



Insight into the natural history of primary biliary cirrhosis: A systemic review of data from placebo-controlled clinical trials

LIVER

Ping Xu¹, Lan Li¹, Guogang Li², Chaohui Yu¹, Youming Li¹

¹Department of Gastroenterology, the First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China

²Department of Surgery, the Second Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China

ABSTRACT

Background/Aims: The natural history of primary biliary cirrhosis (PBC) is extremely variable. The extraction and analysis of available information from placebo-treated patients in randomized controlled trials of PBC treatment would facilitate the study of the natural history of PBC. The aim of the present study was to determine important clinical information regarding the natural history of PBC patients without effective treatment.

Materials and Methods: A search of the PubMed, EMBASE and Cochrane Library databases was performed by two authors. Twelve randomized placebo-controlled clinical trials for PBC patients without decompensated cirrhosis were retrieved for further review. Pooled estimates of biochemical measurements, histological scores and clinical outcomes associated with PBC were calculated in the placebo group.

Results: Placebo-treated PBC patients displayed a significant decrease in serum alkaline phosphatase and very slight fluctuations in the other biochemical parameters during the 2-year follow-up. Meanwhile, histological progression was observed in 39.4% of the placebo-treated patients, and a moderate deterioration in histological scores was noted after 2 years. The pooled 2-year rates of death, transplantation and development of varices were 11.4%, 8.7% and 10.6%, respectively, in placebo-treated PBC patients.

Conclusion: This review provides a foundation for further epidemiologic investigations in untreated patients and ursodeoxycholic acid-resistant patients with PBC. Biochemical responses after 2 years may provide some information on disease progression and therapeutic response in PBC.

Keywords: Primary biliary cirrhosis, natural history, placebo, pooled analysis

INTRODUCTION

Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease caused by attacks of the immune system on the bile ducts, leading over a long period of time to liver fibrosis, biliary cirrhosis and, eventually, liver failure (1). PBC affects between 40 and 130 people per million, and 90% of patients are female (2,3). The only approved pharmacological treatment, ursodeoxycholic acid (UDCA), improves bile flow and liver function, whereas liver transplantation is still required in persons who have progressed to end-stage disease.

The course of PBC varies greatly from one patient to another. Some asymptomatic patients have a mean life expectancy similar to that of the general population, whereas survival is shorter in patients who progress to the symptomatic phase (4-8). The natural history of PBC has dramatically improved with the introduction of

UDCA. UDCA does cause a delay in referral for transplantation in patients with a perfect response to UDCA. However, up to 40% of patients do not respond to UDCA optimally and, accordingly, these patients have an increased risk of disease progression and decreased survival in the absence of liver transplantation (9,10). In the UDCA era, for both practical and ethical reasons, numerous studies were conducted regarding the natural history of PBC patients treated with UDCA; however, few studies were performed for PBC patients who did not undergo therapy. Investigations of the natural history of untreated patients may be helpful in understanding the natural history of patients with UDCA-resistant PBC and in developing criteria for assessing response to UDCA.

With respect to the evaluation of medical interventions on the disease, randomized placebo-controlled clinical

Address for Correspondence: Lan Li E-mail: doctorlilan@163.com

Received: January 17, 2016 **Accepted:** March 31, 2016

© Copyright 2016 by The Turkish Society of Gastroenterology • Available online at www.turkjgastroenterol.org • DOI: 10.5152/tjg.2016.15535

Table 1. Characteristics of studies included in the analysis

Study No.	Author	Year	Country	Study type	Placebo size	Mean age	Gender (M/F)	Active therapy	Duration (months)
1	Vuoristo et al. (14)	1995	Finland	Multicentre	31	57	4/27	UDCA and colchicine	24
2	McCormick et al. (15)	1994	UK	Single centre	8	62	4/4	Thalidomide	6
3	Lindor et al. (16)	1994	USA	Multicentre	91	52	12/79	UDCA	24
	Lindor et al. (17)	1997	USA	Multicentre	91	52	12/79	UDCA	48
	Balan et al. (18)	1994	USA	Multicentre	89	52	12/77	UDCA	24
	Batts et al. (19)	1996	USA	Single centre	29	54	4/25	UDCA	24
4	Parés et al. (20)	2000	Spain	Single centre	93	54.7	6/87	UDCA	>24
5	Hendrickse et al. (21)	1999	England	Single centre	30	57	3/27	MTX	24
6	Poupon et al. (22)	1990	France	Multicentre	68	58	8/60	UDCA	6
	Poupon et al. (23)	1991	France	Multicentre	73	57	8/65	UDCA	24
7	Turner et al. (24)	1994	UK	Single centre	24	57.7	0/24	UDCA	24
8	Battezzati et al. (25)	1993	Italy	Multicentre	44	55	3/41	UDCA	6
9	Combes et al. (26)	1995	USA	Multicentre	74	48.9	6/68	UDCA	24
10	Heathcote et al. (27)	1994	Canada	Multicentre	111	55.4	6/105	UDCA	24
11	Mitchison et al. (28)	1992	UK	Single centre	17	57	1/16	Prednisolone	36
12	Lombard et al. (29)	1993	Denmark	Multicentre	173	54.2	26/147	Cyclosporine A	>24

