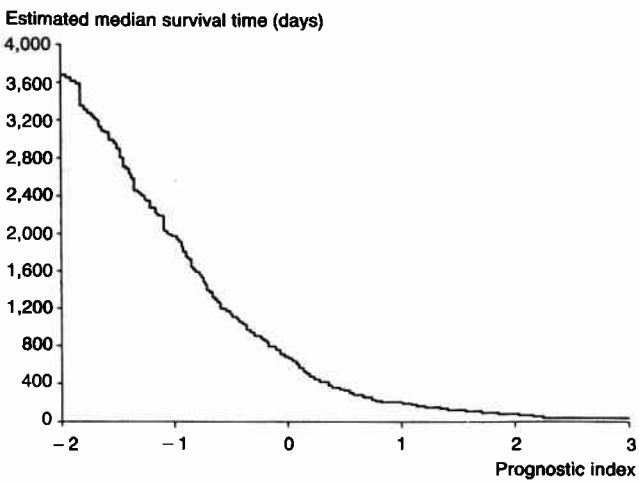

Fig. 2. *Estimated median survival time by prognostic index PI_T in cirrhosis (From:* Schlichting P, Christensen E et al, *1983 (II)).*

Table 2.
Normalized therapeutic index (NTI) for treatment with prednisone in cirrhosis for all combinations of significant therapeutic variables.

Size of largest regenerative nodule in liver biopsy	Ascites	Piecemeal necroses > five hepatocytes: none or few; Antinuclear factor (ANF): −	+	++ or +++	Piecemeal necroses > five hepatocytes: moderate or many; Antinuclear factor (ANF): −	+	++ or +++
≤ normal lobule or undefined	none	0.87	3.22 ++	3.18 +	2.42 +	3.31 ++	3.98 +++
	slight	−2.37 −	−0.15	1.23	1.55	2.41 +	3.11 ++
	moderate or marked	−3.29 −−	−1.97 −	−0.49	0.57	1.32	2.00 +
> normal lobules	none	−3.04 −	−1.87	−0.64	0.38	1.02	1.62
	slight	−4.60 −−−	−3.41 −−	−1.90	−0.47	0.15	0.78
	moderate or marked	−5.22 −−−	−4.21 −−−	−2.82 −	−1.30	−0.74	−0.11

+: significantly beneficial effect of prednisone ($0.01 < p < 0.05$).
++: very significantly beneficial effect of prednisone ($0.001 < p < 0.01$).
+++: highly significantly beneficial effect of prednisone ($p < 0.001$).
−: significantly harmful effect of prednisone ($0.01 < p < 0.05$).
−−: very significantly harmful effect of prednisone ($0.001 < p < 0.01$).
−−−: highly significantly harmful effect of prednisone ($p < 0.001$).
From: *Christensen E et al,* 1985 (IV).

From the latter table the prognostic index PI_T for a patient with primary biliary cirrhosis can be obtained directly in the same way as in Table 1A. As seen from Table 3 low serum bilirubin, younger age, absence of cirrhosis, high serum albumin, absence of central cholestasis and azathioprine therapy were associated with better prognosis. These results extend those reported by *Roll J et al,* (1983).

No variable was found to interact with the treatment, i.e. no therapeutic variable was identified (*Christensen E et al,* 1985 (V)). It should be noted that the beneficial effect of azathioprine was significant only in the multivariate Cox regression model in which the influence of slight imbalance in prognostic variables (in particular bilirubin being slightly higher in the azathioprine than in the placebo group) was taken into account. This emphasizes the value of multivariate in contrast to univariate analysis in this situation (*Armitage P* and *Gehan EA,* 1974; *Brown BW,* 1980; *Altman DG,* 1985; *Christensen E, et al,* 1985 (V); *Christensen E et al,* 1986).

Using Figures 3 and 4, respectively, the probability of surviving 2, 5 and 8 years and the estimated median survival time can be obtained from the prognostic index PI_T. We found a remarkable variation in prognosis, the estimated median survival time varying between more than 8.3 years (corresponding to PI <2.3) and 1.5 months (corresponding to PI of 7.5) (*Christensen E et al,* 1985 (V)).

Since no variable interacted with therapy the relative benefit of azathioprine treatment appears to be the same for any patient. However, in our data the difference in median estimated survival times and hence the gain obtained by active treatment in terms of added survival time is greater in absolute numbers for patients with a relatively good prognosis than for patients with a poorer prognosis (*Christensen E et al,* 1985 (V); *Christensen E et al,* 1986). So far no significant therapeutic variable has been identified in PBC (*Christensen E et al,* 1985 (V); *Neuberger J, Christensen E et al,* 1985; *Dickson RE et al,* 1985; *Matloff DS et al,* 1982; *Roll J,* 1985).

Table 3. *Significant prognostic variables and their regression coefficients in time-fixed Cox regression model for primary biliary cirrhosis.*

Variable	Scoring	Regression coefficient (b)	Standard error (SE(b))	p-value
Serum bilirubin	$\log_{10}$(value in μmoles/l)	2.51	0.32	<0.0001
Age	exp((age in years − 20)/10)	0.0069	0.0016	<0.0001
Cirrhosis	absent: 0 present: 1	0.88	0.22	<0.0001
Serum albumin	value in g/l	−0.050	0.018	0.006
Central cholestasis	absent: 0 present: 1	0.68	0.27	0.01
Therapy	azathioprine: 0 placebo: 1	0.52	0.21	0.01

From: *Christensen E et al,* 1985 (V).

COURSE OF DISEASE

The previous results on prediction of prognosis and therapeutic effect are based on the covariation between the end-point variable and other data at one time during the course e.g. at entry into a controlled clinical trial or at the time of diagnosis. However, the course may not be completely predictable from only one set of observations. Even in patients with similar degree of severity of the disease the course may take different directions; some may improve and others may deteriorate. Therefore, the course of disease may in itself contain additional information on the subsequent prognosis of the patient.

