Primary Biliary Cirrhosis: Prediction of Short-term Survival Based on Repeated Patient Visits

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The progression of primary biliary cirrhosis was studied in 312 patients who were seen at the Mayo Clinic between January 1974 and May 1984. Follow-up was extended to April 30, 1988, by which time 140 of the patients had died and 29 had undergone orthotopic liver transplantation. These patients generated 1,945 patient visits that enabled us to study the change in the prognostic variables of primary biliary cirrhosis (age, bilirubin value, albumin value, prothrombin time and edema) from the time of referral. Also, using this database and the Cox proportional-hazards regression model, we developed an updated model for primary biliary cirrhosis that can be used to predict short-term survival at any time in the course of the disease. This model uses the values of the prognostic variables measured at the latest patient visit. Comparison of predicted survival from the update model and the natural history model of primary biliary cirrhosis showed that the updated model was superior to the original model for predicting short-term survival. This finding applied to both the Mayo Clinic patients and an independent set of 83 Dutch patients. The Mayo updated model is recommended for improving the accuracy of predictions of survival during the 2 yr after a patient visit. (HEPATOLOGY 1994;20:126-134.)

Primary biliary cirrhosis (PBC) is a chronic liver disease for which there is no totally effective treatment other than liver transplantation (1, 2). Considerable effort has been devoted to the development of models to predict the survival of patients who have the disease in an effort to optimize the selection of transplant recipients (3-5). The most common approach has been to use Cox proportional-hazards regression (6) to model survival as a function of clinical, biochemical and histological variables measured at the time of diagnosis or referral to the center. The Mayo PBC model (5), for example, bases its predictions on a risk score calculated from the patient's age, total serum bilirubin value, serum albumin value, prothrombin time and presence or absence of edema and diuretic therapy. This model has been widely used and studied in various patient settings (7-11).

Some investigators have modeled the progression of liver disease in an effort to use the changing values of clinical variables to improve the accuracy of survival predictions (8, 12). As originally presented (5), the Mayo PBC model uses referral values of variables to estimate the probability of surviving up to 7 yr later. Because most patients with PBC make repeated visits to the clinic, it is natural to ask (1) how well the Mayo model predicts survival based on measurements determined later in the course of disease and (2) whether a "better" model can be developed that uses updated risk scores to predict short-term survival. We approach these questions in much the same way as Hughes et al. (13), whose article appeared while ours was in review.

METHODS

Patient Population and Clinical Database. We focused on the same 312 patients with PBC who were used to develop the first version of the Mayo model (5). (The data set for the final version of that model included an additional 106 Mayo patients who had originally been used for cross-validation purposes.) These 312 patients were enrolled in two clinical trials evaluating the use of D-penicillamine for treating PBC (14). Patient accrual took place from January 1974 through May 1984. No benefit of D-penicillamine was found, but the patients have been followed regularly since the trials ended.

For the purposes of the current study, follow-up was extended to April 30, 1988. (This date was not extended further to minimize biases introduced by the increasing frequency of orthotopic liver transplantation in recent years.) By 1988, 140 of the patients had died, 169 were still alive, and three had been lost to follow-up (last known status was in 1986). Of the 312 patients, 29 had undergone transplantation, and seven of these had died by the time of last follow-up. As in the earlier Mayo

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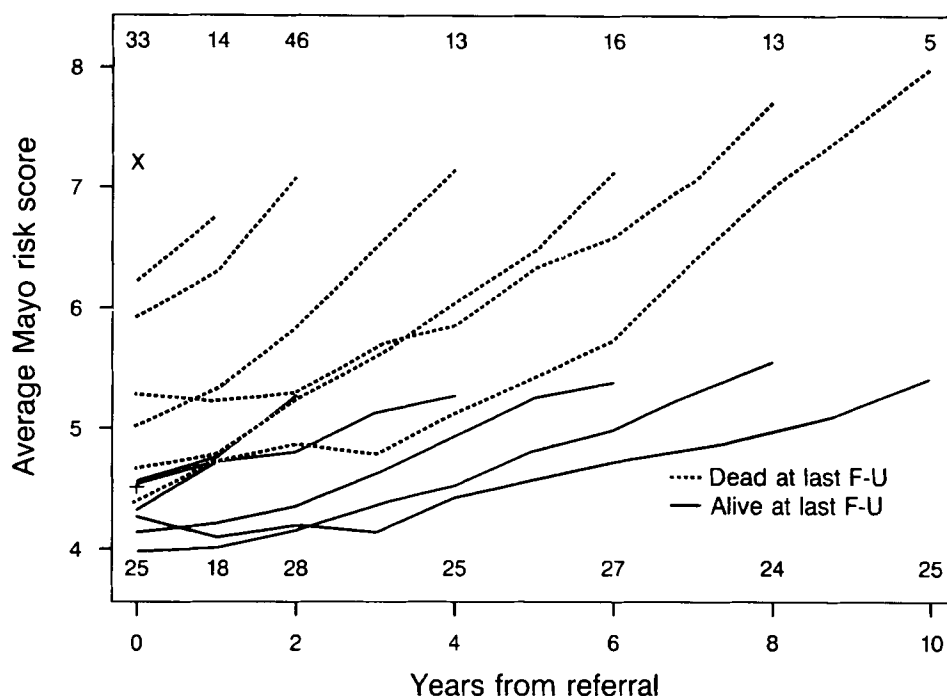
FIG. 1. Progression of Mayo risk score in cohorts based on time of last visit. *Solid lines* indicate average risk scores, interpolated at yearly intervals, for groups of patients who were alive at last follow-up (F-U) (cohort sizes are given at bottom of plot). *Dashed lines* indicate groups of patients who were dead at last follow-up (cohort sizes are provided at top of plot). The cohorts were as follows: only one visit (x = dead at last follow-up; + = alive at last follow-up); last visit 0 to 1 yr after referral; last visit 1 to 2 yr after referral; 2 to 4 yr; 4 to 6 yr; 6 to 8 yr; 8 to 10 yr; and last visit more than 10 yr after referral.

