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Review Article

Prognostic models in chronic liver disease: validity, usefulness and future role

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In MEDICINE prognosis or "fore-knowledge" is prediction of the probable course and outcome of a disease. Patient characteristics (variables), being related to the course and outcome, hold prognostic information and can indicate prognosis. Several prognostic variables can be combined into a prognostic model to improve prognostication.

Thus in principle prognostication may seem simple, but in practice it is far from simple. The most important reason for this is the fundamental biological principle of diversity among individuals caused by genetic recombination during meiosis in all higher species including *Homo sapiens*. This diversity increases adaptability and thereby the probability of survival of the species. In medicine this means that human beings differ in their disposition or susceptibility to contract a given disease and that patients suffering from a certain disease, defined according to the state of the art, will show different manifestations, giving a "spectrum" of variation between patients. Since diseases develop and progress in time, the time-factor will also be important. Thus, patients will present themselves to the doctor at various time-stages of the disease, and they will present different combinations of symptoms and signs, different values of laboratory tests and different findings in paraclinical investigations.

The variation among patients with a given disease makes a complete description difficult and usually only a simplified incomplete description is made, which usually comprises for each variable the average (or proportion) and possibly the variation (e.g. range, standard deviation or standard error). The course and outcome of a disease are often presented as a survival curve which gives the average survival probability for the patient group.

Since the characteristics of individual patients differ from the average, it cannot and does not describe individual patients. Furthermore, a given patient is poorly described by a single characteristic. Description is much improved by considering the particular combination of the characteristics presented by the patient. Thus, the task of the doctor is one of pattern recognition i.e. recognising the combination or structure (pattern) in which the characteristics present themselves in the patient in order to identify the "type" or subgroup to which he/she belongs.

To attack this problem it is necessary to have access to a large data-base, including for each patient the outcome variable and many descriptive variables. A good setting for prospectively collecting data for a data-base is a randomised clinical trial. Besides the prognostic aspect, the impact of therapy on prognosis can be studied in detail (1,2) and perhaps a therapeutic index can be obtained (2,3).

In theory, the prognostic structure in the data can be studied with many different methods (4), but in recent years a widely used approach has been to model the outcome as a "linear" combination (function) of independent predictor variables using multiple logistic or Cox regression analysis (2,4–6). These functions are called linear because they describe a straight line in the n-dimensional space, where n is the number of variables included in the function. They are extensions to higher dimensions of $Y=a+bX$, representing a straight line in the plane defined by the two dimensions X and Y, where a is a numeric constant and b a numeric coefficient.

These methods take into account the pattern of covariation (or correlation) (4,6) between the studied

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variables. The number of different correlation coefficients will be $n(n-1)/2$, where n is the number of variables. If $n=10$, the number of correlation coefficients between the variables will be $10\times9/2=45$. If $n=20$ there will be $20\times19/2=190$ different correlation coefficients. The correlation coefficients between the variables hold very important information about the "variation structure" of the data-set. Variables with high covariation (or correlation) vary together or in parallel from patient to patient and they therefore hold more or less the same information. Generally, the best linear model will tend to include variables which are correlated to the outcome variable but are not strongly intercorrelated (4,6). The coefficients in the linear model reflect their independent contribution to predicting the outcome variable. The model can be used in a given patient to calculate a prognostic index which can be transformed to a probability of surviving a given period of time (2,6).

Since such complex analyses are – to some degree – exploratory or heuristic, the results need some kind of validation before they can be considered "proved". Optimally, the prognostic index should be validated using the data of independent patients to see if the prognostic index predicts the prognosis correctly in these patients. If independent patients are not available, a more limited validation can be obtained by dividing the original patient data into a "model sample" used for the statistical development of the prognostic index and a "test sample" used for testing and validation of the prognostic index (2,6).

This paper reviews and critically evaluates different prognostic models in various chronic liver diseases. The paper does not intend to present a complete review of all published models, but rather to point out the limitations and to suggest ways of improving the situation.