For many diseases serial measurement of single variables is being used routinely to monitor the course of disease, to adjust therapy, or both e.g. blood pressure levels in hypertension, blood glucose levels in diabetes mellitus, serum cholesterol in cardiovascular disease, serum creatinine in renal disease and bilirubin, albumin, aspartate aminotransferase and immunoglobulins in chronic liver disease. The variables are considered as indicators of the degree of disturbed normal function, the degree of decreased functional capacity or the intensity ("activity") of the disease process.

METHODS FOR STUDYING THE COURSE OF DISEASE

Studying the course of chronic disease is a complex task (*Starmer CF et al,* 1980). A major difficulty is the decreasing number of patients observed with increasing time of obser-

vation. In controlled clinical trials this may be ascribed to 1) deaths, 2) withdrawals, 3) drop-outs, or 4) late entry (in relation to the time of completion of the trial). In the latter 3 instances the information on the course is incomplete or censored.

Cross-sectional (transectional) analysis

With this method, which has been used frequently in the literature, one analyzes the values at different times after entry into the study in the patients being observed at that time (*Cook GC et al,* 1971; *Soloway RD et al,* 1972; *Murray-Lyon IM et al,* 1972; *Kirk AP et al,* 1980; *Matloff DS et al,* 1982). The change with time is the result of the combined effects of the real change in the patients and the selection effect caused by loss of patients with time from any cause. With this method the lack of significant change in levels with time does not preclude that progression toward more abnormal values with time actually takes place, if those lost with time mainly belong to the more severely ill of the patients, which will often be the case *(Christensen E et al,* 1985 (VI). For this reason transectional analysis has limited informational value.

Table 3A. *Pocket chart for calculation of therapy-dependent prognostic index PI_T in primary biliary cirrhosis.*

Variable	Points to add (A)	Points to subtract (S)
Serum bilirubin – μmoles/l		
3	12	
4	15	
6	20	
9	24	
12	27	
17	31	
25	35	
35	39	
51	43	
82	48	
120	52	
170	56	
250	60	
325	63	
Age – years		
25	0	
47	1	
58	3	
63	5	
66	7	
70	10	
73	14	
75	17	
77	21	
78	23	
Cirrhosis		
present	9	
absent	0	
Serum albumin		
G/l 16 μmoles/l 243		8
24 365		12
32 486		16
40 608		20
48 730		24
56 851		28
Central cholestasis		
present	7	
absent	0	
Therapy,		
placebo	5	
azathioprine	0	
Sum of points to be added (A) =		
Sum of points to be subtracted (S) =		←
A – S =		
PI_T = (A – S)/10 =		

Note: For each variable only one number should be used in the addition. If a patient has values between those in the table, interpolation should be used.
Based on *Christensen E et al,* 1985 (V).

Life-table analysis

This method which utilizes time from entry to the occurrence of an event allows for incomplete follow-up or censored observations (*Peto R et al,* 1977). Besides death an event may be the occurrence of a symptom, sign or biochemical variable above or below a certain value in patients without the characteristic in question at the time of entry into the trial. Using Kaplan-Meier's estimator the cumulative proportion of patients in whom the event has occurred with time can be estimated. This method, however, treats all data including the quantitative variables as dichotomous variables and utilizes only the time to the first occurrence disregarding later changes (*Christensen E, et al,* 1980 (I)). Only the change in one direction e.g. from less to more abnormal is analyzed. For this reason the method is best suited for the analysis of variables showing progression with time. With these limitations the life table method is an unbiased method which permits comparison of the risk of development of a given characteristic in different subgroups using the logrank test (*Peto R et al,* 1977).

In primary biliary cirrhosis the quantitative variables recorded in the PBC-1 trial was analyzed in this way using as end-point a value beyond the abnormal (upper or lower) 15th percentile of the distribution of the variable in question at the time of entry into the trial (*Christensen E et al,* 1980 (I)). With this type of analysis the rate of progression of incapacitation,

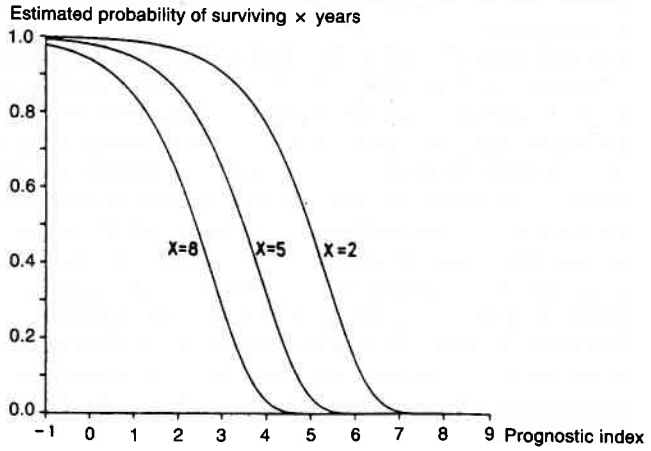

Fig. 3. *Estimated probability of surviving 2, 5 and 8 years by prognostic index PI_T in primary biliary cirrhosis (From:* Christensen E et al, *1985 (V)).*

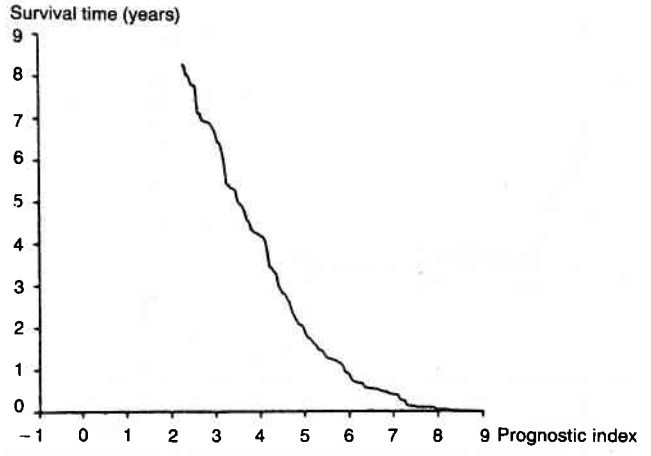

Fig. 4. *Estimated median survival time by prognostic index PI_T in primary biliary cirrhosis (From:* Christensen E et al, *1985 (V)).*

albumin, bilirubin and mitochondrial antibody seemed to be higher than that of cholesterol, IgG, IgA and IgM (*Christensen E et al,* 1980 (I)).

