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A Pugh score of 8 adequately selects patients with parenchymal cirrhosis for liver transplantation

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Abstract. The aim of our study was to develop simple and highly effective scores to estimate prognosis at 1 year for patients with parenchymal cirrhosis and to define the optimum time for liver transplantation with the same degree of accuracy as the prognosis estimation for primary biliary cirrhosis. The prognostic value of 19 variables was studied retrospectively in 91 patients with parenchymal cirrhosis using multivariate analysis and logistic regression. The best prognostic index was obtained with two independent variables: ascites and aminopyrine breath test. Although the receiver operating characteristic (ROC) curve for these two variables was better than the ROC curve for Pugh score, the percentage of correct prediction was excellent for both indices: 92% and 87%, respectively. The critical cut-off value of the Pugh score was 8.8. The prognostic value of a Pugh score ≤ 8 or > 8 was confirmed in a prospective study of 145 cirrhotic patients with 78% correct prediction. During this period, 21 patients with parenchymal cirrhosis received transplants with a preoperative Pugh score of 9.5 ± 2.0 (mean $\pm$ SEM) and 60% 1- and 2-year survival. In conclusion in parenchymal cirrhosis, a Pugh score > 8 indicates a poor prognosis at 1 year. This is a simple, easy and highly effective tool to define the optimal time for liver transplantation in this category of patients.

Key words: Liver transplantation – Pugh score – Parenchymal cirrhosis

As emphasized recently by the Hannover group [10] an important issue for defining optimum time for liver transplantation is the estimation of spontaneous prognosis for the following 1 to 2 years. In the field of primary biliary cirrhosis or sclerosing cholangitis, several prognostic models have been published with certain variables (e.g. age and bilirubin) being consistently included [21]. In the field of parenchymal cirrhosis, however, there is certainly less consistency in the prognostic factors described [2, 4, 5, 7, 9, 14, 16, 17]. The following drawbacks can be emphasized: the high number of variables often kept in the final model, the inclusion of histological features in some studies, the absence of cross-validation, the heterogeneous diagnostic groups and the low predictive value of the model.

The aim of our study was: to construct a powerful prognostic model based on clinical, biological and functional variables in a series of patients with parenchymal cirrhosis; to measure the accuracy of the prediction formula by applying it to another series of cirrhotic patients; to compare the new model with the Pugh score; and finally, to define the cut-off Pugh score value best separating patients with a good prognosis from those who should undergo liver transplantation. In particular, we were interested to know if estimation of quantitative liver function using the aminopyrine breath test could improve the performance of the prediction, as previous investigations showed contradictory results [3, 13, 19].

Patients and methods

Patients

Included in the study were 91 patients with parenchymal cirrhosis (56% of alcoholic origin). Criteria for defining alcoholism included a daily intake of more than 50 g of alcohol for more than 5 years. Criteria for defining cirrhosis included either a positive laparoscopy and/or liver biopsy (82 patients) or clinico-biochemical features and endoscopic demonstration of oesophageal varices (nine patients) suggesting cirrhosis.

In all the patients, a complete history was obtained and physical examination and laboratory analyses were performed on admission. Abdominal ultrasonography, oesophagogastroduodenoscopy, and a 2-h aminopyrine breath test were performed within 72 h as part of a routine work-up. The status of the patient – living or dead – and the cause of death were established after 1 year.

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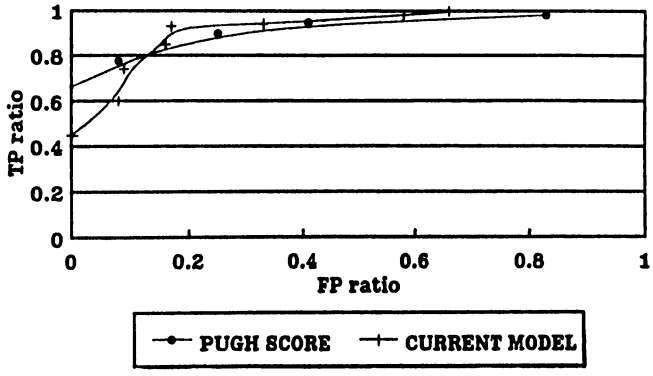

Fig. 1. ROC curves. True positive (TP) ratio (sensitivity) and false positive (FP) ratio (1-specificity) for various cut-off points of the Pugh score (●) and the current model including as variables aminopyrine breath test result and degree of ascites (+)

