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Journal of Hepatology 41 (2004) 344–350

Journal of Hepatology

www.elsevier.com/locate/jhep

Review

Prognostic models including the Child–Pugh, MELD and Mayo risk scores—where are we and where should we go?

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1. Introduction

Improvement of the course and outcome of the patient's disease is a primary objective of doctors. Thus, assessment of the patient's prognosis is an important part of the evaluation, which will have a significant influence on the choice of therapy. It is therefore important to acquire reliable tools for prognostication of individual patients. In chronic liver disease prognostication may be of value particularly in the timing of complex therapeutic procedures such as liver transplantation. Thus, prognostic models may help doctors in the clinical decision making and provide patients with a more reliable assessment of their potential outcome. However, the imprecision of the prognostic estimates should always be considered and communicated to the patients.

The course and outcome of chronic liver disease may be difficult to predict. Many factors need to be considered: the specific diagnosis, the stage, the disease activity, the likely rate of progression and the occurrence of decompensation and complications. Of particular importance is the probable effect of any therapeutic measures taken during the course of the disease. Since many—partly unknown—factors will be operative in a complex interactive way, it may not be possible with simple means to obtain a clear picture, which can be applied with confidence for decision-making. Thus more complex methods analyzing the combined influence of many variables on the course and outcome are necessary [1].

Over a period of decades, a large number of prognostic models have been developed for cirrhosis in general and for various specific chronic liver diseases in particular (for an early and incomplete review see Ref. [2]). The principle behind these prognostic models has been to relate the descriptive characteristics of the patients at a given time—e.g. time of diagnosis or inclusion into a randomized clinical trial—with the occurrence of a well defined endpoint, e.g., death in the subsequent follow-up period. Generally, the prognostic models have been developed by the study of large data-bases of patients with the diagnosis in question being followed-up for a period of time that allows a sufficient number of endpoints to occur. Most frequently, a linear regression analysis technique (e.g. Cox's proportional hazards analysis [3]) is being applied to develop the prognostic model, which includes variables with independent relations with the endpoint. The regression coefficients of the model show how each variable—with its given scoring—contributes to the prediction of the endpoint.

Since most patients are seen not just once but for longer spans of follow-up, there is a need to update prognosis whenever changes—like decompensation, infection, sepsis, variceal bleeding—occur. Such updating of prognosis during the course of the disease can be done using the time-dependent Cox model [3], which utilizes follow-up data in the model design. Therefore, follow-up data need to be available before a time-dependent model can be developed.

Any modelling will to some extent be exploratory or 'heuristic'. Thus validation of models using independent patient data will be needed.

An important point to remember is that current prognostic models—including the time-dependent models—only provide a crude, imprecise estimate of the prognosis of individual patients because they only explain a smaller part of the observed variation in outcome between the patients [1]. A number of important determinants of the course and outcome may not be available or even identified and their interrelationship may be much more complex than can be described with current—rather simple—model types. Therefore prognostic models cannot in any way replace careful clinical assessment of the individual patient. They can only provide some—rather weak—additional information, which may be considered together with all other relevant information in the clinical decision-making.

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doi:10.1016/j.jhep.2004.06.005

2. The course of chronic liver disease

Many chronic liver diseases generally run a rather steady course with phases of improvement and deterioration. Overall the rate of progression may be slow, in particular in the early phases of the diseases. Sooner or later—depending on the 'activity' of the disease—the relatively steady course will develop into a more acute phase of accelerating progression with occurrence of decompensation, complications and death. The prognostic indicators may be different in the early and late phases of the disease [1]. In the early phases the intensity of the disease process or 'activity' (liver cell necrosis and inflammation) will be indicated by the degree of elevation of liver cell enzymes like aspartate amino transferase (AST) or alanine amino transferase (ALT) and elevation of immunoglobulins in the serum. In the late phase, the most important indicators of an advanced stage of disease with a decreased functional capacity and structural alterations (cirrhosis and hepatic decompensation) will be increase of serum bilirubin, decrease in serum albumin, decrease in serum prothrombin index (prolongation in prothrombin time), occurrence of jaundice, ascites, gastro-esophageal varices, variceal bleeding, encephalopathy and an increase in serum creatinine. When decompensation and complications occur, the prognosis will become markedly poorer as can be assessed using a time-dependent prognostic model including such variables. In a large study of the course of laboratory variables in cirrhosis the major changes were seen in the last year (comparison of the intervals 1.4–0.5 and 0.4–0 years) before death from a hepatic cause [4]: bilirubin increased (on average) from 35 to 56 μmol/l, albumin decreased from 35 to 31 g/l and prothrombin index decreased from 55 to 46% of normal.

