Int J Clin Exp Med 2016;9(11):21996-22003
www.ijcem.com /ISSN:1940-5901/IJCEM0030004

*Original Article*

# Identification of the risk factors for liver-related mortality in primary biliary cirrhosis patients: a case-control study in China

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Received April 6, 2016; Accepted September 22, 2016; Epub November 15, 2016; Published November 30, 2016

**Abstract:** Background: Primary biliary cirrhosis (PBC) is an autoimmune liver condition with relatively slow progression, leading to liver failure and death. We retrospectively investigated potential risk factors of liver-related mortality in patients with PBC. Methods: The data of patients with PBC at the First Affiliated Hospital of Zhengzhou University in China from 2007 to 2013 were included, specifically that of 91 deceased and 364 living (control) patients. Univariate and multivariate conditional logistic regression models were applied to determine potential risk factors of liver-related mortality, with calculations of odds ratios (ORs) and 95% confidence intervals (CIs). Results: The following features were statistically similar between the deceased and living patients: age, gender, nationality, the status of anti-human immunodeficiency virus antibody, anti-hepatitis C virus antibody, and hepatitis B surface antigen. A large proportion of deceased PBC patients (92.31%) had died of decompensated cirrhosis; the most common immediate cause was hemorrhagic shock (41.75%), then hepatic encephalopathy (38.45%). Independent risk factors for liver-related mortality were: hepatocellular carcinoma, elevated total bilirubin (TBIL), decreased albumin (ALB) and platelet levels, and non-response to ursodeoxycholic acid ($P$<0.001, all). Cutoff values of TBIL and ALB for prediction of poor prognosis were determined as 38.65 μmol/L and 34.8 g/L, respectively; the areas under the ROC curve were 0.771 and 0.758 ($P$<0.001), respectively. Conclusions: PBC patients with hepatocellular carcinoma, high total bilirubin, low albumin or platelet levels at the initial diagnosis of disease, or who do not response to UDCA, are prone to liver-related death.

**Keywords:** Primary biliary cirrhosis, liver-related mortality, hepatocellular carcinoma, risk factor, case-control study

## Introduction

Primary biliary cirrhosis (PBC) is a cholestatic liver disease of slow progression, with a high female-to-male ratio (9:1) in middle-aged PBC patients [1-3]. Chronic nonsuppurative destruction of the bile ducts in PBC ultimately leads to liver cirrhosis or other adverse outcomes. In recent years, the prevalence of PBC has increased worldwide [4-6].

Currently, the treatment of PBC patients with ursodeoxycholic acid (UDCA) has been proven most efficacious. For those at the terminal stage or with liver failure, liver transplantation is the only curative option [7, 8]. The progression of PBC is accelerated by comorbidities such as hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, or alcohol intake [9]. Nevertheless, the potential risk factors for liver-related mortality in PBC patients have not been fully clarified.

Previous studies have shown that baseline parameters may influence the prognosis of PBC patients; investigations have included histological stage, age, or serum bilirubin or albumin levels [10-13]. Furthermore, clinical symptoms at the time of diagnosis, such as fatigue and pruritus, may indicate acceleration of disease progression [14, 15]. There is evidence that UDCA treatment and sensitivity to medication may improve survival or biochemical test results [16-18].

Although some factors have been shown to affect prognosis in PBC, variations in study designs have left questions regarding the risk