TABLE 1. Descriptive statistics for the follow-up of 312 patients with PBC

	Median	Mean	Minimum	Maximum
No. of years followed (n = 312 pt)	6.3	6.4	0.11	14.3
No. of visits per patient (n = 312 pt)	5.0	6.2	1.0	16.0
No. of years between visits (n = 1,633 visits)	0.97	0.89	0.13	5.77
Duration of intervals, yr[a] (n = 1,945 visits)	0.96	1.03	0.003	11.85

[a]Includes the interval between the last visit and the date of last follow-up.

modeling efforts, patients were censored at the time of transplantation.

Most of the 312 patients made annual visits to the Mayo Clinic after their initial referral. Table 1 summarizes the pattern and frequency of these visits. There were 1,945 total visits, and the median interval between visits was almost exactly 1 yr.

A comprehensive database was established on each patient, summarizing information on clinical, biochemical and demographic risk factors recorded at each visit. Complete data on the five risk factors used in the original Mayo model were available for 1,718 (88.3%) of the 1,945 patient visits. The variable with the most missing values was prothrombin time (data were lacking for 146 visits). The other prognostic variables were more completely recorded: bilirubin data were missing for seven visits, albumin data for 41 visits, and edema data for 72 visits. For the purposes of the statistical modeling described later, missing values of a variable were estimated from the previously recorded value of that variable. Comparison of results obtained this way, with the results based on a data set from which visits with incomplete data were omitted,

showed a minimal effect of this imputation on modeling results.

We tested the predictions of the Mayo-based models on an independent set of 83 patients with PBC who were seen at the University Hospital of Groningen, The Netherlands, between 1968 and 1991. Of these patients, 37 eventually underwent transplantation, and 19 died before receiving a transplant. Follow-up was extended to January 1991. With censoring of patients at the time of transplantation, the median follow-up time was 5.13 yr (range, 0.014 to 17.99 yr). When individual patients' follow-up was divided into intervals corresponding to successive visits, as described earlier, 481 intervals resulted, with a median duration of 11.96 mo (range, 0.033 to 100.2 mo).

Statistical Modeling. The main tool used was the Cox proportional-hazards regression model (6). In this model, each patient is given a risk score:

$$R = \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_k X_k \qquad (1)$$

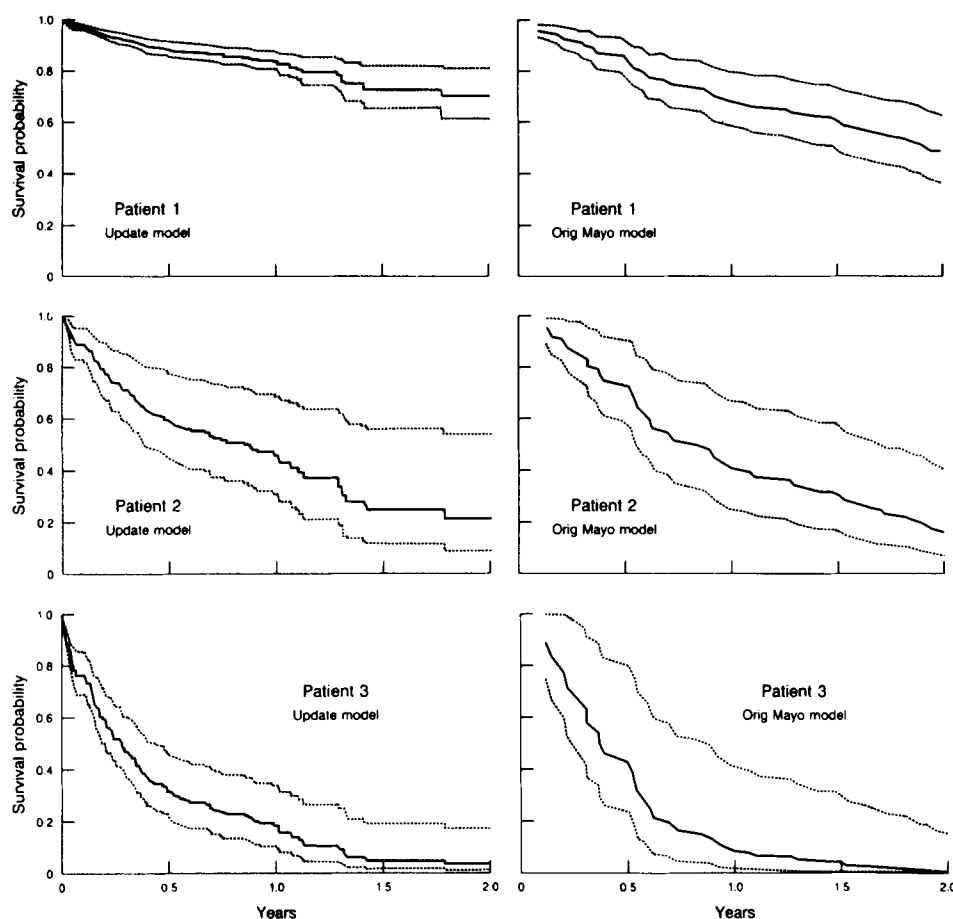in which X_1, X_2 ... X_k are the levels of k prognostic variables

FIG. 2. Predicted survival, and 95% confidence interval, for three patients, calculated according to the updated model *(left)* and the original *(Orig)* Mayo model *(right)*. The updated model and original Mayo risk scores, respectively, are 8.90 and 7.58 for patient 1; 10.39 and 8.50 for patient 2; and 11.17 and 9.48 for patient 3. The curves are based on the complete baseline survivor function (having a step at each failure time), a summary of which is given in Table 3.

