Clinical characteristics and prognosis of Primary biliary cholangitis with esophagogastric varices.

Mingyue Zhang

Medical Center

Huan Xie

Medical Center

Alessio Gerussi

University of Milano–Bicocca: Università degli Studi di Milano-Bicocca

Lin Han

Medical Center

Ying Chen

Medical Center

Jun Zhao

Medical Center

Qingsheng Liang

Medical Center

Baosen Li

Medical Center

Pietro Invernizzi

University of Milano–Bicocca: Università degli Studi di Milano-Bicocca

Zhengsheng Zou

Medical Center

ME Gershwin

University of California Davis

Ying Sun

Medical Center <https://orcid.org/0000-0002-2570-9206>

Research Article

Keywords: Primary biliary cholangitis, esophagogastric varices, Ursodeoxycholic acid, Liver transplantation-free survival, Endoscopic therapy, Risk factors

Posted Date: March 1st, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1368857/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Background and aims The development of esophagogastric varices (EGV) is one of the most common complications in patients with Primary biliary cholangitis (PBC); yet, factors associated with their development have been poorly characterized. In this cohort, we aimed to investigate the clinical factors associated with EGV in patients with PBC.

Methods: The cohort study included patients with PBC who received esophagogastroduodenoscopy screening and ursodeoxycholic acid (UDCA) therapy at baseline. Liver-related death and liver transplantation were assessed as the endpoint, liver transplantation-free survival rates were estimated by using Kaplan–Meier methods, and Cox regression analysis was performed to identify the potential risk factors of endpoint events for PBC with EGV.

Results The 690 patients included in this study had a mean age of 57 years old and 553 (80.1%) were females, 13 (7.9%) in the 165 PBC with no liver cirrhosis and 400 (76.2%) in the 525 PBC with liver cirrhosis had signs of EGV, and 215 (31.2%) patients of the cohort had bleeding esophagogastric varices as the first presentation at diagnosis. The median (Interquartile range) follow-up period was 4.0 (2.0, 6.0) years. During the follow-up duration, 99 patients progressed to liver-related deaths, and 23 patients underwent liver transplantation. The 5-year cumulative LT-free survival was 88.20% (95% CI 83.7-92.7) in PBC without EGV, and 80.90% (95% CI 80.0-89.9), 80.30% (95% CI 69.7-90.9), 75.70% (95% CI 68.3-83.1) among PBC with small, medium and large-sized esophageal varices at baseline, respectively ($p=0.002$). The 10-year cumulative LT-free survival was 68.8% (95% CI 53.9-82.8) in PBC without EGV, and 54.2% (95% CI 36.4-72.0), 51.6% (95% CI 29.9-73.3), 62.1% (95% CI 49.2-75.0) among PBC patients with small, medium and large-sized esophageal varices at baseline, respectively ($p=0.001$). History of endoscopic therapy and UDCA biochemical responder with Paris criteria for PBC with EGV were associated with a statistically significant reduced risk of LT or death ($p=0.001$ and $p=0.007$).

Conclusions Endoscopic therapy and a favorable biochemical profile of UDCA can prolong the LT-free survival of PBC patients with EGV, despite the presence of large-sized esophageal varices.

Introduction

Primary biliary cholangitis(PBC) is an autoimmune disease of the small intrahepatic bile ducts predominantly affecting middle-aged women. First-line therapy is Ursodeoxycholic acid (UDCA); around 20–40% of patients do not respond to UDCA and are at high risk of progression to advanced liver disease. The development of esophagogastric varices(EGV) is one of the most common complications in patients with PBC; yet, factors associated with their development have been poorly characterized. The aim of this study was to investigate clinical factors associated with EGV in patients with PBC.

Patients And Methods

Study design and population

For the current study, a total of 728 hospitalized patients with an established PBC diagnosis were enrolled and followed under identical conditions in the Senior Department of Hepatology at the Fifth Medical Center of General Hospital, Beijing, China. As for international guidelines, a diagnosis of PBC required the presence of a highly positive antimitochondrial antibody (AMA) and chronic cholestasis in the absence of a liver biopsy, or histologic confirmation, and presence of either chronic cholestasis or a positive AMA (1), in this cohort. Patients performed

routine esophagogastroduodenoscopy screening for disclosing the presence or absence of oesophageal or gastric varices, and began UDCA therapy (According to the weight-based dose, 13-15 mg/kg/day) once the diagnosis of PBC was made.