TABLE 1

The Child-Turcotte criteria

Group designation Grading		A 1	B 2	C 3
Serum bilirubin	(mg%) (μmol/l)	<2 <34	2–3 34–51	>3 >51
Serum albumin	(g%) (μmol/l)	>3.5 >532	3.0–3.5 456–532	<3.0 <456
Ascites		none	easily controlled	poorly controlled
Neurological disorder		none	minimal	advanced "coma"
Nutrition		good	fair	poor

From reference 7.

The Child-Turcotte and Pugh Scores

In 1964, Child & Turcotte published their empirical criteria for assessment of hepatocellular functional reserve in cirrhosis (7), shown in Table 1. They comprise 5 variables (serum bilirubin, serum albumin, ascites, neurological disorder and nutrition). For a given patient, each of the 5 variables is graded A, B or C, scored as 1, 2 or 3, respectively. The points can be added to give a combined score between 5 and 15. The A, B and C categories for the combined score have not been generally agreed upon (8).

Pugh et al. (9) have proposed a modification of the Child-Turcotte criteria where nutrition is replaced by the prothrombin time, graded as follows: <4 s prolonged (≅prothrombin index >50%): A; 4–6 s prolonged (≅prothrombin index 38–50%): B; >6 s prolonged (≅prothrombin index <38%): C. For albumin, they use a category C cut-off point of 2.8 g% instead of the 3.0 g% used by Child & Turcotte. They define the following A, B and C grading for the combined score: 5–6: A; 7–9: B; 10–15: C (9).

Although others have confirmed that the Child-Turcotte and Pugh scores hold prognostic information (10,11), they are not completely satisfactory for the following reasons:

Use of cut-off points for quantitative variables

The use of cut-off points for the quantitative variables (albumin, bilirubin, prothrombin time) may (unnecessarily) reduce the prognostic information in those variables. For example, two patients with bilirubin of 3.1 mg% and 20 mg%, respectively, will both be classified as bilirubin category C although their prognosis may be markedly different. Regression models allow utilisation of the full value spectrum of quantitative variables, although it may be necessary to use a transformation (e.g. logarithmic transformation) of the variable to fulfil the assumptions of the regression model (6).

The cut-off points used may not be optimal

The cut-off points defining categories A, B and C seem arbitrary; they have not been selected as a result of a prognostic analysis and they seem not to be optimal. For example, for bilirubin the survival for categories A, B and C is only slightly different (10). A cut-off point higher than 3 mg% between category B and C might be better. Although the definition of cut-off points is crucial for the quantitative variables, well-defined definitions of categories A, B and C for the qualitative variables, like ascites, encephalopathy and nutrition, are also important.

The death risks for A, B and C may not be proportional
The increase in risk from A to B may not be the same as from B to C for each single variable, i.e. "linearity" may not be fulfilled . For example, concerning ascites the risk for category A and B seems to be very nearly the same and markedly less than for category C (10).

The variables may not be equally important
In the calculation of the combined score all five variables are given the same range of weights (1 to 3). This means that the variables are considered to have the same prognostic importance. There are many indications that this may not be true. For example, the prognostic influence of albumin and ascites seems to be markedly greater than that of bilirubin (10). Probably the prognostic influence of encephalopathy is even greater. In the Copenhagen cirrhosis patients, encephalopathy was so closely related to death that it was not feasible to include it in the time-dependent prognostic model (12). Another study demonstrated a 1-year survival after hepatic encephalopathy (without concomitant GI bleeding) of 33% and after encephalopathy associated with bleeding of 15%, the vast majority of the deaths occurring within the first few months (13).

A difference in prognostic influence between the variables and a lack of proportional risks (linearity) for A, B and C mean that the scores for each of the variables cannot in a meaningful way be added together to give a combined score. Expressed in another way: two patients having the same combined score but with different contributions from each of the 5 variables may have markedly different prognoses.

Since the five variables are considerably intercorrelated in a complex way, the correlations need to be taken into account to know how the variables should be combined in the best possible way. This is not done in the combined Child-Turcotte or Pugh scores, but this is what the multiple regression models do. It is also the explanation of why the 5 variables, when analysed together in a Cox regression model, turn out to have markedly different independent associations with the prognosis, and generally only some of the variables will be statistically significant.

