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Survival following the development of ascites and/or peripheral oedema in primary biliary cirrhosis: A staged prognostic model

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Abstract

Objective. Current prognostic models in primary biliary cirrhosis (PBC) have low precision, partly due to the restricted inclusion criteria of some cohorts used for modelling but also because of the prolonged natural course of the disease. It is hypothesized that better precision could be achieved with a staged model, using ascites or peripheral oedema as a new starting-point for prediction. **Material and methods.** The study was based on an established database of 289 consecutive patients, followed between 1977 and 1998. Stepwise Cox regression was used to construct a staged model based on 143 patients who first developed ascites ($n=111$) or peripheral oedema ($n=32$) at entry or during subsequent follow-up. The model was compared with published models using graphical methods and receiver operating characteristics (ROCs).

Results. Mean time from clinical diagnosis of ascites or peripheral oedema to death was 3.1 years. The following variables had independent prognostic significance: \log_{10} (bilirubin) ($p < 0.001$), albumin ($p < 0.001$), age ($p < 0.001$) and history of encephalopathy ($p < 0.001$). Goodness of fit showed that the survival probabilities predicted by the Ascites Stage Model fitted well with the observed data. The Ascites Stage Model (ROC 0.8324 (SE 0.0348)) was a better predictor of survival than the Mayo long-term model (ROC 0.7833 (SE 0.0397)), the Mayo Repeated Patient Visits Model (ROC 0.7779 (SE 0.0399)) and the Royal Free PBC Prognostic Model (ROC 0.7785 (SE 0.0396)). **Conclusions.** The Ascites Stage Model gives a better survival estimate for PBC patients once they have developed ascites or peripheral oedema compared with the current models, and demonstrates an advantage of staged models in diseases with a prolonged natural history.

Key Words: Fluid retention, liver transplantation, primary biliary cirrhosis, prognostic score

Introduction

Primary biliary cirrhosis (PBC) is a chronic inflammatory liver disease characterized by cholestasis, a positive antimitochondrial antibody and lymphocytic predominant portal inflammation, with variable fibrosis leading to cirrhosis in many cases [1]. Death is commonly due to complications of the disease or liver failure. Prolonged survival may occur and asymptomatic cases may have a near normal life expectancy [2]. Although some developments have taken place in medical therapy, effective therapy is limited and evidence that ursodeoxycholic acid slows or stops disease progression is still being debated [3,4]. As a result, liver transplantation remains the mainstay of treatment when patients develop

advanced-stage disease. As there is a prolonged disease course that has variable progression, in the past two decades survival modelling has been used to improve assessment of the optimal timing for transplantation. The most common approach uses Cox's proportional-hazards regression with "time fixed" covariates [5,6]. These models use clinical, biochemical and histological features measured at the time of diagnosis, referral to a centre or randomization in a clinical trial. Some investigators have used the changing value of clinical variables to improve the accuracy of survival prediction, the time-dependent model [7]. Further refinement was derived from validating the same model used at repeated patient visits, which improved the overall accuracy [8,9]. However, modelling from the time of onset of

complications in PBC has not been reported, despite the fact that it is well known that the occurrence of acute complications such as upper gastrointestinal (UGI) bleeding and infection may greatly alter the survival of cirrhotic patients in the acute phase with a marked increase in the hazard function for death, and that the onset of fluid retention changes the prognosis. The limitations of current prediction models also lie in their inclusion of a heterogeneous group of patients, some of whom may have complications of their liver disease at baseline, or the exclusion of such patients as in cohorts based on entry into randomized studies [6,10]. This lessens the applicability of the models to new cohorts. Thus an attempt to refine modelling in PBC by further stratifying patients with complications is a logical approach to improve the predictive power of modelling survival. Ascites or the development of peripheral oedema, being a common clinical complication of all liver cirrhosis [11,12], provides a convenient new baseline stage for predicting survival in PBC patients. In this paper, we developed a model for survival following the advent of ascites and/or peripheral oedema in PBC patients and compared it with more general models published in the literature.