In the CSL-1 trial we found the rate of occurrence of esophageal varices to be 2-3 times higher than that of bleeding from esophageal varices (*Christensen E et al,* 1981).

Trend analysis

In each patient in whom the variable in question has been recorded at 2 or more separate occations the change with time (slope or trend) can be estimated using linear regression. The estimated regression coefficients should be corrected for regression towards the mean which may bias the results (*Blomqvist N,* 1977; *Svärdsudd K et al,* 1980; *Wu M et al,* 1980). Furthermore, if more than 2 separate time points are considered the course may be non-linear and therefore not well described by linear regression. Alternatively one may use polynomial regression models to describe the data (*Woolson RF et al,* 1980). Other problems to be considered when using these methods are: 1) the varying periods of observation of the patients (patients with a short follow-up will contribute fewer values than those with a long follow-up), 2) the courses may not be "syncronized" to the time of entry into the trial or the time of diagnosis (some patients may have a more advanced disease which may progress rapidly, other patients may be diagnosed at an early stage and live for long periods with few signs of progression), and 3) in chronic liver disease the course may be irregular with phases of improvement and phases of deterioration. These problems may be difficult to deal with. We are not aware of any such analyses in chronic liver disease.

Studying the course in groups defined by the minimal duration of observation

With this method which is described in more detail elsewhere (*Christensen E et al,* 1985 (VI)) the total period of observation is divided into intervals according to scheduled follow-up and the course is analyzed in groups of patients having values in all the intervals of each studied period. The patients with the shortest observation can contribute to the first interval only, whereas patients with the longest observation can contribute to all intervals. Thus the studied patient groups overlap, each group including patients with observation times equal to or greater than the period being investigated. By comparison of corresponding values in adjacent groups this method enables estimation of the magnitude and direction of the effect of selection due to the loss of patients with time from any cause including death.

We have used this method to study the course in time of laboratory variables in the CSl-1 trial (*Christensen E et al,* 1985 (VI)). As an example the findings for bilirubin is shown in Figure 5. In the placebo group the course varies somewhat with the total time period being considered. Patients with long observation show initial regression towards normal, patients observed for more than 3 years show a further subsequent regression, while patients observed for at least 1, 2 or 3 years tend to show an increase in bilirubin in the last year of observation. Similar changes were observed in other variables e.g. prothrombin index and albumin (*Christensen E et al,* 1985 (VI)).

The short term reversibility means that levels after a few months may better indicate the degree of permanent liver damage than initial levels. Furthermore, the results show that long term improvement does occur in some patients. In this context it is interesting that a decrease in portal pressure with time has been described to occur in cirrhosis (*Reynolds TB et al,* 1960).

As shown in Figure 5 a more marked initial decrease in bilirubin was found during prednisone than during placebo treatment. Prednisone also increased initial regression towards normal in a number of other variables e.g. prothrombin index, aspartate aminotransferase and gamma globulin (*Christensen E et al,* 1985 (VI)). These findings are in agreement with previous reports on the metabolic, antiinflammatory, immunosuppressive effects of steroid hormone (*David DS et al,* 1970). Some of the findings may be regarded as consequences of an improvement in hepatocellular function due to a beneficial effect of the hormone on selected patients within the investigated group (including autoimmune chronic aggressive hepatitis and alcoholic hepatitis) (*Tanner AR et al,* 1979).

Course in relation to time of death

Since the onset of disease may be insidious and not well defined by the time of diagnosis or the time of entry into a trial, courses cannot be expected to be "synchronized" to that time. This may explain why the courses may be less clear when analyzed in relation to that time.

Since the major changes may be expected to occur within few years prior to death, one may study the course in relation to time of death, summarizing the data in defined time intervals prior to that time (*Christensen E et al,* 1985 (VI)).

By "synchronizing" the courses in the CSL-1 trial in this manner a clearer picture was obtained at least in patients dying from a "hepatic" cause (*Christensen E, et al,* 1985 (VI)). As an example the results for bilirubin are shown in Figure 6. It appears that marked increase is seen in the last year before death from a hepatic cause. The changes before that time are small.

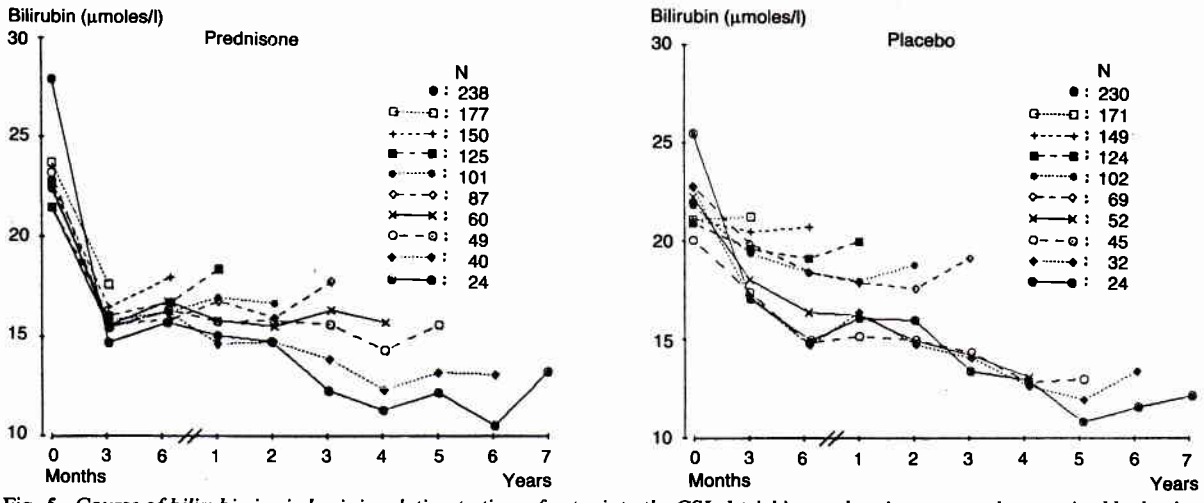

Fig. 5. *Course of bilirubin in cirrhosis in relation to time of entry into the CSL-1 trial in overlapping groups characterized by having complete data in the time span under consideration. Antilogs of means of logarithmic values are presented. N: number of patients. (From:* Christensen E et al, *1985 (VI)).*

