# A Therapeutic Index That Predicts the Individual Effects of Prednisone in Patients With Cirrhosis

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*Our aim was to construct an index that accurately predicts the degree of benefit or harm that prednisone therapy holds for patients with liver cirrhosis. The admission and survival data of 488 patients with cirrhosis who participated in a controlled clinical trial of prednisone in a dosage of 10–15 mg daily (251 patients) versus placebo (237 patients) and who were observed for up to 12 yr were analyzed using Cox's multiple regression model. Four variables each provided significant therapeutic information: antinuclear factor ($p = 0.02$) and large piecemeal necroses ($p = 0.02$) were associated with a beneficial effect, whereas ascites ($p = 0.0004$) and large regenerative nodules ($p = 0.0007$) were associated with a harmful effect of prednisone. From these four variables a therapeutic index was constructed. For a given patient the therapeutic index is a measure of how big the effect will be if prednisone is given. The gain in survival time obtained by administering prednisone according to the therapeutic index was estimated to be 349 yr, mainly confined to 217 patients with a significant positive (121) or negative (96) therapeutic index. The therapeutic index may prove useful for the optimal administration of prednisone treatment in new patients with cirrhosis.*

Previous analyses by the Copenhagen Study Group for Liver Diseases (1) have shown that prednisone decreases survival in patients with ascites and increases survival in nonalcoholic women without ascites. The latter group comprising only women is perhaps less satisfactory biologically because none of the more common liver diseases are confined to one sex (2,3). Patients with chronic aggressive hepatitis benefit from corticosteroid treatment (3–7). However, some patients in whom the histologic criteria of chronic aggressive hepatitis are not fulfilled also seem to benefit from prednisone treatment (8). These results were obtained by stratification of the patients (9), but by that method the influence of only one or few variables can be analyzed simultaneously. The purpose of the present study was to combine all variables that hold significant therapeutic information in a multivariate analysis into a therapeutic index (TI) that can estimate prognosis if prednisone is administered to a given patient.

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*Abbreviations used in this paper*: ANF, antinuclear factor; MSD, median survival difference; MST, median survival time; NTI, normalized therapeutic index; PI, prognostic index; TI, therapeutic index.

## Patients and Methods

During the period 1962–1969, 532 patients with histologically verified liver cirrhosis were included in a controlled clinical trial evaluating the effect of prednisone versus placebo on survival as previously reported (1). This report analyzes the data of 488 patients whose initial biopsy permitted histologic reevaluation using updated, more restrictive criteria (10). With these criteria, cirrhosis was confirmed in 287 patients (59%), probable in 101 (21%), compatible in 89 (18%), and unlikely in 11 (2%) (3,10). The allocation was based on date of birth; 251 patients received prednisone and 237 placebo. The dosage of prednisone was initially 40 mg/day and was reduced in 1–2 mo to a maintenance dose of 10–15 mg/day. During the trial period (up to September 1, 1974), 292 of the 488 patients died, 142 in the prednisone group and 150 in the placebo group. The survival curves were similar in the two groups. The pattern of main cause of death was the same in both groups (11). The frequency of mild hypertension and of bruises was significantly higher during prednisone treatment, whereas the frequency of peptic ulcer, diabetes mellitus, obesity, osteoporosis, muscular atrophia, and infection was not significantly different in the two groups.

The admission and survival data were analyzed using a multivariate regression model for survival data proposed by Cox (12). The variables studied, the checking of model assumptions, and the detailed description of methods used for estimation of regression coefficients and their significance are reported elsewhere (13). Our final Cox regression model had this form:

$$\lambda(t) = \lambda_0(t) \exp (z_{\text{treatment}} b_{\text{treatment}} + z_1 b_1{}^T + \cdots + z_4 b_4{}^T + z_5 b_5 + \cdots + z_{12} b_{12}).$$

Thus the death risk or hazard $\lambda(t)$ is a function of a basal or underlying death risk $\lambda_0(t)$ and of the patient's variables $z_1$ to $z_{12}$ weighted with the corresponding regression coefficients $b_1$ to $b_{12}$. $b_{\text{treatment}}$ is an overall treatment effect coefficient, $z_{\text{treatment}}$ is a treatment indicator (prednisone 0, placebo 1), $b_1{}^T$ to $b_4{}^T$ are regression coefficients for "therapeutic" variables $z_1$ to $z_4$ ($T$ stands for prednisone or placebo), and $b_5$ to $b_{12}$ are regression coefficients for "prognostic" variables $z_5$ to $z_{12}$ (13). If a regression coefficient $b_i$ is positive, higher values (scores) of the corresponding variable indicate higher hazard or worse prognosis; vice versa if $b_i$ is negative. If $b_i$ is zero then $z_i$ has no influence on survival.

The variables included in the model are shown in Table 1. Variables 1–4 are therapeutic and have significantly different regression coefficients for each treatment; variables 5–12 are prognostic and have regression coefficients common to the two treatments as explained in detail previously (13).