Material and methods

The database

In 1992, we reported on the Royal Free Prognostic Index for PBC patients based on person interval to better predict survival and thus subsequent listing for liver transplantation [8]. This model used an established database of a cohort of 289 consecutive PBC patients referred to the Royal Free Hospital from 1 January 1977 to 1 March 1989 [8]. The diagnosis of PBC was established by positive anti-mitochondrial antibodies, alkaline phosphatase level greater than 1.5 times the upper limit of normal and/or liver histology compatible with PBC. In this database, the time of occurrence of complications and the occurrence of comorbid conditions for each patient were recorded including ankle oedema, ascites, encephalopathy (all detected clinically on routine physical examination) and the development of varices (endoscopically or radiologically proven), variceal and non-variceal GI bleeding, urinary tract infection (UTI) and other infections. Death was classified as liver related if it resulted from a complication of liver disease, or non-liver-related disease. Patients who had liver transplantations were censored at the date of surgery, whereas all patients alive without transplantation at the end of the study were censored at the date of the last follow-up. This

original cohort was updated with information up to 8 January 1998, giving an average follow-up of 8.06 (SD 5.55) years, (median 7.19 years, inter-quartile range (IQR) 3.35–11.54 years, range 0.12–25.52 years) from the day of presentation. During the whole follow-up period, 40 (13%) patients were transplanted and 149 (52%) died without transplantation.

Current study

After excluding patients who had not developed fluid retention, 143 patients were left, of whom 99 died during follow-up and 25 had liver transplantation. Of these 143 patients, 111 (77.6%) developed ascites as assessed by clinical examination, while 32 (22.4%) had solely peripheral oedema (defined as clinically detectable pitting oedema). We modelled time to death as a new baseline stage. Only patients who presented with these signs of fluid retention at the time of referral to our centre or developed these signs during follow-up were evaluated. Information was collected at routine visits to the clinic every 3 or 6 months, or at any hospital admission, routine or unexpected, as dictated by the patient's condition. The clinical characteristics and biochemical variables at the time of diagnosis of fluid retention were evaluated as potential predictors of survival. The following variables were evaluated as they have known prognostic importance in PBC, at the time of diagnosis of fluid retention: age, serum bilirubin concentration (as $\log_{10}(\text{bilirubin})$) ($\mu\text{mol/l}$), serum albumin concentration (g/l), serum alkaline phosphatase concentration (U/l), hepatic encephalopathy, presence of UGI bleeding within 6 weeks, history of UGI bleeding beyond 6 weeks, previous diagnosis of non-bleeding varices and septicaemia or spontaneous bacterial peritonitis (SBP).

The average follow-up time from presentation to death was 6.0 years (SD 4.7 years) (median 5.6 years, IQR 2.1–8.5 years, range 0.13–25 years). The mean follow-up time to the diagnosis of fluid retention from presentation was 2.9 years (SD 3.1 years) (median 1.9 years, IQR 0.8–5.0, range 0–12.8 years). The mean interval to death from the diagnosis of fluid retention was 3.1 (SD 3.7 years) (median 1.7 years, IQR 0.6–4.4 years, range 0–16.4 years). Deaths (80 (80.8%) liver-related deaths and 19 (19.2%) non-liver-related deaths) from any cause were treated as an end-point for the purpose of survival analysis. Patients who had liver transplantation were censored at the time of transplantation. The initial time-point for survival modelling was the date of diagnosis of fluid retention.

Development of the statistical model

The Cox proportional hazards regression model was used. This model assumes that the hazards of individuals with different risk factors are related proportionally. The model leads to a prognostic index or risk score (R) for each individual, as follows:

$$R_i = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \dots + \beta_n x_{in} \quad (1)$$

$\beta_0 \dots \beta_n$ are regression coefficients, i indexes the i th individual whose prognostic variables $x_{i1} \dots x_{in}$ are known prognostic variables of interest and a large value in the prognostic index means a higher risk, whereas a smaller value means lower risk. Then by the Cox model proportional hazards assumption, the probability of surviving beyond time (t) is as follows:

$$\Pr(\text{Patient } i \text{ survives } \geq t) = S(t) = S_0(t)^{e^{R_i}} \quad (2)$$

where $S_0(t)$ is the baseline survival function. Thus every worsening of the prognostic variables in the model at the time of diagnosis of ascites, will increase the risk of dying by a multiplicative factor $\exp(R_i)$.