Outcomes

Study entry was defined as the date of UDCA therapy, censoring was performed at the date of last follow-up, liver-related death or date of liver transplantation. All patients had at least 1-year of follow-up, data were collected through the end of January 1, 2020. Patients were excluded if the follow-up data or time were insufficient or unavailable, or they had concomitant liver disease.

Explanatory variables

The following variables at baseline were included: Age at diagnosis, sex, antinuclear antibodies (ANA) anit-SP100 antibody and anti-gp210 antibody serological status, and laboratory parameters, including platelet count, ALB, TBIL, ALT, AST, ALP, GGT, TBA, CHE, TC, IgA, IgG, IgM, INR, PT and creatinine; the imaging and endoscopic findings; a state of edema or ascites associated with cirrhosis. Variables of a 1-year treatment with UDCA: Platelet count, TBIL, ALT, AST, ALP, ALB. Liver cirrhosis was diagnosed by radiological and/or histological evidence. For gastric varices are an extension of esophageal varices, so the degree of oesophageal and gastric varices were recorded by the esophageal varices 3 grades (Small, medium, large) were used for esophageal varices; small varices defined as minimally elevated veins above the esophageal mucosal surface, medium varices defined as tortuous veins occupying less than one-third of the esophageal lumen, and large varices defined as those occupying more than one-third of the esophageal lumen (2). MRS(3), MELD score (4), FIB-4 index (5), and APRI(6) were calculated for each patient at the time of diagnosis. GLOBE score and UK-PBC Risk Score were calculated according the data of UDCA therapy for 1 year by using an online calculator (<https://www.globalpbc.com/globe>, http://www.uk-pbc.com/resources/tools/risk_calculator/).

Statistical analysis

Continuous variables were expressed as mean±standard deviation (SD) if normally distributed, or the median and interquartile range (25th-75th percentiles) if not normally distributed. Categorical variables were expressed as frequencies (percentages). The student's t test (For normal distributions) or Wilcoxon's signed rank test (For non-normal distributions) were used for comparison of continuous variables, and the Chi-square test was implemented for categorical variables. Deviations from the normal distribution were analysed by the Shapiro-Wilk W test. In the logistic regression models, the optimal cut-off values of each continuous variable were determined by the upper limit of normal (ULN), or lower limit of normal (LLN), or by using the maximum of the Youden index for cut-off point selection in the context of ROC curve analysis for some key variables. Kaplan-Meier survival curves were constructed, and log-rank chi-square testing was used to assess the relationship between liver transplantation-free (LTF) survival and variables. Since survival time and prognosis did not follow a normal distribution, Wilcoxon's signed rank test for contrasts, mean survival times were estimated and their 95% CI were calculated. The hazard ratio (HR) and the respective 95% confidence intervals (CIs) were calculated using Cox proportional hazard regression analyses, and factors with a prognostic association in the univariate analysis were entered into a multivariate Cox regression model (Forward sequential method), then the Wald statistic was used to check for the significance of the regression coefficient for each parameter. All the aforementioned statistical tests were two-tailed, and the P value <0.05 was considered to be statistically significant. All statistical analyses were performed by the statistical software SPSS 23.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics of the cohort

The clinical characteristics and laboratory results of the patients with PBC at baseline are displayed in **Table 1**. Out of the 728 patients with PBC receiving UDCA therapy,

Table 1. Characteristics of the study population at baseline			
Demographic characteristics	Total(n=690)	Demographic characteristics	Total(n=690)
Age at diagnosis, years	57±12	ALB (g/L)	34±6
Female,n(%)	553(80.1%)	TBIL (μmol/L)	21.3[14.2, 38.7]
Non-liver cirrhosis, n(%)	165(23.9%)	ALT(U/L)	50[26, 92]
EGV, n(%)		AST (U/L)	66[40, 102]
Yes	13(7.9%)	ALP (U/L)	240[186, 418]
No	152(92.1%)	GGT(U/L)	156[75, 363]
Liver cirrhosis, n(%)	525(76.1%)	TBA(μmol/L)	28[11, 61]
EGV, n(%)		CHE (U/L)	4566± 214
Yes	400(76.2%)	TC(mmol/L)	4.4[3.3, 5.7]
No	125(23.8%)	IgA(g/L)	2.7[1.9, 3.9]
Bleeding EGV, n(%)	215(31.2%)	IgG(g/L)	15.7[12.8, 20.4]
as the first		IgM(g/L)	2.8[1.6, 4.4]
presentation		INR	1.02(0.93, 1.13)
ANA, n(%)	499(72.3%)	Fib-4 index	4.6[2.6, 7.9]
Anti-sp100, n(%)	100(14.5%)	APRI index	1.4[0.8, 2.5]
Anti-gp210, n(%)	232(33.6%)	Mayo Risk Score	5.8[4.8, 6.9]
Platelets count(×10 ⁹ /L)	120[76, 80]	MELD Score	1.9[0.3, 4.5]