Naturally, there will be a wide variation in the course of disease between the patients. Some patients may have a rather inactive disease and may suddenly deteriorate due to 'external' factors like dehydration, infection or sepsis.

3. Prognostic models

The variables far most often included in the prognostic models for cirrhosis are indicators of late stage disease [2]. This applies in particular to the Child–Pugh classification (CPC) [5,6] as well as the model for end-stage liver disease (MELD) [7,8]. CPC, MELD and the Mayo risk score for primary biliary cirrhosis (PBC) [9] are the most widely cited and used models at present. A summary of the advantages and disadvantages of the prognostic models or scores described in the following is shown in Table 1.

3.1. Child–Pugh classification (CPC)

The CPC, which was defined empirically, is based on serum bilirubin, serum albumin, prothrombin time, ascites and encephalopathy [6]. It is very popular and has been widely used as a prognostic tool. Nevertheless, from a methodological point of view it suffers from many weaknesses (Table 1) [2]: the use of cut-off points for the bilirubin, albumin and prothrombin time reduces artificially the prognostic information in these quantitative variables, the applied cut-off levels may not be optimal, the death risks for the three categories defined by each variable may not be proportional, the five variables may not be equally important prognostically, the degree of ascites and encephalopathy may be open to some interpretation, other prognostically important variables e.g. age, gastro-esophageal varices, variceal bleeding and serum creatinine are not included. It has also been shown that prognostic indices based on statistical modelling predict prognosis better than CPC [2]. The fact that CPC, in spite of these methodological weaknesses, does hold significant prognostic information, shows that the prognostic variables included are indeed important.

3.2. Model for end-stage liver disease (MELD)

This model, published in 2000, was developed—using the data of 231 patients who underwent elective transjugular intrahepatic portosystemic shunting (TIPS)—to predict patient survival and to identify patients who would suffer liver-related death within 3 months of the procedure [7]. Liver-related death occurred in 110, in 70 within 3 months. In order to pick a small set of strong prognostic variables, the backward elimination technique was used, retaining in the model only variables with $P < 0.01$. The resultant prognostic model included $\log_e$ bilirubin (mg/dl), $\log_e$ creatinine (mg/dl), $\log_e$ INR (international normalized ratio for prothrombin time) and cause of underlying liver disease (alcohol-related and cholestatic versus other type). In univariate analysis the following variables also showed some association with survival: ascites ($P = 0.02$), encephalopathy ($P < 0.01$), Child-Pugh classification ($P < 0.01$) and score ($P < 0.01$), albumin ($P < 0.01$) and age ($P = 0.07$). However, these variables did not achieve $P < 0.01$ in the multivariate analysis and were thus not retained in the model. The model was validated in 71 independent TIPS patients divided by their model risk score into two groups: low risk ($N = 65$) and high risk ($N = 6$). No significant difference between observed survival and survival estimated by the model was found in each of the two groups using the one-sample logrank test [10,11], which is better suited than the c-statistic referred to below.