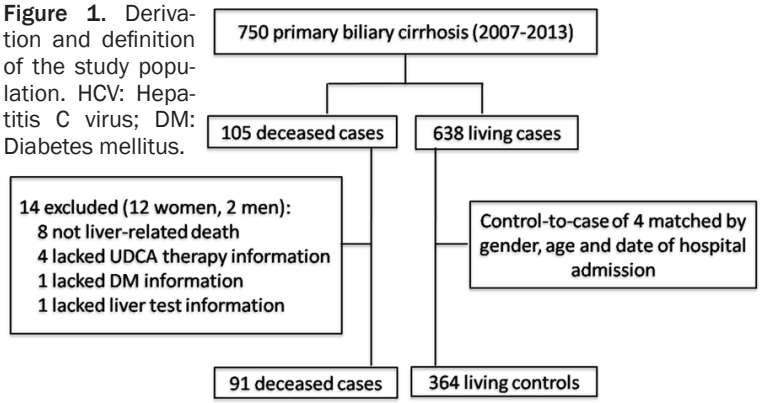


**Figure 1.** Derivation and definition of the study population. HCV: Hepatitis C virus; DM: Diabetes mellitus.

**Table 1.** Clinical and demographic characteristics of PBC patients in case and control groups*

| | Cases (%) | Controls (%) | *P*-value |
|---|---|---|---|
| Subjects, n | 91 | 364 | |
| Age, y | 55 (35-84) | 55 (31-86) | 0.898 |
| Gender | | | 1.000 |
| Male | 11 (12.09) | 44 (12.09) | |
| Female | 80 (87.91) | 320 (87.91) | |
| Nationality | | | 0.084 |
| Han | 89 (97.80) | 343 (94.23) | |
| Others | 2 (2.20) | 21 (5.77) | |
| HBsAg | | | 1.000 |
| Negative | 90 (98.90) | 360 (98.90) | |
| Positive | 1 (1.10) | 4 (1.10) | |

Abbreviations: HBsAg, hepatitis B surface antigen. *Data are presented as the number (frequency) for categorical data, or as median (interquartile range) for continuous data, or as indicated. NA: not applicable.

factors of liver-related mortality. To investigate the potential risk factors for liver-related mortality in PBC patients, this retrospective study utilized the database of the First Affiliated Hospital of Zhengzhou University in China to compare the clinical data of 638 patients at different disease stages with that of 105 deceased PBC patients.

## Material and methods

### *Study population and design*

A total of 750 patients with PBC at the First Affiliated Hospital of Zhengzhou University from January 2007 to December 2013 were enrolled in our study. Among these patients, 105 were deceased and 638 were survived (control group). The patients' clinical and demographic information was acquired from the hospital database.

Diagnosis of PBC was based on at least 2 of the 3 following criteria: biochemical evidence of cholestasis with elevation of alkaline phosphatase activity; the presence of anti-mitochondrial antibodies (AMA); and if a biopsy was performed, histopathological evidence of nonsuppurative cholangitis and the dest-ruction of small or medium-sized bile ducts. Excluded from the study were patients with Wilson's disease, primary sclerosing cholangitis, autoimmune hepatitis, or alpha-1 antitrypsin deficiency. We chose a ratio of 4 control inpatients to one deceased. Control subjects were matched to the deceased patients by gender, age (± 2 years), and duration of hospitalization (± 6 months). Of the 105 deceased patients, 91 had complete clinical histories and test information for inclusion; therefore 504 matched living controls were thus required for the study (**Figure 1**).

The Research Ethics Committee of the First Affiliated Hospital of Zhengzhou University approved this study. Due to the de-identified secondary data that were analyzed in this study, the committee waived the need for written informed consent from the patients.

### *Analysis of clinical factors*

The following clinical features were considered in this analysis of the potential risk factors for liver-related mortality in PBC: disease stage, liver function, status of hepatitis virus infection, blood routine test results, hemostasis examination at the initial diagnosis of PBC, clinical history, comorbidities, clinical manifestations, and the use of UDCA. Liver cirrhosis was determined based on pathological examination of a liver biopsy, or by ≥2 imaging methods (e.g., angiography, computed tomography [CT], abdominal ultrasonography, or magnetic resonance imaging [MRI]) and clinical manifestations. Cirrhosis was confirmed using one imaging method and the presence of complications, such as hepatic encephalopathy, ascites, or esophageal varices, as well as liver fibrosis tests. Hepatocellular car-

**Table 2.** Main death diagnosis and direct causes of death in the case group

| | | n | % |
|---|---|---|---|
| Main death diagnosis | Decompensated cirrhosis | 84 | 92.31 |
| | Hepatocellular carcinoma | 7 | 7.69 |
| Direct death cause | Hemorrhagic shock | 38 | 41.75 |
| | Hepatic encephalopathy | 35 | 38.45 |
| | Septic shock | 9 | 9.90 |
| | Hepatorenal syndrome | 6 | 6.60 |
| | Respiratory failure | 3 | 3.30 |

cinoma (HCC) was diagnosed pathologically, by ≥2 imaging modalities, or by one imaging modality and serum α-fetoprotein (AFP) ≥400 ng/mL. The history of alcohol intake was defined as alcohol consumption ≥4 days/week for ≥5 years [19]. A smoking history was defined as cigarette consumption ≥4 days/week for ≥5 years [19].