TABLE 2. Regression coefficients and standard errors for covariates in the updated model and the original Mayo model

	Updated model		Original Mayo model	
Variable	Coefficient	Standard error	Coefficient	Standard error
Age	0.051	0.011	0.039	0.008
Log bilirubin	1.209	0.121	0.871	0.083
Log prothrombin time[a]	2.754	0.583	2.380	0.767
Log albumin	−3.304	0.474	−2.533	0.648
Edema score	0.675	0.235	0.859	0.271

[a]If INR is used instead of prothrombin time, 6.843 + 1.020 log INR should be used in place of the coefficient for prothrombin time.

(risk factors, or covariates) and $\beta_1, \ldots \beta_k$ are regression coefficients. Each coefficient β_i has the interpretation that every unit increase in the ith covariate, X_i, increases the risk of dying by the multiplicative factor $\exp(\beta_i)$. High-risk scores correspond to poor prognoses. In particular, if $S(t, X)$ denotes the probability that a patient with risk-factor values $X = \{X_1, X_2 \ldots X_k\}$ and risk score R will be alive t years later, and $S_o(t)$ is the survival function for a hypothetical individual having risk score R_o (corresponding to average values of the covariates X), then it follows from the proportional-hazards assumption that

$$S(t,X) = \{S_o(t)\}^{\exp(R - R_o)} \tag{2}$$

Model estimation and assessment were done by computer with the SAS procedure PHGLM (15).

The original Mayo model used a patient's referral, or baseline, values of risk factors to predict future survival. For the current study, we used a different kind of modeling procedure. Each patient's total follow-up was broken up into the number of intervals corresponding to the number of visits at which data were recorded. For example, a patient who visited the clinic at 6 mo and 1 yr after referral and died at

TABLE 3. Baseline survivor function for the updated model

t (mo)	0	3	6	9	12	15	18	21	24
$S_0(t)$	1	0.996	0.992	0.991	0.989	0.986	0.980	0.980	0.978

$S_0(t)$ is the expected survival probability for a patient with an updated-model risk score of 6.119.

TABLE 4. Example of prediction of short-term survival in a patient with primary biliary cirrhosis who visited the clinic from December 14, 1974, to March 10, 1981, and died on July 10, 1981

Parameters	Clinic visit						
	1	2	3	4	5	6	7
Visit date	12/14/74	6/16/75	12/10/75	12/6/75	10/6/77	10/10/78	3/10/81
Age (yr)	42.5	43.0	43.5	44.5	45.3	46.3	48.7
Bilirubin (mg/dl)	3.2	7.0	4.2	13.5	12.0	16.2	14.8
Prothrombin time (sec)	11.0	12.5	11.2	14.1	11.5	11.5	13.0
Albumin (gm/dl)	3.08	3.64	3.10	2.87	2.96	2.99	2.41
Edema score[a]	0.0	0.0	0.0	0.0	0.0	0.5	1.0
Risk score[b]	6.46	7.23	6.87	9.22	8.46	9.17	10.57
Probability of surviving next 6 mo[c]	0.99	0.98	0.98	0.84	0.92	0.84	0.50

[a] 0 for no edema and no diuretic therapy, 0.5 for edema present without diuretic or edema resolved with diuretic therapy, 1.0 for edema despite diuretic therapy.

[b] Risk score: $0.051 * 42.5 + 1.209 * \log_e 3.2 + 2.754 * \log_e 11.0 - 3.304 * \log_e 3.08 + 0.675 \times 0.0 = 6.46$. Risk score with INR: $6.843 + 0.051 * 42.5 + 1.209 * \log_e 3.2 + 1.020 * \log_e 0.791 - 3.304 * \log_e 3.08 + 0.675 \times 0.0 = 6.46$.

[c] Probability of surviving next 6 mo: $0.992^{\exp(6.46 - 6.119)} = 0.99$. Note: Maintain decimal accuracy until final rounding.

2 yr contributed three intervals: referral to 6 mo, 6 mo to 1 yr, and 1 yr to 2 yr. Each interval is considered a short period of follow-up for a unique patient, and the beginning of the interval corresponds to a new time zero and the end corresponds to the time of censoring (if the patient is alive) or death. Thus, the total time since referral is not included in the description of the interval.

Our modeling approach differs somewhat from that used by Christensen et al. (12), who studied patients with cirrhosis. They used Cox regression with time-dependent covariates (6), which assumes a baseline hazard that is modified by constantly changing values of the predictive variables. By postulating a constant hazard and assuming short-term stability of covariates, their application becomes similar to our "time-fixed" approach, which uses covariates measured at the beginning of an interval to predict short-term survival.

