Superiority of the Child–Pugh Classification to Quantitative Liver Function Tests for Assessing Prognosis of Liver Cirrhosis

I. ALBERS, H. HARTMANN, J. BIRCHER & W. CREUTZFELDT
Division of Gastroenterology and Endocrinology, Dept. of Internal Medicine, and
Division of Clinical Pharmacology, Georg August University of Göttingen,
Göttingen, FRG

Albers I, Hartmann H, Bircher J, Creutzfeldt W. Superiority of the Child–Pugh classification to quantitative liver function tests for assessing prognosis of liver cirrhosis. Scand J Gastroenterol 1989, 24, 269–276

To evaluate the prognostic value of quantitative liver function tests in comparison with established prognostic variables, the data of 47 patients with liver cirrhosis were analysed. A total of 16 variables, comprising the galactose elimination capacity and the indocyanine green clearance, the Child–Pugh classification, and several clinical and biochemical variables were subjected to Kaplan–Meier life-table analysis and Cox proportional hazards regression analysis. As independent variables, poor prognosis was associated significantly with increasing Child–Pugh score ($p < 0.00001$), whereas the galactose elimination capacity ($p = 0.03$) and the indocyanine green clearance ($p < 0.001$) were less sensitive indicators. The regression analysis showed prognostic value in decreasing sequence for Child–Pugh classification, age, sex, history of upper GI haemorrhage, and alkaline phosphatase activity. The quantitative liver function tests evaluated in the present work have less prognostic value than routinely accessible variables.

Key words: Child–Pugh classification; fractional indocyanine green clearance; galactose elimination capacity; liver cirrhosis; prognostic factors; quantitative liver function tests

Prof. Dr. med. W. Creutzfeldt, Medizinische Universitätsklinik, Robert-Koch-Straße 40, D-3400 Göttingen, FRG

Assessment of prognosis is an important factor in medical decision-making (1). In patients with liver cirrhosis several indicators are used to predict survival. These comprise clinical, biochemical, and histologic variables found to assess prognosis both as independent indicators of survival and as a combination of these factors as in various score systems (2–7).

It is not yet fully established whether impairment of liver function in cirrhosis of various aetiologies, estimated by quantitative liver function tests, is correlated to prognosis (8). Previous investigations have shown contradictory results. The [^{14}C]aminopyrine breath test was found to predict short-term survival in patients with alcoholic hepatitis (9) and in patients with liver disease who had undergone surgery (10); however, in another study this test did not add any information to the prediction of survival in cirrhosis (11). For the galactose elimination and the indocyanine green clearance as a constant infusion method, Gluud et al. (12) found no significant prognostic information with regard to death in alcoholic cirrhotic men.

The objective of this study was to investigate the prognostic value of two quantitative liver function tests, one of which is thought primarily to assess the functioning liver cell mass (galactose elimination capacity (GEC)) and the other to be dependent also on liver blood flow (fractional indocyanine green clearance (ICG)). Results of these tests were compared to established prognostic indicators.

PATIENTS AND METHODS

Patients

From 1982 to 1985, 47 patients with cirrhosis of the liver were recruited for a follow-up study in which survival time was observed until September 1987. The patients were admitted consecutively to the hospital of the University of Göttingen as in- or out-patients.

The diagnosis of cirrhosis was based on history, physical examination, and clinical and biochemical findings. It was confirmed by liver biopsy in 39 cases. In the other eight patients clotting abnormalities prevented histologic diagnosis. Nevertheless, the constellation of typical physical signs such as ascites, spider angiomatas, oesophageal varices, and typical laboratory findings was accepted as evidence of cirrhosis.

The aetiology of cirrhosis was considered to be excessive chronic alcohol consumption in 64%, chronic type-B hepatitis in 23%, and others in 13% (haemochromatosis, Wilson's disease, autoimmune chronic active hepatitis with cirrhosis).

Procedures

All patients were classified by a modified Child–Turcotte classification in accordance with Pugh et al. (13). This classification comprises ascites, encephalopathy, serum albumin and bilirubin levels, and prothrombin time. Each variable is given a value of 1 to 3 with increasing impairment of liver function.