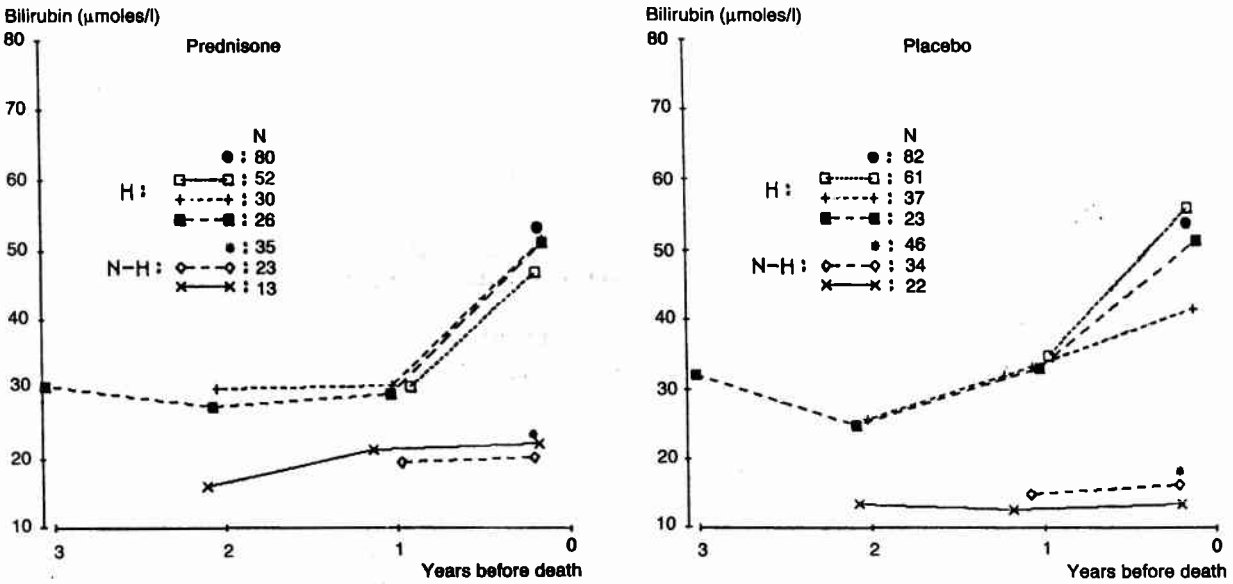

Fig. 6. *Course of bilirubin in cirrhosis in relation to time of death in overlapping groups with complete data in each period of observation. Antilogs of means of logarithmic values are presented. N: number of patients. H: hepatic main cause of death. N-H: Non-hepatic main cause of death. (From:* Christensen E et al, *1985 (VI)).*

Corresponding curves were seen for albumin and prothrombin index (*Christensen E et al,* 1985 (VI)). Thus in regard to these variables cirrhosis follows a rather stationary course until the final, fatal accelerative deterioration occurs. This emphasizes the relatively acute nature of the late stage disease (*Christensen E et al,* 1985 (VI)).

The results on the course of single variables in groups of patients may be difficult to interpret and utilize in clinical practice because the analyses are not well suited to provide information on the prognostic or therapeutic value of the levels of different variables. A variable becomes valuable only if its level (or change) is associated with prognosis or therapeutic effect.

RELATION BETWEEN COURSE OF VARIABLES AND THERAPY-DEPENDENT PROGNOSIS

As an attempt to investigate whether the changes in laboratory variables within the first 3 months of admission to the CSL-1 trial had any relation to estimated prognosis or therapeutic effect, we calculated the product-moment correlation coefficient between the changes and our previously developed prognostic and therapeutic indices, PI_T and TI, being estimates of the patients' prognostic and therapeutic disposition, respectively, at the time of entry into the trial (*Schlichting P, Christensen E et al,* 1983 (II); *Christensen E et al,* 1985 (IV)).

For example during prednisone treatment we found the initial change in aspartate aminotransferase to be negatively correlated with TI, indicating that decrease in this variable is associated with positive values of TI indicative of beneficial effect of prednisone treatment and vice versa (*Christensen E et al,* 1985 (IV)). Furthermore, during prednisone therapy, the initial change in aspartate aminotransferase was found to be positively correlated with $PI_{prednisone}$, indicating that absence of the usual decrease in this variable is associated with high (positive) values of $PI_{prednisone}$ indicative of poor prognosis and vice versa *(Christensen E et al,* 1985 (IV)).

None of the variables which correlated significantly with PI_T or TI contributed to the index in question. The findings suggest that the initial changes in some variables during prednisone treatment may indicate whether prednisone is of benefit to the patient or not (*Christensen E et al,* 1985 (IV)). However, all significant correlations were small indicating that the changes in single variables have relatively little prognostic or therapeutic value.

INDIVIDUAL THERAPY-DEPENDENT PROGNOSIS BASED ON CURRENT STATUS OF THE PATIENT

In the preceding we have described how prognostic and therapeutic information based on variables at the time of entry into the trial can be utilized. However, the situation after that time may rapidly change for better or worse e.g. prognosis may improve if the patient stops drinking or it may become worse if he develops ascites or experiences bleeding from esophageal varices (*Christensen E et al,* 1981). Such changes cannot be accounted for in a prognostic index based on data at the entry into the trial. However, if such changes occurring during the course of the disease can be utilized to update estimates of the therapy-dependent prognosis, more precise estimates may be expected. Time-dependent analysis has been performed in other diseases (*Myers LE et al,* 1980) but not previously in chronic liver disease as far as we know.

Time-dependent analysis

Cox has proposed a multiple regression model for time-dependent variables (*Cox DR,* 1972). This model corresponds to the earlier presented Cox regression model for time-fixed variables with the exception that each variable z_i no longer is constant (equal to the value on admission) but is allowed to vary as a function of time t after entry into the study: $z_i(t)$. Consequently, the hazard of a patient can vary in time corresponding to the variation in the significant therapeutic or prognostic variables. For example if a patient develops GI bleeding, the hazard will probably be increased, if the bleeding can be effectively treated, the risk will probably decrease.