38 patients were excluded due to not achieving the minimum follow-up of 1 year, missing laboratory data or non-liver-related deaths. A total of 690 patients were included, with a median (interquartile range) follow-up period of 4.0 (2.0, 6.0) years. Mean age was 57 years and 553 (80.1%) were females. In the 165 individuals without liver cirrhosis, 13 (7.9%) of them had EGV, among the patients with liver cirrhosis, 400 (76.2%) had signs of EGV. In 215 patients (31.2%) of the cohort, bleeding esophagogastric varices was the first presentation. All cases were AMA positive; 499 (72.3%) were ANA positive, 100 (14.5%) cases were positive for anti-sp100, 232 (33.6%) were positive for anti-gp210 alone, and 36 (5.2%) were positive for both anit-sp100 and gp210. The median TBIL, ALP, INR and MELD score were 21.3 μmol/L, 240 U/L, 1.02, and 1.9, respectively, and the rest was portrayed in table 1. During the follow-up duration, 99 patients succumbed to liver-related deaths, 23 patients underwent liver transplantation, and 34 (4.9%) of the cohort progressed to liver cancer during follow-up, the incidence of HCC in PBC with EGV was 5.8% (24 in 413 patients).

Differences between patients with EGV and those without EGV according to baseline factors

Patients without EGV had significantly higher levels of GGT, ALT, and TC levels, and significantly lower levels of TBIL, INR, TBA, IgA, IgG levels, and APRI Index, FIB-4 Index, Mayo Risk Score and MELD score. **Table 2** shows the differences between patients with EGV and those without according to baseline factors.

Table 2. Differences between patients with EGV and those without according to factors at baseline							
Variable	PBC without EGV (n=277)	PBC with EGV (n=413)	P value	Variable	PBC without EGV (n=277)	PBC with EGV (n=413)	P value
Age at diagnosis, years	57±12	58±11	NS	TBA(μmol/L)	19.0 [8.2,55.3]	32.5 [13.1,65.6]	0.001
Female, n(%)	213(38.5%)	340(61.5%)	NS	TC(mmol/L)	4.9 [3.8,5.9]	3.9 [3.1,5.3]	0.000
ANA+, n(%)	191(69.0%)	308(74.6%)	NS	INR	0.95 [0.89,1.04]	1.06 [0.98,1.16]	0.000
Anti-sp100+, n(%)	40(14.4%)	60(14.5%)	NS	IgA(g/L)	2.4[1.7, 3.4]	2.9[1.9, 4.1]	0.000
Anti-gp210+, n(%)	83(30.0%)	149(36.1%)	NS	IgM(g/L)	2.7[1.6, 4.4]	2.8[1.6, 4.4]	NS
ALP(U/L)	243[188, 431]	238(185, 413]	NS	IgG(g/L)	14.8[12.2, 19.3]	16.8 [13.5,21.0]	0.000
GGT(U/L)	199(95, 452]	139(63, 283]	0.000	APRI Index	0.9(0.6, 1.9]	1.7(1.1,2.9]	0.000
TBIL(μmol/L)	16.8(11.1,36.0]	21.9(15.3, 40.0]	0.000	FIB-4 Index	2.8(1.8,4.9]	6.2(3.9,9.5]	0.000
ALT(U/L)	59(30,111]	43.0(24,69]	0.000	Mayo Risk Score	4.8(4.0,6.1]	6.3(5.5,7.1]	0.000
AST(U/L)	69[41,105)	64.0 [40,100]	NS	MELD Score	0.8(0.0,4.2]	2.3(0.9,4.6]	0.002
NS, not significant.							

LTF-survival according to the degree of EGV

Data comparing the duration of LTF survival by the degree of esophageal varices at baseline are presented in table 3.