*Table 1. Regression Coefficients From the Cox Regression Analysis*

| Variable | Variable number | Scoring | Treatment group(s) | Regression coefficient ($b$) |
|---|---|---|---|---|
| Treatment | 0 | Prednisone: 0; placebo: 1 | Both | 0.150 |
| Antinuclear factor | 1 | −: 0; +: 1; ++ or +++: 2 | Plac | 0.311 |
| | | | Pred | −0.124 |
| Large piecemeal necroses (>5 hepatocytes) | 2 | None or few: 0; moderate or severe: 1 | Plac | 0.728 |
| | | | Pred | −0.739 |
| Ascites | 3 | None: 0; slight: 1; moderate or marked: 2 | Plac | 0.105 |
| | | | Pred | 0.719 |
| Size of largest regenerative nodule in liver biopsy specimen | 4 | ≤ Normal lobule or undefined: 0; > normal lobule: 1 | Plac | −0.607 |
| | | | Pred | 0.729 |
| Sex | 5 | Female: 0; male: 1 | Both | 0.317 |
| Age (yr) | 6 | Age − 60 | Both | 0.049 |
| Prothrombin index (% *of normal*) | 7 | $\log_e$ (value) − 4 | Both | −0.495 |
| Acetylcholine esterase ($\mu mol/min \cdot ml$) | 8 | $\log_e$ (value × 100) − 4 | Both | −0.612 |
| Inflammation in liver connective tissue | 9 | None: 0; slight: 1; moderate: 2; marked: 3 | Both | −0.390 |
| Efferent veins in liver regenerative nodules | 10 | None: 0; few: 1; moderate: 2 | Both | 0.258 |
| Few diffuse focal small liver cell necroses | 11 | Present: 1; otherwise: 0 | Both | 0.310 |
| Eosinophil leukocytes in liver parenchyma | 12 | None: 0; few: 1; moderate: 2; many: 3 | Both | 0.299 |

Plac, placebo; pred, prednisone.

### *Definition and Scoring of Therapeutic Variables*

Antinuclear factor (ANF) was determined by immunofluorescent antibody technique (14,15). On the basis of the intensity of the fluorescence, results were graded as − (negative), + (just visible), ++ (definite), and +++ (bright). [The correlation with results given as dilution titers is reported in the paper by Kristensen et al. (16). If only titers are available, it may be reasonable to classify positive titers below 40 as + and titers of 40 or higher as ++ or +++.]

Piecemeal necrosis (i.e., liver cell necrosis located at the interphase between the connective tissue and the parenchyma) was classified as large if the area (in the tissue section) of the necrosis or hepatocytolysis was larger than that of five adjacent liver cells. Large piecemeal necroses were few if less than one per square millimeter of the biopsy section could be found.

Ascites was graded as slight if it was just detectable by shifting dullness and as moderate or marked if definite abdominal distention was also seen.

Size of largest regenerative nodule: The biopsy specimens were taken using Menghini needles with a diameter of 1.6 mm. Normal lobules were defined as having a diameter of 1.5 mm. The score of 1 was used if a specimen that confirmed cirrhosis (i.e., included at least two complete nodules) also included parts of at least one nodule the diameter of which could be estimated to be >1.5 mm (17). Otherwise the score of 0 was used. Undefined size means that the specimen did not permit assessment of the diameter of regenerative nodules.

### *Derivation of Measures of Therapeutic Effect*

From the model a separate prognostic index (PI) was constructed for prednisone and for placebo treatment:

$$PI_T = \log[\lambda(t)/\lambda_0(t)] = z_{treatment}b_{treatment} + z_1b_1{}^T + \cdots + z_4b_4{}^T + z_5b_5 + \cdots + z_{12}b_{12}.$$

Higher values of $PI_T$ mean higher risk or worse prognosis; lower (including negative) values mean better prognosis. The difference in prognosis during placebo and prednisone treatment, respectively, $PI_{placebo} - PI_{prednisone}$, is a measure of the therapeutic effect of prednisone. Because the prognostic terms (for variables 5–12) are identical in $PI_{placebo}$ and $PI_{prednisone}$, they vanish and the difference reduces to the following simple therapeutic index (TI), which is based on therapeutic variables only (variables 1–4):

$$TI = b_{treatment} + z_1d_1 + \cdots + z_4d_4,$$

where $d_i = b_i{}^{placebo} - b_i{}^{prednisone}$. A positive coefficient $d_i$ implies that higher values (scores) $z_i$ of the corresponding variable are associated with a beneficial effect of prednisone, and vice versa if $d_i$ is negative. A positive value of TI indicates that prednisone should reduce the risk, i.e., increase the survival of the patient; a negative TI indicates the opposite.

The standard error of the therapeutic index [SE(TI)] can be estimated from the covariance matrix for the therapeutic variables and the statistical significance of TI can be evaluated by comparing TI/SE(TI), i.e., the normalized therapeutic index (NTI) with the standardized normal distribution. NTI >1.96 or <−1.96 are considered significant.

To estimate the effect of prednisone treatment on survival time it is necessary to calculate $PI_{placebo}$ and $PI_{prednisone}$. Using the relation in Figure 1, $PI_T$ can be translated to the estimated median survival time ($MST_T$) (18). Now the effect of prednisone treatment can be expressed as the median survival difference ($MSD = MST_{prednisone} - MST_{placebo}$). This is a measure of the gain (positive or negative) of prednisone treatment in terms of time added to or subtracted from the estimated $MST_T$ during placebo treatment.

Examples of calculation of the indices are given in Results.

## Results

### *Therapeutic Variables and Therapeutic Index*

The four variables that each provided significant therapeutic (i.e., therapy-dependent prognostic) information are shown in Table 2 with their regression coefficients in a condensed form. A positive *d* coefficient means that higher values (scores) of the variable are associated with a beneficial effect of prednisone; a negative *d* coefficient means the opposite. Thus positive ANF and large piecemeal necroses are associated with a significantly beneficial effect of prednisone, whereas the presence of ascites and large regenerative nodules in the liver are associated with a significantly harmful effect of prednisone. In a regression model including the variables

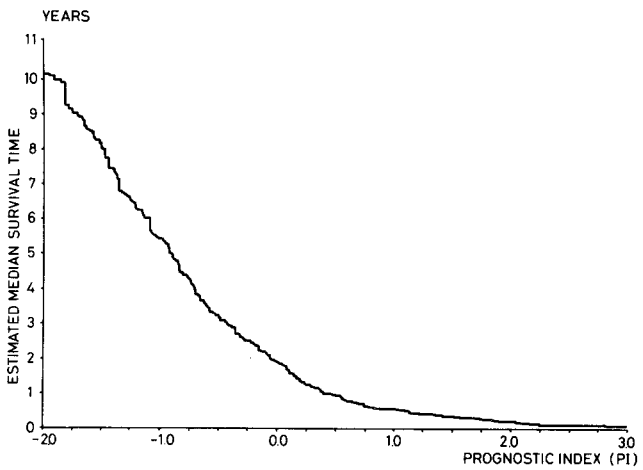


*Figure 1.* Estimated median survival time as a function of the prognostic index (PI) irrespective of the treatment. The curve is estimated as previously described (13,18). Corresponding to the value of PI on the abscissa, one reads the estimated median survival time on the ordinate.