The inclusion of variables in the model and the procedure for classifying variables as "prognostic" or "therapeutic" corresponds to that described earlier. Accordingly the time-dependent Cox regression model can also be reduced to one with r prognostic coefficients common to the treatments and k pairs of therapeutic coefficients significantly different between the treatments (*Christensen E et al,* 1986 (VII)).

In the same way as in the Cox model for time-fixed variables a separate time-dependent prognostic index $PI(t)_T$ (dependent on time t) can be defined for each treatment (T stands for the treatment given, here placebo (=treatment A) or prednisone (=treatment B)) (*Christensen E et al,* 1986 (VII)). A time-dependent therapeutic index TI(t) defined as the difference $PI(t)_{tr.A} - PI(t)_{tr.B}$ and a normalized time-dependent therapeutic

index NTI(t) = TI(t)/SE(TI(t)) can be derived in the same way as for the time-fixed Cox regression model as described earlier in this paper.

Analyzing the data from the CSL-1 trial using the Cox regression model for time-dependent variables we obtained the results shown in Tables 4 and 4A. The following "purely" prognostic variables were significantly associated with a high hazard: marked GI bleeding (necessitating blood transfusion), high age, high daily alcohol consumption, high serum bilirubin, low serum albumin, no or slight inflammation in liver connective tissue, poor nutritional status and high alkaline phosphatase. Prothrombin index and ascites were therapeutic since they interacted significantly with the treatment i.e. the association of these variables with the hazard was significantly stronger during prednisone than during placebo treatment. Thus low prothrombin index and ascites indicated significantly higher hazard during prednisone than during placebo while a high prothrombin index indicated the opposite (*Christensen E et al,* 1986 (VII)).

The time-dependent prognostic index $PI(t)_T$ may be obtained at any time during the course of the disease. It can be obtained very simply using the numbers in Table 4A.

The time-dependent normalized therapeutic index NTI(t) can be obtained very simply from Figure 7 by reading on the ordinate the value which corresponds to the current prothrombin index and degree of ascites. If $NTI(t) > 1.96$ prednisone may be considered beneficial and administered, if $NTI(t) < -1.96$ prednisone may be considered harmful and withheld. Intermediary values of NTI(t) indicates insignificant effect of prednisone treatment (*Christensen E et al,* 1986 (VII)).

Probability of surviving next 3 or 6 months

An important result was that the estimated cumulative underlying hazard function $\hat{\Lambda}_0(t)$ turned out to be linear apart from the last 1.5-2 years where the confidence of the curve is considerably less due to the small numbers of patients at risk at that time (*Christensen E et al,* 1986 (VII)). This indicated that the underlying hazard $\lambda_0(t)$ may be considered constant. 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 varying hazards of the patients could be satisfactorily described alone by the varying levels of the variables in the model (*Christensen E et al,* 1986 (VII)).

To facilitate interpretation of $PI(t)_T$ it may be transformed to an estimate of the conditional probability P(t,h) of surviving a given time interval, h, say 3 or 6 months, after time t given survival to that time. Because the underlying hazard $\lambda_0(t)$ can be considered constant ($=\lambda_0$) then P(t,h) may be estimated as $\hat{P}(t,h) = \exp(-\lambda_0 \cdot h \cdot \exp(PI(t)_T))$. Therefore a graph of the estimated probability of surviving the next 3 or 6 months as a function of $PI(t)_T$ for any time t could be made (*Christensen E et al,* 1986 (VII)). This is shown in Figure 8. Corresponding to the value of $PI(t)_T$ on the abcissa one can read the probability of surviving the next 3 or 6 months on the ordinate.

Table 5 shows an example of estimation of the indices and the probability of surviving the next 3 or 6 months at various times in a given patient.

It is important to keep in mind that the time-dependent Cox model only analyzes the association of the hazard with the current level of the time-dependent variables. The course in time of the variables themselves is not taken into account. Furthermore, after entry into the trial the effect of the therapy being significant in selected patients (*Christensen E et al,* 1985 (IV)) may influence the comparability of the treatment groups after randomization. However, the time-dependent model was designed to adjust for differences between the two treatment groups as far as possible. 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.

COMPARISON OF TIME-FIXED AND TIME-DEPENDENT COX MODELS

The time-dependent Cox regression model included a different set of significant variables than the time-fixed Cox regression model (*Schlichting P, Christensen E et al,* 1983 (II)) as seen from Table 6.

Table 4. *Significant prognostic or therapeutic variables in time-dependent Cox regression model in cirrhosis.*

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.	−1.58	0.22	$<10^{-4}$
		plac.	−0.83	0.19	$<10^{-4}$
Ascites, slight	present: 1, otherwise: 0	pred.	0.96	0.25	$<10^{-4}$
		plac.	0.34	0.27	0.21
Ascites, moderate or marked	present: 1, otherwise: 0	pred.	1.66	0.25	$<10^{-4}$
		plac.	1.17	0.23	$<10^{-4}$
GI bleeding marked	present: 1, otherwise: 0	both	1.41	0.18	$<10^{-4}$
Age (years)	(age at randomization) − 60	both	0.052	0.0085	$<10^{-4}$
Alcohol consumption, daily	none: 0, 10 − 50g: 3, >50 g: 9	both	0.14	0.024	$<10^{-4}$
Bilirubin (μmoles/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	meagre 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	$<10^{-3}$

Plac.: placebo. Pred.: prednisone.
From: *Christensen E, et al.* 1986 (VII).

A main reason for the differences is the frequency with which the variables have been recorded after entry into the trial (*Christensen E et al,* 1986 (VII)). The Cox regression model for time-dependent variables requires that the value of each variable in each patient observed 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. 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 association less, perhaps insignificant. Since the frequency of investigations to some degree depends on the ease with which they can be performed, the clinical variables and simple laboratory tests are being favored in a time dependent analysis at the expense of more special tests including liver biopsies.