Statistical analysis was performed with STATA version 8.2 (4905 Lakeway Drive, College Station, Tex., USA). The influence on survival of each baseline variable was assessed by unadjusted analysis using the standard Cox regression. For model estimation, a multivariable survival model was then derived using both forward and backward stepwise Cox regression, with "P-to-enter" of 0.05. Both procedures resulted in the selection of the same model. The assumption of proportional hazards was tested using the procedure "stphtest" in STATA, which is based on a test proposed by Grambsch & Therneau [13].

Goodness of fit

Both graphical and arithmetical methods were used to assess how well the model fitted the data in our study population. Kaplan-Meier plots were used to compare the actual survival data with survival predicted graphically by the model. The study group was further split into three groups, low-, medium- and high-risk, using the predicted survival, choosing the cut-off points so there were about 33 deaths, i.e. equal numbers, within each group. The predicted survival curve was calculated by averaging the estimated survival curve for each patient. The predicted survival and actual survival data were then compared graphically. The same graphical method was applied to compare the goodness of fit with our data, of the Royal Free Prognostic Model (Model 5) [8], derived from the same data set, which does not have prothrombin time as a prognostic

variable, and the Mayo Prognostic Model [6] which does.

For estimating the Mayo Risk Score, the prothrombin time values required imputation, as these values were not routinely measured during follow-up and or at the time of diagnosis of fluid retention. The relationship between our risk factors and prothrombin time was modelled using the 80 patients with observed prothrombin times (out of the complete data set of 289 patients) and then this model was used to predict the missing prothrombin times using multiple regression. As a check on the results, the measured prothrombin times (as $\log_e(\text{prothrombin time in seconds})$) at the time of diagnosis of fluid retention were compared with the imputed values. The values of two sets of data were similar, with the imputed values having a slightly lower mean (observed mean of the measured prothrombin time in $\log_e(\text{prothrombin time})$ 2.733 (SD 0.242) versus the imputed 2.729 (SD 0.185), $p=0.8615$ by Student's t -test), minimum (2.146 for imputed value and 2.437 for measured value) and maximum (3.254 for imputed value and 3.265 for measured value).

The goodness of fit was assessed numerically at the median survival time for each model, as follows. First, the observed number of deaths by the median follow-up time was calculated. Then, using the model under consideration, the probability of dying before the median follow-up time was evaluated for each patient. The observed deaths and predicted probabilities were then compared using the receiver operating characteristic (ROC) [14]. Statistical significance was at the 5% level throughout.

Results

At the time of diagnosis of fluid retention, the median bilirubin concentration was 57 $\mu\text{mol/l}$ (IQR 21–147 $\mu\text{mol/l}$, range 4–660 $\mu\text{mol/l}$). The median albumin was 34 g/l (IQR 30–39 g/l, range 18–51 g/l) and 31 (27%) patients had a history of encephalopathy (Table I). Diuretics were prescribed in 130 (90%) patients after diagnosis of fluid retention. As expected, patients who had only peripheral oedema (32 patients) had less severe liver disease compared with patients with ascites: mean age was 57.7 (SD 11.0), median bilirubin 16 (IQR 10–51) $\mu\text{mol/l}$, median albumin 39 (IQR 34.25–41.75) g/l, and 6% had encephalopathy.

Using unadjusted analyses, the covariates which were statistically significantly ($p < 0.05$) related to survival of PBC patients after diagnosis of fluid retention were: age, bilirubin ($\log_{10}(\text{bilirubin})$) and albumin concentration, history or presence of encephalopathy, previous UGI bleeding within 6 weeks

Table I. Characteristics of 143 PBC patients at the time of diagnosis of fluid retention.