M: male; F: female; DCA: ursodeoxycholic acid; MTX: methotrexate

trials constitute the gold standard in clinical research. Valuable information about the natural history of the disease could be collected from placebo-controlled trials. Because the placebo does nothing to directly cause a change in PBC, patients treated with placebos may be the most suitable subjects for the study of the natural history of PBC patients (11,12). The extraction and analysis of available information from randomized placebo-controlled trials of PBC treatment could facilitate the study of the natural history of PBC.

In this study, data on PBC patients who were treated with placebos were extracted from eligible randomized placebo-controlled trials for meta-analysis. The aim of the present study was to determine important clinical information on the natural history of PBC patients.

MATERIALS AND METHODS

Study design

The systemic review was conducted according to the guidelines of PRISMA (Preferred Reporting Items of Systematic Reviews and Meta-Analyses) (13). Studies that conform to the following criteria were accepted: (i) a randomized placebo-controlled clinical trial in patients with PBC; (ii) minimum 24 weeks of treatment and (iii) primary outcomes that include at least one of the following: biochemical data, histological data, rate of liver transplantation, rate of complication and mortality. Trials were excluded for the following reasons: (i) relevant data

were not extractable; (ii) patients had decompensated cirrhosis; (iii) patients had features of other coexistent liver diseases; (iv) patients had other diseases that may lead to abnormal liver function or may limit life expectancy and (v) patients in the placebo group were treated with basic active drugs, such as UDCA. Review studies, case reports, retrospective analyses, letters and abstracts were excluded from the review. If a study which met the inclusion criteria lacked original data, we attempted to obtain these data by contacting the original authors. The study was conducted in accordance with the Helsinki Declaration, and the research procedure was approved by the ethics committee of the first affiliated hospital of Zhejiang University.

Systematic literature search

Two authors independently retrieved and reviewed the published literature in the PubMed (1966 to December 2015), EMBASE (1974 to December 2015) and Cochrane Library (2015, Issue 12) databases, limiting their searches to the English language. The search terms were 'primary biliary cirrhosis', 'placebo' and 'randomized controlled trial'. We further searched the reference lists of the retrieved articles to obtain additional trials.

Data extraction and quality assessment

Data extraction was performed by two independent reviewers. The recorded data included first author's name, year of publication, country of publication, study protocol, sample size, randomized method, sex, mean age, severity of disease, schedules of medications, follow-up time, biochemical and histological outcome

Table 2. Methodological quality of trials included in the analysis

Author	Randomisation method	Blind	Explanation for drop outs / withdrawals	Allocation concealment	ITT analysis
Vuoristo et al. (14)	Y	Double blind	Y	Unclear	Y
McCormick et al. (15)	Unclear	Double blind	Y	Unclear	N
Lindore et al. (16,17)	Y	Double blind	Y	Unclear	N
Balan et al. (18)	Y	Double blind	N	Unclear	N
Batts et al. (19)	Y	Double blind	N	Unclear	Y
Parés et al. (20)	Y	Double blind	Y	Unclear	N
Hendrickse et al. (21)	Y	Double blind	Y	Unclear	Y
Poupon et al. (22,23)	Unclear	Double blind	Y	Unclear	Y
Turner et al. (24)	Unclear	Double blind	Y	Unclear	Y
Battezzati et al. (25)	Y	Double blind	Y	Unclear	N
Combes et al. (26)	Unclear	Double blind	Y	Unclear	Y
Heathcote et al. (27)	Y	Double blind	Y	Unclear	Y
Mitchison et al. (28)	Y	Double blind	Y	Unclear	Y
Lombard et al. (29)	Y	Double blind	Y	Unclear	Y

ITT: intent-to-treat

Table 3. Changes between pre- and post-treatment in biochemical variables in placebo-treated patients with PBC: pooled results