Other important prognostic variables are not included
Important variables such as age, oesophageal varices and GI bleeding, which have been shown to hold significant additional prognostic information (see below) are not included (12,14–18).

Prognostic indices based on statistical analyses have been shown to predict the prognosis better (10,14). Nevertheless, the Child-Turcotte criteria and the Pugh modification are still widely used, probably because they are quite simple to apply and because other better prognostic models have achieved less publicity and are, incorrectly, considered difficult to use.

Other General Scores in Cirrhosis

In 1983, the Copenhagen Study Group for Liver Diseases reported the results of a Cox regression analysis of the data of 488 patients with cirrhosis (15). The following eight variables had a significant prognostic effect: sex, age, prothrombin, acetyl cholinesterase, eosinophil leucocytes in liver parenchyma, liver cell necrosis, inflammation in liver connective tissue, and efferent veins in parenchymal nodules. The variables could be combined to give a prognostic index which was validated using a split sample technique.

Since then a number of similar analyses has been made in patients with cirrhosis of mixed aetiology. The most important of the models (12,16–18) are summarised in Table 2. In these models a number of additional independent prognostic variables have been identified (e.g. male gender, high age, oesophageal varices, GI bleeding, continued abuse of alcohol, low acetylcholine esterase, high gamma globulins) as well as those included in the Child-Turcotte and Pugh scores. However, there is a considerable variation between the variables included in the models, probably reflecting the heterogeneity of the patient samples. In the studies from Barcelona (17) and from Copenhagen (12), the results were validated using a split-sample testing technique.

The Copenhagen study utilised both the admission and follow-up data in a time-dependent Cox regression model (12). The results are summarised in the pocket chart shown in Table 3. Using the pocket chart a prognostic index can be obtained by the simple addition of numbers. Furthermore, the pocket chart directly presents numbers which illustrate the relative importance of each variable. For example, for ascites the difference between none and marked is 12 points, for nutrition the difference between normal and cachectic is 6 points, for albumin the difference between 40 and 20 g/l is 8 points, for the prothrombin index the difference between 70% and 20% is 10 points, and for age the difference between 40 and 70 years is 15 points. The histologic variable (which has relatively little influence) can be left out with little loss of information.

Using the pocket chart, the prognostic index is not more difficult to calculate than the Child-Turcotte or Pugh score, but it provides a better estimate of prognosis. The index can be translated into an estimate of surviving the next 3 or 6 months, as shown in Fig. 1. The index is particularly well suited to the follow-up monitoring of patients, since it gives a quantitative

TABLE 2

Independent variables associated with a poor prognosis in cirrhosis

Variable	Model				
	Palermo compens.	Palermo decompens.	Barcelona compens.	Rome	Copenhagen
Reference:	(16)	(16)	(17)	(18)	(12)
Male sex	×		×	×	
High age	×		×	×	×
Ascites				×	×
Poor nutrition					×
Oesophageal varices	×	×		×	
Hepatocellular carcinoma		×			
Hepatic stigmata			×		
Encephalopathy		×			
GI bleeding		×			×
Continued abuse of alcohol		×			×
Low prothrombin index	×	×	×		×
Low albumin					×
Low acetylcholinesterase		×		×	
High gamma globulins		×	×		
High serum bilirubin			×	×	×
High gamma glutamyl transpeptidase		×			
High alkaline phosphatase			×		×
HBsAg positivity	×	×			
High SGOT		×			
Inflammation in liver connective tissue					×

SGOT=serum glutamic-oxaloacetic transaminase.
compens.=compensated.
decompens.=decompensated.

measure of disease severity and thereby an indication of improvement or deterioration during the course of the disease. The index can help in deciding if and when to perform a liver transplantation in the patient.