Most of our modeling used the five variables in the original Mayo model: $\log_e$ (bilirubin in mg/dL), $\log_e$ (albumin in g/dL), $\log_e$ (prothrombin time in seconds), age in years and edema score. The edema variable was coded as 0 for no edema and no diuretic therapy; 0.5 for edema present without diuretic therapy or edema resolved with diuretic therapy; and 1 for edema despite diuretic therapy. Recently, "international normalized ratio" (INR) has replaced prothrombin time at Mayo. Although prothrombin time was used for statistical modeling, we present methods for survival prediction using prothrombin time or INR. Because a key question is whether a patient's covariate history influences prognosis, we also created 6-mo "delta" variables, representing the change in the value of a covariate in the 6 mo preceding the focal visit. If a visit had not occurred 6 mo (actually, 5 to 7 mo) before the focal visit, an estimated value of the 6-mo change was obtained by linear interpolation from the most recent visit.

The goodness-of-fit of a Cox regression model to observed survival data can be assessed by comparing the actual survival with that predicted by the model for groups of patients, or patient intervals, with nonoverlapping levels of risk (5). Risk scores were computed for each patient using the original Mayo model applied to variables measured at the beginning of an interval. The risk scores were then ranked and divided into several groups, such that there were roughly equal numbers of deaths in each group. The average predicted survival curve for each group was found by computing the estimated survival function for each patient and then taking the arithmetic average of these functions within groups. The actual group survival experience was computed by the Kaplan-Meier method (16) and compared graphically with the average predicted curve. One-sample logrank tests (17) were used to compare individual patients' predicted survival with their observed survival, and a separate test was done for each risk group.

We used this method to assess the goodness-of-fit of the updated model in conjunction with a "data-splitting" approach (18). The data set was randomly divided into two portions: a model-building set consisting of 973 intervals (62 of them ending in death and 10 in transplantations), and a validation set consisting of 972 intervals (61 deaths and 10 transplantations). A Cox model with the usual five covariates was fit to the first set of data, and the predictions of this model were compared with the observed survival in four groups formed from the validation data set, as explained earlier.

This general method was also used to determine how well the Mayo update model predicted survival of the 83 Dutch patients.

RESULTS

Progression of Risk Score. Figure 1 illustrates the progression of risk score in mutually exclusive cohorts of the 312 Mayo patients with PBC. The cohorts are based on the time of the patient's last visit and on the patient's last recorded status. For example, the solid line that ends at 6 yr represents the average risk score among the 27 patients whose last visit occurred between 6 and 8 yr
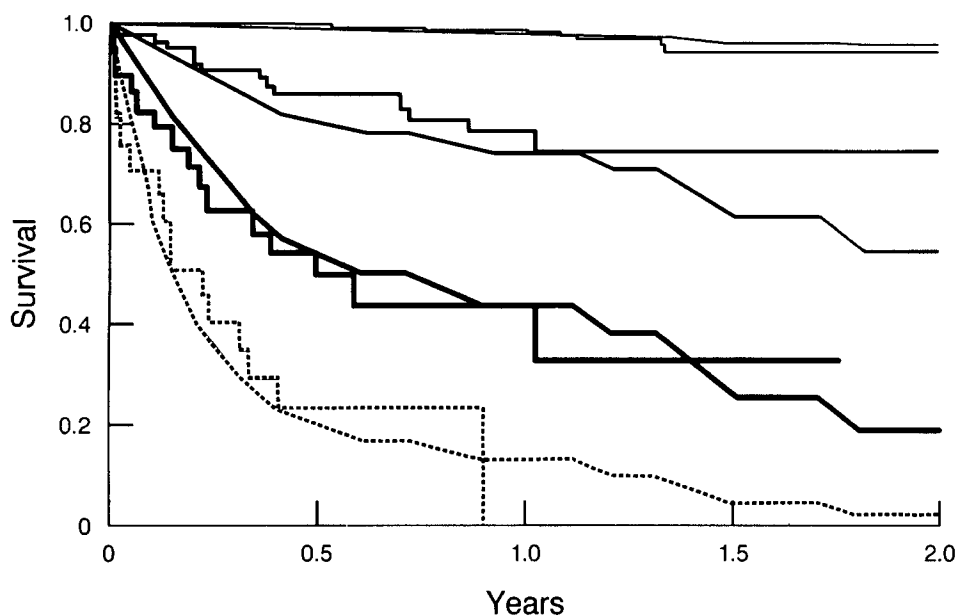
FIG. 3. Observed "survival" of 972 randomly chosen intervals *(lines with steps)* compared with survival predicted by an update model fit to the other 973 intervals *(smoother curves)*. The validation intervals were divided into four risk groups, each including 15 or 16 deaths. The number of intervals, range of Mayo risk scores, and logrank p value for comparing observed to predicted survival are (1) (lowest risk) 851 intervals, risk scores 1.28 to 7.42, p = 0.73; (2) 73 intervals, risk scores 7.43 to 8.49, p = 0.35; (3) 28 intervals, risk scores 8.50 to 9.09, p = 0.77; and (4) (highest risk) 20 intervals, risk scores 9.10 to 11.62, p = 0.91.

after referral and who were alive at the time of last follow-up. The dotted lines denote similarly defined cohorts of patients who died during the study. As pointed out by Christensen et al. (19), presenting data separately for these different cohorts avoids the biases inherent in a plot of average-risk score vs. time for the entire data set, in which the summaries at successive time points pertain to different subpopulations of patients.