Table 3. Duration of LTF survival by the degree of esophageal varices at baseline

Esophageal Varices	n	Means(years)	95% CI(years)	P value		
Non	277	14.7	12.7-16.8	0.002 ^a		
Small	95	10.0	8.6-11.4	0.014 ^b		
Medium	122	9.8	8.8-10.9	0.032 ^b	0.023 ^c	
Large	196	10.8	11.4-14.1	0.006 ^b	0.964 ^c	0.012 ^d

a. Overall comparisons, b. Compared with non-esophageal varices, c. Compared with small of esophageal varices, d. Compared with medium of esophageal varices

In this cohort, the patients with EGV at baseline had a significantly shorter survival time compared to the patients without EGV, the 5-year cumulative LTF survival were 88.2% (95% CI 83.7%-92.7%) in patients without EGV, and the 10-year cumulative LTF survival were 68.8% (95 CI 53.9%-82.8%), respectively, the 5-year cumulative LTF survival in patients with small-sized esophageal varices was 80.9% (95% CI 80.0-89.9) and 80.3% (95% CI 69.7-90.9), 75.7% (95% CI 68.3-83.1) among medium and large-sized varices, respectively [p=0.002]; the 10-year cumulative LTF survival rates were 54.2% (95% CI 36.4-72.0), 51.6% (95% CI 29.9-73.3) and 62.1% (95% CI 49.2-75.0), respectively [p=0.001] (Table 4.). During follow-up, each of the four groups had patients who developed varices in which endoscopic therapy for variceal hemorrhage was performed, including those PBC patients without EGV at baseline. However, endoscopic therapy was carried out at a statistically higher rate in patients with large-sized varices (p=0.000).

Table 4. Endoscopic therapy rates for variceal hemorrhage during follow-up and LTF survival according to the degree of esophageal varices at baseline					
Esophageal Varices at baseline	Non	Small	Medium	Large	P value
History of endoscopic therapy for Variceal Hemorrhage during follow-up, n(%)	105(37.9%)	22(23.2%)	55(45.1%)	108(55.1%)	0.000
5-year cumulative LTF survival,%(95%CI)	88.2(83.7-92.7)	80.9(80.0-89.9)	80.3(69.7-90.9)	75.7(68.3-83.1)	0.002
10-year cumulative LTF survival,%(95%CI)	68.8(53.9-82.8)	54.2(36.4-72.0)	51.6(29.9-73.3)	62.1(49.2-75.0)	0.001

The effect of EGV on LTF survival in PBC patients

During the follow-up period, we analyzed the LTF survival by the Kaplan-Meier method to identify the effect of EGV on the prognosis of PBC patients (Fig.1), the results revealed that PBC patients without EGV survived significantly longer than those with EGV (P=0.002). By contrast the age at diagnosis, the observed LTF survival of PBC in the elderly with EGV at diagnosis correlated with a statistically significant worse prognosis than the patients without EGV (P=0.041), but the PBC patients with middle-age at diagnosis and those having a young-age with EGV were not statistically different from patients without EGV, respectively (P_{Middle-age}=0.060, P_{Young-age}=0.086). Regardless of the patient's sex, appearance of EGV were correlated with a worse prognosis, (P_{Female}=0.007, P_{Male}=0.010). When comparing the prognosis between the autoantibodies-positive and negative patients, we found that for ANA-positive

and negative patients, as long as EGV were present, the prognosis was not good ($P_{ANA^-}=0.009$, $P_{ANA^+}=0.007$); the same finding was depicted in anti-sp100-negative ($P<0.001$) or gp210-negative ($P=0.001$) patients. However, for anti-sp100-positive and anti-gp210-positive patients, EGV had no correlation with the prognosis ($P_{sp100^+}=0.461$, $P_{gp210^+}=0.129$).

The effect of EGV on LTF survival of PBC patients with unfavorable and favorable UDCA biochemical profiles

Regarding the 1-year response rate to UDCA according to the Paris criteria and Barcelona criteria, there was no significant differences between patients with EGV and those without (Paris criteria, $P=0.492$; Barcelona criteria, $P=0.069$), but the prognostic model of the globe score in PBC patients with EGV was significantly higher than those without EGV ($P=0.000$), and the results were similar in terms of the UK-PBC risk score ($P=0.009$). In order to assess the effect of EGV on LTF survival of PBC patients receiving UDCA therapy, the Kaplan-Meier method was used to plot cumulative survival functions according to meeting the biochemical criteria for response after 1 year of UDCA and presence of EGV or not. In this study cohort, the LTF survival rates were higher in biochemical responders than non-biochemical responders, both according to the Paris or Barcelona criteria ($P_{Paris}<0.001$, $P_{Barcelona}=0.012$), and EGV was associated with an increase of liver-related death or the risk of liver transplantation. LTF survival in PBC patients with EGV was significantly lower than in those without EGV, both in adequate and inadequate responders. The survival curves were revealed in figure 2.