Addition of the values leads to the modified Child's risk grades for each patient with 5 and 6 giving class A, 7–9 class B, and 10–15 class C, respectively (Table I).

Ascites was classified as none, slight, or moderate to severe in accordance with the results of the clinical examination and ultrasonography. Slight ascites was also assumed if the patients required aldosterone antagonists (>100 mg spironolactone daily) or loop diuretics for past ascites, even when at presentation no ascites could be detected. Actual portal-systemic encephalopathy was graded 0 to 4+ (14). Grade 1 to 2 encephalopathy was assumed if the patient was in need of continuous therapy with lactulose and neomycin. The severity of coagulation disorders was graded with the prothrombin time, with 70% and 40% as limits for mild and severe impairments.

Quantitative liver function tests were carried out in all patients and repeated in 12 patients of the survivor group. The GEC with 0.5 g/kg intravenously was determined by the method of Tygstrup (15) with peripheral venous blood sampling and a correction factor of 5 min for uneven distribution of galactose (16). The fractional ICG was performed with a bolus injection of 0.5 mg/kg intravenously, as described elsewhere by Caesar et al. (17).

The day of the patients' first presentation, when clinical and laboratory data were collected and quantitative liver function tests were performed, was used as zero time for the follow-up period of observation. All patients were evaluated during the stable state of liver disease.

Statistical analysis

The data were analysed with 30 September 1987 as closing date, resulting in a median period of observation of 34 months (range, 11 days to 62 months). The analysis was carried out in two

Table I. Grading of severity of liver disease in accordance with the Child–Pugh classification

Measurement	Numerical score for increasing abnormality		
	1	2	3
Ascites	None	Slight	Moderate to severe
Encephalopathy	None	Slight to moderate	Moderate to severe
Bilirubin (mg/dl)	<2	2–3	>3
Albumin (g/l)	>35	28–35	<28
Prothrombin time (%)	>70	40–70	<40

Table II. Clinical and laboratory data collected from 47 cirrhotics

Demographic data
Sex
Age
Clinical variables
Ascites
Encephalopathy
History of upper GI haemorrhage
Laboratory variables
Prothrombin time
Albumin
Bilirubin
Alkaline phosphatase activity
Serum aspartate aminotransferase
Serum alanine aminotransferase
Gamma-glutamyltranspeptidase
Cholinesterase
Others
Child–Pugh classification
Galactose elimination capacity (GEC)
Fractional indocyanine green clearance (ICG)

steps. To identify independent prognostic variables, 16 clinical and laboratory variables, including GEC and ICG (Table II), were analysed by the life-table method of Kaplan & Meier (18) with the aid of a commercial computer program, BMDP P1L (19).

Differences in survival curves—that is, in the probabilities of survival during the follow-up period, were tested with the nonparametric rank test in accordance with Mantel & Cox (20).

Discrete variables were computed directly, whereas continuous variables were stratified (21). To detect the cutoff points of the best discrimination between the various survival curves several different stratifications were performed. The nonparametric rank test proposed by Mantel & Cox was also applied to examine the best fit for stratified variables.

Second, the Cox proportional hazards regression analysis with survival time as dependent variable was applied to evaluate the relationship between survival and a set of variables (covariates) associated with survival (BMDP program P2L) (19). The regression model is formulated in terms of the relation of the investigated covariates with the hazard—that is, the risk of death within a given time interval. The relation of the covariates to survival is expressed as the predictor variables multiplied by their corresponding estimated regression coefficients (22). The goodness of fit of the model was investigated by a partial likelihood function, and the decision to include or to exclude the respective regressor variable was based on a chi-square test (19).