No. of Patients	143
Mean age (SD)	58.8 (11.0)
Male:Female	18:125
Mean (SD) follow-up in years (Median (IQR))	6.0 (4.7) (5.6 (2.1–8.5))
Use of diuretics* [#]	130 (90%)
Median bilirubin (IQR) (reference range: 5–17 mol/l)	57 (21–147)
Median albumin (IQR) (reference range: 35–50 g/l)	34 (30–39)
Median alkaline phosphatase (IQR) (reference range: 42–128 U/l)	544 (325–750)
Median prothrombin time (IQR) (reference range: 12–16 s)	14 (13–15.75)
History and or presence of hepatic encephalopathy*	31 (27%)
History of upper GI bleeding within 6 weeks of diagnosis of fluid retention*	36 (25%)
History of UGI bleeding more than 6 weeks from the diagnosis of fluid retention*	40 (28%)
History of diagnosis of non-bleeding varices*	50 (35%)
Diagnosis of UTI at or before diagnosis of fluid retention*	40 (28%)
SBP or septicaemia at or before diagnosis of fluid retention*	10 (7%)
Death during follow-up*	99 (69%)
Liver transplantation during follow-up*	25 (18%)

Abbreviations: PBC = primary biliary cirrhosis; IQR = interquartile range; UGI = upper gastrointestinal; UTI = urinary tract infection.

*Number (percent).

[#]Prescription of diuretics after the diagnosis of ascites made in the corresponding RFH (Royal Free Hospital) clinic/admission.

and previous diagnosis of non-bleeding oesophago-gastric varices (Table II).

Using backward and forward stepwise selections, four variables at the time of diagnosis of fluid retention were found to be independent significant covariates for survival in PBC. These were age ($p < 0.001$), serum albumin concentration (g/l) ($p < 0.001$), \log_{10} (bilirubin) ($\mu\text{mol/l}$) ($p < 0.001$) and presence or history of encephalopathy ($p < 0.001$). The corresponding coefficients are presented in Table III. The test of the proportional hazards assumption showed that the Cox model's proportional hazards assumption held for all four covariates (joint $p = 0.721$). As result, the equation for the best model of survival at the time of diagnosis of ascites for PBC patients was:

$$\begin{aligned}
 R = & 1.138 \{ \text{Log}_{10} [\text{bilirubin } (\mu\text{mol/l})] \} \\
 & - 0.081 [\text{albumin (g/L)}] \\
 & + 0.053 (\text{age at the time of diagnosis of ascites}) \\
 & + 1.010 (\text{history of encephalopathy at the time} \\
 & \quad \text{of diagnosis of ascites}) \quad (3)
 \end{aligned}$$

The presence or history of encephalopathy equals 1, whereas its absence equals zero.

Using the prognostic index, the patients were divided into three risk groups: $R < 2.2$, $2.2 \leq R \leq 3.4$ and $R > 3.4$. The goodness of fit to the data is shown in Figure 1 for all patients as well as low-, intermediate- and high-risk groups. The predicted survival agreed well with the observed survival data in all risk groups (ROC 0.8324 (SE 0.0348)). The mean prognostic index in the group with peripheral

Table II. Regression coefficients and standard errors of known prognostic variables in PBC at the time of diagnosis of fluid retention.

Variables at the time of diagnosis of fluid retention	Coefficient	SE*	<i>p</i> -value
Age	0.033	0.010	0.001
Log_{10} (bilirubin in $\mu\text{mol/l}$)	1.225	0.217	<0.001
Albumin (g/l)	-0.119	0.019	<0.001
Alkaline phosphatase (U/l)	0.000	0.000	0.995
History and/or presence of hepatic encephalopathy	1.395	0.242	<0.001
History of UGI bleeding within 6 weeks of diagnosis of fluid retention	0.736	0.222	0.001
History of UGI bleeding beyond 6 weeks of diagnosis of fluid retention	0.078	0.218	0.719
History of diagnosis of non-bleeding varices	0.706	0.212	0.001
Diagnosis of UTI at or before diagnosis of fluid retention	-0.419	0.228	0.067
SBP or septicaemia at or before diagnosis of fluid retention	0.290	0.462	0.530

Abbreviations: PBC = primary biliary cirrhosis; UGI = upper gastrointestinal; UTI = urinary tract infection; SBP = spontaneous bacterial peritonitis.

*Standard error.