The prognostic information of more special tests like aminopyrine breath test (11,19,20), galactose elimination capacity (GEC) (20), indocyanine green (ICG) intrinsic hepatic clearance (20), plasma noradrenalin (21), portal venous pressure (21,22), and splanchnic angiographic findings (23) have been investigated, but generally little information can be obtained in addition to that from the clinical variables and simple biochemical tests. The reason for this is that the special tests are to some degree correlated to the clinical variables and the simple biochemical tests which can easily be obtained in the clinical situation. Generally, the simpler the tests and the more easily they can be obtained, the greater the chance that they will be generally accepted as prognostic indicators in clinical practice.

Alcoholic Liver Disease

In 1983, Orrego et al. proposed a Combined Clinical and Laboratory Index (CCLI) for global assessment of the severity of alcoholic liver disease (24). The empirically constructed index was based on 12 variables, which in univariate analyses showed significant association with the 1-year survival. However, when applying multivariate statistical methods to the data, only 4 of the variables were significantly associated with a poor prognosis (encephalopathy, low albumin, prolonged prothrombin time, and low haemoglobin) (24). The remaining variables seemed to be more or less redundant because of close correlations with the 4 significant variables, showing the value of using multivariate statistical methods for the development of prognostic indices.

Since then, other prognostic analyses have been performed in alcoholic liver diseases (25–27) (summarised in Table 4). The European study (27) also included patients with alcoholic steatosis. This may explain some of the variation between the variables selected in the models. The Copenhagen study (25) also tested the CCLI and found that its predictions were less accurate than those Orrego et al. made in their patients (24). Otherwise, these highly different models have not yet been tested in independent patients.

Chronic Hepatitis B

Reports on the natural history of chronic hepatitis B are scarce (28,29). The course of the disease is sometimes very long. De Jongh et al. (29) found in 98 patients followed up for a mean of 4.3 years that only age, bilirubin, and ascites were independently related

TABLE 3

Pocket chart for calculation of current prognostic index in cirrhosis

Variable			Points to add
Age (years)		20	0
		30	5
		40	11
		50	16
		60	21
		70	26
		80	31
Current alcohol consumption	none		0
	10–50 g/day		4
	>50 g/day		13
Ascites	none		0
	slight		3
	moderate or marked		12
GI bleeding		no	0
		yes	14
Nutritional status	normal or fat		0
	meagre or cachectic		6
Serum bilirubin	<4 mg/100 ml or <70 μmol/l		0
	≥4 mg/100 ml or ≥70 μmol/l		9
Serum albumin	g/l	μmol/l	
	15	228	14
	20	304	10
	30	456	6
	40	608	2
	50	760	−1
Prothrombin index (% of normal)		10	22
		15	19
		20	16
		30	13
		40	11
		55	8
		70	6
		105	3
		150	0
Alkaline phosphatase (IU/l)		37	0
		70	2
		107	4
		180	6
		290	8
		400	10
Liver connective tissue inflammation			
	Unknown		0
	None or slight		4
	Moderate or marked		−2
Sum of points S=			
Prognostic index PI(t)=S/10−6=.			

Note: For each variable only one number should be used in the addition. If a patient has values between those in the table, interpolation should be used.
From reference 12 (slightly modified).

to survival. For patients with compensated liver cirrhosis, HBeAg positivity was also a prognostic factor.

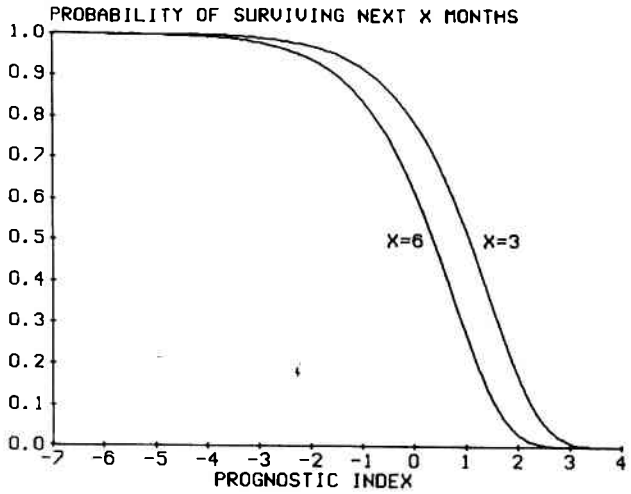

Fig. 1. Estimated probability of surviving the next 3 or 6 months as a function of the current prognostic index in cirrhosis as presented in Table 3. From reference 12.