RESULTS

During the follow-up period 22 of the investigated 47 patients died (19 men, 3 women), and 2 patients were lost to follow-up. In 20 cases death was due to progressive liver failure or acute gas-

Table III. Initial findings for surviving and nonsurviving patients included in the study ($n = 45$*)

Variable	Surviving (n, or $\bar{x} \pm$ SD)	Nonsurviving† (n, or $\bar{x} \pm$ SD)
Sex (M/F)	13/10	19/3
Mean age (years)	47 ± 13	61 ± 11
Aetiology of cirrhosis		
Hepatitis B	4	6
Alcoholic	14	15
Others	5	1
Child–Pugh classification		
Class A	19	4
Class B	4	12
Class C	0	6
Quantitative liver function tests		
GEC (mg/min/kg)	5.1 ± 1.1	4.4 ± 1.3
ICG (min^{-1})	0.11 ± 0.05	0.07 ± 0.05

* Two patients lost to follow-up were excluded from the table.
† Two patients died of other than hepatic causes.

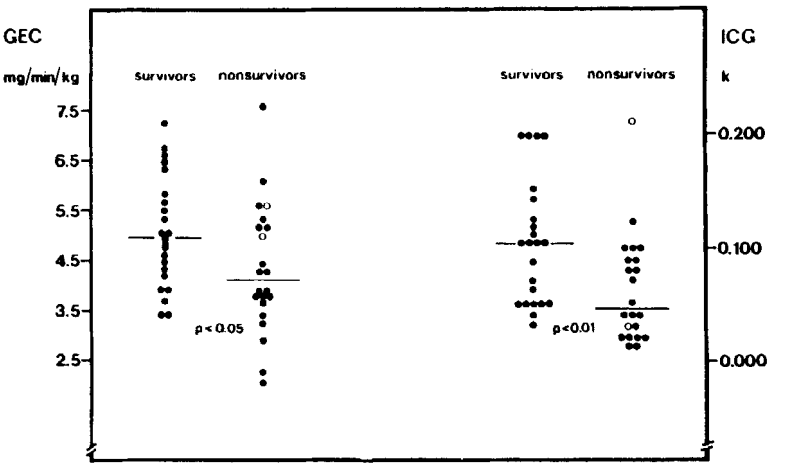

Fig. 1. Galactose elimination capacity (GEC) and fractional indocyanine green clearance (ICG) subdivided in accordance with the patients' survival state at the end of the study ($n = 45$; 2 lost to follow-up excluded). Open circles denote patients who died of nonhepatic causes. Statistics: median and t test.

trointestinal bleeding, whereas in 2 patients it was related to extrahepatic causes: 1 male patient with haemochromatosis died of congestive heart failure, and 1 female patient with alcoholic cirrhosis and insulin-dependent diabetes mellitus died of unknown cause, presumably as a result of hypoglycaemia. These two patients were excluded from further analysis. Mean survival time in the other nonsurviving patients was 14.7 ± 12.6 months ($\bar{x} \pm$ SD).

Distribution of sex, age, aetiology, Child-Pugh classification, and mean results of the quantitative liver function tests in the patients is shown in Table III. Individual results of GEC and fractional ICG at first presentation for survivors and nonsurvivors, as given in Fig. 1, show an overlap between the groups, even though the differences were found statistically significant.

The time course of the quantitative liver function tests in 12 of the surviving patients, as shown

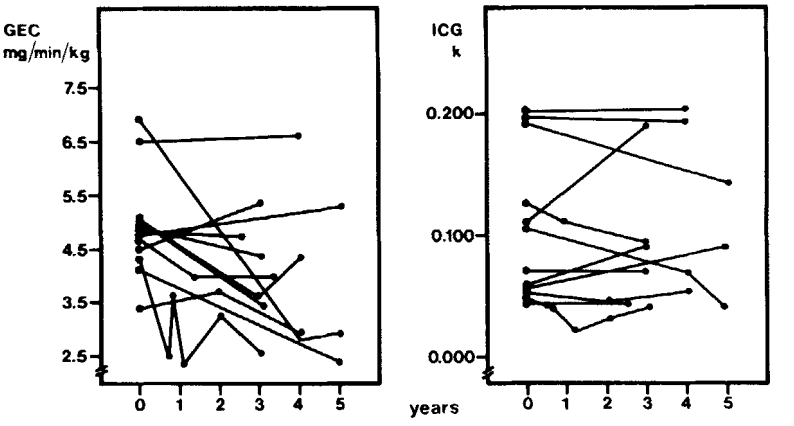

Fig. 2. Time course of galactose elimination capacity (GEC) and fractional indocyanine green clearance (ICG) in 12 surviving patients. The first value marks the respective entry into the study.

in Fig. 2, was quite variable. Few patients showed improvements, some remained unchanged, and others showed deterioration.