Final survival prediction model for PBC with present or absent EGV

we conducted multivariate analysis using Cox proportional-hazards regression models by the full set of variables to compare stratum specific hazard ratios in the PBC patients with or without EGV. The results showed that $CHE<ULN$ and $INR>1.2ULN$ at baseline in PBC patients with EGV were associated with a statistically significant higher liver-related death or liver transplantation rate than those without EGV ($CHE<ULN$, HR 2.584, 95%CI 1.382-4.834, $P=0.003$; $INR>1.2ULN$, HR 1.775, 95%CI 1.108-2.841, $P=0.017$), and the same relationship was observed when $TBIL>1.2ULN$, $AST>2.3ULN$ after 1 year of UDCA treatment, and non-biochemical responders according to the Paris criteria, with a history of endoscopic therapy in PBC patients with EGV was associated with a statistically significant reduction in the hazard of hepatic-related death or liver transplantation (Table 5.).

Table 5. Final survival prediction model to the PBC presence of EGV

Variable	HR	95% CI	P value
CHE			0.003
≥ULN at baseline	1		
<ULN at baseline	2.584	1.382-4.834	
INR			0.017
≤1.2ULN at baseline	1		
>1.2ULN at baseline	1.775	1.108-2.841	
History of endoscopic therapy			0.001
Yes	1		
No	2.112	1.359-3.281	
TBIL			0.007
≤1.2ULN after 1 year of UDCA therapy	1		
>1.2ULN after 1 year of UDCA therapy	2.168	1.241-3.788	
AST			
≤2.3ULN after 1 year of UDCA therapy	1		
>2.3ULN after 1 year of UDCA therapy	2.642	1.011-2.667	0.045
Biochemical responder with Paris criteria			0.007
Yes	1		
No	2.148	1.237-3.731	

For the patients without EGV, AST>2.3ULN, INR>1.2ULN at baseline, CHE<ULN after 1 year of UDCA treatment, and GLOBE SCORE>1.125 were the independent parameters of liver-related death or liver transplantation (Table 6).

Table 6. Final survival model. Cox regression for PBC patients without EGV

Variable	HR	95% CI	P
AST			0.005
≤2.3ULN at baseline	1		
>2.3ULN at baseline	3.082	1.411-6.731	
CHE			0.000
≥ULN after 1 year of UDCA therapy	1		
<ULN after 1 year of UDCA therapy	21.232	4.820-93.529	
INR			0.012
≤1.2ULN at baseline	1		
>1.2ULN at baseline	2.642	1.243-5.616	
GLOBE SCORE			0.017
≤1.125	1		
>1.125	2.801	1.206-6.503	

Dissscussion

Advanced stages of PBC indicated an increased incidence of complications, and the prognosis of PBC patients mainly depends on the progression of liver cirrhosis and its complications. UDCA can delay part of the histologic progression of PBC, and improve the prognosis(7–9), but in the advanced stages of PBC, UDCA can not effectively prevent the occurrence of liver disease-related complications, which are associated with an increased risk of death or liver transplantation due to PBC (10). The overall number of hospitalizations and in-hospital mortality among patients with PBC is increasing (11). Proper assessment of the PBC's prognosis was important for helping the patients avoid the risk of developing serious complications, and prolongs their survivals. Decompensated cirrhosis is very common at the time of PBC diagnosis (12), in some asymptomatic PBC, EGV, even variceal bleeding were present at diagnosis (13). Variceal bleeding is the most life-threatening adverse event of cirrhosis (14), including PBC (15). Endoscopic prophylaxis before or after variceal bleeding plays a critical role in the management of variceal hemorrhage in patients with medium- and large-sized varices, even patients with small varices who have alarming signs (14). Appropriate endoscopic screening, prevention and effective management of EGV are very important for reducing both the incidence and the mortality due to bleeding from EGV (16). Endoscopic screening should be performed on PBC patients with suspected cirrhosis at the time of diagnosis (1). In the current study, we aimed to investigate the clinical factors associated with EGV in patients with PBC, and we found that varices were present in 7.9% of patients without liver cirrhosis and 76.1% of those with liver cirrhosis; serious complications of upper gastrointestinal bleeding caused by EGV were seen in 31.2% of patients at the time of diagnosis. Similar to other works, we found the good biochemical response to UDCA after 1 year was associated with an excellent long-term survival (Paris criteria, 14.6 years vs 8.7 years, $P = 0.000$; Barcelona criteria, 13.2 years vs 11.5 years, $P = 0.097$), and there was no significant differences with respect to the biochemical response to UDCA when comparing the PBC patients with and without EGV, either by the Paris criteria or by the Barcelona criteria, but the duration of LTF survival in PBC patients with EGV was significantly shorter (9.4–11.7 years vs 12.7–16.8 years, $P = 0.001$). Variceal

