ORIGINAL ARTICLE

Predictors of liver failure in primary biliary cirrhosis

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Abstract

Background. The disease progression of patients with primary biliary cirrhosis (PBC) varies significantly, and the prognostic markers that identify those patients who will develop liver failure have been scarcely studied from a Chinese cohort.
Aims. We aimed to determine the predictive factors of liver failure in patients with PBC.
Methods. Patients who were first diagnosed as PBC with hepatic compensation between January 2007 and December 2009 were enrolled in this cohort study.
Results. Altogether 398 patients were finally included. Of these patients, 80% were women, 98% had positive antimitochondrial antibodies, and 45% had positive antinuclear antibodies (ANA). To December 2012, a total of 38 patients developed liver failure. According to the outcome, patients who developed liver failure had had higher serum concentration of baseline total bilirubin (TBil) ($p = 0.013$) and total bile acid (TBA) ($p < 0.001$), and lower concentrations of baseline total cholesterol (Tch) ($p = 0.008$), than patients who did not develop liver failure. Additionally, the proportion of ANA positivity was statistically different between the two groups ($p = 0.009$). In the established model for predicting liver failure in PBC, three variables were finally selected out, including Tch (odds ratio (OR) 0.552, 95% confidence interval (CI) 0.394–0.774, $p < 0.001$), TBA (OR 1.006, 95% CI 1.002–1.010, $p = 0.002$), and ANA (+ versus –, OR 5.518, 95% CI 1.155–26.376, $p = 0.032$).
Conclusions. ANA, Tch, and TBA are predictors of liver failure in PBC.

Key words: *Primary biliary cirrhosis, liver failure, predictor*

Introduction

Primary biliary cirrhosis (PBC) is an autoimmune liver disease characterized by the destruction of intrahepatic bile ducts, which can lead to hepatic cirrhosis and eventually liver failure and death (1,2). Ursodeoxycholic acid (UDCA) is the only drug accepted internationally for the treatment of PBC (3-5). However, a recent meta-analysis of 16 randomized clinical trials demonstrated no significant benefits of UDCA on all-cause mortality or liver transplantation in patients with PBC (6). In fact, the disease progression varies markedly among patients with PBC (7); moreover, substantial divergences of clinical characteristics exist because of variations in the populations under different studies (8,9). Thus, it is necessary in the early stage to determine the prognostic variables associated with the development of end-stage liver disease, so that physicians can closely monitor the disease progress and adjust treatment measures in a timely manner before fatal events occur. In the present study, we aim to study the clinical characteristics

and risk factors associated with the development of liver failure in a prospective cohort with PBC.

Patients and methods

Patients

Patients who were first diagnosed as PBC with hepatic compensation between January 2007 and December 2009 in Beijing 302 Hospital were enrolled in this cohort study. All of these included patients had received UDCA therapy at the initial diagnosis of PBC. Exclusion criteria included the concurrence of autoimmune hepatitis or extra-hepatic autoimmune diseases; infection with hepatitis A, B, C, D, E, Epstein–Barr virus, cytomegalovirus, or human immunodeficiency virus; the presence of other forms of liver diseases such as alcoholic liver disease, drug-induced hepatitis, or Wilson's disease; the use of corticosteroids or immunosuppressive drugs for a period of more than 2 weeks; and UDCA non-responders. Liver failure in this study was defined as coagulopathy (prothrombin activity (PTA) ≤40% or international normalized ratio (INR) ≥1.5) and jaundice (serum total bilirubin (TBil) ≥171 μmol/L or a daily increase ≥17.1 μmol/L).

The study was performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the ethics committee of Beijing 302 Hospital.

Laboratory tests

Biochemical profiles, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBil), gamma glutamyl transferase (GGT), alkaline phosphatase (ALP), albumin, total cholesterol (Tch), and total bile acid (TBA) were measured using standard laboratory procedures. Normalized serum concentrations of ALT, AST, TBil, GGT, ALP, albumin, Tch, and TBA were, respectively, <40 U/L, <40 U/L, <17.1 μmol/L, 7–32 U/L, 40–150 U/L, 35–55 g/L, 2.8–5.2 mmol/L, and 0–10 μmol/L.

Serum autoantibodies, including antimitochondrial antibodies (AMA) and antinuclear antibodies (ANA), were tested using indirect immunofluorescence with standard methods (Euroimmun Medizinnische Labordiagnostika AG, Lubeck, Germany), and sera were considered to be positive when they produced a reaction at a dilution of ≥1:100. Immunoglobulin (Ig) was assayed by means of immunological turbidometry (Diasys Diagnostic Systems, Shanghai, China). Normal serum concentrations of IgA, IgG, and IgM

were 0.69–3.28 g/L, 7.23–16.6 g/L, and 0.63–2.77 g/L, respectively.