Several important conclusions can be drawn from Figure 1. (1) There was a progressive increase in risk score among all patients, reflecting increasing disease severity and poorer prognosis with time. (2) Risk scores were generally higher for the patients who died than for those who were still alive at study closure, as would be expected. (3) The rate of change of risk score (slope of curve) appears higher among patients who died, a finding suggesting that deterioration may accelerate as the disease progresses. (4) Patients with the longest follow-up tended to be those with the lowest risk scores at referral. All of these points suggest that the Mayo risk score consistently reflects the severity of illness as PBC progresses and that the Mayo model — or some variant of it — might be useful for predicting survival based on covariates measured at any stage of disease, not just the time of referral.

Statistical Modeling. A new survival model was based on the 1,945 intervals of patient experience, as explained in the Methods section. Survival was modeled as a function of the same five variables used in the original Mayo model. Because only 107 of the 1,945 intervals were longer than 2 yr, we based the model only on the 123 deaths occurring within 2 yr of a visit; patients surviving longer than 2 yr were censored at that time. Thus, our survival predictions are only to 2 yr.

Table 2 shows the regression coefficients for the new model, along with those from the original Mayo model for comparison. The biggest differences in regression coefficients between the models were for bilirubin and albumin; in both cases, the coefficient from the update model is more extreme than that from the original Mayo model. The standard errors of the regression coefficients are roughly comparable between models.

Three pieces of evidence suggest that current covariate values, when used in the updated model, capture much of the information needed to predict short-term survival. First, a variable for time from referral is not statistically significant when added to the updated model ($\beta = -0.044$, p = 0.11). Second, changes in covariates in the 6 mo preceding a visit do not provide additional predictive power; none of the regression coefficients for "delta" variables added one at a time to the five-variable model was statistically significant. Third, a plot of $S_o(t)$, using the Breslow (20) estimator, showed a linear decrease of log $S_o(t)$ vs. time from referral. Thus, there is no statistical evidence, at least, that the relationship between risk score and prognosis depends substantially on the history of the disease process in the individual patient.

To use the updated model to calculate S(t), a patient's probability of surviving t years beyond the present, (1) combine the regression coefficients in Table 2 with the patient's covariate values to obtain the risk score, R, as explained in the Methods section (Equation 1); (2) obtain the baseline survivor function, $S_o(t)$, from Table 3; and (3) calculate
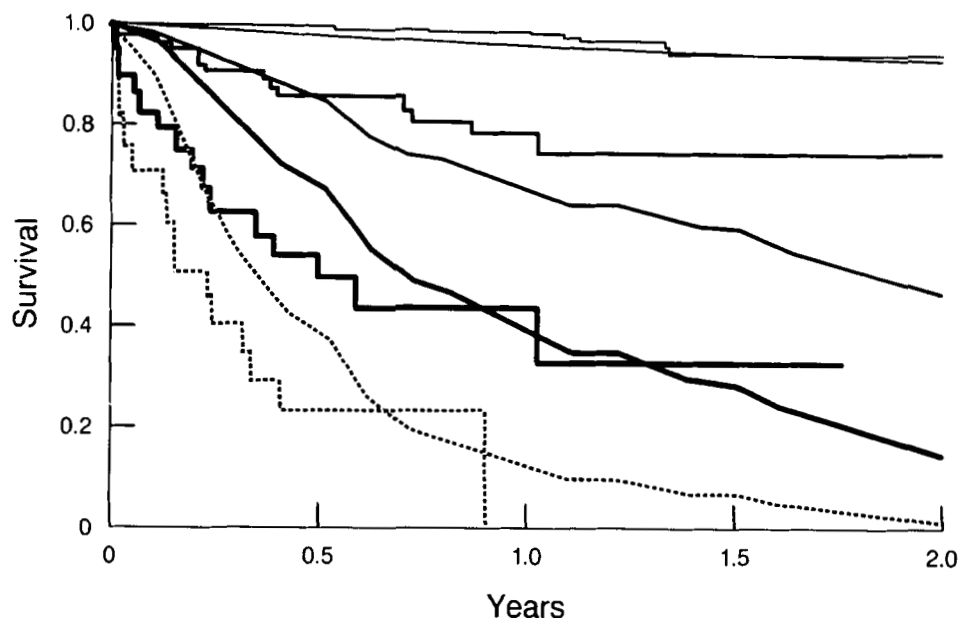
FIG. 4. Observed "survival" of 972 randomly chosen intervals *(lines with steps)* compared with survival predicted by the original Mayo model *(smoother curves)* for the same risk groups described in the legend to Figure 3. Logrank p values for the four groups, from lowest to highest risk, are 0.011, 0.12, 0.21, and 0.0025, respectively.

$$S(t) = \{S_o(t)\}^{exp(R-6.119)} \quad (3)$$

Table 4 gives an illustration of using the updated model for a patient who visited the clinic seven times. The patient visited on Dec. 14, 1974, at which time the patient was 42.5 yr old. The total serum bilirubin value was 3.2 mg/dL, the prothrombin time was 11 sec, the albumin value was 3.08 gm/dL, and the edema score was 0.0. The risk score was calculated to be 6.46, as follows: $0.051 * 42.5 + 1.209 * \log_e 3.2 + 2.754 * \log_e 11.0 - 3.304 * \log_e 3.08 + 0.675 \times 0.0 = 6.46$. If INR is used, the risk score is calculated as $6.843 + 0.051 * 42.5 + 1.209 * \log_e 3.2 + 1.020 \log_e 0.791 - 3.304 * \log_e 3.08 + 0.675 \times 0.0 = 6.46$. The probability of surviving for the next 6 mo is 99%: $0.992^{exp(6.46-6.119)} = 0.99$. Table 4 shows the gradual decline in the probability of surviving the next 6 mo until the year before death, when a sharp decline occurs.