Table III. Regression coefficients and standard errors of the Royal Free Ascites Stage Model.

Covariate	Coefficient	Standard error	p-value	95% CI	
Age	0.053	0.0113	<0.001	0.031	0.075
Encephalopathy	1.01	0.236	<0.001	0.547	1.47
Albumin (g/l)	-0.081	0.022	<0.001	-0.124	-0.038
Log ₁₀ (bilirubin in μmol/l)	1.14	0.272	<0.001	0.606	1.67

oedema was 1.28 (SD 0.47) and it was distributed amongst low risk (71%) and intermediate risk (29%) groups with no such patients in the high-risk group.

Comparison with other models

A comparison was made using the goodness of fit of the Royal Free Survival Model as described in our previous report [8] (Figure 2). Although this model was estimated using the same cohort of 289 patients, it tended to overestimate death in the whole group with fluid retention, but also in the low- and intermediate-risk groups. However, it tended to underestimate survival in the high-risk group. Despite this, the fitted curves lie within the 95% confidence interval (CI) of the observed survival.

Conversely evaluating goodness of fit, the Mayo Model tended to overestimate the risk of death in the whole group (Figure 3), including low- and intermediate- and high-risk groups, but less so in the last one.

The Royal Free Ascites Stage Model (ROC 0.8324 (SE 0.0348)) fitted the data substantially better than either the Royal Free Survival Model [8] (ROC 0.7785 (SE 0.0396)) or the Mayo Long-Term Survival Model [6] (ROC 0.7833 (SE 0.0397)), both of which overestimated the risk of death (Figures 2 and 3), and also the Mayo Repeat Patient Visits Model [9] fits (ROC 0.7779 (SE 0.0399)), which underestimated the risk of death for our population (Figure 4), including in each stratified risk group. The latter finding could be due to the imputed prothrombin times being too large, but this in fact is not the case; the values have a similar range to the observed ones and are not statistically different.

Example using the Royal Free Ascites Stage Model

The Royal Free Ascites Stage Model can be calculated with a calculator or computer program using the information in Tables III and IV, where the latter gives the survival probability $S_o(t)$ at various time points calculated using the mean of the covariates $R=2.50$ (6). The prognostic index R of a PBC patient who has developed recent fluid retention can be calculated as in the equation using information on age, bilirubin, albumin and history of the presence of

encephalopathy. The survival probability can then be predicted by the equation:

$$S(t) = S_o(t)^{\exp(R-2.50)} \tag{4}$$

An example taken from patients in our study is shown to illustrate its potential use.

Example: The use of the Royal Free Ascites Stage Model and comparison between the Mayo Models, and the Royal Free Prognostic Model

A 50-year-old PBC patient (serial number 279) presented to us on 2 March 1978, bilirubin 38 μmol/l (2.2 mg/dl), albumin 39 g/l (3.9 g/dl), prothrombin time 11.0 s with no encephalopathy and no ascites or peripheral oedema. The risk score calculated by the Mayo Model [6] was:

$$R = 0.039 \times 50 + 0.871 \times \log_e(2.2) - 2.533 \times \log_e(3.9) + 2.38 \times \log_e(11.0) + 0.859 \times 0 = 4.90$$

The expected probability values for survival as computed from the survival function $S_o(t)$ [6] at 2 years and 4 years were 0.949 and 0.853, respectively.

Ascites was diagnosed on 22 March 1979. The prognostic markers at this time were: age 51, bilirubin 68 μmol/l (4.0 mg/dl), albumin 34 g/l (3.4 g/dl), prothrombin time 13.4 s, and there was one episode of hepatic encephalopathy, and diuretic therapy was started. The patient died on 23 June 1981 of liver failure, 40.3 months after presentation and 27.5 months after development of ascites. The prediction for survival probability at the time of diagnosis of ascites can be calculated by different models shown as follows:

A. Mayo Model [9] by repeated patient visits

$$R = 0.051 \times 50 + 1.209 \times \log_e(4.0) - 3.304 \times \log_e(3.4) + 2.754 \times \log_e(13.4) + 0.675 \times (1) = 8.01$$

The expected survival probability values computed from the survival function $S_o(t)$ [9] at 1 year and 2 years were 0.929 and 0.863, respectively.

