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Prognosis of untreated primary sclerosing cholangitis

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INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by inflammation and fibrosis of the intra- and extrahepatic bile ducts. Although immunological and genetic factors seem to be involved in the pathogenesis, the aetiology of PSC remains unknown.

Long-term studies have established PSC as a progressive disease[1–8], which ultimately may lead to biliary cirrhosis, liver failure and death. The mean age at time of diagnosis is 35–40 years and two-thirds of patients are males. Up to half of patients are symptomatic at diagnosis, and the majority have associated inflammatory bowel disease, mainly ulcerative colitis. The initial presentation and the subsequent rate of disease progression are highly variable among patients. In most patients the rate of progression is relatively slow, with median survival being about 12 years; however, the development of cholangiocarcinoma, which occurs in about 10%, worsens the prognosis considerably[9,10]. Recently it has been demonstrated in more studies that patients with only small duct PSC – comprising about 10% of patients – have a much better prognosis and a much lower risk of developing cholangiocarcinoma than patients with large duct PSC[11–14].

Several large studies have described the natural history of PSC, including patient characteristics at diagnosis, survival and its association with variables describing the patients – most frequently at the time of diagnosis[15–24].

SURVIVAL

The median survival time has been found to be about 12 years in more of the larger studies; however, median survival times up to 18 years have been reported in a Dutch study[24]. In another smaller series of referred and probably highly

selected patients a median survival of less than 1 year from referral was observed[17]. This shows the wide variation in course and outcome of the disease.

CHARACTERISTICS AT TIME OF DIAGNOSIS AND ASSOCIATION WITH PROGNOSIS

It is obvious that the course of disease, which can be observed, will be dependent on: (a) the time of diagnosis in relation to the start of the disease, i.e. the diagnostic delay; and (b) the rate of progression of the disease. Because of the insidious nature of the disease it may be difficult to determine the starting time. Although diagnosis of asymptomatic cases does occur, most frequently the diagnosis is made only following the occurrence of symptoms, which may occur after many years of asymptomatic disease. Even in the symptomatic phase the course may be irregular with phases of deterioration and improvement for many years. Furthermore, the rate of disease progression may differ considerably between patients even if they are at the same stage. In later phases of the disease the rate of progression may accelerate towards liver insufficiency over a short period of time (months). These characteristics of the disease explain the variability of the results obtained in regard to variables found to be associated with prognosis.

Tables 1–3 present a summary of the variables found to be associated with survival in univariate analysis in the published studies. In most of the reports a strong association between older age and a poorer survival has been found establishing age at diagnosis as a strong prognostic variable (Table 1).

In the study comprising referred patients[17] a long duration of history was strongly associated with a poor prognosis.

The same study found a worse survival in males. In other studies there have been only weak insignificant trends towards a poorer prognosis in males than in females; however, in one study there was a trend in the other direction[19].

The presence of symptoms and the association with inflammatory bowel disease have in some studies been found to be associated with poorer prognosis.

Some milder signs and symptoms, such as pruritus, fatigue, weight loss, fever and abdominal pain, have been reported in some studies to be associated with a poorer prognosis (Table 1); however, the symptoms and signs most frequently associated with poorer prognosis include features of advanced later-stage disease such as ascites, jaundice, varices, variceal bleeding, hepatomegaly and splenomegaly (Table 1).

The biochemical variables most frequently associated with a poorer prognosis (Table 2) include: (a) indicators of cholestasis, such as high bilirubin, high alkaline phosphatase, high cholesterol; (b) indicators of inflammatory activity and liver cell destruction such as high AST, high gamma-globulin; and (c) indicators of decreased liver cell function, portal hypertension and hypersplenism, such as low albumin, prolonged prothrombin time, low haemoglobin, and low platelet count.

Macroscopic structural variables being associated with poorer survival (Table 3) include presence of common bile duct stricture, extrahepatic PSC, and cholangiographic score with markedly abnormal cholangiogram in regard to both intrahepatic and extrahepatic strictures. The prognostic value of strictures

Table 1 Clinical variables associated with poorer prognosis in PSC in univariate analysis

	Study (main author) and ref.									
	Wiesner[15]	*Farrant*[16]	*Ismail*[17]	*Dickson*[18]	*Schrumpf*[19]	*Broomé*[20]	*Okolicsanyi*[21]	*Kim*[22]	*Boberg*[23]	*Ponsioen*[24]
Year	1989	1991	1991	1992	1994	1996	1996	2000	2002	2002
Number of patients	174	126	48	426	77	305	117	405	330	174
Variables										
Older age	+++			+++	++	+++	++	++	+++	+++
Male gender			+					(+)		
Long duration of history			+++							
Presence of symptoms	++					+++				
Inflammatory bowel disease	+			+						
Pruritus						+++			++	
Fatigue									+++	
Weight loss									++	
Fever						+			+	
Abdominal pain						+			+++	
Ascites	+++			+++		+++		++	+++	
Jaundice	+++			+++		+++			+++	
Varices		++							+++	
Variceal bleeding	+++			++		+++		++		
Hepatomegaly	+	++		+++				++	+++	
Splenomegaly	+++	++		+++				++	+	

+++, $p < 0.001$; ++, $p < 0.01$; +, $p < 0.05$; (+), $p < 0.10$.