Figure 2 shows predicted survival curves for three patients (risk scores), calculated with both the updated model and the original Mayo model. For healthier patients, the updated model makes more optimistic survival predictions than does the original Mayo model. For more severely ill patients, the predicted survival curves are similar. The confidence intervals for the survival curves, computed by the method of Tsiatis (21), appear to be narrower for the updated method for two of the three patients in Figure 2.

Validation. Figures 3 and 4 show the results of the validation based on data splitting. For each of four sets of patient intervals in the validation set, grouped according to Mayo risk score, we compared the observed survival with that predicted from the starting covariate values either by an updated model fit to the building data set (Fig. 3) or by the original Mayo model (Fig. 4), as explained in the Methods section. The

updated model yielded excellent agreement between predicted and observed survival, whereas the plot and logrank tests for the original Mayo model (Fig. 4) showed statistically significant underestimation of survival probabilities for the lowest-risk group and overestimation of survival probabilities for the highest-risk group.

We also compared the performances of the two models on an independent data set derived from 83 Dutch patients with PBC. Figure 5 shows observed survival for 471 patient intervals divided into two risk groups and predicted survival curves based on the original Mayo model and the new updated model. Both models make adequate predictions for the higher-risk group, but the original Mayo model underestimates survival for the lower-risk group.

A final comparison of the models can be made based on the Dutch patient data, rather than the visit data. In Figure 6, a validation is done on patients' whole experiences rather than intervals between visits; that is, survival for each of the 83 patients is predicted from his or her covariate values at referral, with censoring at the time of transplantation. The numbers are too small to allow meaningful statistical comparisons, but the updated model again appears to make more accurate predictions than the original Mayo model. Whether we analyze intervals between visits or intervals between referral and last follow-up, the updated model better predicts short-term survival of the Dutch patients than does the original Mayo model.

DISCUSSION

The original Mayo model for PBC (5) uses data collected at the time of referral to predict deaths that may occur many years later. It seems prudent to use data
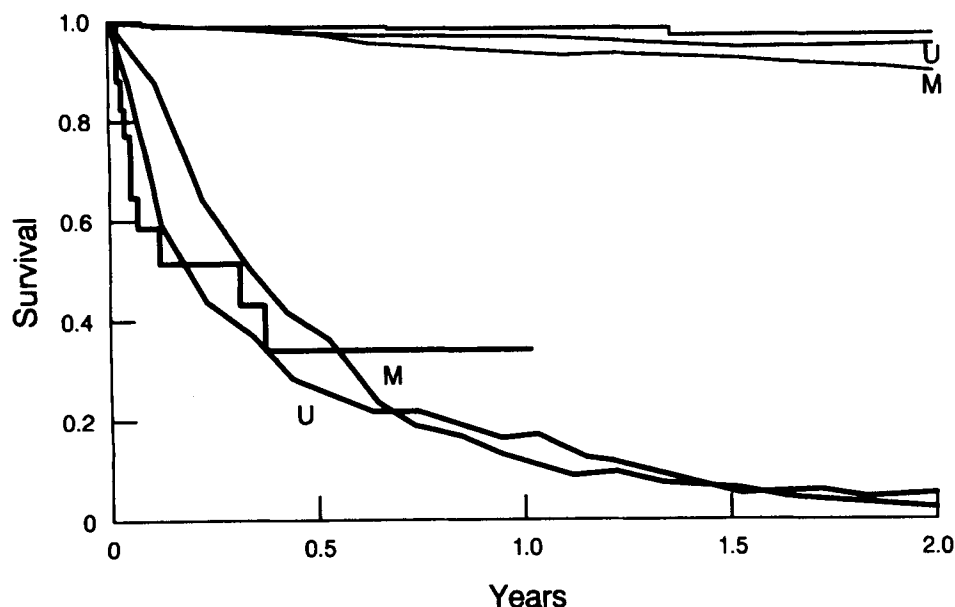
FIG. 5. Observed "survival" of 481 Dutch patient intervals (lines with steps) compared with predicted survival (smoother curves) for two risk groups of intervals having 9 to 10 deaths each. Predicted curves are from the original Mayo model (M) and the updated model (U). The number of intervals and range of risk scores are (1) for the low-risk group, 464 intervals, risk scores 1.73 to 8.72; and (2) for the high-risk group, 17 intervals, risk scores 8.84 to 11.51. Logrank p values for comparing observed with predicted survival are 0.27 (low risk) and 0.20 (high risk) for the updated model and 0.0026 (low risk) and 0.98 (high risk) for the original Mayo model.
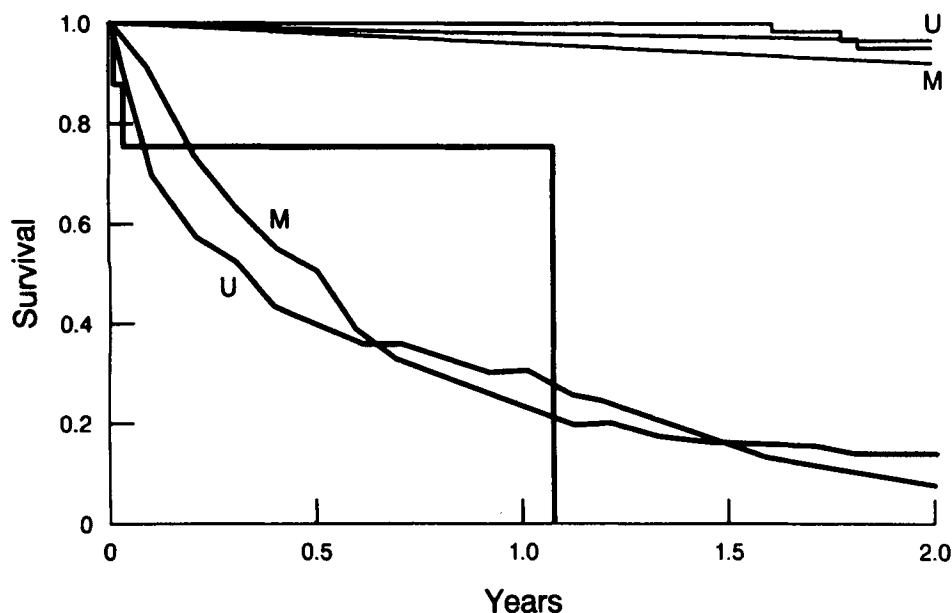