Among the variables which were significant in the time-fixed Cox model seven (acetylcholinesterase, antinuclear factor and 5 histologic variables) were not significant in the time-dependent model probably because these variables were recorded less frequently than the others. Only one histologic variable (liver connective tissue inflammation) being the most significant histologic variable in the time-fixed model maintained its significance in the time-dependent model. Albumin, which was recorded more regularly, replaced acetylcholinesterase to which it is positively correlated. Actual alcohol consumption, which is correlated to the male sex, has replaced this time-fixed variable. Prothrombin index has become a therapeutic variable, probably partly because corticosteroid hormones increase prothrombin index (*Ozsoylu S et al,* 1962; *David DS et al,* 1970). New prognostic variables include GI bleeding which varies highly with time (*Christensen E et al,* 1981) and alkaline phosphatase, bilirubin and nutritional status. The latter two being included in the Child-Turcotte criteria had a weak prognostic influence

Table 4A. *Pocket chart for easy calculation of current therapy-dependent prognostic index $PI(t)_T$ in cirrhosis.*

Variable	Points add (A) pred.	Points add (A) plac.	Points subtract (S) pred.	Points subtract (S) plac.
	both		both	
Treatment (placebo)				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 (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 µmoles/l or ≥4 mg%	9			
Serum albumin				
g/l 15 µmoles/l 228			12	
20 304			16	
30 456			20	
40 608			24	
50 760			27	
Liver connective tissue inflammation,				
none or slight			0	
moderate or marked			6	
unknown			4	
Nutritional status, meagre 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 =				

Note: for each variable only one number (if applicable) should be used in the addition. If a patient has values between those in the table, interpolation should be used.
Plac.: for placebo treated patients.
Pred.: for prednisone treated patients.
Both: for both placebo and prednisone treated patients.
Based on: *Christensen E et al,* 1986 (VII).

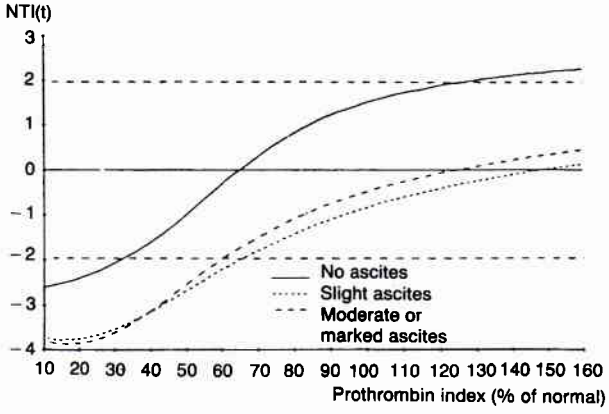

Fig. 7. *Time-dependent normalized therapeutic index NTI(t) as a function of prothrombin index and the degree of ascites in cirrhosis (From:* Christensen E et al, *1986 (VII)).*

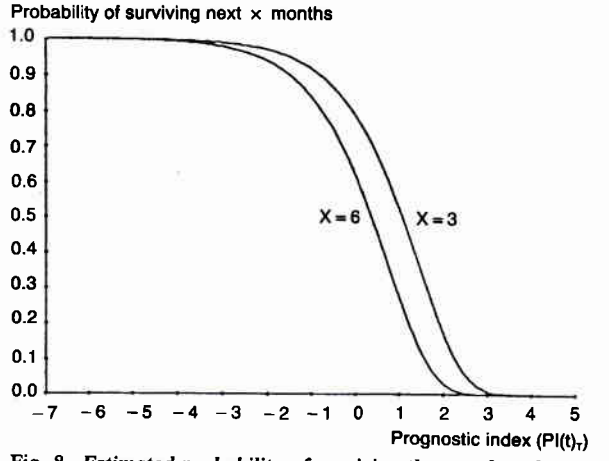

Fig. 8. *Estimated probability of surviving the next 3 or 6 months as a function of the time-dependent prognostic index $PI(t)_T$ in cirrhosis (From:* Christensen E et al, *1986 (VII)).*

Variable	Entry	6 mo.	12 mo.	18 mo.	23.5 mo.
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	>50 g	10-50 g	10-50 g	10-50 g	10-50 g
Bilirubin (μmoles/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, meagre 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
Probability of surviving 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
Probability of surviving 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

Table 5.
Example with $PI(t)_T$ calculated at various times in a prednisone treated male patient with cirrhosis who died of hepatic failure 25 months after entry into the trial.

From: *Christensen E et al,* 1986 (VII).

Table 6. *Significance of variables in different prognostic models in cirrhosis.*

Variable	Time-dependent Cox model		Time-fixed Cox model	
	progn. effect	ther. effect	progn. effect	ther. effect
Clinical				
Age	+	−	+	−
Sex	−	−	+	−
Ascites	+	+	+	+
GI bleeding	+	−	−	−
Current alcohol consumption	+	−	−	−
Nutritional status	+	−	−	−
Laboratory				
Prothrombin index	+	+	+	−
Bilirubin	+	−	−	−
Albumin	+	−	−	−
Alkaline phosphatase	+	−	−	−
Acetylcholinesterase	−	−	+	−
Antinuclear factor (ANF)	−	−	+	+
Histologic				
Liver connective tissue inflammation	+	−	+	−
Large piece-meal necroses	−	−	−	+
Macronodular cirrhosis	−	−	+	+
Small focal liver cell necroses	−	−	+	−
Efferent veins in parenchymal nodules	−	−	+	−
Eosinophil leucocytes in liver parenchyma	−	−	+	−

From: *Christensen E et al,* 1986 (VII).

at the entry into the trial (*Christensen E, et al,* 1984 (III)). Age and ascites had similar effects in the two models. However, ascites has a more marked prognostic influence in the time-dependent model than in the time fixed-model. This may be explained by development of more abnormal values (e.g. marked ascites) before death in patients who had less abnormal or normal values (i.e. no ascites) at the time of entry into the trial. This demonstrates the value of the follow-up information.

VALIDATION OF RESULTS

It is generally considered good practice first to make the hypothesis and then the experiment to prove or disprove it. If feasible this principle should be followed. For certain problems the method may be less useful.