Study	Changes for biochemical variables (delta mean)									
	Albumin (g/L)	AST (U/L)	ALT (U/L)	ALP (U/L)	GGT (U/L)	TB (μmol/L)	Cholesterol (mmol/L)	Triglycerides (mmol/L)	IgG (g/L)	IgM (g/L)
After two years of placebo treatment										
Vuoristo et al. (14)	-0.3	-2	3	-332	59	-10.2	-0.5	-0.1	-0.9	1.1
Balan et al. (18)							-0.54	0.014		
Parés et al. (20)	-0.3	0	-14	-97	-7	8.55	-0.36			
Hendrickse et al. (21)	-0.7									
Poupon et al. (23)	-1.2	2	2.8	-36	-32.64	14.4	-0.1		0.8	0.644
Turner et al. (24)	-1	17.5		84.5		3.5			-0.1	-0.65
Combined	-0.695:	3.503:	-2.775:	-88.011:	-0.469:	4.116:	-0.317:	-0.098:	-0.029:	0.105:
(Pooled result:										
95% CI)	-1.14 to -0.25	-0.64–7.65	-15.33–9.78	-175.80 to -0.23	-26.16–25.22	-2.62–10.86	-0.53 to -0.11	-0.13 to -0.06	-0.64–0.58	-0.73–0.94
After six months of placebo treatment										
McCormick et al. (15)		11.25		27		-37.25				
Poupon et al. (22)	-0.1	-1.2	0.8	22.5	20.48	2.3	0.2		0.48	0.23
Battezzati et al.(25)	-0.5					0.342	-13		1.47	0.37
Combined	-0.474:	3.363:		23.004:		0.571:	-6.402:		1.298:	0.365:
(Pooled result:										
95% CI)	-0.77 to -0.18	-8.40–15.12		-58.64–104.65		-3.29–4.43	-19.34–6.53		0.56–2.03	0.13–0.60

AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; GGT: γ-glutamyl transferase; TB: total bilirubin

measurements, and clinical outcome. The quality of the included articles was ranked using the Jadad composite scale. We also assessed the adequacy of allocation concealment in accordance with the guidelines of the Cochrane Collaboration.

Statistical analysis

The differences in laboratory tests and histological scores before and after placebo treatment were presented as the mean and standard deviation. The pooled estimates of these differences in

the placebo arm were calculated using Meta-Analyst software (version 3.13, Tufts Medical Center; Boston, MA, USA). The pooled rate of each outcome in the placebo arm was calculated using R software (version 3.1.2). The Chi-square test was used to detect statistical heterogeneity. The I^2 statistic was used to determine the degree of inconsistency across studies due to heterogeneity. The fixed effect model was used to pool study data if the I^2 statistic was $\leq 50\%$; otherwise, the random effects model was used.

RESULTS

Description of trials

The search strategy yielded 135 articles. From these, we identified 56 potentially relevant articles by reviewing their titles and abstracts. Of the 56 articles selected for full-text review, 40 articles were excluded because they failed to meet the inclusion criteria. Only 16 articles, including 12 studies which reported sufficient data on PBC patients in the placebo arm, fulfilled the criteria for consideration in the review (14-29).

Table 4. Changes of the histological scores in PBC patients receiving two years of placebo therapy: pooled results

Study	N	Changes for histological scores	95% CI	Weight
Batts et al. (19)	29	0.1	-0.191–0.391	0.014
Parés et al. (20)	45	0.69	0.650–0.730	0.748
Poupon et al. (23)	45	1.4	1.225–1.575	0.039
Hendrickse et al. (21)	30	0.29	0.212–0.368	0.199
Pooled	149	0.629	0.266–0.992	

The main characteristics of the 12 studies included in the meta-analysis are summarized in Table 1. Of these, 5 were single centre studies and 7 were multi-centre studies. A total of 769 patients served as placebo controls. The average age was 54.8 years, and 693 (90.1%) of the patients were women. The sample sizes in the placebo groups of each study varied greatly, ranging from 8 to 173 patients. All patients were diagnosed with PBC based on the presence of clinical and histological features compatible with a diagnosis of PBC. Patients with decompensated cirrhosis and those who used drugs that might affect the course of PBC were excluded from the study. The quality of the included studies, as evaluated by the Jadad scoring system and allocation concealment classification, can be found in Table 2.