FIG. 6. Observed survival of 83 Dutch patients (lines with steps) compared with survival predicted from covariates at referral (smoother curves) for two risk groups with three deaths each. Predicted curves are from the original Mayo model (M) and the updated model (U). The number of patients and range of risk scores are (1) for the low-risk group, 75 patients, risk scores 1.73 to 7.54; and (2) for the high-risk group, 8 patients, risk scores 8.26 to 11.37. Logrank p values for comparing observed to predicted survival are 0.56 (low risk) and 0.28 (high risk) for the updated model and 0.36 (low risk) and 0.59 (high risk) for the original Mayo model.

from subsequent patient visits to refine survival predictions, as suggested by Christensen (22) and Neuberger et al. (23), and, in fact, the Mayo model is almost certainly being used in that way in current clinical practice. It is therefore important to determine whether variables

measured at any stage of disease can be used to make accurate survival predictions and whether details of the patient's recent clinical history add to our ability to predict survival.
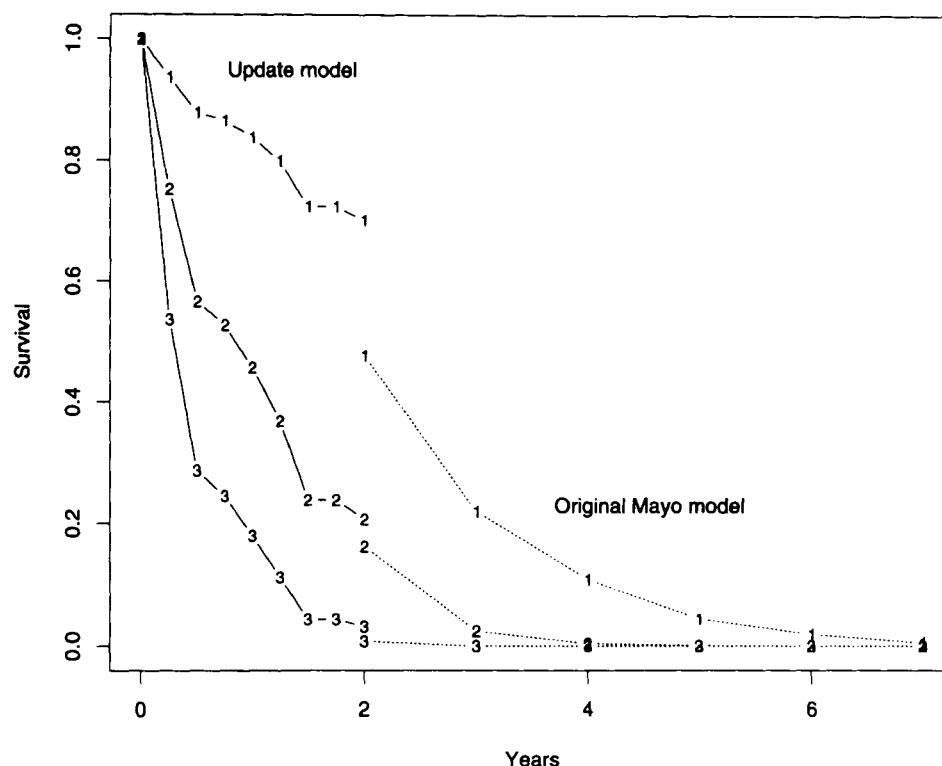
Data from the repeated visits by the 312 Mayo Clinic

FIG. 7. Predicted survival for the same three patients (1, 2, and 3) as in Figure 2, using the updated model for 0 to 2 yr *(solid lines)* and the original Mayo model for 2 to 7 yr *(dotted lines)*. We recommend that the updated model be used for 0 to 2 yr, and the original Mayo model be used for 3 yr and beyond.

patients clearly show progressive deterioration in the clinical variables composing the Mayo-model risk score. Because the risk score gradually increases over time (Fig. 1), it could be a useful predictor of survival at any stage of disease. This possibility is supported by the statistical modeling, which failed to demonstrate a significant effect of time from referral when it was added to the updated Cox model. There are suggestions from Figure 1 that (1) within cohorts, the rate of change of risk score increases with time from referral, as shown by Klion et al. (8), and (2) the mean risk score appears to increase at a faster rate in patients who died than in those who were still alive at last follow-up—findings that suggest that a patient's clinical history could be informative for prognosis. This possibility was not supported by the modeling, however, in which none of the "delta" variables (changes in risk factors during the preceding 6 mo) added significant predictive power to the updated model.