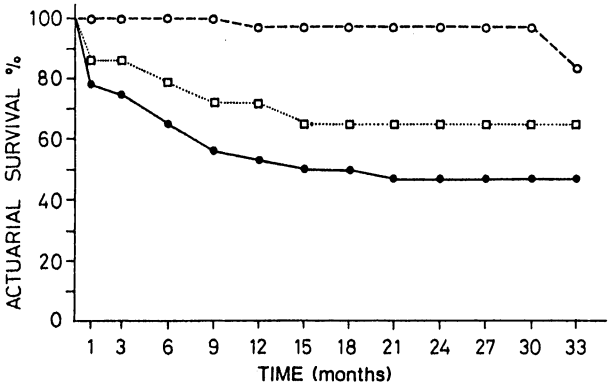

Fig. 2. Actuarial survival of patients with parenchymal cirrhosis (n = 145) according to the Pugh classification. ○, Pugh A (n = 46); □, Pugh B (n = 59); ●, Pugh C (n = 40)

In the prospective study, 166 other patients with parenchymal cirrhosis (60% of alcoholic origin) were studied. During the follow-up period, 50 patients with parenchymal cirrhosis were considered for liver transplantation; 21 were transplanted and 29 were turned down.

Statistical methods

In the first series of 91 patients with parenchymal cirrhosis, survival curves were analysed using the actuarial method of Mantel [11]. Variables that achieved statistical significance ($P < 0.01$) in univariate analysis using chi-squared tests were subsequently included in the multivariate analysis. Multivariate analysis of the prognostic variables mentioned above was performed using a stepwise logistic regression procedure [8].

From the regression equation, histograms of predicted probabilities of success were computed for each individual belonging either to the group 'successes' (alive at 1 year) or to the group 'failures' (dead at 1 year). From these histograms, a probability cut-off point could be selected to maximize the proportions of correctly predicted successes and failures. Such studies were carried out for mortality specifically related to liver disease (death due to hepatic failure or severe gastrointestinal bleeding).

Comparison of the discriminative effeciency of the logistic equations including either the best of our 18 variables [2] or the Pugh score was done using the same stepwise logistic regression procedure in terms of probability of correct classification, goodness of fit, accuracy of adjustment of the data to the model and receiver operating characteristic (ROC curves) [12]. The cut-off Pugh score separating patients alive and dead at 1 year was determined.

In the second series of patients, the percentage actuarial survival according to Pugh score (Child-Pugh A = score 5–6; Child-Pugh B = score 7–9; Child-Pugh C = score 10–15) was analysed. The percentage actuarial survival was calculated in this prospective series according to the best cut-off Pugh score and the cut-off point < 0.7 or > 0.7, both obtained in the first series of patients and derived from the logistic equations including as prognostic variables either the Pugh score or aminopyrine breath test result and degree of ascites.

Results

First series of patients with parenchymal cirrhosis

The logistic equation including the Pugh score as predictive parameter was:

$$\ln(p/1-p) = -0.939(\pm 0.242) \times \text{Pughscore} + 9.332$$

Where ln denotes natural logarithm and p the cut-off point. The number in parentheses is the standard error of regression coefficients and 9.332 is a constant. Taking 0.75 as the cut-off point, the Pugh score obtained from this equation is 8.76, i.e. 9.

Comparison of this last equation with a previously published equation [2], including as predictive variables the aminopyrine breath test result and the degree of ascites, revealed for percentage correct prediction of death and survival at 1 year, goodness of fit and accuracy of adjustment (log likelihood) values of 92% vs 87%, 0.999 vs 0.459, and −34.904 to −17.250 vs −34.904 to −20.206, respectively.

The ROC curve of the two variables (aminopyrine breath test result and degree of ascites) was better than the ROC curve of the Pugh score (Fig. 1). For the same true positive of 90%, false positive would be 17% for the current model and 25% for the Pugh score.