Most controlled clinical trials in chronic disease are designed prospectively to answer a single usually rather broad question. Considering the tremendous investment in time and resources that goes into the conduct of a clinical trial, additional analyses of the data are not only well justified but indispensable to ensure maximum utilization of the data. Otherwise valuable time would be lost and a much slower progress would result.

However, the powerful descriptive tool of multivariate analysis should be considered explorative or heuristic. Therefore the results obtained need some form of confirmation before they can be considered "proved". Preferably, therefore, multivariate analyses should be accompagnied by some sort of evaluation or validation of the results, i.e. the therapy-dependent prognosis predicted from the results of the analysis should be compared with the survival observed in patients who did not contribute to the analysis. Various methods may be used (*Peduzzi PN et al,* 1982).

1. TESTING IN NEW PATIENTS

This is the best way of validating results. We used this method in the PBC-1 trial (*Christensen E et al,* 1985 (V)) where the final Cox regression model was used to estimate the prognosis of independent patients with PBC treated with placebo in another controlled clinical trial conducted in a similar way (*Neuberger J, Christensen E et al,* 1985). When divided into 3 groups according to the value of the prognostic index the observed and predicted survival curves were compared and found to be similar (P of no difference = 0.4).

2. DATA SPLITTING

This method may be used if data from another similar controlled trial are not available. Here the statistical model being estimated using one part of the data is used to predict outcome for the remaining subjects, and predicted and observed outcome in these are compared to assess the predictive power of the model (*Greenberg R et al,* 1974; *Cox DR,* 1975; *Peduzzi PN et al,* 1982).

We have used this procedure for evaluation of the results of the Cox regression analyses of the CSL-1 trial (*Schlichting P, Christensen E et al,* 1983 (II); *Christensen E et al,* 1986 (VII)). A random sample comprising 75% of the analyzed patients was obtained. Using the data of these patients the coefficients for the variables included in the final Cox regression model were estimated. These coefficients were used in the final model to estimate the therapy-dependent prognosis in the remaining 25% of the patients. The group comprising 25% of the patients was divided into 3 groups according to the estimated prognostic index. In the Cox model for time fixed variables the estimated survival in each of these 3 groups was compared with the observed survival and no significant difference was found (*Schlichting P, Christensen E et al,* 1983 (II)). In the Cox regression model for time dependent variables the number of deaths expected in each subsequent half year interval was estimated in the 3 groups and these numbers were compared with the numbers of deaths observed (*Christensen E et al,* 1986 (VII)). No significant difference between observed and expected numbers of deaths in the 3 groups was found. Nevertheless, for higher

values of $PI(t)_T$ indicative of poorer prognosis, risk tended to be overestimated, especially in the first half year after entry into the trial. For lower values of $PI(t)_T$ indicative of better prognosis, risk tended to be underestimated (*Christensen E et al,* 1986 (VII)). The reason for these tendencies was that in the calculation of the expected numbers of death the influence of possible change during the next 6 months, in particular the possibility of improvement in patients with high $PI(t)_T$ and of deterioration in patients with low $PI(t)_T$ (regression toward the mean) was not taken into account. When the time fixed Cox regression model was validated in a similar way it was revealed that $PI(t)_T$ predicted outcome more accurately than PI_T which may be considered as an average over time of $PI(t)_T$-values. PI_T was found to underestimate the hazard in high risk patients as determined by $PI(t)_T$ and to overestimate hazard in low risk patients (*Christensen E et al,* 1986 (VII)).

3. JACKKNIFE OR "LEAVING CURRENT PATIENT OUT" METHOD

In this method estimates of the regression coefficients of the final multivariate model is obtained from the data after leaving out the data of one patient from the analysis (*Lachenbruch PA et al,* 1968). The regression coefficients are used to calculate the prognostic index for the excluded patient. This procedure is repeated for all the patients, i.e. the number of analyses needed corresponds to the number of patients. In this way the obtained prognostic index for each patient is unbiased because it is based on data to which the patient in question did not contribute. By combining the prognostic indices with the cumulative underlying hazard as described previously in this paper, survivorship functions can be estimated. By comparing the survivorship functions estimated for groups of patients defined according to the value of their prognostic indices with the actual survival curves in these groups, the validity of the model can be tested. This method is probably best suited for evaluation of results based on rather few patients where leaving out data of one patient may have a substantial influence (*Christensen E et al,* 1983). If the number of patients is large, the effect of leaving out one patient's data will be small and the amount of computation will be big.

In multivariate analyses some variables may randomly be found to have a significant prognostic or therapeutic association (*Lee KL et al,* 1980). This problem naturally increases with the number of variables analyzed and hence the number of statistical tests performed. Therefore it is important to evaluate the results in the light of common clinical knowledge and biologic principles to see if the results are "reasonable". This seemed to be the case for most of the prognostic and therapeutic variables identified in our studies (*Schlichting P, Christensen E et al,* 1983 (II); *Christensen E et al,* 1985 (IV); *Christensen E et al,* 1985 (V); *Christensen E et al,* 1986 (VII)).

Even if the validation procedure does not reveal significant differences between observed and predicted outcome this does not guarantee that there is no difference. There is always a possibility of committing type 2 errors.

CONCLUSION AND PERSPECTIVES

The main result from the investigations performed is the demonstration of association of certain variables with prognosis and therapeutic effect in chronic liver disease. Clinical and paraclinical variables are only meaningful if they provide prognostic or therapeutic information. In isolation the variables are of little importance in clinical practice. Multivariate analyses are needed to describe the pattern of covariation between the variables, their relative importance and their independent association with the therapy-dependent prognosis. Univariate methods are unable to do this. Even though multivariate methods may be used to adjust for imbalance in known prognostic variables, they cannot make data bases replace randomized clinical trials (*Byar DP,* 1980) because randomization always will be necessary to "neutralize" the influence of all unknown prognostic variables. In addition, multivariate methods are in no way perfect. They often need certain assumptions to be fulfilled and these must be checked whenever such analyses are being performed. One difficulty is the selection of covariates finally included in the regression model (*Byar DP & Corle DK,* 1977). Slight and perhaps random differences in prognostic influence of variables which are correlated may determine which are finally included in the model (*Schlichting P, Christensen E, et al,* 1983 (II)). The obtained regression models are in no way unique. In some instances slightly different models might have been obtained with nearly the same degree of prognostic information. The models obtained are thus dependent on which variables have been recorded and in time-dependent models also on the frequency with which they have been recorded (those recorded frequently have a greater chance of being included as prognostic variables than those recorded infrequently, other things being equal). Therefore the results should in no way be regarded as final. Instead they should be regarded as temporary practical solutions to practical problems. This emphasizes the need for continual adjustment of the indices by new controlled clinical trials. Ideally any new patient should contribute to this process by being included in new ongoing controlled clinical trials of high quality (*Chalmers TC et al,* 1981) with relevant endpoints (*Miettinen OS et al,* 1983). In this context the "atypical" patients should be given the same therapeutic attention as the "typical".