Our new updated model makes more accurate predictions of short-term survival than does the original Mayo model, for both the original Mayo patients with PBC (Fig. 3 compared with Fig. 4) and for an independent set of Dutch patients with PBC (Figs. 5 and 6). The main shortcoming of the original Mayo model seems to be an underestimation of the survival probabilities for relatively low-risk patients. Because only 53 of the 418 patients (13%) used to construct the final version of the original Mayo model died within 2 yr of referral (the

"time zero" for that modeling), it is not surprising that the model is less well suited for prediction of short-term survival than is the updated model.

We recommend that the updated model be used for predictions up to and including 2 yr and that the original Mayo model be used for predictions of 3 yr and beyond. For low-risk patients, this switching of models can result in an inflection of the survival curve between 2 and 3 yr, but for higher-risk patients, the discontinuity between models is hardly noticeable (Fig. 7).

In conclusion, the original Mayo model remains the tool of choice for prediction of survival for 3 yr and beyond, but for periods up to and including 2 yr, the updated model should provide more accurate and precise estimates of survival probabilities for patients with PBC.

REFERENCES

1. Gordon RD, Iwatsuki S, Tzakis AG, Esquivel CO, Todo S, Makowka L, Starzl TE. The Denver-Pittsburgh Liver Transplant Series. In: Terasaki PI, ed. Clinical transplants 1987. Los Angeles: UCLA Tissue Typing Laboratory, 1987:43-50.
2. Esquivel CO, Van Thiel DH, Demetris AJ, Bernardos A, Iwatsuki S, Markus B, Gordon RD, et al. Transplantation for primary biliary cirrhosis. Gastroenterology 1988;94:1207-1216.
3. Roll J, Boyer JL, Barry D, Klatskin G. The prognostic importance of clinical and histologic features in asymptomatic and symptomatic primary biliary cirrhosis. N Engl J Med 1983;308:1-7.
4. Christensen E, Neuberger J, Crowe J, Altman DG, Popper H, Portmann B, Doniach D, 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.

5. Dickson ER, Grambsch PM, Fleming TR, Fisher LD, Langworthy A. Prognosis in primary biliary cirrhosis: a model for decision making. HEPATOLOGY 1989;10:1-7.

6. Cox DR. Regression models and life-tables. J R Stat Soc B 1972;34:187-220.

7. Jeffery GP, Hoffman NE, Reed WD. Validation of prognostic models in primary biliary cirrhosis. Aust N Z J Med 1990;20:107-110.

8. Klion FM, Fabry TL, Palmer M, Schaffner F. Prediction of survival of patients with primary biliary cirrhosis: examination of the Mayo Clinic model on a group of patients with known endpoint. Gastroenterology 1992;102:310-313.

9. Markus B, Dickson ER, Grambsch PM, Fleming TR, Mazzaferro V, Klintmalm GBG, Wiesner RH, et al. Efficacy of liver transplantation in patients with primary biliary cirrhosis. N Engl J Med 1989;320:1709-1713.

10. Grambsch PM, Dickson ER, Wiesner RH, Langworthy A. Application of the Mayo primary biliary cirrhosis survival model to Mayo liver transplant patients. Mayo Clin Proc 1989;64:699-704.

11. Bonsel GJ, Klompmaker IJ, van't Veer F, Habbema JDF, Slooff MJH. Use of prognostic models for assessment of value of liver transplantation in primary biliary cirrhosis. Lancet 1990;335:493-497.

12. Christensen E, Schlichting P, Kragh Andersen P, Fauerholdt L, Schou G, Vestergaard Pedersen B, 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.

13. Hughes MD, Raskino CL, Pocock SJ, Biagini MR, Burroughs AK. Prediction of short-term survival with an application in primary biliary cirrhosis. Stat Med 1992;11:1731-1745.

14. Dickson ER, Fleming TR, Wiesner RH, Baldus WP, Fleming CR, Ludwig J, McCall JT. Trial of penicillamine in advanced primary biliary cirrhosis. N Engl J Med 1985;312:1011-1015.

15. SAS Institute, Inc. SUGI Supplemental Library User's Guide. Version 5 ed. Cary, North Carolina: SAS Institute, Inc., 1986.

16. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-481.

17. Harrington DP, Fleming TR. A class of rank test procedures for censored survival data. Biometrika 1982;69:553-566.

18. Picard RR, Berk KN. Data splitting. Am Statist 1990;44:140-147.

19. Christensen E, Schlichting P, Fauerholdt L, Juhl E, Poulsen H, Tygstrup N, and the Copenhagen Study Group for Liver Disease. Changes of laboratory variables with time in cirrhosis: prognostic and therapeutic significance. HEPATOLOGY 1985;5:843-853.

20. Breslow N. Covariance analysis of censored survival data. Biometrics 1974;30:89-99.

21. Tsiatis AA. A large scale study of the estimate for the integrated hazard function in Cox's regression model for survival data. Ann Stat 1981;9:93-108.

22. Christensen E. Prognostication in primary biliary cirrhosis: relevance to the individual patient. HEPATOLOGY 1989;10:111-113.

23. Neuberger JM, Gunson BK, Buckels JAC, Elias E, McMaster P. Referral of patients with primary biliary cirrhosis for liver transplantation. Gut 1990;31:1069-1072.