*Table 2. Treatment Effect Coefficients From Cox Regression Analysis*

| Variable | Variable number | Scoring | Regression coefficient | | SE[a] | p |
|---|---|---|---|---|---|---|
| | | | $b_{treat}$ | $d$ ($b_{plac}-b_{pred}$) | | |
| Treatment | 0 | 1 | 0.150 | — | 0.173 | 0.39 |
| Antinuclear factor | 1 | −: 0; +: 1; ++ or +++: 2 | — | 0.435 | 0.188 | 0.02 |
| Large piecemeal necroses (>5 hepatocytes) | 2 | None or few: 0; moderate or severe: 1 | — | 1.465 | 0.635 | 0.02 |
| Ascites | 3 | None: 0; slight: 1; moderate or marked: 2 | — | −0.614 | 0.174 | 0.0004 |
| Size of largest regenerative nodule in liver biopsy specimen | 4 | ≤Normal lobule or undefined: 0; >normal lobule: 1 | — | −1.336 | 0.395 | 0.0007 |

Plac, placebo; pred, prednisone; treat, treatment. [a] Standard error or regression coefficient.

shown in Table 1 the following variables showed an insignificant tendency ($0.05 < p < 0.20$) toward a beneficial effect of prednisone: histologic features of chronic active hepatitis, high alkaline phosphatase activity, marked periportal fibrosis, and marked pericellular fibrosis. Previous hepatitis, lymphocytes in liver connective tissue, high alcohol intake, and poor nutritional status showed insignificant tendencies toward a harmful effect of prednisone. Sex and age showed no tendency toward an interaction with prednisone treatment, but the male sex was closely correlated with high alcohol intake.

Using the regression coefficients in Table 2, the TI (defined in Methods) can be calculated.

If a patient presents with the following therapeutic variables: ANF: ++ ($z_1 = 2$), severe piecemeal necroses > five cells ($z_2 = 1$), no ascites ($z_3 = 0$), and regenerative nodules greater than normal lobules ($z_3 = 1$), then TI = $0.150 + 2 \times 0.435 + 1 \times 1.465 + 0 \times (-0.614) + 1 \times (-1.336) = 1.149$. The positive value suggests a beneficial effect of prednisone. The standard error of TI [SE(TI)] can be estimated to be 0.709. Because NTI (the normalized therapeutic index = standardized normal deviate) is 1.62 (1.149/0.709), the suggested beneficial effect of prednisone is not quite significant ($p = 0.10$), but the indication nevertheless is that prednisone may be effective in this patient.

The four therapeutic variables can exist in 36 combinations. For each combination Table 3 gives the corresponding NTI and its statistical significance. The effect of prednisone varies widely with the particular combination of variables in the patient. The TI and its significance need not be calculated in each new case but may be read directly from Table 3 against the particular combination of the

*Table 3. Normalized Therapeutic Index for All Combinations of the Therapeutic Variables*

| Size of largest regenerative nodule in liver biopsy specimen | Ascites | Piecemeal necroses > five hepatocytes: None or few; ANF: − | ANF: + | ANF: ++ or +++ | Piecemeal necroses > five hepatocytes: Moderate or severe; ANF: − | ANF: + | ANF: ++ or +++ |
|---|---|---|---|---|---|---|---|
| ≤Normal lobule or undefined | None | $-0.87^{}$ (47.3%) | $3.22^{++}$ (12.3%) | $3.18^{+}$ (9.4%) | $2.42^{+}$ (0.6%) | $3.31^{++}$ (1.0%) | $3.98^{+++}$ (1.2%) |
| | Slight | $-2.37^{-}$ (5.3%) | $-0.15^{}$ (2.9%) | $1.23^{}$ (1.2%) | $1.55^{}$ (0%) | $2.41^{+}$ (0%) | $3.11^{++}$ (0.2%) |
| | Moderate or marked | $-3.29^{--}$ (4.9%) | $-1.97^{-}$ (2.3%) | $-0.49^{}$ (1.2%) | $0.57^{}$ (0%) | $1.32^{}$ (0.6%) | $2.00^{+}$ (0%) |
| >Normal lobules | None | $-3.04^{-}$ (5.1%) | $-1.87^{}$ (0.8%) | $-0.64^{}$ (1.2%) | $0.38^{}$ (0%) | $1.02^{}$ (0%) | $1.62^{}$ (0%) |
| | Slight | $-4.60^{---}$ (1.0%) | $-3.41^{--}$ (0.4%) | $-1.90^{}$ (0%) | $-0.47^{}$ (0%) | $0.15^{}$ (0%) | $0.78^{}$ (0%) |
| | Moderate or marked | $-5.22^{---}$ (0.4%) | $-4.21^{---}$ (0.2%) | $-2.82^{-}$ (0%) | $-1.30^{}$ (0%) | $-0.74^{}$ (0%) | $-0.11^{}$ (0.2%) |

Values in parentheses are percentages of patients with the particular combination. Superscript breakdown: +, index significantly positive ($0.01 < p < 0.05$); ++, index very significantly positive ($0.001 < p < 0.01$); +++, index highly significantly positive ($p < 0.001$); −, index significantly negative ($0.01 < p < 0.05$); −−, index very significantly negative ($0.001 < p < 0.01$); −−−, index highly statistically negative ($p < 0.001$). ANF, antinuclear factor.