Recently a large EUROHEP study on the survival and prognostic factors in 366 patients with chronic hepatitis B and compensated cirrhosis has been performed (30). The 10-year survival was 68% in these patients. A Cox regression analysis showed high age, low serum albumin, low platelets, splenomegaly, high bilirubin, and HBeAg positivity to be independently associated with a poor prognosis. The results were also presented in a pocket chart from which a prognostic index can easily be derived and, using a graph, translated to a probability of surviving 5 or 10 years (30). Although this prognostic index has not been validated using independent data, it may possibly be used as a surrogate marker for evaluation of treatment effects related to survival.

Chronic Hepatitis C

Hepatitis C becomes chronic in about 3/4 of cases, but little is known about the long-term survival of these patients. Usually the disease progresses very slowly and only after a considerable number of years may cirrhosis and its complications develop.

A large – not yet fully published – EUROHEP study of the natural history of 356 patients with compensated cryptogenic cirrhosis, most of whom have chronic hepatitis C infection, showed a 10-year survival of 78% (31). High age, hepatic stigmata on physical examination, high bilirubin and low platelets were associated with a poor prognosis. These factors can also be combined to give a prognostic index which may be a suitable surrogate marker for evaluation of treatment effects related to survival.

TABLE 4

Independent variables associated with a poor prognosis in alcoholic liver disease

Variable	Models			
Reference:	Toronto (24)	Copenhagen (25)	Paris (26)	European (27)
Female gender		×		
High age		×	×	
Ascites		×		
History of alcoholism of long duration				×
Encephalopathy	×		×	
Low haemoglobin	×			
Low prothrombin index	×		×	×
Low albumin	×			
Low acetylcholinesterase		×		
High bilirubin			×	
High immunoglobulin M				×
High alkaline phosphatase				×
High gamma glutamyl transpeptidase			×	
High serum creatinine				×
High white blood cell count				×
Little liver cell steatosis				×

TABLE 5

Independent variables associated with a poor prognosis in primary biliary cirrhosis

Variable	Time fixed models						Time dependent models		
Reference:	Yale (38)	European (33)	Mayo (39)	Glasgow (40)	Oslo (41)	London (42)	European (43)	Mayo (44)	London (45)
High bilirubin	×	×	×	×	×	×	×	×	×
Low serum albumin		×	×			×	×	×	×
Low prothrombin index			×					×	
Low immunoglobulin M							×		
High age	×	×	×	×		×	×	×	×
Hepatomegaly	×					×			
Peripheral oedema			×					×	
Ascites				×		×	×		×
Oesophageal varices						×			
GI bleeding				×	×		×		
Cirrhosis	×	×		×		×	×		
Histologic cholestasis		×		×			×		
Mallory bodies				×					

Primary Biliary Cirrhosis

Primary biliary cirrhosis is an intrahepatic, chronic, nonsuppurative, destructive cholangitis which ultimately leads to cirrhosis. The natural history and the survival time are highly variable (32). Although some treatments such as azathioprine (33), colchicine (34), cyclosporin A (35) and ursodeoxycholic acid (36) have some beneficial effects, no medical treatment has been demonstrated to be effective in stopping progression of the disease. Therefore, in the advanced cases liver transplantation is the only effective therapeutic measure.

In 1979, Shapiro demonstrated the paramount importance of serum bilirubin as a prognostic factor (37). Since then, many studies have identified prognostic variables (32,33,38–45) and devised prognostic indices (33,38–45). Table 5 summarises the independent prognostic variables identified in the studies. The European and the Mayo models have been validated using independent patient data. The Mayo model has been used to improve comparison with historic controls (36), but such a procedure is a poor substitute for randomised clinical trials, which should always be preferred.