*Statistical analysis*

Data are presented as the mean ± standard deviation or the percentage (number) of patients. The Mann-Whitney U test and the chi-squared test were used for analyzing the non-parametric and independent variables, respectively. Univariate and multivariable conditional logistic regression models were used to calculate the odds ratio (OR) and 95% CI (confidence interval). Variables with a *P*-value <0.05 in a univariate analysis were subsequently adjusted by age and gender for a multiple logistic regression analysis. We determined the cutoff value of continuous risk factors for predicting the liver-related mortality by the receiver operator characteristic curve (ROC). A forward selection process was applied for model establishment. SPSS software (v16.0, SPSS, Chicago, IL, USA) was used for statistical analysis. A *P*-value <0.05 was considered statistically significant.

## Results

*General characteristics of the study population*

To estimate the risk factors for liver-related mortality in PBC, 91 deceased patients and 364 living patients (controls) identified from our database of 750 Chinese PBC patients over nearly 7 years of follow-up time were enrolled in this study (**Figure 1**; **Table 1**). Between the deceased PBC patients and the control group, there were no significant differences in mean age, gender, nationality, anti-HIV antibody, anti-HCV antibody and hepatitis B surface antigen (HBsAg) status. A large proportion of deceased PBC patients died of decompensated cirrhosis (92.31%, 84/91, and others died of HCC (7.69%, 7/91; **Table 2**).

In addition, the direct causes of mortality in deceased PBC patients were analyzed. Hemorrhagic shock was the most common direct cause of death (41.75%, 38/91), followed by hepatic encephalopathy (38.45%, 35/91). Other direct causes of death causes were septic shock (9.90%, 9/91), hepatorenal syndrome (6.60%, 6/91), and respiratory failure (3.30%, 3/91).

*Risk factors in the univariate model*

We first determined the potential risk factors of liver-associated death in PBC patients by applying an unadjusted univariate conditional logistic regression analysis (**Table 3**). PBC patients who had received a diagnosis of liver cirrhosis (any stage) had a 9.40-fold greater risk of mortality that did patients with chronic hepatitis only (95% CI=4.35-18.503), while the risk was 34-fold greater for those with HCC (95% CI=4.362-85.16). Diabetes mellitus and fatigue were associated with increased crude ORs for PBC-associated mortality. The use of UDCA and response to UDCA were associated with a lower risk of mortality.

Other risk factors for PBC-associated mortality were: reduced albumin (ALB) and platelet count (PLT) levels; and increased total bilirubin (TBIL), aspartate aminotransferase (AST), AST/PLT ratio index (APRI), prothrombin time (PT), and international normalized ratio (INR). However, other factors, such as HBsAg positivity, AMA positivity, hypertension, history of smoking, history of alcohol abuse, and alanine transaminase (ALT), were all excluded from the univariate model.

*Risk factors in the multivariate model*

The following were included in multivariate logistic regression analysis: initial diagnostic stage, AST, TBIL, PLT, APRI, ALB, PT, INR, fatigue, type 2 diabetes mellitus, use of UDCA, and response to UDCA (**Table 4**). Adjustments