In a subsequent paper, MELD was investigated in a broader sample of patients not undergoing TIPS [8]. The model was found to predict 3 months survival reasonably well, the concordance (c)-statistic (i.e. the area under the receiver-operating-characteristic (ROC) curve [12]) being 0.78 to 0.87 in the investigated patient groups. Interestingly the cause of the liver disease could be omitted from the model, virtually without changing the c-statistics values [8]. This shows that the patients at this stage—in spite of

Table 1
Advantages and disadvantages of some prognostic models

Model or score	Advantages	Disadvantages
CPC [6]	Simple to use Variables easy to obtain Does hold some prognostic information	Use of cut-off points reduces prognostic information Cut-off point used for variables not optimal The five variables not equally important The points for each variable may not be additive Some variables (ascites, encephalopathy) open to some interpretation Some important variables not included
MELD [7]	Statistically sound Useful irrespective of specific diagnosis. Variables objective	Some important variables may be missing
Change in MELD score (ΔMELD) [19]	As above Can indicate disease progression or regression	As above
Mayo risk score [9]	Does not need a liver biopsy	Long term prognostication not very precise Does not utilize follow-up data
Abbreviated Mayo risk score [22]	As above. Simple to use	As above
Time-dependent model for cirrhosis [2,23]	Can up-date prognosis during course of disease Holds stronger prognostic information Includes all important prognostic variables Simple pocket chart prognostication is possible	Some variables open to some interpretation Not tested in independent patients
Time-dependent Mayo risk score [25]	Can up-date prognosis during course of disease Holds stronger prognostic information	

different etiology of the cirrhosis—more or less had arrived at the final common pathway of liver insufficiency.

MELD has been praised for having a sound statistical and clinical validity, relying on a few, readily available, objective variables and being generalizable to a heterogeneous group of patients (Table 1). More studies have found MELD to hold nearly the same degree of prognostic information as CPC or perhaps slightly more [13–16].

Being developed from advanced stage (TIPS) patient data, MELD should most likely also work satisfactorily in transplantation candidates being for the most part in a similarly advanced stage. In fact MELD has been found useful as an objective criterion for allocation of patients to liver transplantation [17,18] thus de-emphasizing waiting time as a determining factor.

3.3. Change in MELD score (ΔMELD)

A single MELD score summarizes the status of the patient at a given time. By repeating the MELD score determination after a certain period, e.g., 30 days, the magnitude and direction of change (ΔMELD) over the period considered is obtained. This measure of disease progression gives additional prognostic information [19] (Table 1), which may be used as a tiebreaker for organ allocation in patients waiting for a liver transplantation with the same MELD score [19,20].

3.4. The Mayo risk score

This prognostic score for PBC, which was published in 1989, includes age of the patient, serum bilirubin, serum albumin, prothrombin time and severity of edema [9]. This score, which does not need a liver biopsy, has been validated using independent patients [21] and is used by many centres. For easy application in liver transplant candidates the Mayo risk score has been modified to an abbreviated risk score in a format similar to the CPC by introducing cut-off levels for age, bilirubin, albumin and prothrombin time [22]. This simplified risk score contain nearly the same prognostic information as the original score [22]. Since both versions of the Mayo Risk Score are based on baseline data only, long term prognostication is not very precise (Table 1).

3.5. Time-dependent prognostic models

The idea of utilizing follow-up information to update prognostic estimates has been pursued in prognostic models based on time-dependent Cox proportional hazards analysis. We published the first time-dependent model in cirrhosis in 1986 [23]. It is based on the analysis of 415 patients

followed-up for up to 12 years. During this period 248 patients died and none were transplanted. After start the patients were followed-up at 3, 6 and 12 months and thereafter once a year. Thus a total of 3603 sets of data at different time points contributed to the time-dependent model. The final model included the following prognostic variables: age, current alcohol consumption, ascites, GI bleeding, nutritional status, serum bilirubin, serum albumin, prothrombin index and alkaline phosphatase (all $P < 0.001$) [23]. The degree of liver connective tissue inflammation also had slight influence in the model. However, this variable can be omitted from the prognostic index. The occurrence of hepatic coma preceded death so closely that we did not find it justified to include this variable in the model. The model, which was validated using cross-validation, was found to predict prognosis markedly better than a previous time-fixed model developed from the same data. The model is particularly well suited to monitor patients during follow-up. Whenever changes in the clinical status occur, the model can update prognosis by estimating the current probability of surviving the next 3 or 6 months. The model is presented slightly modified as an easy-to-use pocket chart in Ref. [2]. It could be interesting if others could validate this model using their data. Other time-dependent models have been developed, e.g., in PBC and primary sclerosing cholangitis [2,24–26]. Thus the Mayo risk score for PBC also exists in a time-dependent version including the original variables [25], but in this new model their prognostic influence is stronger because follow-up data have also been taken into account in the modeling (Table 1). All the time-dependent models have been found to hold stronger prognostic information than the corresponding time-fixed models and have also been found more useful to update prognosis during follow-up.