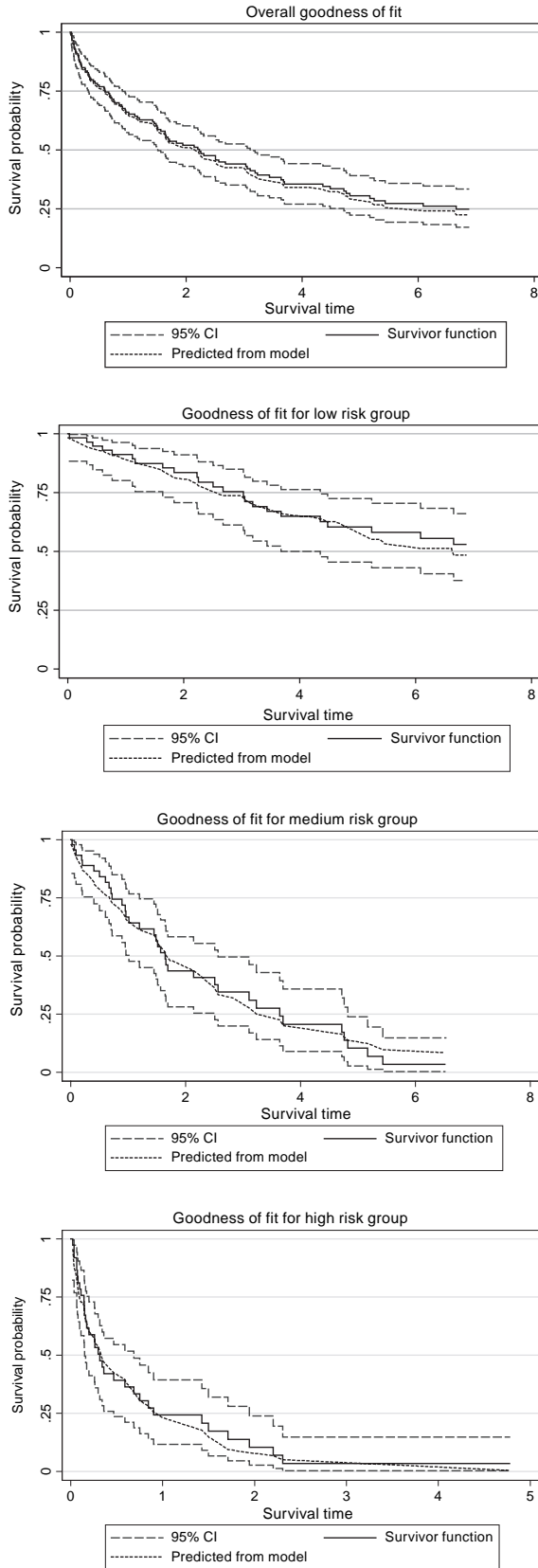


Figure 1. Goodness of fit comparing the Royal Free Ascites Stage Model in the whole group, and the low-, intermediate- and high-risk groups with fluid retention.

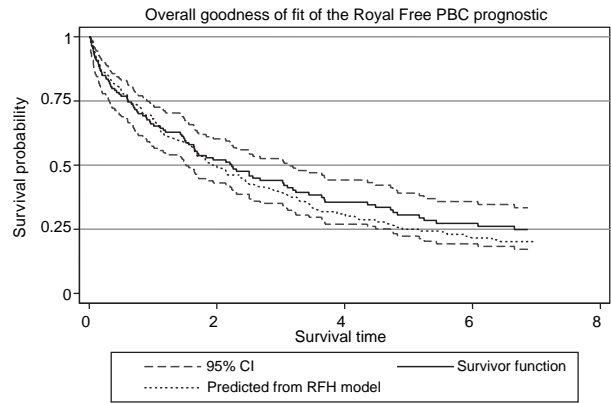


Figure 2. Overall goodness of fit for the Royal Free Prognostic Model [8].

