0270-9139/89/1001-0111$02.00/0
HEPATOLOGY
Vol. 10, No. 1, pp. 111-113, 1989
Printed in U.S.A.
Copyright © 1989 by the American Association for the Study of Liver Diseases

Editorial

Prognostication in Primary Biliary Cirrhosis: Relevance to the Individual Patient

At the time of diagnosis, patients with primary biliary cirrhosis (PBC) show a wide spectrum of disease severity (1), ranging from asymptomatic with a survival indistinguishable from normal (2) to very severely ill with a markedly reduced life expectancy (1, 2).

Although small therapeutic effects have been reported for azathioprine (3) and colchicine (4), no known drug effectively stops the progression of the disease (5). Therefore, liver transplantation is being performed with increasing frequency in patients with advanced disease (6). In order to ensure correct timing of transplantation (neither too early, nor too late), interest in how to estimate prognosis reliably in the individual patient has grown, and various statistical methods have been applied to combinations of clinical, biochemical and histological data of patients with PBC in an attempt to identify variables which predict the survival time of the patient.

PREDICTORS OF SURVIVAL WITHOUT TRANSPLANTATION

Since PBC is an intrahepatic, chronic, nonsuppurative, destructive cholangitis which ultimately leads to cirrhosis, indicators of cholestasis severity and cirrhosis might be expected to have some prognostic value.

Ten years ago, Shapiro et al. (7) reported that the bilirubin level was an important prognostic factor in PBC. They noted that, after a relatively stable phase of varying length, the bilirubin showed an accelerated increase prior to death (7). A similar course is seen in other types of cirrhosis as well (8). Shapiro et al. specifically found that after two successive bilirubin values above 2 mg per dl obtained 6 months apart, the patient lived an average of 4.1 years (95% confidence interval 2.7 to 6.2 years); after two successive bilirubin values above 6 mg per dl, the average survival time was 2.1 (1.6 to 2.7) years, and after two values above 10 mg per dl, the survival time was 1.4 (1.1 to 1.8) years (7). Even though these observations have never been validated in an independent sample, the paramount importance of the bilirubin level as a prognostic factor in PBC has been confirmed in all subsequent studies evaluating prognosis (1–3, 9).

In a study based on data from the international trial evaluating the effect of azathioprine vs. placebo (3, 10), it was found that in addition to an increased bilirubin level, old age and presence of cirrhosis were also independent factors indicative of a poor prognosis (1). These results were obtained by simpler statistical analyses of subgroups using stratification (11). However, using such methods, the influence of only a few variables can be analyzed simultaneously. In contrast, the Cox multiple regression model for survival data (12, 13) can assess the influence of many different variables simultaneously, provided that certain assumptions are fulfilled (13).

In 1983, Roll et al. (2) published the first results using the Cox regression analysis method and found that elevated bilirubin, old age and hepatomegaly were independent risk factors associated with a poor prognosis, whereas the presence of portal fibrosis without bridging fibrosis or cirrhosis was associated with a better prognosis.

Using the Cox regression model to analyze the data obtained from the international azathioprine trial, the following variables were found independently to define a poor prognosis: an elevated serum bilirubin, old age, cirrhosis, low serum albumin and central cholestasis (3). In addition, azathioprine treatment was associated with a slightly better survival (3). All of these variables could be combined to create a prognostic index to estimate the survival of individual patients (3). The prognostic index is easy to estimate using a pocket chart (14), and by applying simple diagrams, it can be transformed to a probability of surviving a given time or an estimated median survival time (3, 14). It has been shown using an independent sample that survival predicted by the prognostic index corresponds rather closely to the observed survival if the patients are divided into three groups having a good, medium or poor prognosis (3). Confidence limits for the survival curves predicted by the model have been reported as well (3). Confidence limits for predicted survival curves can be obtained using a published Cox regression analysis computer program (15) modified for standard error estimation (3, 16).

In this issue of *Hepatology,* Dickson et al. (9) from the Mayo Clinic report a new pragmatic prognostic model which includes age, bilirubin, albumin, prothrombin time and the severity of edema, and omits the use of variables requiring a liver biopsy. The analysis is based on patients included in a trial evaluating the effect of D-penicillamine vs. placebo in patients with advanced histologic disease, either Stage 3 or 4 (17), and another unpublished trial comparing the same therapies in patients with early Stage 1 and 2 diseases. The authors claim that D-penicillamine had no effect in either of the two trials, but the data from the latter trial have not yet been presented.

Address reprint requests to: Erik Christensen, M.D., Dr.Med., Medical Department F, Glostrup University Hospital, Ndr. Ringvej 29, DK-2600 Copenhagen, Glostrup, Denmark.

Nonetheless, the authors combined the data from all of these patients without adjustment for therapy in their analysis.

These authors claim that the model fits the observed survival data of the patients if these are divided into five risk score groups [Fig. 1 of Ref. (9)]. Unfortunately, no confidence limits, either for the observed or for the predicted survival curves of the five risk score groups, are provided in the figure. When one looks more closely at their figure, it appears that the observed survival curve (Kaplan-Meier estimate) for the third risk group follows the predicted survival for the second risk group up to 1.5 years and, from about 2 to 4 years, it follows the predicted survival curve for the fourth risk group, yet the observed survival curve for the fourth risk group lies below the corresponding predicted survival curve from year 1 and beyond.