Survival analysis by the life-table method is shown in Fig. 3. The overall mortality in all patients included in the study was 51% at the end of the period of observation. Eleven of the investigated 16 variables showed independent prognostic value. The correlation of the Child–Pugh classification to survival was highly significant ($p < 0.00001$) (Fig. 3B). The results of GEC and ICG were of less but statistically significant prognostic value (GEC, $p = 0.03$; ICG, $p < 0.001$; Fig. 3C, D).

The other variables with independent association to poor prognosis comprise the following demographic data and features of history and clinical examination: age >55 years ($p < 0.007$), male sex ($p < 0.01$), ascites ($p < 0.001$), and encephalopathy ($p < 0.003$). The following biochemical variables showed prognostic value: serum bilirubin >1.5 mg/dl ($p < 0.0005$), prothrombin time <70% of normal ($p < 0.014$), alkaline phosphatase >200 U/l ($p < 0.04$), and serum albumin <28 g/l ($p < 0.05$).

Variables with no independent association with prognosis were aspartate aminotransferase ($p = 0.10$), alanine aminotransferase ($p < 0.2$), gamma-glutamyltranspeptidase ($p = 0.31$), cholinesterase ($p = 0.32$), and a history of GI haemorrhage ($p = 0.75$).

The final model from Cox proportional hazards regression analysis includes in decreasing order of priority the following variables of prognostic value: Child–Pugh classification, age, sex, history of upper GI haemorrhage, and alkaline phosphatase. GEC and ICG did not add prognostic information of statistical significance in this