Pooled biochemical changes

Nine articles reported available data on biochemical changes in the placebo group. After six months of placebo treatment, the pooled estimate of the change in the albumin level was -0.47 g/L (95% CI, -0.77 to -0.18). The changes in serum levels of aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin (TB) and cholesterol were 3.36 U/L (95% CI, -8.40 to 15.12), 23.00 U/L (95% CI, -58.64 to 104.65), 0.57 μ mol/L (95% CI, -3.29 to 4.43) and -6.40 mmol/L (95% CI, -19.34 to 6.53), respectively, in patients who were receiving placebos.

Additionally, the changes in serum IgG and IgM concentration were 1.30 g/L (95% CI, 0.56 to 2.03) and 0.37 g/L (95% CI, 0.13 to 0.60), respectively (Table 3). Together, our studies found a slight decrease in serum albumin within six months. Serum IgG and IgM concentrations increased marginally within six months.

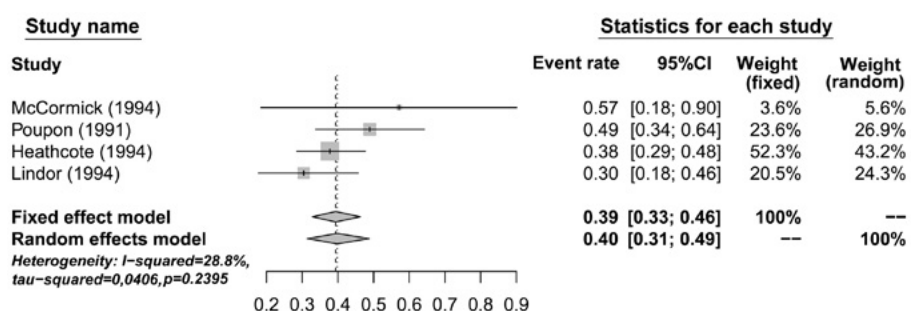


Figure 1. Pooled estimate of histological progression rate in placebo-treated patients with PBC

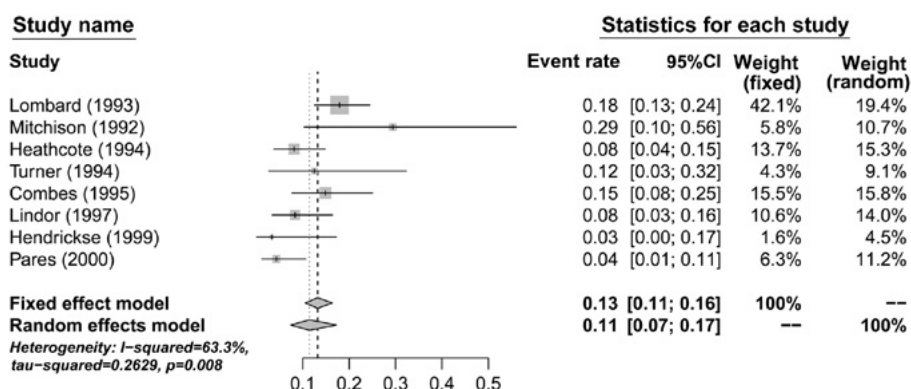


Figure 2. Pooled estimate of mortality in placebo-treated patients with PBC

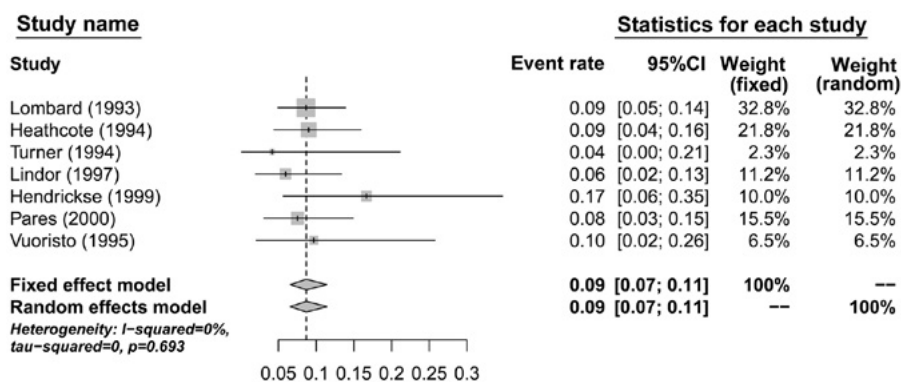


Figure 3. Pooled estimate of the rate of liver transplantation in placebo-treated patients with PBC