Dickson et al. (9) also compare their model with that developed from the international azathioprine trial (3) and find a very high correlation ($r = 0.92$) between risk scores obtained from the two models. This finding should not be particularly surprising, as the two models have three variables (bilirubin, age and albumin) in common, of which bilirubin and age had by far the greatest impact on both models.

As might be expected, the Mayo model (9) appeared to predict survival slightly better in the Mayo cross-validation patients [Fig. 3 of Ref. (9)]. The reader should be aware of the fact that the statistical comparison between the observed and predicted survival curves using the one-sample log-rank test needs to be interpreted with great caution because the predicted survival curves are random and not fixed, as is assumed by the test. As a result, the p values obtained in this situation are too low. Clearly, confidence limits for the predicted curves (3) would have been useful, but, unfortunately, they were not estimated by the authors.

Figure 3 in the paper by Dickson et al. (9) demonstrates the overlap concerning individual survival times (*e.g.* some patients in the low-risk group die *before* some patients in the high-risk group), which is seen also using the European model [Fig. 7 of Ref. (3)]. Thus, neither model can yield a precise estimate for an individual patient's prognosis.

One obvious reason for this imprecision of both models is that the prognostic variables utilized do not contain sufficient prognostic information; better prognostic variables need to be identified. In this context, it may be useful to study whether inclusion of quantitative liver function tests such as the aminopyrine breath test (18), galactose elimination capacity (19) and serum hyaluronate (20) in the prognostic models for PBC can increase their predictive power. However, in a large group of cirrhotic patients of mixed etiologies, the aminopyrine breath test did not provide prognostic information additional to that of the Child-Turcotte criteria (21).

Another and perhaps more important reason for the imprecision of the current prognostic models is that they have utilized data recorded at only one time during an often long course of individual patient's disease. One cannot expect precise prognostic estimates to be obtained from such information. Although the course of PBC is one of progression, fluctuations in symptoms, signs and biochemical variables do occur. Moreover, diagnoses are often made during an exacerbation which brings the patient to the doctor. Thus, data obtained at such a time may reflect the prognosis less precisely than later "steady-state" data (8). Furthermore, one might reasonably expect that the utilization of follow-up data in a statistical model for prognosis estimation would improve the model's predictive pover. In this regard, it should be noted that it is possible for time-dependent variables to be incorporated in the Cox regression model (12, 13, 22).

PREDICTORS OF EARLY MORTALITY AFTER TRANSPLANTATION

An important application of any model defining liver disease prognosis is the ability to time liver transplantation correctly. The physician caring for liver disease patients is faced with the problem of defining the time when the prognosis for an individual patient is better with a transplant than without it. This is not easy, as the prognosis following a transplant depends on factors quite different from those that determine prognosis without a transplant.

Following a liver transplantation, mortality is concentrated within the first few postoperative months (6). The major causes of early death are sepsis and bleeding (6, 23). In a study from Pittsburgh comprising 93 liver transplanted patients (including 27 patients with PBC), the following *pretransplant* variables were associated with an early death: elevated creatinine (>1.7 mg per dl), markedly elevated bilirubin (>18.6 mg per dl), encephalopathy, ascites, elevated white blood cell count (>7,632 cells per mm^2) and elevated polymorphonuclear cell count (>5,300 cells per mm^2) (24). Of these variables, the plasma creatinine >1.7 mg per dl showed the greatest accuracy of prediction of early death (24). However, these results, which were never validated using an independent sample of patients, may not be an optimal utilization of the data because: (i) continuous variables like creatinine and bilirubin levels were dichotomized (above and below a certain cut-off value), a method whereby important information may be lost; (ii) the actual length of the survival was not utilized, and (iii) the specific type of liver disease of the patients studied was not taken into account.

HOW CAN WE USE THE CURRENTLY AVAILABLE INFORMATION?

In patients transplanted for PBC, the observed survival after the transplantation has been reported as significantly better than the expected survival without transplantation as estimated by the European (25) and Mayo models (26), despite an initial high postoperative mortality. In one of the studies, the estimated median survival time before transplantation was 5 months, but in four patients it was more than 1 year (25). As a practical guideline, it might be reasonable to begin to consider a transplantation if the estimated survival is less than 1 year [corresponding to a European prognostic index >5.9 (3) or a Mayo risk score >8.2 (9)]. Once the

estimated survival time is less than 6 months (European prognostic index >6.7 and Mayo risk score >8.97), transplantation should be performed before the development of encephalopathy, marked decompensation, renal failure and infection because these factors have been shown to increase the early mortality after transplantation (24).