Second series of patients with parenchymal cirrhosis

The percentage actuarial survival according to the Pugh score is depicted in Fig. 2. Actuarial survival at 12 and 24 months was 97% and 97% for Child-Pugh A, 72% and 65% for Child-Pugh B, 52% and 45% for Child-Pugh C. The percentage actuarial survival of patients with a Pugh score of 9 or more (which derives from the first study mentioned above) and equal to or less than 8 in comparison with percentage actuarial survival according to a p value < 0.7 or > 0.7 is represented in Fig. 3. Percentage survival at 12 and 30 months was, respectively, 88% and 84% for a Pugh score ≤ 8, 85% and 79% for a p value > 0.7, 40% and 33% for a Pugh score > 8 and 49% and 41% for a p value < 0.7. The percentage correct prediction of death and survival at 1 year was 77% for a Pugh score ≤ 8 or > 8 and 72% for a p value < 0.7 or > 0.7 in this prospective series of patients.

The Pugh score was calculated retrospectively for the 50 patients considered for liver transplantation. The

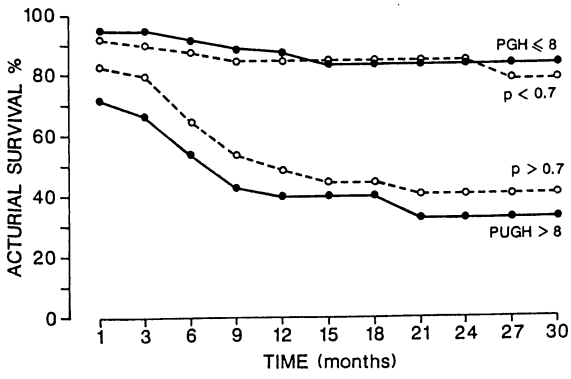

Fig. 3. Actuarial survival of patients with parenchymal cirrhosis (n = 145) according to Pugh score (≤ 8 or > 8) and cut-off point (< 0.7 or > 0.7) from the following equation: ln (p/1-p) = −1.95 ascites + 1.64 aminopyrine breath test − 0.93. This equation had a 91 % predictive value in the first series of patients [9]

29 patients turned down and the 21 transplant recipients had, respectively, during their work-up Pugh scores of 9.9 ± 1.6 and 9.5 ± 2.0 (mean ± standard deviation; $P > 0.05$). These two categories had, respectively, a 24-month actuarial survival of 60 % and 22 %.

Discussion

The prognostic model previously described by us [2], and including at presentation the two variables aminopyrine breath test result and degree of ascites, was compared with the well-establilshed prognostic indicator, the Pugh score.

In the first series of patients, which is in a way a retrospective study, the model with two variables was superior to the model including the Pugh score in terms of percentage correct prediction, goodness of fit, accuracy of adjustment and comparative ROC curves. However, the Pugh score was acceptable as it was correct in 87 % of cases. In the second series of patients studied prospectively, the excellent prognostic value of the Pugh score was validated.

We were mostly interested in trying to define the cut-off value of the Pugh score which best predicts those patients who will die of cirrhosis within 1 year. We propose that a Pugh score of 8 entirely fullfils this requirement. Indeed, this number was obtained from the prognostic equation including the Pugh score in the first series of patients and taking a cut-off point of 0.75 which best separated successes (patients alive at 1 year) and failures (patients dead at 1 year). Moreover the predictive value of a Pugh score of 8 was validated in the prospective study, being here even more efficient than the prognostic model including as variables aminopyrine breath test result and ascites. As emphasized by Wasson et al. [20], the accuracy of the prediction formula can differ in the initial study and in the test sample. This underlines [18] the importance of testing the prediction formula in another group of similar patients.

We conclude from our observations that a Pugh score of more than 8 is adequate for defining optimum time for liver transplantation and is as good as weights generated by a mathematical approach, and can be satisfactory for routine clinical practice. The potential value of a Pugh score of more than 8 as an index of a bad prognosis was further confirmed in a series of 50 patients considered by our group for liver transplantation on the basis of an intuitive combination of clinical and biochemical data suggesting imminent hepatic failure [18]. Retrospective estimation of the Pugh score disclosed that the mean value was more than 8 in both the group receiving transplants and the group turned down.

Estimation of the spontaneous prognosis of cirrhotic patients should improve in the future in terms of sensitivity and predictive value. We suggest that a Pugh score ≤ 8 or > 8 should be used as a reference standard when evaluating new prognostic tests or models. Repeated determination of the measurements, with multivariate analysis utilizing follow-up information to update prognosis, as proposed by Christensen et al. [6], would be a reasonable approach.

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