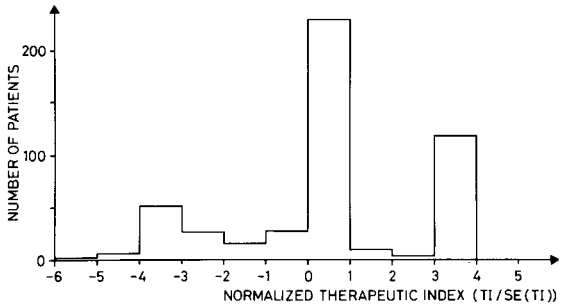


*Figure 2.* Distribution of the normalized therapeutic index [TI/SE(TI)] in the 488 patients.

patient's therapeutic variables. Some combinations are found in few or no patients. For these combinations the value of the TI represents an effect predicted from our (additive) model. The validity of the value of the TI for these combinations could not be tested directly from our data. Considering only the eight combinations occurring in >2% (accounting for ~90%) of the patients, the main result can be summarized as follows: prednisone seems beneficial if ANF is positive unless ascites or large regenerative nodules can be detected.

The distribution of the patients' TIs is shown in Figure 2. A significantly positive index (NTI >1.96) was found in 121 patients, whereas 96 patients had a significantly negative index (NTI <−1.96). The simple survival curves of these two groups are shown in Figures 3 and 4. They indicate that the effect of prednisone is markedly beneficial for NTI >1.96 (Figure 3) and markedly harmful for NTI <−1.96 (Figure 4). The $PI_{placebo}$ values (estimating "spontaneous" prognosis) were so similar in the groups that the marked differences in survival could not be explained by differences in prognostic factors between prednisone- and placebo-treated patients.

### *Predicting Effect of Prednisone on Survival Time*

The TI predicts whether prednisone will improve survival or not, but not the actual increase or decrease in survival time. This will also depend on prognostic factors. These factors (variables 5–12 in Table 1) are used in the $PI_T$ (defined in Methods).

The model predicts that the patient expected to benefit most from prednisone treatment should have moderately or markedly positive ANF ($z_1 = 2$), moderate or severe large piecemeal necroses ($z_2 = 1$), no ascites ($z_3 = 0$), and small regenerative nodules in the biopsy ($z_4 = 0$) (upper right position in Table 3).

For such a patient having the (median) prognostic variables of male sex ($z_5 = 1$), age 60 yr ($z_6 = 0$), prothrombin index 65% of normal ($z_7 = 0.17$), acetylcholine esterase activity 1.72 $\mu$mol/min · ml ($z_8 = 1.15$), moderate liver connective tissue inflammation ($z_9 = 2$), few efferent veins

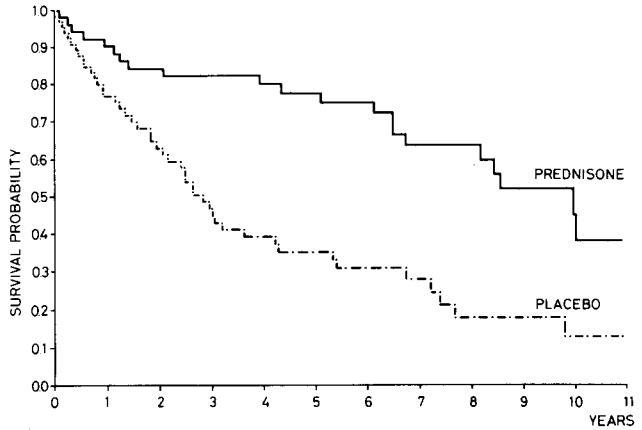


*Figure 3.* Actual survival curves of 121 patients [prednisone 56 (mean $PI_{plac} = -0.68$), placebo 65 (mean $PI_{plac} = -0.64$)] with significantly positive therapeutic indices (NTI >1.96). PI, prognostic index; NTI, normalized therapeutic index.

in liver regenerative nodules ($z_{10} = 1$), few diffuse focal small liver cell necroses not present ($z_{11} = 0$), and no eosinophil leukocytes in the liver parenchyma ($z_{12} = 0$), $PI_{prednisone}$ is −1.98 and $PI_{placebo}$ is 0.51. Using Figure 1, we find that the estimated median survival time during prednisone treatment is >10.3 yr and during placebo treatment 1.2 yr. [For the latter figure SE could be estimated to be 0.8 yr (see Appendix).] Thus the estimated gain of prednisone treatment in this type of patient is >10.3 − 1.2 = >9.1 yr added survival time. This beneficial effect of prednisone is illustrated in Figure 5.

Similarly, for the most unfavorable combination of the therapeutic variables (lower left position in Table 3), the prognostic variables being unchanged, $PI_{prednisone}$ is 1.174 and $PI_{placebo}$ is −1.24. Using Figure 1, we find that the estimated median survival time for prednisone is 0.6 yr (estimated SE = 0.2 yr) and for placebo 7.4 yr (estimated SE = 2.1 yr). Thus the estimated loss of survival time by using prednisone is 7.4 − 0.6 = 6.8 yr (SE = 2.1 yr). The harmful effect of prednisone is illustrated in Figure 6.