Table 2 Biochemical variables associated with poorer prognosis in PSC in univariate analysis

	Study (main author) and ref.									
	Wiesner[15]	*Farrant*[16]	*Ismail*[17]	*Dickson*[18]	*Schrumpf*[19]	*Broomé*[20]	*Okolicsanyi*[21]	*Kim*[22]	*Boberg*[23]	*Ponsioen*[24]
Year	1989	1991	1991	1992	1994	1996	1996	2000	2002	2002
Number of patients	174	126	48	426	77	305	117	405	330	174
Variables										
High bilirubin	+++	+	++	+++	++	+++	++	++	+++	
High alkaline phosphatase		+		(+)		++	+	+	++	
High cholesterol							+++			
High AST	(+)			+++		++	++	++	(+)	
High gamma-globulin	+									
Low albumin	+++			+++	(+)	++	++	++	+++	
Prolonged prothrombin time								++	+++	
Low haemoglobin	+++			+++	(+)		++	++	+++	
Low platelet count	++				(+)			++	(+)	

+++, $p < 0.001$; ++, $p < 0.01$; +, $p < 0.05$; (+), $p < 0.10$.

Table 3 Histological and structural variables associated with poorer prognosis in PSC in univariate analysis

	Study (main author) and ref.									
	Wiesner[15]	*Farrant*[16]	*Ismail*[17]	*Dickson*[18]	*Schrumpf*[19]	*Broomé*[20]	*Okolicsanyi*[21]	*Kim*[22]	*Boberg*[23]	*Ponsioen*[24]
Year	1989	1991	1991	1992	1994	1996	1996	2000	2002	2002
Number of patients	174	126	48	426	77	305	117	405	330	174
Variables										
Common bile duct stricture		+								
Extrahepatic PSC						+++				
High cholangiographic score										+++
Ductopenia	++									
Cholestasis	+++	++								
Piecemeal necrosis	+++									
Portal fibrosis		++								
Advanced histological stage	+++	+++		+++		+++				
Cirrhosis			++							

+++, $p < 0.001$; ++, $p < 0.01$; +, $p < 0.05$; (+), $p < 0.10$.

on cholangiography, in particular intrahepatic strictures, is supported by other studies[25–26].

Microscopic structural variables being associated with poorer survival (Table 3) include early lesions such as ductopenia, cholestasis, and piecemeal necrosis, and later more advanced features such as portal fibrosis, advanced histological stage and cirrhosis.

Recently the intrahepatic or small duct form of PSC comprising about 10 percent of the patients was studied more closely[11–14]. Small duct PSC seems to have a more benign course with a better survival and less risk of cholangiocarcinoma.

Over the years less emphasis has been put on liver biopsy findings as a source of prognostic information. No study after 1996 includes histological variables among the prognostic indicators.

PROGNOSTIC MODELS

Prognostic variables have been combined into prognostic models mainly using the Cox model for proportional hazards[27]. In such models each included variable contributes in proportion to its independent association with survival. Since most of the variables recorded for the PSC patients are intercorrelated to a higher or lesser degree, only the strongest prognostic variables will be included in the prognostic models.

Table 4 gives an outline of the variables included in various prognostic models. The models differ markedly, reflecting differences in the patient samples from which they have been developed. Beyond the differences in distribution of types and stages of PSC the variables recorded and analysed at baseline vary considerably between the studies. The most important indicator of a poor prognosis is a high serum bilirubin, this variable being included in nearly all the models. Other important independent predictors of a poor prognosis include high age, low albumin and advanced histological stage. However, variables such as hepatomegaly, splenomegaly, variceal bleeding, inflammatory bowel disease, low haemoglobin, high alkaline phosphatase, high AST, high cholesterol, and a high cholangiographic score are also included in some models as independent indicators of a poor prognosis.

The Child–Pugh score is inferior to the prognostic models specific for PSC[8,28].

TIME-DEPENDENT PROGNOSTIC MODEL

The time-fixed models referred to above utilize only the baseline data. This limits the applicability of the models because the stage and activity of the disease may change soon after baseline and thus change the prognosis. Generally the time-fixed models cannot predict reliably more than a few years ahead, and even then the prognostic estimates may not be very precise.