bleeding can be catastrophic and fatal for patients with PBC, and markedly increase the probability of death or liver transplantation. However, the LTF survival seemed to be influenced by UDCA therapy, the risks of liver-related death or liver transplantation elicited a statistically significant reduction in UDCA-treated patients with adequate response, irrespective of the presence or absence of EGV. The GLOBE scores and UK-PBC risk scores can be used to accurately evaluate the prognosis of PBC patients (17, 18). In the current cohort, both of the scores were much higher in the group with EGV than in the one without. Moreover, the data provided further evidence that EGV were associated with significantly higher mortality. Nonetheless, the Cox regression analyses for PBC patients with EGV indicated that the relative risk reduction of death or liver transplantation was associated with a history of endoscopic therapy, when we compared the LTF survival between PBC with small of esophageal varices and large-sized varices, the results showed there was no statistically significant differences in the two groups, but the group with large-sized varices had a significantly higher of endoscopic therapy for variceal hemorrhage during follow-up. Therefore, for the patients with EGV, even in the PBC with large-sized varices, getting prompt endoscopic therapy to manage such bleeding both for hemostasis of active bleeding and bleeding prophylaxis, was effective in prolonging the survival time. Apart from bleeding, stage IV PBC is also closely associated with an increased incidence of hepatocellular carcinoma (HCC) (19). The incidence of HCC in the advanced stages of PBC was reported to be 5.9% (20). In this study, the incidence of HCC during follow-up were 4.9%, and 5.8% in PBC patients with EGV, respectively. Some evidence showed that the male gender was associated with a poor prognosis in PBC(21, 22) (23) and a significantly worse transplant-free survival. However, male patients with PBC exhibited similar survival when compared with female patients in this study cohort, though the mean duration of LTF survival in males, either with or without EGV, were shorter than in females, but there was no statistically significant difference between genders, which was similar to the conclusions made by other scholar(24). Anti-gp210 is considered as a biomarker of disease severity in PBC, Yang F, et al have reported that the probability of 5-year adverse outcome-free survivals was significantly better in anti-gp210 negative patients(25). In this series, anti-gp210 antibodies were detected in 33.6% of patients, there was no statistically significant difference in the positive rate of anti-gp210 between patients with and without EGV ($P = 0.096$). In a nutshell, PBC patients with EGV delineated a poor prognosis compared to those without EGV, but in anti-gp210 positive PBC patients, the presence of EGV or not had the similar LTF survival, and the same survival findings were made regarding anti-sp100 positive PBC patients. Based on these observations, the presence of anti-gp210 and anti-sp100 antibodies may influence the survival time of PBC patients(26).

In summary, good biochemical response to UDCA after 1 year of therapy is associated with a LTF survival, but the survival will be affected by the appearance of EGV. Once the diagnosis of PBC is made, endoscopic screening for EGV formation is necessary. For UDCA responders with EGV, endoscopic therapy is used to treat and prevent rebleeding, which may improve the survival of PBC patients with EGV.

Abbreviations

PBC	Primary biliary cholangitis
EGV	Esophagogastric varices
UDCA	Ursodeoxycholic acid
ALB	Albumin
TBIL	Total bilirubin
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ALP	Alkaline phosphatase
GGT	Gamma-glutamyltransferase
TBA	Total bile acids
CHE	Cholinesterase
TC	Total cholesterol
INR	International normalized ratio
PT	Prothrombin time
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
AMA	Antimitochondrial antibody
MRS	The Mayo risk score
MELD	Model for End-stage Liver Disease
FIB-4	Fibrosis index based on four factors
APRI	AST to platelet ratio index
LTF	Liver transplantation-free

Declarations

Acknowledgements

We thank all the staffs and patients for their participation in this study.