Statistical analysis

Data analyses were performed using SAS 9.2 software (SAS Institute Inc., Cary, NC, USA). Continuous data were expressed as medians (interquartile range). Categorical data were expressed as the number of subjects. Group comparisons were performed using the Wilcoxon rank sum test for continuous variables, and chi-square test or Fisher exact test for categorical variables. Logistic regression was used for evaluating prognostic predictors of liver failure. A probability (p) value of less than 0.05 was considered statistically significant.

Results

Demographic and clinical characteristics

Finally, 398 patients were included. In these patients, 317 (80%) were female and 81 (20%) were male. The average age was 57 (12) years. A total of 389 patients had positive AMA, and 9 had negative AMA; 182 patients had positive ANA, and 216 had negative ANA. In the years 2007, 2008, and 2009, 80, 147, and 171 patients were enrolled (Figure 1). To December 2012, a total of 38 patients had developed liver failure (Figure 2).

Univariate analysis for baseline variables in PBC

According to the outcome, patients who developed liver failure had had higher serum concentrations of baseline TBil (43.7 μmol/L versus 23.2 μmol/L, p = 0.013) and TBA (92.5 μmol/L versus 46.0 μmol/L, p < 0.001) and lower serum concentrations of baseline Tch (3.09 mmol/L versus 4.52 mmol/L, p = 0.008) than patients who did not develop liver failure (Table I). In addition, the proportion of ANA positivity differed between the two groups. Thus, a majority of the patients who developed liver failure had positive ANA (65.79% versus 43.61%, p = 0.009).

Predictors of liver failure in PBC

Three variables were eventually selected out to predict the development of liver failure in PBC using logistic regression, including Tch (odds ratio (OR) 0.552, 95% confidence interval (CI) 0.394–0.774, p < 0.001), TBA (OR 1.006, 95% CI 1.002–1.010, p = 0.002), and ANA (+ versus –, OR 5.518, 95% CI 1.155–26.376, p = 0.032) (Table II).

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│ Evaluation of clinical information at entry │
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Exclusion criteria:
(I) Concurrence of autoimmune hepatitis or extra-hepatic autoimmune diseases;
(II) Infection with hepatitis A, B, C, D, E, Epstein-bar virus, cytomegalovirus or human immunodeficiency virus;
(III) Presence of other forms of liver diseases such as alcoholic liver disease, drug-induced hepatitis or Wilson's disease;
(IV) Use of corticosteroids or immunosuppressive drugs (≥ 2weeks);
(V) Non-responders to ursodeoxycholic acid

398 patients with hepatic compensation were enrolled, including 80 in the year of 2007, 147 in 2008 and 171 in 2009

Follow-up: check-up in hospital pr telephone interview

A total of 38 patients developed liver failure to December 2012

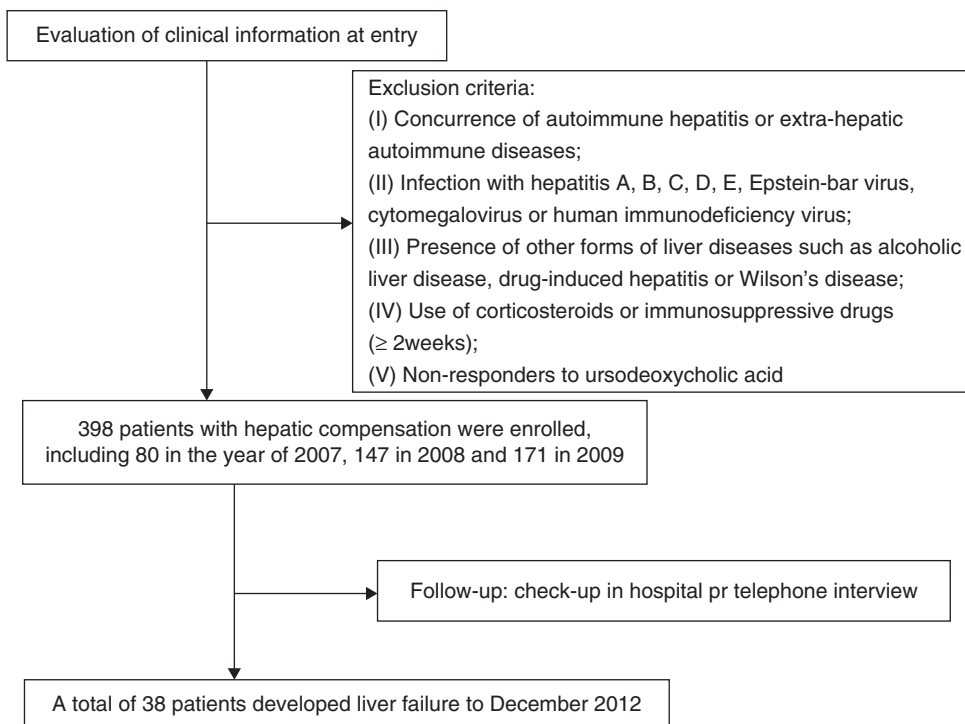Figure 1. Patient enrollment.