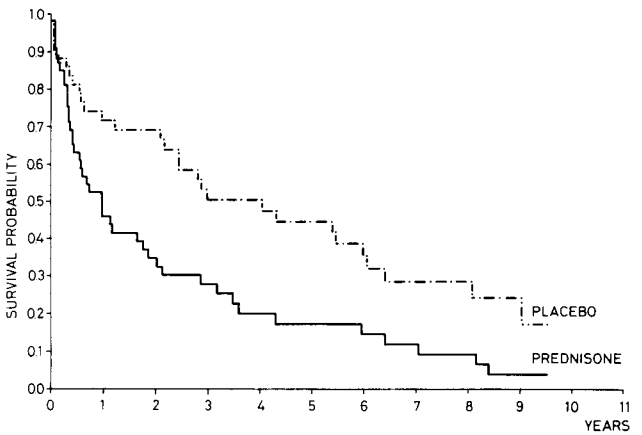


*Figure 4.* Actual survival curves of 96 patients [prednisone 54 (mean $PI_{plac} = -0.54$), placebo 42 (mean $PI_{plac} = -0.67$)] with significantly negative therapeutic indices (NTI <−1.96). PI, prognostic index; NTI, normalized therapeutic index.

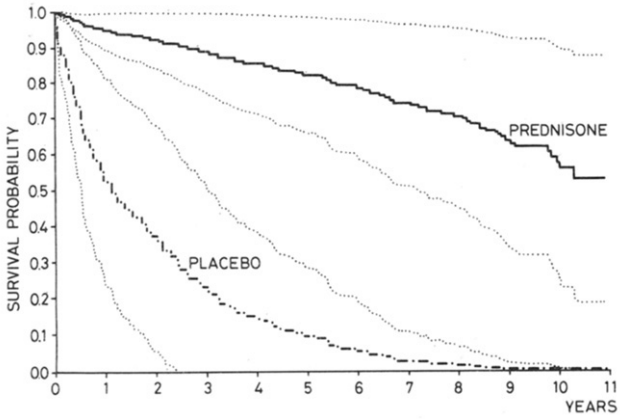


*Figure 5.* Survival curves and 95% confidence limits (*dotted lines*) estimated for the most favorable combination of the therapeutic variables (see Table 3) and the following prognostic variables: male sex ($z_5 = 1$), age 60 yr ($z_6 = 0$), prothrombin index 65% of normal ($z_7 = 0.17$), acetylcholine esterase activity 1.72 $\mu$mol/min · ml ($z_8 = 1.15$), moderate liver connective tissue inflammation ($z_9 = 2$), few efferent veins in liver regenerative nodules ($z_{10} = 1$), few diffuse focal small liver cell necroses not present ($z_{11} = 0$), and no eosinophil leukocytes in the liver parenchyma ($z_{12} = 0$). The method of estimation has previously been published (13,18).

### *Gain Obtained by "Optimal" Administration of Prednisone*

For each patient, median survival time was estimated ($PI_T$ and Figure 1) both for actual "random" treatment and for optimal treatment defined according to the sign of TI [positive: prednisone; negative: not prednisone (placebo)]. The distributions of the estimated median survival times are shown in Figure 7. The gain obtained by optimal treatment allocations is substantial. The total increase in expected survival time for 10 yr (see Appendix) obtained by optimal treatment allocation is estimated to be 349 yr in the 488 patients. This gain is not evenly distributed but mainly confined to those having a significantly positive (121 or 25%) or negative (96 or 19%) TI.

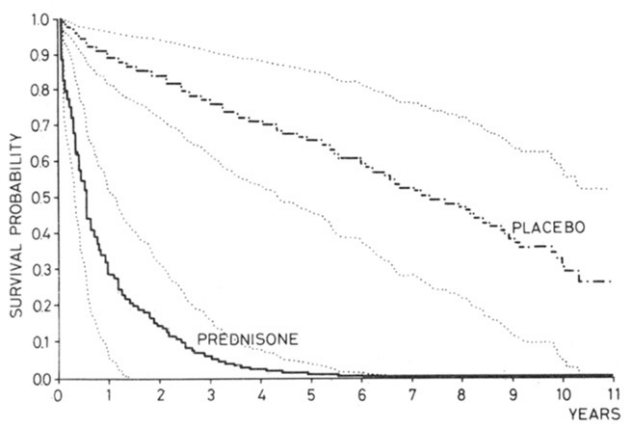


*Figure 6.* Survival curves and 95% confidence limits (*dotted lines*) estimated for the most unfavorable combination of the therapeutic variables (see Table 3) and the prognostic variables described in the legend to *Figure 5*. The method of estimation has previously been published (13,18).

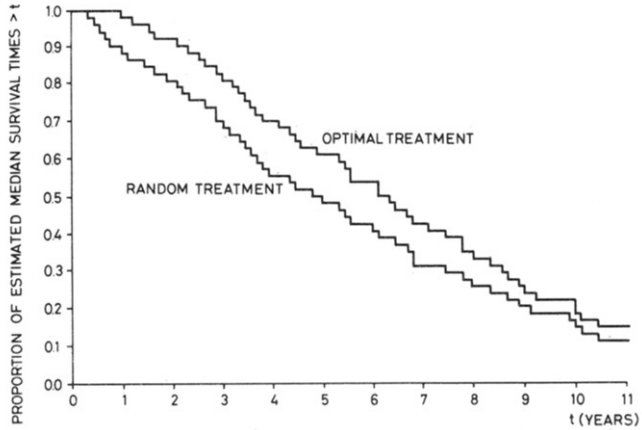


*Figure 7.* Cumulative distribution of estimated median survival times for the actual random treatment allocation and optimal treatment allocation according to the sign of the therapeutic index (TI) [positive: prednisone; negative: not prednisone (placebo)].

### *Characterization of Patients With Different Therapeutic Index*

Table 4 shows the distribution of pertinent variables in three groups defined by the TI.

The group with a significantly harmful effect of prednisone is characterized by relatively high frequency of men, alcoholics, and individuals with advanced disease clinically, biochemically, and histologically.

The group with a significantly beneficial effect of prednisone is characterized by relatively high frequency of women and individuals with "active" disease clinically, biochemically, and histologically. Three-fourths of the patients in this group are nonalcoholic women without ascites.