Author contributions

Collected the data and performed data analysis: M-YZ, HX, YC, JZ and Q-SL. Drew and revised the figures and tables: AG and LH. Drafting of the manuscript, M-YZ and YS. Study design and study supervision: YS, M-EG, Z-SZ, PI and B-SL. Data interpretation, and critical review/revision of the manuscript: YS, M-EG, AG and PI.

Funding

Supported by the National Natural Science Foundation of China grants [81873564].

Conflict of interest No author has conflicts of interest to disclose.

Consent to participate This study was conducted in accordance with the principles of Declaration of Helsinki, the study protocol was approved by the Human Research Ethics Committee at the Fifth Medical Center of PLA General Hospital.

Consent for publication Informed consent for publication was obtained from all authors.

Human and animal research This article does not contain any studies with animals performed by any of the authors

Authors and Affiliations

Mingyue Zhang^{1,2}, Huan Xie¹, Alessio Gerussi³, Lin Han¹, Ying Chen¹, Jun Zhao¹, Qingsheng Liang¹, Baosen Li, Pietro Invernizzi³, Zhengsheng Zou¹, M Eric Gershwin⁴, Ying Sun¹

1 Senior Department of Hepatology, the Fifth Medical Center of PLA General Hospital, Beijing, 100039, China;

Mingyue Zhang, Huan Xie, Lin Han, Ying Chen, Jun Zhao, Qingsheng Liang, Baosen Li, Zhengsheng Zou & Ying Sun

2 Graduate School of PLA General Hospital, Beijing, 100853, China;

Mingyue Zhang

3 Division of Gastroenterology, Center for Autoimmune Liver Diseases, Department of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy

Alessio Gerussi & Pietro Invernizzi

4 Division of Rheumatology, Allergy and Clinical Immunology, School of Medicine, University of California, Davis, 451 Health Sciences Drive, Suite 6510, Davis, CA, 95616, USA.

M Eric Gershwin

References

1. Lindor KD, Bowlus CL, Boyer J, Levy C, Mayo M. Primary Biliary Cholangitis: 2018 Practice Guidance from the American Association for the Study of Liver Diseases. *Hepatology* 2019;69:394-419.
2. Garcia-Tsao G, Sanyal AJ, Grace ND, Carey W, Practice Guidelines Committee of the American Association for the Study of Liver D, Practice Parameters Committee of the American College of G. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology* 2007;46:922-938.
3. Dickson ER, Grambsch PM, Fleming TR, Fisher LD, Langworthy A. Prognosis in primary biliary cirrhosis: model for decision making. *Hepatology* 1989;10:1-7.
4. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, et al. A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001;33:464-470.
5. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, M SS, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology*

2006;43:1317-1325.