3.6. Optimal timing of liver transplantation

This procedure should neither be too early, i.e., when survival with transplantation will be poorer than without, nor too late, i.e., when the risk of dying before transplantation can be made is high and the chance of tolerating and surviving the procedure is poor. The MELD model has been used for pre-transplant prediction of post-transplant survival [17,27–30] with varying success. Since the determinants for survival will not necessarily be the same with and without a transplant, the same prognostic model cannot be expected to be useful in both cases [17]. A separate model will be needed for pre-transplant prediction of post-transplant survival developed from data of patients who actually were transplanted. Then a comparison of the two separate prognostic estimates with and without transplantation can be included in the decision-making about the procedure [31]. Only if prognosis would be better with a transplant than without should the procedure be indicated, but other clinically relevant information should be considered as well.

4. Status and future

4.1. How much of the variation in survival do prognostic models explain?

For multiple regression model the coefficient of determination R^2 is an information criterion, which expresses the proportion of the variance in the outcome variable being explained by the independent variables included in the model.

For Cox's proportional hazards model several corresponding measures have been proposed [32,33]. It is desirable that the variation explained is routinely evaluated in prognostic models [32]. This is seldom done. Survival models usually explain only 10 to 45% of the variation in the data used for their development [32]. That our current prognostic knowledge is so limited may come as a surprise to many. Statistical significance of prognostic variables in the model says little about their predictive ability [2,34].

4.2. How much do prognostic models reduce prediction errors?

Schemper [34] suggests the term 'absolute prediction error' as a unified concept of predictive accuracy and explained variation. Denoting the absolute prediction error (absolute difference between observed and expected survival probability) without the model as E and with the model as E_M, the improvement in prediction obtained using the model or error reduction can be expressed as $E_{reduc} = E - E_M$. The relative gain in predictive accuracy or the proportion of the variation which is explained by the model, i.e., the variance reduction is $V_{reduc} = (E - E_M)/E$. Using data from the Mayo model for PBC [9], the absolute predictive error in survival probability without the model E was 0.38, and with the model 0.23 [34] over the 12 years observation period. Thus this model decreased the absolute errors of prediction of survival probability by 0.15, i.e., $E_{reduc} = 0.15$. The relative gain in predictive accuracy or the proportion of the variation explained by this model or variance reduction was $V_{reduc} = (0.38 - 0.23)/0.38 = 0.40$ or 40%, a relatively high number [34]. At present the absolute prediction error reduction is not being calculated in published prognostic models.

4.3. The performance of prognostic models is poorer in independent patients

The variance and prediction error reduction of prognostic models described above refer to the relation of the model to the data used for its estimation (the model sample). However, models are particularly well adjusted to the model sample data [1] and usually the performance of the model will be considerably poorer in independent patients [35].

Thus prognostic models need testing in new patients

preferably from other centres to prove their general usefulness or validity [36]. Such validation is an important step in the assessment and further refinement of prognostic models [37].