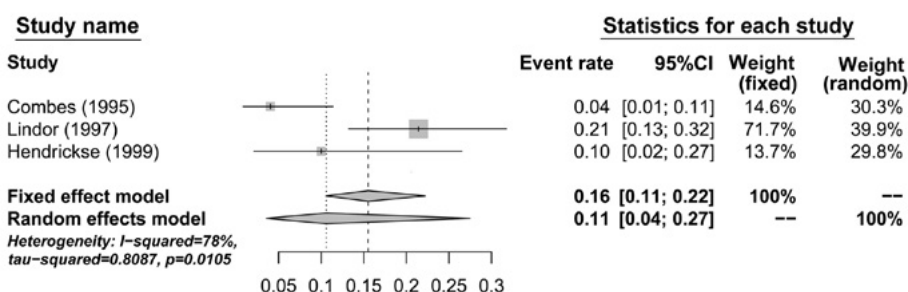


Figure 4. Pooled estimate of the rate of development of varices in placebo-treated patients with PBC

After two years of placebo treatment, the pooled estimate of the change in albumin level was -0.70 g/L (95% CI, -1.14 to -0.25). The changes in serum levels of AST, alanine aminotransferase (ALT), γ -glutamyl transferase, ALP and TB were 3.50 U/L (95% CI, -0.64 to 7.65), -2.78 U/L (95% CI, -15.33 to 9.78), -0.47 U/L (95% CI, -26.16 to 25.22), -88.01 U/L (95% CI, -175.79 to -0.23), and 4.12 μ mol/L (95% CI, -2.62 to 10.86), respectively in patients who were receiving placebos. Additionally, the changes in cholesterol and triglycerides were -0.32 mmol/L (95% CI, -0.53 to -0.11) and -0.10 mmol/L (95% CI, -0.13 to -0.06), respectively. Four studies provided data on changes in serum immunoglobulin concentration after two years of placebo treatment; the IgG and IgM changes were -0.03 g/L (95% CI, -0.64 to 0.58) and 0.11 g/L (95% CI, -0.73 to 0.94), respectively (Table 3). Together, our studies found a slight decrease in serum albumin within 2 years. However, we also observed a significant decrease in serum ALP and marginal decreases in cholesterol and triglycerides, which was unexpected.

Pooled histological changes

Liver biopsy specimens of the 149 patients in the placebo groups from four studies were staged and scored according to the Ludwig criteria. After two years of placebo treatment, the pooled estimate of the change in histological scores was 0.63 (95% CI, 0.27 to 0.99) (Table 4). In addition, four studies including 204 patients provided data on the histological progression rate after two years of placebo treatment. Progression in the histological stage was observed in 39.4% of patients, ranging from 32.8% to 46.3% (Figure 1). There was no significant level of heterogeneity between the studies ($I^2=28.8\%$; $p=0.2395$).

Pooled incidence of clinical events

Of the 606 patients in the placebo group from eight studies, 71 died during at least 2-year follow-up. Detailed causes of death for 71 patients were extracted from eight studies. The two leading causes of death were hepatic failure and gastrointestinal bleeding. Only 46 of 546 patients underwent liver transplantation. All patients who underwent liver transplantation developed cirrhosis, and most of these patients reached the terminal stage.

The pooled estimate of 2-year mortality for PBC was 11.4%, ranging from 7.4% to 17.2% (Figure 2). There was a statistically significant level of heterogeneity between the studies ($I^2=63.3\%$; $p=0.008$). The pooled estimate of rate of liver transplantation within 2 years was 8.7%, ranging from 6.6% to 11.4% (Figure 3). There was no significant level of heterogeneity between the studies ($I^2=0$; $p=0.693$). For complications associated with cirrhosis, gastroesophageal varices developed in 10.6% of patients (95% confidence interval, 3.6% to 27.5%) during 2-year follow-up (Figure 4), with a statistical heterogeneity between the studies ($I^2=78\%$; $p=0.0105$).

DISCUSSION

Despite considerable advances in our understanding of the natural history of PBC following the introduction of UDCA, little improvement has been made in the natural history of untreated patients. In our study, we have pooled some data regarding blood chemistry measurements, histological scores and clinical outcomes in placebo-treated patients with PBC. These data will be helpful to understand clinical manifestations, progression

and prognosis for untreated PBC patients as well as for patients refractory to UDCA.