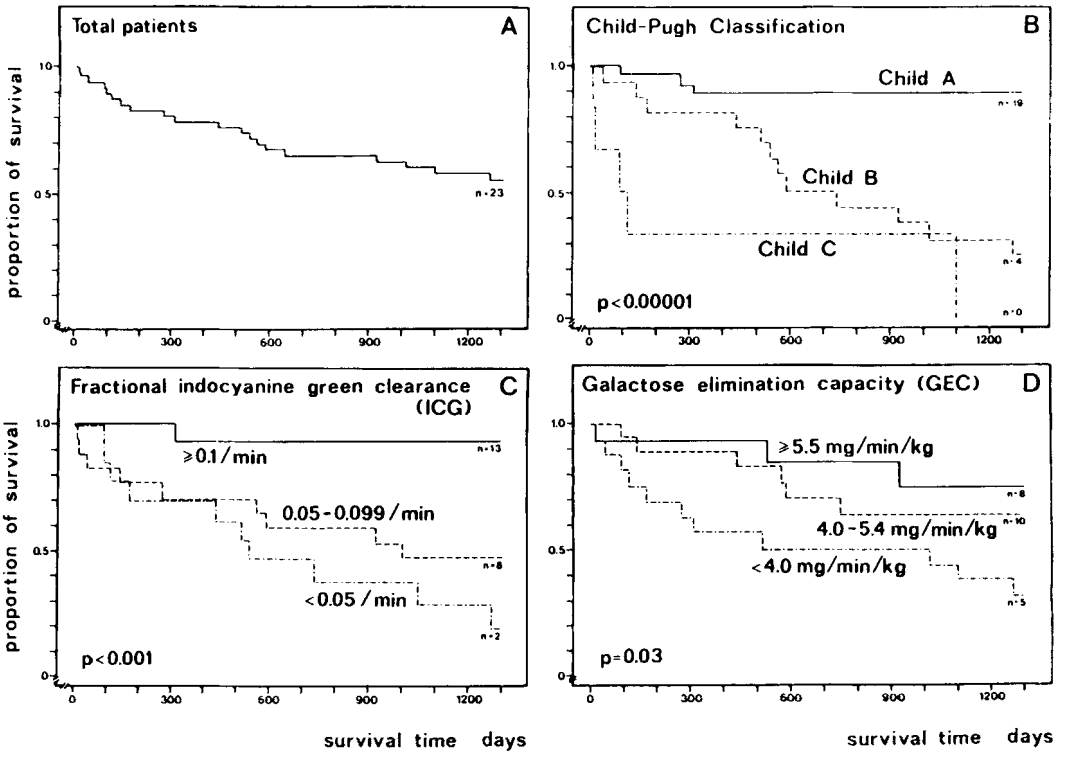

Fig. 3. Life-table analysis for independent prognostic indicators: panel A, all patients; panel B, subdivisions in accordance with the Child–Pugh classification; panel C and D, evaluation of GEC and ICG tests. *P* values are given by the nonparametric rank test proposed by Mantel and Cox.

Table IV. Variables with prognostic value in the final model obtained from Cox proportional hazards regression analysis

Variable*	df†	Log likelihood	Chi-square	P value	Relative risk‡
Constant		−62.6			
+Child–Pugh	1	−54.2	16.6	<0.0001	2.22 (0.93–5.30)
+Age	2	−49.3	10.0	0.002	1.12 (1.05–1.20)
+Sex	3	−46.6	5.4	0.02	14.78 (1.57–139.11)
+History of GIH	4	−44.3	4.5	0.034	0.28 (0.09–0.81)
+AP	5	−42.6	3.5	0.05	1.01 (1.00–1.01)

* Child–Pugh = Child–Pugh classification; GIH = upper GI haemorrhage; AP = alkaline phosphatase activity.
† df = Degrees of freedom.
‡ Relative risk with 95% confidence interval.

model. In the backward regression, GEC was removed at the seventh and ICG at the eighth step. For the variables included in the final Cox model the estimated regression coefficients, log likelihood for the model's fit, and p values from the chi-square test are shown in Table IV.

DISCUSSION

The results from this study show prognostic value for several variables including data from history, physical examination, and biochemical findings, which reflect the severity of liver cirrhosis. These results are in agreement with previous observations (3, 23–27).

As a combination of physical and biochemical variables, the Child classification (28) has proved to be of prognostic value in patients who underwent portosystemic shunt operation (29–32) and also in medically treated patients (23, 33). Each of the five variables proposed by Child and Turcotte also has independent prognostic value (7, 25–27). Christensen et al. (23), however, considered the prognostic significance of the Child–Turcotte classification incomplete. It was therefore proposed that this classification should be supplemented by additional prognostic information by using a prognostic index consisting of at least 12 variables.

In this study the Child classification modified by Pugh was used to group the patients. Previously, a valuable association with prognosis has been established (24, 34, 35). The advantage of the Child–Pugh classification consists in the better applicability in the grading of the patients and in the replacement of the nutritional status by the prothrombin time, which as an independent variable was found to be more closely associated to survival (7, 27).

For the Pugh modification Infante-Rivard et al. (24) suggested a slightly higher predictive value when using a multivariate model with indicator and continuous variable rather than the original scale with equivalent weight of each variable. In our study the simple Child–Pugh classification itself shows a highly significant association with survival both in the univariate analysis of Kaplan and Meier and in the multivariate Cox regression analysis. Compared with the Infante-Rivard modification the Child–Pugh classification has the merit of easy applicability in clinical practice.

Although diminished functioning of liver parenchyma cells in cirrhosis could be expected to show a better association with prognosis, the quantitative liver function tests were of no significant prognostic value in the regression analysis. As an independent indicator of prognosis, however, ICG had the same prognostic value as the presence of ascites (both $p < 0.001$), whereas GEC showed only a weak association with survival time ($p < 0.03$). These findings support the view that the quantitative liver function tests reflect only a single biochemical or haemodynamic variable, in contrast to 'hepatic function', which comprises several different processes.

The indicators of advanced liver disease included in the Child–Pugh classification, such as ascites, encephalopathy, increased serum bilirubin, decreased prothrombin time, and serum albumin, are part of the clinical picture of decom-

pensation and may be of high prognostic value because they are indicators of complications specific for advanced liver disease. In contrast, the two investigated quantitative liver function tests are thought to reflect the 'functioning liver cell mass' and possibly parenchymal blood flow, for which no critical level is known to be associated with decompensation or with survival. In fact, in a recent investigation we found that the relation of GEC and of ICG to complications of cirrhosis was not very close (36). It appears, therefore, that the physiologic derangements that are related to the manifestations of decompensation are more critical for survival of patients with cirrhosis than 'liver function' as expressed by the two tests.