As indicated in Table 5, three of the Cox models (43–45) are time-dependent models utilising follow-up information. These indices can thus be used to update prognosis whenever changes in the condition occur. They are thus well suited for monitoring patients dur-

ing the course of the disease and may therefore be particularly useful for optimal timing of liver transplantation. The time-dependent models give more reliable predictions because they utilise the data more efficiently. The European models have been presented as pocket charts by which prognosis can easily be estimated (2,43). The European time-dependent model exists in a version with and without histologic variables (43).

Some of the above models have been used to substantiate the value of liver transplantation by demonstrating that the survival observed after the procedure is better than without transplantation, as predicted by the models (46–48). Such evidence is markedly weaker than what could have been obtained in controlled clinical trials, but since such have not, and probably will not, be performed, the predictions provided by the prognostic indices have become necessary in the evaluation of the transplantation procedure.

Furthermore, a prognostic model has been devised for prediction of survival after transplantation for primary biliary cirrhosis (49). Thus it is possible to predict survival time both with and without transplantation, and the procedure would accordingly be justified only if the former were longer than the latter.

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis is a chronic progressive destructive biliary disease of unknown aetiology. The median survival is about 12 years but it varies markedly between individual patients (50–53). Until now, no medical treatment has been demonstrated to be effective in stopping progression of the disease. At present, transplantation is the only effective treatment.

Four prognostic indices have so far been reported (50–53). The independent prognostic variables identified are presented in Table 6. Three models included bilirubin and all four included high age and advanced histologic stage as independent prognostic variables.

The first three prognostic models have been evaluated in an independent smaller series with regard to their ability to discriminate between patients needing and patients not needing a transplantation (54). None of the models provided a complete distinction between the two groups, but the model of Dickson et al. (52) gave the best discrimination (54).

TABLE 6

Independent variables associated with a poor prognosis in primary sclerosing cholangitis

Variable	Models			
	Mayo	King's	Multi-cent.	Sweden
Reference:	(50)	(51)	(52)	(53)
High bilirubin	×		×	×
High alkaline phosphatase		×		
Low haemoglobin	×			
High age	×	×	×	×
Hepatomegaly		×		
Splenomegaly		×	×	
Inflammatory bowel disease	×			
Advanced histologic stage	×	×	×	×

Why is the Precision of Prognostic Models Not Very High?

Generally the precision of prognostic models in predicting the prognosis for a given patient is not very high. This is reflected in the rather wide confidence limits of the estimated survival probability (33,39,43). Even though time-dependent models utilise the prognostic information better and only predict for a limited period, the confidence limits of the estimated survival probabilities from these models are still rather wide (43).

The reasons for this imprecision include:

Statistical significance is not equivalent to predictive ability

Variables are usually included in a model if they are statistically significant. However, statistical significance is a rather weak criterion, meaning only that the prognostic association is unlikely to have occurred by chance. With increasing sample size, increasingly weaker associations may become statistically significant. Thus in very large samples, variables with very weak (unimportant) prognostic information may achieve statistical significance. Thus for the logistic regression and Cox models we need better information criteria corresponding to the coefficient of determination R^2 of simple multiple regression analysis which directly gives the proportion of the variance in the outcome variable being explained by the predictor variables in the model.

The prognostic variables are only weakly informative

The descriptive variables which we use for prognosis explain only a small part of the observed variation in survival among patients. The biological variation is much larger than can be accounted for by the recorded variables. In addition, many of the variables which we record are not central to the fundamental disease process but are side events or epi-phenomena.

Too few variable recordings are being used

Variables at diagnosis or at admission to hospital typically show short-term regression toward normal (2,55)

and may therefore be less informative than later steady-state values.

The changes during the course of the disease are not utilised

The initial course of the disease may give additional indication about the subsequent course. Such information about the course of variables over time is at present not utilised sufficiently in existing models. The time-dependent Cox model uses only the current variable recordings, not their previous course.

Variables may interact in a highly complex manner

Even though the prognostic models obtained so far may seem complex, they generally follow a simple scheme: they are linear, i.e. they represent straight lines. A given change in one variable represents a given change in death risk, irrespective of the other variables being low or high. This linear structure may be too simple to give a valid description. The variables may interact: i.e. the effect of a change in one variable on the death risk may depend on the value of other variables. Although it is possible to discover and take simple interactions into account, more complex interactions may be very difficult to identify and describe with present statistical tools.