**Table 3.** Univariate conditional logistic regression analysis of potential risk factors for PBC mortality

| Variables | Cases (%) | Controls (%) | uOR (95% CI) | B | *P* value |
|---|---|---|---|---|---|
| Follow-up time (month) | 8 (3-77) | 34 (3-84) | 0.735 (0.667-0.810) | -0.308 | 0.000 |
| Initial diagnostic stage | | | | | |
| Chronic hepatitis | 7 (7.69) | 126 (34.62) | 1.000 | - | - |
| LC | 77 (84.62) | 238 (65.38) | 9.403 (4.35-18.503) | 2.205 | 0.000 |
| HCC | 7 (7.69) | 0 | 34.000 (4.362-85.16) | 3.552 | 0.001 |
| HBsAg | | | | | |
| Negative | 90 (98.90) | 360 (98.90) | 1.000 | - | - |
| Positive | 1 (1.10) | 4 (1.10) | 1.000 (0.139-7.177) | 0.000 | 1.000 |
| HBcAb | | | | | |
| Negative | 52 (57.14) | 212 (58.24) | 1.000 | - | - |
| Positive | 39 (42.86) | 152 (41.76) | 1.037 (0.684-1.570) | 0.036 | 1.000 |
| AMA | | | | | |
| Negative | 3 (3.30) | 19 (5.22) | 1.000 | - | - |
| Positive | 88 (96.70) | 345 (94.78) | 1.686 (0.466-6.103) | 0.522 | 0.426 |
| ALB | 29 (13-40) | 35 (18-52) | 0.828 (0.784-0.874) | -0.189 | 0.000 |
| TBIL | 52.8 (7.3-645.7) | 22.9 (3.3-585.1) | 1.009 (1.006-1.012) | 0.009 | 0.000 |
| ALT | 60.0 (3-803) | 53 (7-2740) | 1 (0.998-1.001) | 0.000 | 0.778 |
| AST | 94 (11-1601) | 67 (17-1262) | 1.002 (1.000-1.004) | 0.002 | 0.029 |
| ALP | 260 (37-829) | 249 (58-3036) | 1 (0.999-1.001) | 0.000 | 0.533 |
| PLT | 85 (23-325) | 143 (10-443) | 0.991 (0.987-0.995) | -0.009 | 0.000 |
| APRI | 1.09 (0.16-7.18) | 0.55 (0.05-16.3) | 1.483 (1.178-1.867) | 0.394 | 0.001 |
| PT | 13.3 (9.4-45.4) | 11.3 (8.3-28.9) | 1.427 (1.258-1.618) | 0.355 | 0.000 |
| INR | 1.15 (0.79-1.77) | 0.99 (0.79-3.25) | 11.756 (3.212-43.030) | 2.464 | 0.000 |
| Fatigue | | | | | |
| No | 27 (29.67) | 151 (41.48) | 1.000 | - | - |
| Yes | 64 (70.33) | 213 (58.52) | 1.670 (1.019-2.737) | 0.513 | 0.042 |
| Pruritus | | | | | |
| No | 62 (68.13) | 278 (76.37) | 1.000 | - | - |
| Yes | 29 (31.87) | 86 (23.63) | 1.543 (0.920-2.591) | 0.434 | 0.100 |
| Diabetes mellitus | | | | | |
| No | 73 (80.22) | 327 (89.84) | 1.000 | - | - |
| Yes | 18 (19.78) | 37 (10.16) | 2.341 (1.221-4.488) | 0.851 | 0.010 |
| Hypertension | | | | | |
| No | 85 (93.41) | 312 (85.71) | 1.000 | - | - |
| Yes | 6 (6.59) | 52 (14.29) | 0.412 (0.169-1.005) | -0.886 | 0.051 |
| Alcohol intake | | | | | |
| No | 85 (93.41) | 343 (94.23) | 1.000 | - | - |
| Yes | 6 (6.59) | 21 (5.77) | 1.185 (0.424-3.313) | 0.170 | 0.747 |
| Smoking | | | | | |
| No | 90 (98.90) | 344 (94.51) | 1.000 | - | - |
| Yes | 1 (1.10) | 20 (5.49) | 0.174 (0.022-1.359) | -1.747 | 0.095 |
| Blood transfusion | | | | | |
| No | 89 (97.80) | 348 (95.60) | 1.000 | - | - |
| Yes | 2 (2.20) | 16 (4.40) | 0.500 (0.115-2.175) | -0.693 | 0.355 |
| Use of UDCA | | | | | |
| No | 10 (10.99) | 11 (3.02) | 1.000 | - | - |
| Yes | 81 (89.01) | 353 (96.98) | 0.275 (0.117-0.648) | -1.291 | 0.003 |
| Response to UDCA | | | | | |
| No | 62 (68.10) | 117 (32.10) | 1.000 | - | - |
| Yes | 29 (31.90) | 247 (67.90) | 0.212 (0.127-0.353) | -1.550 | 0.000 |

Abbreviations: uOR, unadjusted odds ratio; CI, confidence interval; LC, liver cirrhosis; HCC, hepatocellular carcinoma; HBsAg, hepatitis B surface antigen; HbcAb, hepatitis B core antibody; AMA, anti-mitochondrial antibodies; ALB, albumin; TBIL, total bilirubin; ALT, alanine transaminase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; PLT, platelet count; APRI, AST/PLT ratio index; PT, prothrombin time; INR, international normalized ratio; UDCA, ursodeoxycholic acid.