Our studies have not shown any deterioration upon 6-month placebo treatment in blood chemistry measurements, except albumin and immunoglobulin. We reported a slight decrease in serum albumin in patients during 6-month studies. Meanwhile, we observed mild increases in serum IgG and IgM concentrations with time. The pooled analyses found that placebos could not prevent this deterioration of liver function. Similarly to what was observed during a 6-month follow-up, a slight deterioration in serum albumin level was observed in the placebo patients during a 2-year follow-up. In contrast, serum IgG and IgM concentrations remained practically unchanged over 2 years. Of particular significance is the observation that serum ALP levels decreased significantly at the end of the study in the placebo patients along with a slight decline in the levels of cholesterol and triglycerides. A possible explanation for why the ALP, cholesterol and triglycerides in the placebo groups decreased during follow-up is that these values fluctuate in the course of PBC; thus, this result should be interpreted with some caution. The current study provides important data regarding the natural history of untreated PBC and supports the notion that serum biochemical values have no obvious deterioration during a long course of this disease. In addition, our data suggest that biochemical measurements at the 2-year mark are not suitable for assessing therapeutic responses to UDCA in PBC patients, confirming the results observed by Papastergiou et al. (30). However, a greater number of patients with a longer period of follow-up will be required to obtain conclusive evidence.

Although the histological assessment of PBC is an invasive technique that is limited by sampling variation, subjective interpretations and limited frequency of biopsies, it is considered to be the gold standard for staging the progression of PBC. In our studies of PBC patients receiving a 2-year placebo therapy, moderate worsening of histological scores was noted; also, progression of the histological stage occurred in 39.4% of patients in comparison with the unexpected changes in the biochemical parameters. As noted, histological progression occurs relatively rapidly in most PBC patients, confirming the results reported by Locke et al. (31); thus, trials of a relatively short duration are likely to be informative when evaluating the risk for histological development. Together, these data may assist clinicians in assessing disease progression as well as in designing future clinical trials.

We used hard endpoints, such as death or transplantation. The mortality during 2-year follow-up in our study was 11.4%, which is in agreement with recent studies (6,7). In the majority of PBC patients who died, end-stage liver disease was the primary cause of death, and only a minority died of extrahepatic causes. The pooled estimated 2-year probability of transplantation was 8.7%. The high incidence of liver transplantation in the placebo group may reflect considerable clinical deterioration. However, there is no unified consensus about the indications

and timing of liver transplantation, which affects the incidence of liver transplantation.

The development of portal hypertension, particularly gastroesophageal varices, has been identified as one of the factors for risk of death in PBC patients (32). Symptoms related to portal hypertension in PBC usually develop after the onset of cirrhosis but occasionally can be found in precirrhotic stages. In our study, gastroesophageal varices developed in 10.6% of patients during a 2-year follow-up. This finding is in contrast to the report from Mayo et al. (33), who observed the development of varices in 20.5% of PBC patients. This difference could be due to the fact that our follow-up was shorter (2 years vs 7.3 years).

There are several limitations to this study due to the limitations of the available data. First, we did not analyse the prognostic indices for predicating the natural history and indicating when transplant referral occurred for patients with PBC because the required data could not be extracted from the included studies. Second, patients have miscellaneous manifestations and outcomes at various times during the course of PBC; however, the potential heterogeneity could not be analysed due to unavailability of the data. We grouped and pooled all the patients without decompensated cirrhosis, regardless of their age, sex or severity of illness. Despite this limitation, our pooled analysis provided a general picture of biochemical and histological changes and clinical outcomes in a relatively large sample of PBC patients. Third, in the available studies, the duration of follow-up was variable, ranging from 6 months to more than 3 years; however, 2 years is the most commonly used duration. Although most of the patients progressed through histological stages within 2 years (31), the progressions of PBC are quite diverse. However, it is highly unlikely that a long-term placebo-controlled trial of PBC treatment will be conducted in the future. Although this would be the most rigorous method to confirm the conclusions of this study, it is impossible to perform such a trial due to practical and ethical issues (34).

In conclusion, this study demonstrated the natural history of placebo-treated PBC patients. It showed that serum ALP levels decreased significantly and other biochemical parameters fluctuated slightly or were practically unchanged within 2 years. Meanwhile, histological progression occurred in more than one-third of PBC patients over a 2-year period. Thus, biochemical responses at the 2-year mark may provide little information on disease progression and therapeutic response. Furthermore, the 2-year rates of death, transplantation and development of varices were 11.4%, 8.7% and 10.6%, respectively. This information will further enhance the current understanding of the natural history of untreated patients and UDCA-resistant patients and will facilitate the development of new therapies for PBC.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of the first affiliated hospital of Zhejiang University.

Informed Consent: N/A.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - P.X., Y.L.; Design - L.L., G.L., C.Y.; Supervision - P.X., L.L., Y.L.; Funding - L.L.; Materials - L.L., G.L., C.Y.; Data Collection and/or Processing - P.X., L.L.; Analysis and/or Interpretation - P.X., L.L., Y.L.; Literature Review - G.L., C.Y.; Writer - P.X., L.L., G.L.; Critical Review - C.Y., Y.L.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: This study was supported by the Zhejiang Provincial Medical and Healthy Science Foundation of China (2015KYB135).