The solutions presented in this paper have been developed in an attempt to meet the need to treat each patient on an individual basis according to his/her needs i.e. the principle of finding which treatment is best for which patient. This is an attempt to break the all too common practice to treat all patients in the same way on the basis of average results, irrespective the characteristics of the patient.

The analysis have resulted in therapeutic and prognostic indices which, by summarizing the information presented by a new patient to single numbers, may indicate prognosis and effect of therapy in individual patients. Thus rational means has been provided for exerting an individual approach in the management of patients with chronic liver disease. The time-dependent indices provide means for close monitoring of patients which may be of value if special therapeutic procedures such as liver transplantation are being considered (*Scharschmidt BF,* 1984; *Van Thiel DH et al,* 1984; *Vierling JM,* 1984).

Further developments and refinements of statistical methods as well as more studies and analyses are needed to optimize management of individual patients, which is the primary goal of doctors. In recent years a marked development has already taken place and there is every indication that new and better statistical methods will be developed and applied in the future. To stimulate this process a close cooperation between clinicians and statisticians is necessary. The statisticians need inspiration from practical clinical problems and clinicians need the expertise of statisticians to ensure maximum validity of analyses and results.

SUMMARY

In a given disease the manifestations and course of disease may vary markedly between the patients. This complicates prediction of the prognosis and treatment effect in individual patients. Most controlled clinical trials present only the "average" effect e.g. the therapy-dependent survival in the studied patient group.

To estimate the therapy-dependent prognosis in individual patients it is necessary to utilize the covariation between survival time and variables characterizing each patient including the therapy given.

This paper describes current methods for identification of

variables which covary with survival time (prognostic variables) or the effect of therapy (therapeutic variables). Analyzing data from two large controlled clinical trials in patients with chronic liver disease: 1) the multicenter trial of prednisone versus placebo in cirrhosis conducted by the Copenhagen Study group for Liver diseases (CSL-1) and 2) the multinational trial of azathioprine versus placebo in primary biliary cirrhosis (PBC-1) we have developed indices for prediction of prognosis and therapeutic effect using Cox's multiple regression model for censored survival data. Using the indices one can estimate the therapy-dependent prognosis in new patients from their base-line data. Furthermore, a time-dependent index by which the risk of a given patient can be estimated repeatedly to update prognosis during the course of the disease is presented. To simplify application "pocket charts" have been devised by which a prognostic index for a patient can easily be obtained at the bedside. By simple graphs, a prognostic index can be translated to estimates of the probability of surviving a given time or the median survival time predicted for the patient.

The indices have been validated by comparing the survival predicted by the indices with the observed survival in new patients or using data splitting.

The results allow a more differentiated treatment strategy based on the characteristics of the individual patient. Even if the results apply to chronic liver disease, the general principles are valid for study of the individual therapy-dependent prognosis in other diseases.

SUMMARY IN DANISH

Ved en given sygdom vil manifestationer og forløb ofte udvise en betydelig individuel variation. Dette forhold vanskeliggør forudsigelse af prognose og behandlingseffekt for den enkelte patient. De fleste kontrollerede forsøg angiver kun den »gennemsnitlige« effekt eller terapi-afhængige prognose, hyppigt i form af overlevelseskurver for det undersøgte patientmateriale.

For at estimere den terapi-afhængige prognose for den enkelte patient er det nødvendigt at udnytte sam- eller kovariationen imellem overlevelsesvarigheden og såkaldte baggrundsvariabler, der karakteriserer de enkelte patienter.

Arbejdet beskriver metoder til identifikation af variabler, der kovarierer med prognosevariablen (prognostiske variabler) eller behandlingseffekten (terapeutiske variabler). Ved analyse af data fra to store kontrollerede kliniske forsøg – 1) en af Københavns studiegruppe for leversygdomme gennemført multicenterundersøgelse af effekten af prednison over for placebo ved cirrhose (CSL-1) og 2) en fra dansk side ledet multinational undersøgelse af effekten af azathioprin over for placebo ved primær biliær cirrhose (PBC-1) – har vi udviklet indices til forudsigelse af prognose og terapeutisk effekt ved hjælp af Cox's multiple regressionsmodel for censurerede overlevelsesdata. Med disse indices kan den terapi-afhængige prognose estimeres for en ny patient ud fra hans/hendes baggrundsvariabler. Endvidere er udviklet et »tidsafhængigt« indeks, hvorved man kan opdatere prognosen under sygdomsforløbet. For at forøge den kliniske anvendelighed er resultaterne »oversat«, så indices kan beregnes ved sygesengen ved addition af simple talværdier. Ved hjælp af enkle diagrammer kan en given prognostisk indeksværdi omsættes til et estimat af 1) sandsynligheden for at overleve en given tid eller 2) den mediane overlevelsesvarighed for den pågældende patient.

Indices er blevet valideret ved iagttagelse af rimelig overensstemmelse imellem den ved hjælp af indices forudsagte overlevelse og den observerede overlevelse for uafhængige patienter.

Resultaterne muliggør en mere differentieret behandlingsstrategi baseret på den enkelte patients karakteristika. Selv om resultaterne gælder for patienter med kronisk leversygdom, vil de generelle principper kunne overføres til analyser af den individuelle terapi-afhængige prognose ved andre sygdomme og behandlinger.

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