It has been postulated that repeated application of quantitative liver function tests might be a rational procedure to define the rate of progression of a liver disease and by this means to lead to a more accurate prediction of prognosis. The time course of GEC and ICG observed in the 12 surviving patients (Fig. 2) shows considerable variation. This supports the contention that a single measure of the 'functioning liver cell mass' at a given time does not predict the subsequent time course for a particular patient and therefore is not closely related to prognosis.

For the time being single measurements of GEC and ICG cannot in clinical practice be given priority in the assessment of prognosis of patients with cirrhosis. This study, however, confirms the high independent prognostic value of the Child–Pugh classification.

ACKNOWLEDGEMENTS

The authors thank Dr. Robert Eggers and R. Muche for valuable assistance in mathematical and statistical problems and Mrs. H. Steinmetz and Ms. S. Zachmann for technical assistance.

REFERENCES

1. Creutzfeldt W, Beck K. Erhebungen über Ätiologie, Pathogenese, Therapieerfolge und Überlebenszeit an einem unausgewählten Krankengut von 560 Patienten mit Leberzirrhose. Dtsch Med Wochenschr 1966, 91, 682–689
2. Orrego H, Blake JE, Blendis LM, Medline A. Prognosis of alcoholic cirrhosis in the presence and absence of alcoholic hepatitis. Gastroenterology 1987, 92, 208–214
3. D'Amico G, Morabito A, Pagliaro L, Marubini E, the Liver Study Group of 'V. Cervello' Hospital. Survival and prognostic indicators in compensated and decompensated cirrhosis. Dig Dis Sci 1986, 31, 468–475
4. Moreau R, Sicot C. Evaluation du prognostic à court terme des cirrhotiques admis en réanimation, à l'aide de 4 indices de gravité. Gastroenterol Clin Biol 1985, 9, 871–876
5. Schlichting P, Christensen E, Andersen PK, Fauerholdt L, Juhl E, Poulsen H, Tygstrup N, the Copenhagen Study Group for Liver Diseases. Prognostic factors in cirrhosis identified by Cox's regression model. Hepatology 1983, 3, 889–895
6. Neuberger J, Altman DG, Christensen E, Tygstrup N, Williams R. Use of a prognostic index in evaluation of liver transplantation for primary biliary cirrhosis. Transplantation 1986, 41, 713–716
7. Orrego H, Israel Y, Blake JE, Medline A. Assessment of prognostic factors in alcoholic liver disease: toward a global quantitative expression of severity. Hepatology 1983, 3, 896–905
8. Bircher J. Assessment of prognosis in advanced liver disease: to score or to measure, that's the question. Hepatology 1986, 6, 1036–1037
9. Schneider JF, Baker AL, Haines NW, Hatfield G, Boyer JL. Aminopyrine *N*-demethylation: a prognostic test of liver function in patients with alcoholic liver disease. Gastroenterology 1980, 79, 1145–1150
10. Gill RA, Goodman MW, Golfus GR, Onstad GR, Bubrick MP. Aminopyrine breath test predicts surgical risk for patients with liver disease. Ann Surg 1983, 198, 701–704
11. Villeneuve JP, Infante-Rivard C, Ampelas M, Pomier-Layrargues G, Huet PM, Marleau D. Prognostic value of the aminopyrine breath test in cirrhotic patients. Hepatology 1986, 6, 928–931
12. Gluud C, Henriksen JH, Nielsen G, the Copenhagen Study Group for Liver Diseases. Prognostic indicators in alcoholic cirrhotic men. Hepatology 1988, 8, 222–227
13. Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973, 60, 646–649
14. Conn HO, Lieberthal MM. Assessment of mental state. In: Conn HO, Lieberthal MM, eds. The hepatic coma syndromes and lactulose. The Williams & Wilkins Co., Baltimore, 1979, 169–188
15. Tygstrup N. Determination of the hepatic elimination capacity (Lm) of galactose by single injection. Scand J Clin Lab Invest 1966, 18, 118–125
16. Bircher J, Blankart R, Halpern A, Häcki W, Laissue J, Preisig R. Criteria for assessment of functional impairment in patients with cirrhosis of the liver. Eur J Clin Invest 1973, 3, 72–85
17. Caesar J, Shaldon S, Chiandussi L, Guevara L, Sherlock S. The use of indocyanine green in