4.4. Why are current prognostic models rather poor prediction tools?

(A) *Statistical models do not use the full information in the prognostic variables*. Models may express the prognostic information in the included variables incorrectly or insufficiently. Failure of the model to adequately describe the information in the data may be caused by the model being too simple or the model assumptions not being met [3,38]. Thus important variables may be missing or scored inadequately, e.g., quantitative variables may be reduced to binary by scoring values above and below a certain threshold as one or zero, irrespective the numeric value. This leads to unnecessary loss of prognostic information. Sometimes a quantitative variable needs to be log-transformed for model assumptions to be fulfilled. Thus checking of model assumptions with the assistance of a qualified statistician is essential [3,38]. Most models are 'linear' assuming an additive effect of the variables on the prognostic index. Such a linear relationship may be too simple. The variables may have a much more complicated structure which needs to be described by more complex models, which include interaction terms [3]. A flexible model class is neural networks, which can fit complex data structures [39]. Since the number of parameters to fit may be large, the risk of over-fitting is markedly increased. The prognostic precision of neural networks is in most cases practically the same as that of Cox proportional hazards models [39,40] but if Cox model assumptions cannot be met, neural networks may be applied.

(B) *The prognostic variables currently used are not sufficiently informative*. Our knowledge of the disease processes is incomplete. We do not have sufficient information about the important determinants of the disease. We mostly record epi-phenomena not central to the disease process. Variables like ascites, bilirubin, albumin, creatinine, prothrombin time, are selected, secondary or indirect indicators of some aspect of liver function. They cannot be expected to hold precise information about the central processes determining the disease.

With an increased understanding of molecular biology including the influence of certain genotypes [41] there is hope of obtaining a much more precise information about the central determinants for the course of defined liver diseases. In hepatocellular carcinoma the presence of the mutant p53 gene is strongly associated with increased invasiveness of the tumor [42]. In chronic hepatitis C the host genetic background may influence the natural outcome of the disease. Thus the interleukin-10 GG genotype has been demonstrated to be associated with persistent infection [43]. In lymphoma [44] and in breast cancer [45] a number of molecular markers are increasingly replacing less specific variables in the evaluation of prognosis. These are just a few examples. Much more progress in the field of molecular biology and gene technology will be seen in the future.

The further identification and inclusion of molecular key variables in prognostic models will gradually replace most—if not all—of the prognostic variables being used now. This development will lead to a marked improvement of the precision of prognostic estimates for individual patients. For this development to take place, sophisticated genetic analyses will need to be available to most of the patients. A greater insight in the molecular biology behind the diseases will also pave the way for better therapies including gene therapy [46].

4.5. How should current prognostic models be used?

Because of the considerable imprecision of current prognostic models they cannot reliably estimate prognosis of individual patients. An individual prognostic estimate can only be used as an additional piece of information to be considered together with all other relevant clinical information in the decision-making [1].

When applied repeatedly in the same patient a time-dependent prognostic index may be useful in estimating progression over time. Such information may be included together with other relevant information in the decision-making about liver transplantation.

For groups of patients the average and distribution of their prognostic indices are summarized measures of the seriousness of the disease. Such measures are well suited to describe and compare the composition of different patient groups in regard to stage of progression and patient mix [1].

Because a prognostic index includes variables strongly associated with disease progression, it can inspire further pathogenetic studies. It can also have an educational value for students and untrained doctors.

4.6. How can we improve prognostic models?

Prognostic variables.. We need to include follow-up data to a greater extent in the prognostic modelling. We need better prognostic variables that are central to the disease process. Hopefully, gene technology and molecular biology will increase our knowledge in this respect.

Prognostic models should be developed on sufficiently large databases of consecutive patients followed-up for sufficiently long periods of time. Closer cooperation between centres and countries would promote the acquisition of sufficient amounts of data including the full spectrum of the disease in question. Such cooperative efforts should be supported and promoted by the hepatological societies. Statistical expertise needs to be directly involved in any prognostic modelling to ensure the maximum quality of analyses and results.

Publication of prognostic models should present detailed

information on checking of model assumptions and all details of the model including variable scoring, regression coefficients, standard errors, *P*-values, a suited information criterion and an estimate of the absolute prediction error (see above). Whenever possible, means of calculating 95% confidence limits of individual prognostic estimates should be provided. For Cox proportional hazards models the underlying cumulative hazard or survival function [3] should also be presented. This function is necessary to transform the prognostic index or score to estimates of survival probability [3].