In one study, by Boberg et al.[23], follow-up data have been utilized to develop a so-called time-dependent Cox regression model[27]. In utilizing the follow-up data this model is based on a much larger amount of data being related to subsequent survival. This means that the resulting model can give more precise predictive estimates. The time-dependent model is well suited for monitoring of patients.

Table 4 Variables with independent association with poorer prognosis in PSC (multivariate analysis)

	Study (main author) and ref.									
	Wiesner[15]	*Farrant*[16]	*Ismail*[17]	*Dickson*[18]	*Schrumpf*[19]	*Broomé*[20]	*Okolicsanyi*[21]	*Kim*[22]	*Boberg*[23]	*Ponsioen*[24]
Year	1989	1991	1991	1992	1994	1996	1996	2000	2002	2002
Number of patients	174	126	48	426	77	305	117	405	330	174
Variables										
Older age	+++	++		+++	++	+		++	+++	(+)
Long duration of history			(+)							
Hepatomegaly		++								
Splenomegaly		+		++						
Variceal bleeding								++		
Inflammatory bowel disease	+++									
High bilirubin	+++		+++	+++	++	+++		++	+++	
Low albumin							(+)	++	+++	
Low haemoglobin	+++						+			
High alkaline phosphatase		++								
High AST							+	++		
High cholesterol							+++			
Advanced histological stage	+++	+		+++		++				
High cholangiographic score										+++

+++, $p < 0.001$; ++, $p < 0.01$; +, $p < 0.05$; (+), $p < 0.10$.

Whenever changes occur during the course of the disease a new updated short-term prognostic estimate can be made for the next time period by applying the current values of the prognostic variables in the model.

Boberg et al.[23] performed both a time-fixed analysis and a time-dependent analysis on their series of 330 patients from five European centres followed for a median of 8.4 years after diagnosis. Both analyses identified age, bilirubin and albumin as independent predictors of prognosis. However, the prognostic information of bilirubin and albumin was much stronger, i.e. the regression coefficients were numerically larger, in the time-dependent than in the time-fixed model. Accordingly, the 1-year survival probabilities estimated from the time-dependent model corresponded better with the observed survival than those estimated from the time-fixed model in 18 PSC patients dying within 1 year after diagnosis. Using an additive regression analysis the authors made the interesting observation that the influence of albumin was significant only in the first 5 years after diagnosis[23].

APPLICABILITY OF THE PROGNOSTIC MODELS

Generally the prognostic models 'explain' only a quite small part of the variation of the survival time seen in patients; the vast majority of the variation is not explained. This limits the applicability of the prognostic models[29]. Individual estimates of survival are imprecise, even if a time-dependent model is used. The confidence interval of the survival estimates will most often be very wide. Thus a prognostic estimate can serve only as a crude guide to prognosis, and thus only be a supplement to other relevant clinical information needed to decide if and when special therapeutic procedures will be needed. Of particular importance is the decision of if and when to perform liver transplantation[30,31], which may be necessary for end-stage PBC patients because of the inefficiency of medical and other conservative therapies[32]. The timing of liver transplantation is difficult[33,34] and a decision regarding the procedure should not be based on prognostic estimates alone. Instead the prognostic information should be considered together with all other clinically relevant data to ensure the best possible foundation for the decision.

PERSPECTIVES

Prognostic modelling for PSC is difficult for the following reasons: the disease is rather rare, accumulation of large databases requires close cooperation between many centres, the clinical course of the disease is very long, and the number of endpoints is limited. Furthermore, the course of the disease is not steadily progressing but will present short-term phases of improvement and deterioration. The transition from one stage to another (asymptomatic to symptomatic, symptomatic to decompensated, decompensated to terminal) is insidious and not well defined. The prognostic determinants may well differ in the various phases. This will complicate a useful description. In addition different medical and conservative therapies may modify the course in various ways.

At present a large number of rather different prognostic models are available. Probably their prognostic information is rather similar, although this has not been investigated. It would be desirable if general agreement could be obtained on a common prognostic model to be used for PSC[35,36]. To obtain such an agreement, cooperative studies on combined databases from all centres seem necessary.

Thus the challenge for the future in improving the description of the natural history and its determinants is substantial. A wider application of time-dependent Cox regression analysis, which can model both deterioration and improvement, may lead to some further progress. The pattern of intercorrelation between the descriptive variables at various phases during the course of the disease should be studied further to evaluate if interaction terms between variables should be included in the models. Furthermore, modelling of the course of the prognostic variables themselves may also result in some progress[35]. Close cooperation with qualified statisticians, to ensure the best quality of the analyses, is essential in this process[35,36]. In addition the search should continue for better descriptive variables, which characterize as precisely as possible the core problem(s) in the disease, preferably in molecular terms[37]. Such information will most likely improve the prognostication markedly compared to the current prognostic models, which are mainly based on peripheral epiphenomena secondary to the core problem(s) defining the disease.

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