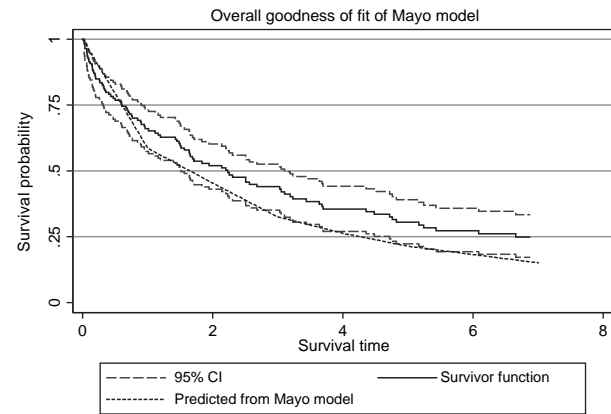


Figure 3. Overall Goodness of Fit for the Mayo model [6].

B. Royal Free Prognostic Model [8]

$$R = [0.55 \times (51) + 21 \times \log_{10}(69) - 1 \times (39) + 8 \times (1) - 55] / 10 = -1.43$$

The expected survival probability values at 1 year and 2 years were 0.888 and 0.621, respectively.

C. Royal Free Ascites Stage Score

$$R = 1.138 \times \text{Log}_{10}(69) - 0.081 \times [(39\text{g/l})] + 0.053 \times (61.78) + 1.010 \times (1) = 3.22$$

The expected survival probability values at 1 year and 2 years were 0.545 and 0.301, respectively.

In this real patient, the development of ascites and an episode of hepatic encephalopathy severely increased the risk of death, as is experienced in day-to-day clinical practice in all forms of cirrhosis. The ascites stage model captured these risks better in this PBC patient as compared to other models, resulting in a better prediction of the probability of death.

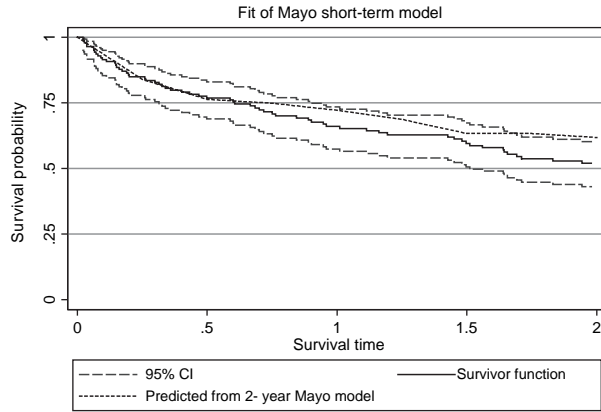


Figure 4. Goodness of fit for the Mayo Repeated Patient Visits (short-term) Model [9].

Discussion

In this study, an evaluation of modelling survival in PBC patients was made using the development of one of its complications, fluid retention detected clinically, as a new starting-point for prediction. The advantage of choosing fluid retention as a baseline stage lies in its nature of being a common and well-recognized clinical complication giving rise to a poorer prognosis in all aetiologies of cirrhosis [11,12].

The aim of modelling the progression of disease in PBC is to improve the estimates of survival of individual patients and thus to confer better timing for listing and/or transplantation. Although validated in different cohorts [6], time-fixed models [6,10,15–17] are not entirely accurate [18]. In addition, there are other shortcomings. Baseline modelling assumes that the form of both the baseline hazard function and risk relationships with the covariates are the same, no matter where in the course of the disease the prediction is determined. In reality it is more likely that the relationship between albumin, bilirubin, age and other key predictors will vary depending on when a patient has varices, ascites, etc.