6. Loaeza-del-Castillo A, Paz-Pineda F, Oviedo-Cardenas E, Sanchez-Avila F, Vargas-Vorackova F. AST to platelet ratio index (APRI) for the noninvasive evaluation of liver fibrosis. *Ann Hepatol* 2008;7:350-357.
7. Harms MH, de Veer RC, Lammers WJ, Corpechot C, Thorburn D, Janssen HLA, Lindor KD, et al. Number needed to treat with ursodeoxycholic acid therapy to prevent liver transplantation or death in primary biliary cholangitis. *Gut* 2020;69:1502-1509.
8. John BV, Khakoo NS, Schwartz KB, Aitchenson G, Levy C, Dahman B, Deng Y, et al. Ursodeoxycholic Acid Response Is Associated With Reduced Mortality in Primary Biliary Cholangitis With Compensated Cirrhosis. *Am J Gastroenterol* 2021;116:1913-1923.
9. Huet PM, Vincent C, Deslaurier J, Cote J, Matsutami S, Boileau R, Huet-van Kerckvoorde J. Portal hypertension and primary biliary cirrhosis: effect of long-term ursodeoxycholic acid treatment. *Gastroenterology* 2008;135:1552-1560.
10. Paumgartner G. Ursodeoxycholic acid for primary biliary cirrhosis: treat early to slow progression. *J Hepatol* 2003;39:112-114.
11. Galoosian A, Hanlon C, Tana M, Cheung R, Wong RJ. Race/Ethnicity and Insurance-Specific Disparities in In-Hospital Mortality Among Adults with Primary Biliary Cholangitis: Analysis of 2007-2014 National Inpatient Sample. *Dig Dis Sci* 2020;65:406-415.
12. Takeshita E, Kumagi T, Matsui H, Abe M, Furukawa S, Ikeda Y, Matsuura B, et al. Esophagogastric varices as a prognostic factor for the determination of clinical stage in patients with primary biliary cirrhosis. *J Gastroenterol* 2003;38:1060-1065.
13. Vlachogiannakos J, Carpenter J, Goulis J, Triantos C, Patch D, Burroughs AK. Variceal bleeding in primary biliary cirrhosis patients: a subgroup with improved prognosis and a model to predict survival after first bleeding. *Eur J Gastroenterol Hepatol* 2009;21:701-707.
14. Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. *Hepatology* 2017;65:310-335.
15. Harms MH, Lammers WJ, Thorburn D, Corpechot C, Invernizzi P, Janssen HLA, Battezzati PM, et al. Major Hepatic Complications in Ursodeoxycholic Acid-Treated Patients With Primary Biliary Cholangitis: Risk Factors and Time Trends in Incidence and Outcome. *Am J Gastroenterol* 2018;113:254-264.
16. Zuckerman MJ, Elhanafi S, Mendoza Ladd A. Endoscopic Treatment of Esophageal Varices. *Clin Liver Dis* 2022;26:21-37.
17. Carbone M, Sharp SJ, Flack S, Paximadas D, Spiess K, Adgey C, Griffiths L, et al. The UK-PBC risk scores: Derivation and validation of a scoring system for long-term prediction of end-stage liver disease in primary biliary cholangitis. *Hepatology* 2016;63:930-950.
18. Lammers WJ, Hirschfield GM, Corpechot C, Nevens F, Lindor KD, Janssen HL, Floreani A, et al. Development and Validation of a Scoring System to Predict Outcomes of Patients With Primary Biliary Cirrhosis Receiving Ursodeoxycholic Acid Therapy. *Gastroenterology* 2015;149:1804-1812 e1804.
19. Liang Y, Yang Z, Zhong R. Primary biliary cirrhosis and cancer risk: a systematic review and meta-analysis. *Hepatology* 2012;56:1409-1417.
20. Jones DE, Metcalf JV, Collier JD, Bassendine MF, James OF. Hepatocellular carcinoma in primary biliary cirrhosis and its impact on outcomes. *Hepatology* 1997;26:1138-1142.

21. John BV, Aitcheson G, Schwartz KB, Khakoo NS, Dahman B, Deng Y, Goldberg D, et al. Male Sex Is Associated With Higher Rates of Liver-Related Mortality in Primary Biliary Cholangitis and Cirrhosis. *Hepatology* 2021;74:879-891.
22. Lleo A, Jepsen P, Morenghi E, Carbone M, Moroni L, Battezzati PM, Podda M, et al. Evolving Trends in Female to Male Incidence and Male Mortality of Primary Biliary Cholangitis. *Sci Rep* 2016;6:25906.
23. Myers RP, Shaheen AA, Fong A, Burak KW, Wan A, Swain MG, Hilsden RJ, et al. Epidemiology and natural history of primary biliary cirrhosis in a Canadian health region: a population-based study. *Hepatology* 2009;50:1884-1892.
24. Cheung AC, Lammers WJ, Murillo Perez CF, van Buuren HR, Gulamhusein A, Trivedi PJ, Lazaridis KN, et al. Effects of Age and Sex of Response to Ursodeoxycholic Acid and Transplant-free Survival in Patients With Primary Biliary Cholangitis. *Clin Gastroenterol Hepatol* 2019;17:2076-2084 e2072.
25. Yang F, Yang Y, Wang Q, Wang Z, Miao Q, Xiao X, Wei Y, et al. The risk predictive values of UK-PBC and GLOBE scoring system in Chinese patients with primary biliary cholangitis: the additional effect of anti-gp210. *Aliment Pharmacol Ther* 2017;45:733-743.
26. Levy C, Bowlus CL. Role of Antinuclear Antibodies in Primary Biliary Cholangitis. *Am J Gastroenterol* 2020;115:1604-1606.

Figures

Figure 1

The effect of EGv on LTF survival according to the factors at baseline. 1a. Based on the EGv; 1b. Based on the age at diagnosis; 1c. Based on the gender; and 1d Based on the autoantibodies

2a

2b

Figure 2

The LTF survival according to the biochemical profile of UDCA and presence of EGv. 2a. According to Paris criteria; and 2b. According to Barcelona criteria.