The group with an insignificant effect of prednisone shares some characteristics with the group having a harmful effect of prednisone (high incidence of men and alcoholism), but in regard to many variables, it takes up an intermediate position. However, the distribution of some variables indicates less advanced disease in this group as compared with the other groups.

It should be noted that of the 98 patients with chronic aggressive hepatitis, a significantly positive TI was found in 57 who almost all had positive ANF (Table 3). The remaining 41 had either an insignificant TI or a significantly negative TI.

*Table 4. Variables in Subgroups Defined by the Therapeutic Index*

| Variable | TI/SE(TI) <−1.96 n = 96 | −1.96 to 1.96 n = 271 | >1.96 n = 121 | p for heterogeneity[a] |
|---|---|---|---|---|
| General | | | | |
| Median age (*yr*) | 60 | 59 | 61 | 0.14 |
| Sex (male) (%) | 77 | 70 | 22 | $3 \times 10^{-10}$ |
| Median duration of history (*mo*) | 6 | 6 | 6 | 0.27 |
| Clinical | | | | |
| Ascites (%) | 74 | 11 | 1 | |
| Peripheral edema (%) | 49 | 18 | 21 | $7 \times 10^{-9}$ |
| Alcoholism (%) | 54 | 49 | 18 | $2 \times 10^{-9}$ |
| Hepatomegaly >5 cm below curvature (%) | 46 | 25 | 12 | $2 \times 10^{-6}$ |
| Spider nevi (%) | 44 | 32 | 19 | $6 \times 10^{-4}$ |
| Esophageal varices on x-ray (%) | 13 | 9 | 6 | 0.29 |
| Pain in liver (%) | 28 | 20 | 46 | $9 \times 10^{-7}$ |
| Collagenosis (%) | 3 | 5 | 18 | $5 \times 10^{-6}$ |
| Nonalcoholic women without ascites (%) | 8 | 25 | 74 | $<1 \times 10^{-10}$ |
| Laboratory | | | | |
| Median acetylcholine esterase ($\mu mol/min \cdot ml$) (2.0–6.1) | 2.06 | 2.59 | 2.70 | $5 \times 10^{-4}$ |
| Median albumin (g%) (<4.4) | 3.33 | 3.80 | 3.68 | $1 \times 10^{-3}$ |
| Median prothrombin (% *of normal*) (>70%) | 57 | 71.5 | 66 | $1 \times 10^{-5}$ |
| Median bilirubin (mg%) (<1.0) | 1.4 | 1.0 | 1.1 | $5 \times 10^{-3}$ |
| Median alkaline phosphatase (*King Armstrong Units*) (<10.0) | 14.1 | 12.0 | 15.6 | 0.01 |
| Median aspartate aminotransferase ($mmol/L \cdot h$) (<1.7) | 2.6 | 3.0 | 4.4 | $6 \times 10^{-6}$ |
| Median $\gamma$-globulin (g%) (<1.1) | 1.80 | 1.60 | 2.00 | $8 \times 10^{-5}$ |
| Positive antinuclear factor (%) | 15 | 14 | 97 | |
| Histologic | | | | |
| Macronodular cirrhosis (%) | 36 | 4 | 0 | |
| Lobular architecture totally destructed (%) | 69 | 54 | 36 | $7 \times 10^{-6}$ |
| Efferent veins in regenerative nodules (%) | 57 | 44 | 27 | $6 \times 10^{-5}$ |
| Cholestasis (%) | 16 | 13 | 4 | 0.01 |
| Mallory bodies (%) | 27 | 24 | 9 | $7 \times 10^{-4}$ |
| Steatosis (%) | 63 | 73 | 55 | $1 \times 10^{-3}$ |
| Moderate or marked connective tissue inflammation (%) | 52 | 58 | 74 | $2 \times 10^{-3}$ |
| Moderate or marked lymphocyte infiltration in connective tissue (%) | 46 | 51 | 68 | $3 \times 10^{-3}$ |
| Moderate or marked eosinophil cell infiltration in connective tissue (%) | 1 | 6 | 16 | $2 \times 10^{-4}$ |
| Chronic aggressive hepatitis (%) | 8 | 12 | 47 | $3 \times 10^{-11}$ |
| Moderate or severe small piecemeal necroses (%) | 19 | 21 | 56 | $1 \times 10^{-10}$ |
| Moderate or severe large piecemeal necorses (%) | 0 | 1 | 12 | |

[a] Tested by $\chi^2$ test (qualitative variables) or the Kruskal–Wallis nonparametric test (quantitative variables).

## Discussion

In controlled clinical trials it is common to investigate the therapeutic effect in subgroups defined by stratification according to one or few variables (9). However, with increasing stratification, the rapidly decreasing number of individuals in each stratum or subgroup implies a rapidly decreasing power of the appropriate statistical test. Therefore, stratification is of limited use if many variables are to be studied.

The multivariate method presented here, which utilizes the data of all the patients at the same time, has identified more variables that hold significant independent therapeutic information. It provides the means to condense this information to one number (the TI). For a given patient, the TI estimates how big the effect will be if he receives the treatment. Furthermore, it is possible to estimate how much the treatment will affect the survival time. The statistical assumptions of our particular version of the Cox model have been tested and were not found to be violated (13). In particular, we found no indication of the assumption of additivity in the model being violated.

Not all patients fit well within current disease classification schemes. Some are atypical with characteristics compatible with more than one diagnosis. Some patients not fulfilling the histologic criteria of chronic aggressive hepatitis (e.g., some nonalcoholic women without ascites) seem to benefit from steroid treatment (8). For these reasons we performed the multivariate analysis on the total group of patients with cirrhosis.