Combination of data and models. It may be possible to improve existing prognostic models by performing analyses on combined databases from various centres. It may even be possible to combine published prognostic models from various centres using advanced statistical methodology [47].

5. Conclusions

Prognostic modelling is important to understand better the determinants of the course and outcome of chronic liver disease. Over the years a large number of prognostic models have been developed. A new contribution is the MELD, which from a methodological point of view is preferable to the CPC, that for many years have been dominant. However, even the best prognostic models have a quite limited predictive ability. They are not sufficiently precise to be useful for individual prognostication. The information provided by prognostic models should only be used as a supplement to any other relevant clinical information in the decision-making for the patient. To obtain better prognostic models in the future we need to identify more informative prognostic variables being central to the disease process, to utilize follow-up information to a greater extent, to combine databases and models from different centres and countries and to directly involve highly qualified statisticians in the modelling process to ensure maximum validity of analyses and results.

References

[1] Orlandi F, Christensen E. A consensus conference on prognostic studies in hepatology. J Hepatol 1999;30:171–172.
[2] Christensen E. Prognostic models in chronic liver disease: validity, usefulness and future role. J Hepatol 1997;26:1414–1424.
[3] Christensen E. Multivariate survival analysis using Cox's regression model. Hepatology 1987;7:1346–1358.
[4] 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.
[5] Child IICG, Turcotte JG. Surgery and portal hypertension. In: Child CG III, editor. The liver and portal hypertension. Philadelphia: Saunders; 1964. p. 50–58.
[6] Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;60:646–649.
[7] Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, Ter Borg PCJ. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology 2000;31:864–871.
[8] Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33:464–470.
[9] 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.
[10] Breslow NE. Analysis of survival data under the proportional hazards model. Int Stat Rev 1975;1:45–58.
[11] Harrington DP, Fleming TR. A class of rank test procedures for censored survival data. Biometrika 1982;69:553–566.
[12] Hanley JA, McNeil BJ. The meaning and use of the area under the receiver operating characteristic (ROC) curve. Radiology 1982;143:29–36.
[13] Salerno F, Merli M, Cazzaniga M, et al. MELD score is better than Child–Pugh score in predicting 3-month survival of patients undergoing transjugular intrahepatic portosystemic shunt. J Hepatol 2002;36:494–500.
[14] Schepke M, Roth F, Fimmers R, et al. Comparison of MELD, Child–Pugh, and Emory model for the prediction of survival in patients undergoing transjugular intrahepatic portosystemic shunting. Am J Gastroenterol 2003;98:1167–1174.
[15] Botta F, Giannini E, Romagnoli P, et al. MELD scoring system is useful for predicting prognosis in patients with liver cirrhosis and is correlated with residual liver function: a European study. Gut 2003;52:134–139.
[16] Angermayr B, Cejna M, Karnel F, et al. Child–Pugh versus MELD score in predicting survival in patients undergoing transjugular intrahepatic portosystemic shunt. Gut 2003;52:879–885.
[17] Wiesner RH, McDiarmid SV, Kamath PS, et al. MELD and PELD: application of survival models to liver allocation. Liver Transpl 2001;7:567–580.
[18] Wiesner R, Edwards E, Freeman R, et al. United Network for Organ Sharing Liver Disease Severity Score Committee. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology 2003;124:91–96.
[19] Merion RM, Wolfe RA, Dykstra DM, Leichtman AB, Gillespie B, Held PJ. Longitudinal assessment of mortality risk among candidates for liver transplantation. Liver Transpl 2003;9:12–18.
[20] Kamath PS, Kim WR. Is the change in MELD score a better indicator of mortality than baseline MELD score? Liver Transpl 2003;9:19–21.
[21] 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.
[22] Kim WR, Wiesner RH, Poterucha JJ, et al. Adaptation of the Mayo primary biliary cirrhosis natural history model for application in liver transplant candidates. Liver Transpl 2000;6:489–494.
[23] 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.
[24] Christensen E, Altman DG, Neuberger J, De Stavola BL, Tygstrup N, Williams R. Updating prognosis in primary biliary cirrhosis using a time-dependent Cox regression model. PBC1 and PBC2 trial groups. Gastroenterology 1993;105:1865–1876.
[25] Murtaugh PA, Dickson ER, Van Dam GM, et al. Primary biliary cirrhosis: prediction of short-term survival based on repeated patient visits. Hepatology 1994;20:126–134.
[26] Boberg KM, Rocca G, Egeland T, et al. Time-dependent Cox regression model is superior in prediction of prognosis in primary sclerosing cholangitis. Hepatology 2002;35:652–657.