REFERENCES

- Selmi C, Bowlus CL, Gershwin ME, Coppel RL. Primary biliary cirrhosis. *Lancet* 2011; 377: 1600-9. [\[CrossRef\]](#)
- Verma A, Jazrawi RP, Ahmed HA, et al. Optimum dose of ursodeoxycholic acid in primary biliary cirrhosis. *Eur J Gastroenterol Hepatol* 1999; 11: 1069-76. [\[CrossRef\]](#)
- Boonstra K, Kunst AE, Stadhouders PH, et al. Rising incidence and prevalence of primary biliary cirrhosis: a large population-based study. *Liver Int* 2014; 34: e31-8. [\[CrossRef\]](#)
- Al-Harthy N, Kumagi T. Natural history and management of primary biliary cirrhosis. *Hepat Med* 2012; 4: 61-71.
- Ishibashi H, Komori A, Shimoda S, Ambrosini YM, Gershwin ME, Nakamura M. Risk factors and prediction of long-term outcome in primary biliary cirrhosis. *Intern Med* 2011; 50: 1-10. [\[CrossRef\]](#)
- Floreani A, Caroli D, Variola A, et al. A 35-year follow-up of a large cohort of patients with primary biliary cirrhosis seen at a single centre. *Liver Int* 2011; 31: 361-8. [\[CrossRef\]](#)
- Myers RP, Shaheen AA, Fong A, et al. Epidemiology and natural history of primary biliary cirrhosis in a Canadian health region: a population-based study. *Hepatology* 2009; 50: 1884-92. [\[CrossRef\]](#)
- Baldursdottir TR, Bergmann OM, Jonasson JG, Ludviksson BR, Axelsson TA, Björnsson ES. The epidemiology and natural history of primary biliary cirrhosis: a nationwide population-based study. *Eur J Gastroenterol Hepatol* 2012; 24: 824-30. [\[CrossRef\]](#)
- Corpechot C, Chazouillères O, Poupon R. Early primary biliary cirrhosis: biochemical response to treatment and prediction of long-term outcome. *J Hepatol* 2011; 55: 1361-7. [\[CrossRef\]](#)
- Corpechot C, Abenavoli L, Rabahi N, et al. Biochemical response to ursodeoxycholic acid and long-term prognosis in primary biliary cirrhosis. *Hepatology* 2008; 48: 871-7. [\[CrossRef\]](#)
- Yu CH, Xu CF, Ye H, Li L, Li YM. Early mortality of alcoholic hepatitis: a review of data from placebo-controlled clinical trials. *World J Gastroenterol* 2010; 16: 2435-9. [\[CrossRef\]](#)
- Loomba R, Wesley R, Pucino F, Liang TJ, Kleiner DE, Lavine JE. Placebo in nonalcoholic steatohepatitis: insight into natural history and implications for future clinical trials. *Clin Gastroenterol Hepatol* 2008; 6: 1243-8. [\[CrossRef\]](#)
- Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol* 2009; 62: e1-34. [\[CrossRef\]](#)
- Vuoristo M, Färkkilä M, Karvonen AL, et al. A placebo-controlled trial of primary biliary cirrhosis treatment with colchicine and ursodeoxycholic acid. *Gastroenterology* 1995; 108: 1470-8. [\[CrossRef\]](#)
- McCormick PA, Scott F, Epstein O, Burroughs AK, Scheuer PJ, McIntyre N. Thalidomide as therapy for primary biliary cirrhosis: a double-blind placebo controlled pilot study. *J Hepatol* 1994; 21: 496-9. [\[CrossRef\]](#)
- Lindor KD, Dickson ER, Baldus WP, et al. Ursodeoxycholic acid in the treatment of primary biliary cirrhosis. *Gastroenterology* 1994; 106: 1284-90. [\[CrossRef\]](#)
- Lindor KD, Jorgensen RA, Thorneau TM, Malinchoc M, Dickson ER. Ursodeoxycholic acid delays the onset of esophageal varices in primary biliary cirrhosis. *Mayo Clin Proc* 1997; 72: 1137-40. [\[CrossRef\]](#)
- Balan V, Dickson ER, Jorgensen RA, Lindor KD. Effect of ursodeoxycholic acid on serum lipids of patients with primary biliary cirrhosis. *Mayo Clin Proc* 1994; 69: 923-9. [\[CrossRef\]](#)