ROUTES FOR FURTHER PROGRESS

As mentioned above, a time-dependent Cox regression model for PBC would probably refine current estimates of survival without transplantation. Furthermore, a Cox regression model relating posttransplant survival to pretransplant data of patients with PBC might improve the pretransplant prediction of survival after a transplantation for such patients. If such a model became available, it might be possible, in a given patient, to compare the survival time predicted *with* transplantation with that predicted *without* transplantation (3, 9), and thus the decision for transplantation could be made if the former were longer than the latter, Such a method for deciding for or against transplantation would appear justified and reasonable, as no data from controlled clinical trials assessing such decision making are yet available. It appears most unlikely, for ethical reasons, that controlled clinical trials addressing this point will ever be performed.

ERIK CHRISTENSEN, M.D., DR.MED.
Medical Department F
Glostrup University Hospital
DK-2600 Copenhagen Glostrup
Denmark

REFERENCES

1. 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; 78:236–246.
2. Roll J, Boyer JL, Barry D, et al. The prognostic importance of clinical and histologic features in asymptomatic and symptomatic primary biliary cirrhosis. N Engl J Med 1983; 308:1–7.
3. Christensen E, Neuberger J, Crowe J, et al. Beneficial effect of azathioprine and prediction of prognosis in primary biliary cirrhosis. Final results of an international trial. Gastroenterology 1985; 89:1084–1091.
4. Kaplan MM, Alling DW, Zimmerman HJ, et al. A prospective trial of colchicine for primary biliary cirrhosis. N Engl J Med 1986; 315:1448–1454.
5. Wiesner RH, Grambsch PM, Lindor KD, et al. Clinical and statistical analyses of new and evolving therapies for primary biliary cirrhosis. Hepatology 1988; 8:668–676.
6. Bismuth H, Castaing D, Ericzon GB, et al. Hepatic transplantation in Europe. First report of the European liver transplant registry. Lancet 1987; 2:674–676.
7. Shapiro JM, Smith H, Schaffner F. Serum bilirubin: a prognostic factor in primary biliary cirrhosis. Gut 1979; 20:137–140.
8. Christensen E, Schlichting P, Fauerholdt L, et al. Changes of laboratory variables with time in cirrhosis: prognostic and therapeutic significance. Hepatology 1985; 5:843–853.
9. Dickson ER, Grambsch PM, Fleming TR, et al. Prognosis in primary biliary cirrhosis: model for decision making. Hepatology 1989; 9:1–7.
10. Crowe J, Christensen E, Smith M, et al. Azathioprine in primary biliary cirrhosis: a preliminary report of an international trial. Gastroenterology 1980; 78:1005–1010.
11. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analyses and examples. Br J Cancer 1977; 35:1–39.
12. Cox DR. Regression models and life tables (with discussion). J R Stat Soc B 1972; 34:187–220.
13. Christensen E. Multivariate survival analysis using Cox's regression model. Hepatology 1987; 7:1346–1358.
14. Christensen E. Individual therapy-dependent prognosis based on data from controlled clinical trials in chronic liver disease (Thesis). Dan Med Bull 1988; 35:167–182.
15. Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. New York: John Wiley & Sons, 1980.
16. Tsiatis AA. A large sample study of Cox's regression model. Ann Stat 1981; 9:93–108.
17. Dickson ER, Fleming TR, Wiesner RH, et al. Trial of penicillamine in advanced primary biliary cirrhosis. N Engl J Med 1985; 312:1011–1015.
18. Baker AL, Krager PS, Kotake AN, et al. The aminopyrine breath test does not correlate with histologic disease severity in patients with cholestasis. Hepatology 1987; 7:464–467.
19. Lindskov J. The quantitative liver function as measured by the galactose elimination capacity. II. Prognostic value and changes during disease in patients with cirrhosis. Acta Med Scand 1982; 212:303–308.
20. Nyberg A, Engström-Laurent, Lööf L. Serum hyaluronate in primary biliary cirrhosis—a biochemical marker for progressive liver damage. Hepatology 1988; 8:142–146.
21. Villeneuve J-P, Infante-Rivard C, Ampelas M, et al. Prognostic value of the aminopyrine breath test in cirrhotic patients. Hepatology 1986; 6:928–931.
22. Christensen E, Schlichting P, Andersen PK, et al. Updating prognosis and therapeutic effect evaluation in cirrhosis using Cox's multiple regression model for time-dependent variables. Scand J Gastroenterol 1986; 21:163–174.
23. Cuervas-Mons V, Martinez AJ, Dekker A, et al. Adult liver transplantation: an analysis of the early causes of death in 40 consecutive cases. Hepatology 1986; 6:495–501.
24. Cuervas-Mons V, Millan I, Gavaler JS, et al. Prognostic value of preoperatively obtained clinical and laboratory data in predicting survival following orthotopic liver transplantation. Hepatology 1986; 6:922–927.
25. Neuberger J, Altman DG, Christensen E, et al. Use of a prognostic index in evaluation of liver transplantation for primary biliary cirrhosis. Transplantation 1986; 41:713–716.
26. Dickson ER, Grambsch P, Markus BM, et al. Transplantation markedly improves survival in PBC patients: application of the Mayo model on Pittsburgh transplant patients (Abstract). Gastroenterology 1988; 94:A535.