Important prognostic variables may be unknown

In spite of our seemingly detailed knowledge of many disease processes, we may still have much to discover, including better prognostic variables closely connected with the fundamental processes of the disease in question. However, if new prognostic variables are to be useful in clinical practice, they should be easily obtainable.

What can Prognostic Indices or Scores be Used For?

Guides to prognosis

Because of their imprecision, prognostic scores or indices can only be used as guides to prognosis, not more than that. They are usually not better at predicting prognosis than experienced specialists, who can also take into account more subtle impressions which are not so easily described and recorded.

Summarised description of patients

A prognostic index is a summarised description of the seriousness of the disease expressed in one number, which is obtained as a combination of all the prognostic variables weighted according to their relative prognostic influence. Therefore a group of patients may be very well described by the distribution (e.g. histogram) of their prognostic indices. In particular, such information would improve the description of patients included in randomised clinical trials. A cumulative distribution of the prognostic indices could preferably be presented for each of the treatment groups to document their baseline prognostic comparability, which could then be tested with a distribution test (e.g. the two-sample Kolmogorov-Smirnov test).

Illumination and inspiration of pathogenetic studies

Because prognostic analyses and models are designed to identify variables strongly associated with the outcome (death or survival), and thereby also with the progression of the disease, they can illuminate the pathogenesis of the disease process. Knowing which variables are associated with progression of the disease and which are not can inspire further pathogenetic studies and thereby possibly the discovery of new prognostic variables.

Possible use as a surrogate marker in evaluation of treatments?

Since many cases of chronic liver disease develop over many (e.g. 5, 10 or 20) years, a need has arisen for (surrogate) markers which can describe the degree of progression of the disease at the earlier stages, and thus be used instead of harder end-points (death or complication such as gastrointestinal bleeding, coma, decompensation) for evaluation of therapies in controlled clinical trials (56).

However, there are serious problems in using surrogate markers in the evaluation of treatments. One particularly important problem is the following: even if the surrogate marker in untreated patients has been demonstrated to be related to the outcome, it is still possible that the treatment being investigated may influence the surrogate marker without having an effect on the course of the disease, i.e. the changes produced by the treatment are purely "cosmetic". The situation will be increasingly complex if the treatment effect varies between individuals (2,3,12,57) (which may be a more common feature than previously thought) and especially if the variables characterising responders and non-responders contribute to the surrogate marker index (3,12). Such problems, which have only been studied sporadically (2), may be much more prominent than we would expect. For these reasons use of prognostic indices as surrogate markers in the evaluation of treatments should be used only if hard (or semi-hard) endpoints cannot be obtained in sufficient numbers within a reasonable time, even in large international multicenter trials.

The Need for Simplification and Agreement on Fewer Up-to-date Indices in the Future

Until now, quite a few prognostic models have been published for various chronic liver diseases. Some of these have been validated using independent patient data. Even if the indices are the results of complex statistical analyses, they are not difficult to use because the results can be presented in simple pocket charts and diagrams, with which a crude estimate of the probability of surviving a given time can be calculated at the bedside.

However, for a given disease the models vary somewhat concerning the variables included. This is only to be expected because of differences in the patient samples and the fact that selection of variables is mainly made according to statistical criteria and less frequently according to clinical knowledge. It is difficult to know which of the models is the best for a given disease. Probably their prognostic information is rather similar, although this has not yet been fully investigated. Nevertheless, the existence of so many different models is likely to cause confusion as to which to use. There seems to be a need for some simplification and standardisation. It would be desirable if general agreement could be obtained on one prognostic index to be used as the prognostic index for a given disease to succeed the Child-Turcotte and Pugh criteria. To obtain such an agreement, cooperative studies on combined data bases from different centres should be considered. Use of good prognostic indices generally agreed upon would make comparison of results from different centres easier and would promote scientific progress.

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