- Batts KP, Jorgensen RA, Dickson ER, Lindor KD. Effects of ursodeoxycholic acid on hepatic inflammation and histological stage in patients with primary biliary cirrhosis. *Am J Gastroenterol* 1996; 91: 2314-7.
- Parés A, Caballería L, Rodés J, et al. Long-term effects of ursodeoxycholic acid in primary biliary cirrhosis: results of a double-blind controlled multicentric trial. UDCA-Cooperative Group from the Spanish Association for the Study of the Liver. *J Hepatol* 2000; 32: 561-6. [\[CrossRef\]](#)
- Hendrickse MT, Rigney E, Giaffer MH, et al. Low-dose methotrexate is ineffective in primary biliary cirrhosis: long-term results of a placebo-controlled trial. *Gastroenterology* 1999; 117: 400-7. [\[CrossRef\]](#)
- Poupon RE, Eschwege E, Poupon R. Ursodeoxycholic acid for the treatment of primary biliary cirrhosis. Interim analysis of a double-blind multicentre randomized trial. The UDCA-PBC Study Group. *J Hepatol* 1990; 11: 16-21. [\[CrossRef\]](#)
- Poupon RE, Balkau B, Eschwege E, Poupon R. A multicenter, controlled trial of ursodiol for the treatment of primary biliary cirrhosis. UDCA-PBC Study Group. *N Engl J Med* 1991; 324: 1548-54. [\[CrossRef\]](#)
- Turner IB, Myszor M, Mitchison HC, Bennett MK, Burt AD, James OF. A two year controlled trial examining the effectiveness of ursodeoxycholic acid in primary biliary cirrhosis. *J Gastroenterol Hepatol* 1994; 9: 162-8. [\[CrossRef\]](#)
- Battezzati PM, Podda M, Bianchi FB, et al. Ursodeoxycholic acid for symptomatic primary biliary cirrhosis. Preliminary analysis of a double-blind multicenter trial. Italian Multicenter Group for the Study of UDCA in PBC. *J Hepatol* 1993; 17: 332-8. [\[CrossRef\]](#)
- Combes B, Carithers RL Jr, Maddrey WC, et al. A randomized, double-blind, placebo-controlled trial of ursodeoxycholic acid in primary biliary cirrhosis. *Hepatology* 1995; 22: 759-66. [\[CrossRef\]](#)
- Heathcote EJ, Cauch-Dudek K, Walker V, et al. The Canadian Multicenter Double-blind Randomized Controlled Trial of ursodeoxycholic acid in primary biliary cirrhosis. *Hepatology* 1994; 19: 1149-56. [\[CrossRef\]](#)
- Mitchison HC, Palmer JM, Bassendine MF, Watson AJ, Record CO, James OF. A controlled trial of prednisolone treatment in primary biliary cirrhosis. Three-year results. *J Hepatol* 1992; 15: 336-44. [\[CrossRef\]](#)
- Lombard M, Portmann B, Neuberger J, et al. Cyclosporin A Treatment in Primary Biliary Cirrhosis: Results of a Long-Term Placebo Controlled Trial. *Gastroenterology* 1993; 104: 519-26.
- Papastergiou V, Tsochatzis EA, Rodriguez-Peralvarez M, et al. Biochemical criteria at 1 year are not robust indicators of response to ursodeoxycholic acid in early primary biliary cirrhosis: results from a 29-year cohort study. *Aliment Pharmacol Ther* 2013; 38: 1354-64. [\[CrossRef\]](#)
- Locke GR 3rd, Thorneau TM, Ludwig J, Dickson ER, Lindor KD. Time course of histological progression in primary biliary cirrhosis. *Hepatology* 1996; 23: 52-6. [\[CrossRef\]](#)
- Patanwala I, McMeekin P, Walters R, et al. A validated clinical tool for the prediction of varices in PBC: the Newcastle Varices in PBC Score. *J Hepatol* 2013; 59: 327-35. [\[CrossRef\]](#)
- Mayo MJ, Parkes J, Adams-Huet B, et al. Prediction of clinical outcomes in primary biliary cirrhosis by serum enhanced liver fibrosis assay. *Hepatology* 2008; 48: 1549-57. [\[CrossRef\]](#)
- Lindor KD, Thorneau TM, Jorgensen RA, Malinchoc M, Dickson ER. Effects of ursodeoxycholic acid on survival in patients with primary biliary cirrhosis. *Gastroenterology* 1996; 110: 1515-8. [\[CrossRef\]](#)