Subsequent models, such as the person interval model or the repeat patient visits model [8,9] and time-dependent model [7], used additional information obtained on subsequent follow-up. However, they only predict short-term survival limited to

about 2 years. Theoretically, the time-dependent model is a solution for improving precision of estimation but the need for constant updates of the time-varying covariates throughout the period in which the prediction is limited to 6 months for each update makes it quite difficult to use in practice. We felt that a stage model might improve the overall estimation of survival, particularly considering the prolonged natural history of PBC. This type of model is particularly suited to estimating survival over longer time intervals, for example by dividing the clinical course into two phases (or more) at a stage marked by the advent of a complication with known prognostic significance, such as ascites or peripheral oedema, and deriving a second model at this stage. The overall confidence interval for the entire model is improved through shortening the time between the estimation and death. The advent of ascites and/or peripheral oedema detected clinically, as a stage baseline, is not subject to the assumption of proportional hazard where a single visit is arbitrarily defined as the starting-point in the natural course of the disease. While survival still varies considerably after development of ascites (IQR 0.6–4.4 years in our study population), the Ascites Stage Model is an improvement on the Mayo Model in terms of overall prediction, particularly in the low-risk and the intermediate-risk groups, where it would be most useful.

Our ascites model uses clinical and laboratory patient characteristics which are readily obtainable in the daily clinical setting. These are the same, i.e. age, bilirubin and albumin, as previous published models based on referral [8] or at the time of entry into clinical trials [6,10,16]. However, their relative weight differs after diagnosis of ascites, as reflected in their regression coefficients and the scoring. Compared with our Royal Free Prognostic Model [8] based on the same cohort, the regression coefficients are lower for bilirubin, whilst those for age and albumin remain similar. The presence or a history of hepatic encephalopathy becomes a significant prognostic factor in this model, which is absent from other models.

One-sample, log-rank tests have been used to compare the observed and predicted survival curves in modelling prognosis [6,9]. However, there are

Table IV. Underlying survival function for the Royal Free Ascites Stage Model (derived at the mean of covariates R=2.50).

Time (years)	6 months	1 year	1.5 years	2 years	2.5 years	3 years	3.5 years
$S_0(t)$	0.854	0.744	0.663	0.557	0.468	0.416	0.322
Time (years)	4 years	4.5 years	5 years	5.5 years	6 years	6.5 years	7 years
$S_0(t)$	0.281	0.250	0.190	0.143	0.126	0.126	0.103

Abbreviations: R = risk score; $S_0(t)$ = baseline survival function.

concerns about the p -value obtained by log-rank tests being too low, thus over-sensitive, with a tendency to reject a null hypothesis by finding false-positive results [18]. In order to obtain a fairer comparison of the observed survival and the predicted data generated by different methods, we tested the goodness of fit using the ROC method showing the difference between the Kaplan-Meier survival curve and the mean survival curve predicted by the model. As might be expected, our model gives a better estimate for the study population compared with other models because of its better stratification for this group of patients using ascites and/or peripheral oedema as a stage. Clearly, an independent population is also needed to validate our model and to provide further comparison with published models.

Interestingly our population had a 2-year survival estimate of 50% compared with a population ($n=216$) of mainly alcoholic cirrhosis patients ($n=146$) [11] in whom the baseline for survival estimation was admission to hospital for treatment (66% with previous ascites). A further study with mainly viral-induced cirrhosis [12] ($n=134$) had patients referred as outpatients as a baseline (79% with previous ascites) and the 2-year survival was 62.5%. This variability shows that the estimation of survival with ascites probably needs to be performed within each disease aetiology.

The value of a staged prognostic model is that it allows a more precise estimate of prognosis when there has been a change in the patient's condition [7]. This model is useful, as predicted survival curves for individual survival estimates are less precise over long periods of time than for groups of patients, even if there is a good correspondence between observed and predicted survival curves. Incorporating another, different model for predicting the advent of fluid retention in PBC patients would be useful to form a sequential two-stage model. We recently evaluated the risk of developing ascites in PBC, which can be predicted by the value of serum bilirubin, albumin, history of bleeding varices within 6 weeks and a history of diagnosis of varices within 3 months [19].

The evaluation of modelling survival in PBC using the development of one of its complications, fluid retention, as a new baseline stage suggests that it better predicts survival in PBC patients who develop fluid retention compared to baseline time-fixed models using goodness of fit as well as ROC assessment. The Ascites Stage Model gives a reasonably accurate prediction of both short-term and long-term intervals of survival. Development of similar models based on well-defined clinical com-

plications, such as variceal haemorrhage, may be warranted in the future, to further refine precision in survival modelling in PBC and to enable more optimal listing for liver transplantation.

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