The analysis shows that large piecemeal necroses and a high concentration of antinuclear antibody are associated with a beneficial effect of prednisone. On the other hand, ascites and large regenerative nod-

ules in the liver biopsy specimen are associated with a harmful effect of prednisone treatment. The presence of histologic features of chronic aggressive hepatitis showed an insignificant trend toward a beneficial effect of prednisone. This variable was correlated with the ANF, and omission of the latter from the model made the former a statistically significant variable. Of the following three variables: sex, alcoholism, and ascites [defining the group of nonalcoholic women without ascites known to benefit from prednisone treatment (1)], only ascites was associated with a significant interaction with the treatment. Alcoholism had a weak, insignificant association with a harmful effect of prednisone treatment, and the sex did not tend to interact with the treatment.

It is interesting that aspartate aminotransferase and γ-globulin, often considered as valuable indicators of activity and hence of efficacy of prednisone treatment in chronic aggressive hepatitis, did not hold independent therapeutic information in the model. The reason for this is probably that high levels of aspartate aminotransferase and γ-globulin are unspecific findings. Thus high levels of aspartate aminotransferase may be found in alcoholic hepatitis, which probably benefits little from prednisone treatment (19–21). Furthermore, in chronic aggressive hepatitis the therapeutic significance of aspartate aminotransferase is probably different in HBsAg-positive and HBsAg-negative patients. It should be emphasized that the demonstrated considerable therapeutic disadvantage of large regenerative nodules, indicative of advanced disease (17), refers to the findings in percutaneous liver biopsies obtained using the Menghini technique (10).

Thus our results confirm 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 (3–8). However, less typical patients may also benefit from prednisone treatment if their TI, which combines the four significant therapeutic variables, is positive.

The TI may be calculated for any new patient using a pocket calculator. However, due to the simple scoring of the therapeutic variables, the index can take only 36 different values, which have been calculated in Table 3. So, for a new patient the index need not be calculated but can be read directly from Table 3 against the particular combination of the four therapeutic variables in the patient. As seen from Table 3 some combinations are more common than others, and some combinations have not been seen in our patients. For these combinations the TI is extrapolated and cannot be tested directly with our data. For 90% (disregarding combinations occurring in <2%) of the patients the therapeutic information may be summarized as follows: prednisone seems beneficial (NTI >1.96) if ANF is positive, unless ascites or large regenerative nodules can be detected.

The analysis is based on overall survival, i.e., the influence of side effects of prednisone treatment in regard to mortality is included and therefore accounted for in the results. However, the nonfatal side effects of prednisone, described in Methods, are not accounted for in the TI. This fact may indicate that positive values of TI should lead to administration of prednisone treatment only if the index is above a certain value. If only the effect on survival is considered important, all positive values of TI indicate beneficial effect of prednisone, but only values of the normalized therapeutic index above 1.96 are statistically significant.

The distribution of the TI revealed three major groups (Figure 2) with either beneficial, insignificant, or harmful effects of prednisone. Further analysis of these three groups revealed distinctive differences in a number of variables (Table 4). The patients with a significantly harmful effect of prednisone correspond rather closely to the patients with decompensated cirrhosis (predominantly male alcoholic patients). In these advanced cases the protein catabolic and other side effects of prednisone seem to outweigh any possible beneficial effects; death from bleeding varices tends to be increased by prednisone in patients with ascites (22). The patients with an insignificant effect of prednisone have a less advanced, compensated alcoholic liver disease with a high incidence of steatosis. The patients with a significantly beneficial effect of prednisone have an active disease with intensive hepatocellular damage and repair and pronounced enzymatic and immunologic abnormalities, but only about half of the patients fulfill the histologic criteria of chronic aggressive hepatitis, indicating that these may be too narrow in regard to decision about treatment and that other features of activity are important (7). 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 HBsAg-positive type of the disease (23). It is interesting to note that of the 98 patients with chronic aggressive hepatitis, 57 had a significantly positive TI (virtually all of whom had positive ANF, see Table 3), 8 had a significantly negative TI, and 33 had an insignificant TI. It is conceivable that the HBsAg-positive patients would be in the latter two groups (24–27). Therefore, if HBsAg had been available it would probably not have improved the therapeutic classification significantly.

By computation of the PI for prednisone and placebo treatment, respectively, it is possible to

predict the gain or loss from prednisone treatment in terms of the time added to or subtracted from the survival. The actual amount of time depends on the prognostic factors. For a given value of the TI, the number of years gained may be greater if the prognostic factors are favorable than if they are not. The total gain obtained by allocating each patient to the treatment indicated by his TI compared with random treatment allocation is 349 yr of added survival. However, this gain is mainly confined to the 217 patients (44%) with either significantly positive (121) or negative (96) TI.

Because our analysis is retrospective and has involved many statistical tests, there is a risk that some of our findings may be accidental. However, our statistical model has been validated on independent data as previously described (13), the identified therapeutic variables are biologically meaningful, the TI could reclassify our rather heterogenous patients into three relatively well-separated groups with biologically meaningful characteristics, and the marked difference in survival between prednisone- and placebo-treated patients with significantly positive or negative TIs (Figures 3 and 4) cannot be explained by differences in prognostic variables. For these reasons it is likely that the TI will be of value for identification of patients who benefit from prednisone treatment. However, the TI has not been validated prospectively on new patients in other centers, which would be the ultimate test of the TI. Furthermore, the TI presented may not be the best possible at all places or at all times, inasmuch as cirrhosis is not a firm nosological entity, and because new tests may contain better therapeutic information. However, evaluation of such tests by a new randomized clinical trial would not be justified with extreme groups (NTI $>1.96$ or $<-1.96$), but should be restricted to the intermediate group. Another difficulty is that the results will appear with a big delay in time, much more slowly than the invention of new tests, because it takes years to detect differences in mortality. In spite of this the version of Cox's regression model presented here appears to be well suited for development of new TIs.