Discussion

PBC is a chronic and progressive cholestatic disease, and its pathogenesis remains unclear (10-12). Due to lack of curative therapeutics, liver failure is an evitable severe outcome in the majority of such patients. So, studying factors associated with the development of liver failure has vital and practical value. Beijing 302 Hospital is the largest hospital specializing in hepatology in China. Therefore, such an investigation

Figure 2. Cumulative incidence of liver failure in patients with primary biliary cirrhosis during follow-up.

on the risk of incipient liver failure in a large number of PBC patients possesses certain representativeness.

Previous studies have shown that patients with PBC often have higher serum concentrations of cholesterol (13-15). Because the synthetic and metabolic process of cholesterol is closely associated with the function of the liver, the development and progression of liver diseases can influence the serum concentrations of cholesterol. In our study, patients with lower total serum cholesterol concentrations were more likely to develop liver failure than patients with higher concentrations.

TBA has been less studied than other serum markers in the evaluation of the prognosis of PBC. Based on our study, it was an independent risk factor for liver failure in PBC. As previously shown, cholestasis is a main physiopathological characteristic of PBC. It can cause the accumulation of hydrophobic bile acids in the liver, which are toxic to cellular membranes (16,17). So, an increase of serum TBA may mirror the disease severity in PBC.

It has been reported that ANA can be found in 30%–50% of all PBC patients, and disease-specific ANA are associated with a more severe and rapidly progressing disease (18-20). In the present study, ANA were detected in 46% of the patients and proved to be related to the occurrence of liver failure. Regarding other early variables, such as ALP, GGT, and IgM, no correlations with the development of liver
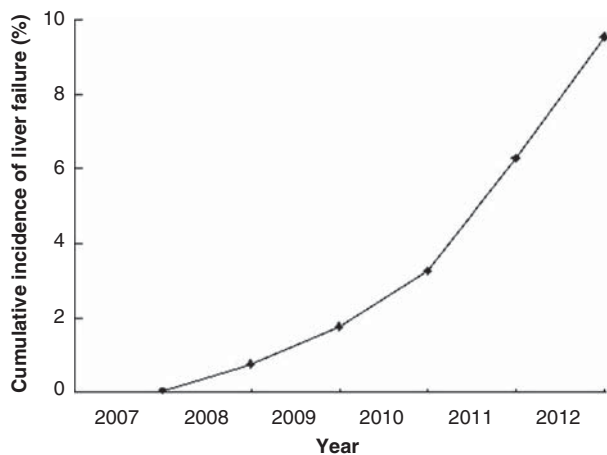
Table I. Comparison of baseline characteristics at entry between patients with and without liver failure.

Parameters	Patients not developing liver failure (*n* = 360)	Patients who developed liver failure (*n* = 38)	*p* value
Sex (male/female)	75/285	6/32	0.463
Age (years)	55 (15)	60 (11)	0.056
ALT (U/L)	52 (58)	56 (70)	0.899
AST (U/L)	70 (61)	88 (85)	0.094
ALT (U/L)	169 (118)	176 (112)	0.736
GGT (U/L)	217 (288)	238 (278)	0.552
Total bilirubin (µmol/L)	23.2 (44.5)	43.7 (46.3)	0.013
Albumin (g/L)	36 (7)	35 (6)	0.905
Total cholesterol (mmol/L)	4.52 (2.91)	3.09 (2.11)	0.008
Total bile acid (µmol/L)	46.0 (91.0)	92.5 (97.0)	< 0.001
IgA (g/L)	2.81 (1.67)	3.81 (3.76)	0.070
IgM (g/L)	2.81 (3.23)	2.01 (1.65)	0.099
IgG (g/L)	15.69 (8.49)	17.92 (8.94)	0.224
AMA (+/–)	352/8	37/1	0.599
ANA (+/–)	157/203	25/13	0.009

Continuous data were expressed as median (interquartile range).

Table II. Predictors of liver failure in primary biliary cirrhosis.

Parameters	Odds ratio (95% CI)	Standardized odds ratio (95% CI)	*p* value
Total cholesterol (mmol/L)	0.552 (0.394–0.774)	0.313 (0.162–0.606)	< 0.001
Total bile acid (µmol/L)	1.006 (1.002–1.010)	1.397 (1.130–1.727)	0.002
ANA (+ versus –)	5.518 (1.155–26.376)	5.518 (1.155–26.376)	0.032

failure were observed, though some of them had definitely diagnostic value.

In conclusion, ANA positivity, a lower serum concentration of Tch, and higher serum concentration of TBA are all associated with the development of liver failure in PBC.

Acknowledgements

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