[27] Onaca NN, Levy MF, Netto GJ, et al. Pretransplant MELD score as a predictor of outcome after liver transplantation for chronic hepatitis C. Am J Transplant 2003;3:626–630.
[28] Saab S, Wang V, Ibrahim AB, et al. MELD score predicts 1-year patient survival post-orthotopic liver transplantation. Liver Transpl 2003;9:473–476.
[29] Hayashi PH, Forman L, Steinberg T, et al. Model for end-stage liver disease score does not predict patient or graft survival in living donor liver transplant recipients. Liver Transpl 2003;9:737–740.
[30] Kim WR. Pretransplant disease severity and posttransplantation outcome. Liver Transpl 2003;9:124–125.
[31] Christensen E, Gunson B, Neuberger J. Optimal timing of liver transplantation for patients with primary biliary cirrhosis: use of prognostic modeling. J Hepatol 1999;30:285–292.
[32] Schemper M, Stare J. Explained variation in survival analysis. Stat Med 1996;15:1999–2012.
[33] Schemper M, Henderson R. Predictive accuracy and explained variation in Cox regression. Biometrics 2000;56:249–255.
[34] Schemper M. Predictive accuracy and explained variation. Stat Med 2003;22:2299–2308.
[35] Diamond GA. Future imperfect: the limitations of clinical prediction models and the limits of clinical prediction. J Am Coll Cardiol 1989; 14:12A–22A.
[36] Justice AC, Covinsky KE, Berlin JA. Assessing the generalizability of prognostic information. Ann Intern Med 1999;130:515–524.
[37] Altman DG, Royston P. What do we mean by validating a prognostic model? Stat Med 2000;19:453–473.
[38] Harrell Jr FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15:361–387.
[39] Ohno-Machado L. A comparison of Cox proportional hazards and artificial neural network models for medical prognosis. Comput Biol Med 1997;27:55–65.
[40] Ohno-Machado L. Modeling medical prognosis: survival analysis techniques. J Biomed Inform 2001;34:428–439.
[41] Blum HE. Molecular therapy and prevention of hepatocellular carcinoma. Hepatobiliary Pancreat Dis Int 2003;2:11–22.
[42] Jeng KS, Sheen IS, Chen BF, Wu JY. Is the p53 gene mutation of prognostic value in hepatocellular carcinoma after resection? Arch Surg 2000;135:1329–1333.
[43] Knapp S, Hennig BJ, Frodsham AJ, et al. Interleukin-10 promoter polymorphisms and the outcome of hepatitis C virus infection. Immunogenetics 2003;55:362–369.
[44] Takahara M, Kishibe K, Bandoh N, Nonaka S, Harabuchi Y, P53 N-. and K-Ras, and beta-catenin gene mutations and prognostic factors in nasal NK/T-cell lymphoma from Hokkaido, Japan. Hum Pathol 2004; 35:86–95.
[45] Glinsky GV, Higashiyama T, Glinskii AB. Classification of human breast cancer using gene expression profiling as a component of the survival predictor algorithm. Clin Cancer Res 2004;10:2272–2283.
[46] Garcia-Banuelos J, Siller-Lopez F, et al. Cirrhotic rat livers with extensive fibrosis can be safely transduced with clinical-grade adenoviral vectors. Evidence of cirrhosis reversion. Gene Ther 2002;9:127–134.
[47] van Houwelingen HC. Validation, calibration, revision and combination of prognostic survival models. Stat Med 2000;19:3401–3415.