## Appendix

Direct estimation of the standard error of the median survival difference [SE(MSD)] is possible but demands the total data base (18) and is therefore not feasible. However, by using the relation TI/SE(TI) = NTI = MSD/SE(MSD) (≈standardized normal deviate), SE(MSD) may be estimated as MSD/NTI. Thus a 95% confidence interval of MSD may be estimated as MSD $\pm$ 1.96 $\times$ MSD/NTI.

The expected survival time is given by the area $\int_0^\infty S(t)dt$ under the survival function $S(t)$ as previously described (18). This area may not be estimated very accurately because the estimated survival function $\hat{S}(t)$ (13,18) may not reach zero even for high values of $t$. Instead attention can be focused on the expected survival time during $T$ years defined by $\int_0^T S(t)dt$. In Results the gain in survival for the 488 patients during optimal compared to actual random treatment allocation is estimated from the expected survival times for 10 yr.

## References


1. Copenhagen Study Group for Liver Diseases. Sex, ascites and alcoholism in survival in patients with cirrhosis. N Engl J Med 1974;291:271–3.
2. Christensen E, Crowe J, Doniach D, et al. Clinical pattern and course of disease in primary biliary cirrhosis based on an analysis of 236 patients. Gastroenterology 1980;78:236–46.
3. Schlichting P, Fauerholdt L, Christensen E, et al. Prednisone treatment of chronic liver disease. I. Chronic aggressive hepatitis as a therapeutic marker. Liver 1982;2:104–12.
4. Cook GC, Mulligan R, Sherlock S. Controlled prospective trial of corticosteroid therapy in active chronic hepatitis. Q J Med 1971;40:159–85.
5. Soloway RD, Summerskill WHJ, Baggenstoss AH, et al. Clinical biochemical and histological remission of severe chronic active liver disease. A controlled study of treatments and early prognosis. Gastroenterology 1972;63:820–33.
6. Wright EC, Seeff LB, Berk PD, et al. Treatment of chronic active hepatitis. An analysis of three controlled trials. Gastroenterology 1977;73:1422–30.
7. Editorial. Immunosuppressive therapy for chronic active hepatitis. Lancet 1978;ii:507–8.
8. Schlichting P, Christensen E, Fauerholdt L, et al. Prednisone and chronic liver disease. II. Clinical versus morphological criteria for selection of patients for prednisone treatment. Liver 1982;2:113–8.
9. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. Br J Cancer 1977; 35:1–39.
10. Schlichting P, Fauerholdt L, Christensen E, et al. Clinical relevance of restrictive morphological criteria for the diagnosis of cirrhosis in liver biopsies. Liver 1981;1:56–61.
11. Schlichting P, Christensen E, Fauerholdt L, et al. Main causes of death in cirrhosis. Scand J Gastroenterol 1983;18:881–8.
12. Cox DR. Regression models and life tables (with discussion). J R Statist Soc B 1972;34:187–220.
13. Schlichting P, Christensen E, Andersen PK, et al. Prognostic factors in cirrhosis identified by Cox's regression model. Hepatology 1983;3:889–95.
14. Faber V, Elling P. Antinuclear factors (ANF) as determined by the immunofluorescent antibody technique. Acta Med Scand 1965;177:309–19.
15. Anderson SG, Addison IE, Dixon HG. Antinuclear-factor serum (homogeneous). An international collaborative study of the proposed research standard 66/233. Ann NY Acad Sci 1971;177:337–45.
16. Kristensen FB, Høier-Madsen M, Møller S. Organ-non-specific antinuclear antibodies (ANA) demonstrated on cultured human fibroblasts compared with a single graduating of fluorescence intensity on rat liver sections. (English abstract and tables). Ugeskr Læger 1982;144:1845–8.
17. Fauerholdt L, Schlichting P, Christensen E, et al. Conversion of micronodular cirrhosis into macronodular cirrhosis. Hepatology 1983;3:928–31.

18. Andersen PK, Christensen E, Fauerholdt L, et al. Measuring prognosis using the proportional hazards model. Scand J Statist 1983;10:49–52.
19. Maddrey WC, Boitnott JK, Bedine MS, et al. Corticosteroid therapy of alcoholic hepatitis. Gastroenterology 1978;75: 193–9.
20. Tygstrup N, Christensen E, Juhl E. Randomisierte Klinische Therapiestudien in der Hepatologie. Internist (Berlin) 1979; 20:565–70.
21. Depew W, Boyer T, Omata M, et al. Double-blind controlled trial of prednisolone therapy in patients with severe acute alcoholic hepatitis and spontaneous encephalopathy. Gastroenterology 1980;78:524–9.
22. Christensen E, Fauerholdt L, Schlichting P, et al. Aspects of the natural history of gastrointestinal bleeding in cirrhosis and the effect of prednisone. Gastroenterology 1981;81:944–52.
23. Dietrichson O, Juhl E, Nielsen JO, et al. The relevance of a serological classification of chronic hepatitis. Acta Pathol Microbiol Scand 1973;81:519–24.
24. Lam KC, Lai CL, Trepo C, et al. Deleterious effect of prednisolone in $HB_sAg$-positive chronic active hepatitis. N Engl J Med 1981;304:380–6.
25. Romeo F, Cannao G, Polosa P. Contraindication of prednisolone treatment in chronic active type-B hepatitis of moderate severity. Ital J Gastroenterol 1982;14:220–4.
26. Wu PC, Lai CL, Lam KC, et al. Prednisolone in $HB_sAg$-positive chronic active hepatitis: histologic evaluation in a controlled prospective study. Hepatology 1982;2:777–83.
27. European CAPO-group. EASL multicenter randomized clinical trial of low-dose steroid treatment in chronic active $HB_sAg$ positive liver disease (abstr.). Liver 1984;4:75.