measurement of hepatic blood flow and as a test of hepatic function. Clin Sci 1961, 21, 43–57
18. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Statist Assoc 1958, 53, 457–481
19. Dixon, WJ. BMDP statistical software. University of California Press, Berkeley, Los Angeles, 1981
20. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, Mantel N, 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
21. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, Mantel N, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. Br J Cancer 1976, 34, 585–612
22. Cox DR. Regression models and life-tables (with discussion). J R Statist Soc 1972, B 34, 187–220
23. Christensen E, Schlichting P, Fauerholdt L, Gluud C, Andersen PK, Juhl E, Poulsen H, et al. Prognostic value of Child–Turcotte Criteria in medically treated cirrhosis. Hepatology 1984, 4, 430–435
24. Infante-Rivard C, Esnaola S, Villeneuve JP. Clinical and statistical validity of conventional prognostic factors in predicting short-term survival among cirrhotics. Hepatology 1987, 7, 660–664
25. Llach J, Ginès P, Arroyo V, Rimola A, Titó L, Badalamenti S, Jiménez W, et al. Prognostic value of arterial pressure, endogenous vasoactive systems, and renal function in cirrhotic patients admitted to the hospital for the treatment of ascites. Gastroenterology 1988, 94, 482–487
26. Milani A, Marra L, Siciliano M, Rossi L. Prognostic significance of clinical and laboratory parameters in liver cirrhosis—a multivariate statistical approach. Hepatogastroenterology 1985, 32, 270–272
27. Christensen E, Schlichting P, Andersen FK, Fauerholdt L, Schou G, Pedersen BV, Juhl E, et al. Updating prognosis and therapeutic effect evaluation in cirrhosis with Cox's multiple regression model for time-dependent variables. Scand J Gastroenterol 1986, 21, 163–174
28. Child CG, Turcotte JG. Surgery and portal hypertension. In: Child CG, ed. The liver and portal hypertension. W.B. Saunders Co., Philadelphia, 1964
29. Campbell DP, Parker DE, Anagnostopoulos CE. Survival prediction in portacaval shunts. Am J Surg 1973, 126, 748–751
30. Turcotte JG, Lambert MJ. Variceal hemorrhage, hepatic cirrhosis, and portacaval shunts. Surgery 1973, 73, 810–817
31. Conn HO, Resnick RH, Grace ND, Atterbury CE, Horst D, et al. Distal splenorenal shunt vs. portal-systemic shunt: current status of a controlled trial. Hepatology 1981, 1, 151–160
32. Conn HO. A peak at the Child–Turcotte classification. Hepatology 1981, 1, 673–676
33. Sarin SK, Chari S, Sundaram KR, Ahuja RK, Anand BS, Broor SL. Young *v* adult cirrhotics: a prospective comparative analysis of the clinical profile, natural course and survival. Gut 1988, 29, 101–107
34. *Pascal JP, Cales P, a multicenter study group.* Propranolol in the prevention of first upper gastrointestinal tract hemorrhage in patients with cirrhosis of the liver and esophageal varices. N Engl J Med 1987, 317, 856–861
35. Sauerbruch T, Weinzierl M, Köpcke W, Paumgartner G. Long-term sclerotherapy of bleeding esophageal varices in patients with liver cirrhosis. Scand J Gastroenterol 1985, 20, 51–58
36. Albers I, Hartmann H, Creutzfeldt W. Vergleich quantitativer Leberfunktionsprüfungen zu klinischen, laborchemischen und bioptischen Befunden bei Patienten mit Lebererkrankungen. Z Gastroenterol 1988, 26, 130–136

Received 1 August 1988
Accepted 9 November 1988