**Table 4.** Multivariate conditional logistic regression analysis of potential risk factors for PBC mortality

| Variables | aOR (95% CI) | B | *P* value |
|---|---|---|---|
| Age | 1.002 (0.982-1.022) | 0.002 | 0.859 |
| Gender | | | |
| Male | 0.991 (0.523-1.877) | -0.009 | 0.977 |
| Female | 1.000 | - | - |
| Chronic hepatitis | 1.000 | - | - |
| LC | 1.339 (0.491-3.650) | 0.292 | 0.568 |
| HCC | 23.654 (2.601-215.077) | 3.164 | 0.005 |
| AST | 1.002 (0.998-1.005) | 0.002 | 0.409 |
| TBIL | 1.007 (1.003-1.011) | 0.007 | 0.001 |
| PLT | 0.995 (0.991-1.000) | -0.005 | 0.038 |
| APRI | 0.900 (0.637-1.272) | -0.105 | 0.551 |
| ALB | 0.891 (0.831-0.956) | -0.115 | 0.001 |
| PT | 1.091 (0.918-1.296) | 0.087 | 0.324 |
| INR | 0.172 (0.000-106.709) | -1.759 | 0.592 |
| Fatigue | | | |
| No | 1.000 | - | - |
| Yes | 1.383 (0.711-2.690) | 0.324 | 0.339 |
| Diabetes mellitus | | | |
| No | 1.000 | - | - |
| Yes | 2.217 (0.910-5.402) | 0.796 | 0.080 |
| Use of UDCA | | | |
| No | 1.000 | - | - |
| Yes | 0.544 (0.171-1.731) | -0.608 | 0.303 |
| Response to UDCA | | | |
| No | 1.000 | - | - |
| Yes | 0.292 (0.160-0.533) | -1.232 | 0.000 |

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; LC, liver cirrhosis; HCC, hepatocellular carcinoma; AST, aspartate aminotransferase; TBIL, total bilirubin; PLT, platelet count; APRI, AST/PLT ratio index; ALB, albumin; PT, prothrombin time; INR, international normalized ratio; UDCA, ursodeoxycholic acid.

were made for possible confounders (i.e., age and gender). Factors associated with a lower risk of death were: PLT elevated by $1\times10^9$/L (adjusted OR [aOR]=0.995, 95% CI: 0.991-1.000), ALB elevated by 1 g/L (aOR=0.891, 95% CI: 0.831-0.956), and response to UDCA (aOR=0.292, 95% CI: 0.160-0.533). Independent risk factors for liver-related mortality were: HCC at the initial diagnosis (aOR=23.654, 95% CI: 2.601-215.077, *P*=0.005) and TBIL elevated by 1 μmol/mL (aOR=1.007, 95% CI: 1.003-1.011).

*Receiver operator characteristics*

Because our multivariate analysis identified levels of TBIL, ALB, and PLT at initial diagnosis as independent risk factors associated with PBC-associated mortality, we further determined the cutoff values of these continuous factors for predicting the survival of PBC patients by ROC analysis. As shown in **Figure 2**, the cutoff values of TBIL, ALB and PLT were 38.65 μmol/mL, 34.8 g/L, and $118\times10^9$/L respectively, while the areas under the ROC were 0.771, 0.758, and 0.682 respectively. Negative predictive values of these three factors were 90.63%, 92.79% and 89.35%, respectively, which suggested that patients with levels of ALB and PLT above the cutoff value and TBIL under the cutoff value are at a lower risk for mortality.

## Discussion

In this study, a hospital-based case-control study was conducted to identify the risk factors for liver-related mortality in Chinese patients with PBC. HCC, TBIL, ALB, and PLT levels at initial diagnosis were identified as the risk factors for liver-related mortality in these patients. We also found that, after controlling for potential confounders, response to UDCA therapy could reduce liver-related mortality.

The mortality rate of PBC patients is higher than that of the general population; the severity of disease has been significantly associated with the prognosis [8, 10, 20]. In the present study, the control subjects were matched by age, gender, and the duration of hospitalization to explore potential factors that have not been previously considered. It has been reported that older age and gender were associated with the prognosis of PBC, and especially the development of HCC [21-23]. These variables were not included in the statistical models. There have been studies showing that early histological stages and asymptomatic patients were associated with better outcomes, while patients at later stages and with symptoms tended to have a higher risk of liver cirrhosis and mortality [8, 10]. In the present study, the univariate analysis showed that patients with HCC and liver cirrhosis had a higher risk of mortality. However, after adjusting for confounding

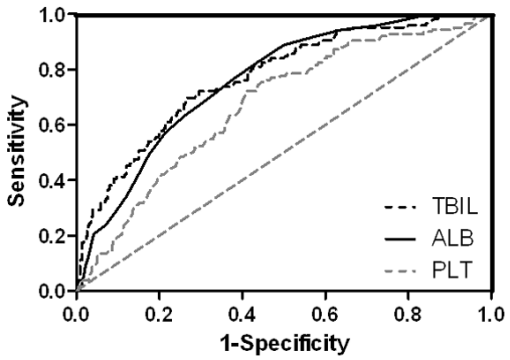


**Figure 2.** ROC curves of ALB, TBIL and PLT for prediction of liver-related mortality in PBC patients.

variables, only HCC was identified as an independent risk factor for PBC mortality, with a risk 23.654-fold higher than in patients without HCC.

The mainstay of therapy for PBC is UDCA (13-15 mg/kg/d); treatment with UDCA may influence the history and prognosis of PBC. Several studies have suggested that UDCA therapy could improve some biochemical test results and could reduce the rates of liver transplantation or death. In other words, the biochemical response to UDCA may predict the long-term outcomes of PBC [16-18]. Ter Borg et al. [13] and Corpechot et al. [24] reported that PBC patients, if treated at an early stage, had a survival rate comparable to that of a standardized general population [13, 24]. Moreover, placebo-controlled trials have shown that UDCA therapy could improve histological features and delay histological progression [25, 26]. However, there have been several studies that failed to show a beneficial effect of UDCA in PBC [27-29], perhaps because the follow-up periods were not sufficiently long to provide a convincing conclusion. In our study, the subjects were followed for approximately 7 years, and we conclude that a favorable response to UDCA can reduce the rate of mortality in PBC patients, as in earlier studies.

At an early stage, PBC has no influences on all-cause mortality, while the presence of viral infection, such as HBV or HCV infection, accelerates disease progression [9]. However, in the present study it appears that HBsAg positivity was not associated with risk of PBC mortality. This may be because few patients were co-infected with HBC or HCV. Several studies have reported that ALB, TBIL, ALP, PLT, and APRI were associated with adverse outcomes or predicted complications of PBC [13, 30-33]. In our study, the unadjusted univariate analysis indicated that ALB, TBIL, AST, PLT, APRI, PT, and INR at initial diagnosis were associated with liver-related mortality in PBC. After adjusting for confounding variables, only ALB, TBIL and PLT remained as independent risk factors. This finding could predict prognosis to some extent.

It should be noted that the current study has several limitations. Although we analyzed many potential factors, a number of other factors (such as blood glucose level) were not included for analysis because of the potential association with alcohol intake and diabetes mellitus. Secondly, histological stage is a pivotal factor for evaluating disease progression. However, because biopsies were not consistently performed, determination of clinical stage was based on biochemical tests and clinical manifestations, and not on histological results. Thirdly, medical interventions such as drugs for diabetes mellitus and hypertension, with the exception of UDCA, may influence the prognosis of disease, but in this study we could not obtain details because the patients could not provide clear indications. Fourthly, anti-glycoprotein-210 and anti-centromere antibodies have been identified as risk factors for PBC progression [21]. At our hospital, testing for these parameters has only recently begun and we lacked the information for the patients in this study. Finally, this was a single-center study, although the patients came from all over the country. Our results warrant a multicenter, prospective study to confirm our conclusions.

In summary, we demonstrated that HCC, reduced ALB and PLT, and increased TBIL levels at initial diagnosis were the independent risk factors for liver-related mortality in patients with PBC. Moreover, PBC patients who responded favorably to UDCA treatment had a lower risk for liver-related mortality. All of these conditions should be systemically considered when evaluating the progression of PBC.

## Disclosure of conflict of interest

None.

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