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Original Article

Patients with AMA/anti-sp100/anti-gp210 Positivity and Cholestasis Can Manifest Conditions Beyond Primary Biliary Cholangitis

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Abstract

Background and Aims: The diagnostic value of primary biliary cholangitis (PBC)-specific antibodies in patients with elevated alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) levels, and other identifiable causes, was unclear. Our study aimed to determine whether etiological treatments in PBC-specific antibody-positive patients could improve liver biochemical tests, thereby distinguishing them from individuals with PBC. ***Methods:*** We enrolled patients who were positive for PBC-specific antibodies and elevated ALP and/or GGT levels but with other identifiable etiologies. Changes in liver biochemistry following non-ursodeoxycholic acid etiological treatments were monitored. ***Results:*** A total of 155 patients with positive PBC-specific antibodies and elevated ALP and/or GGT levels due to non-PBC diseases were enrolled. Among them, 100 patients were diagnosed with non-PBC liver diseases, mainly metabolic-associated fatty liver disease, drug-induced liver injury, and autoimmune hepatitis. Additionally, 55 patients had non-liver diseases, predominantly connective tissue diseases. The median follow-up duration was 15.9 (4.7–25.6) months. Among 141 patients who completed follow-up after receiving etiological treatments, 85.1% (120/141) showed improvement in ALP and/or GGT levels, with 51.8% (73/141) achieving normalization of both ALP and GGT. However, 68 patients continued to exhibit elevated ALP and/or GGT, with 55 patients displaying isolated GGT elevation and 11 patients showing liver histological changes not consistent with PBC. ***Conclusions:*** PBC-specific antibodies, along with elevated ALP and GGT levels, may occur in various non-PBC diseases. Etiological treatments may improve or even resolve cholestatic biochemistry. For these patients, initiating etiological treatment rather than immediately starting ursodeoxycholic acid therapy would be justified.

Keywords: Primary biliary cholangitis-specific antibodies; Diagnosis; Ursodeoxycholic acid; UDCA; Treatment; Etiological treatments.

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Introduction

A serological hallmark of primary biliary cholangitis (PBC) is the presence of anti-mitochondrial antibodies (AMA), anti-sp100 antibodies, or anti-gp210 antibodies. Meta-analysis has demonstrated that AMA exhibits high sensitivity and specificity, both exceeding 90%, whereas anti-sp100 and anti-gp210 antibodies show lower sensitivity (16.7% to 27.2%) but high specificity (97.6% to 98%).[1–3] Therefore, major international guidelines recommend that in patients with intrahepatic cholestasis and the presence of PBC-specific antibodies, a diagnosis of PBC can be made without the need for a liver biopsy.[4–7]

However, caution is warranted when interpreting the diagnostic value of PBC-specific antibodies across different clinical settings. For instance, in individuals with isolated AMA positivity but lacking cholestatic biochemical evidence, the likelihood of developing PBC remains very low, even after up to five or seven years of follow-up.[8,9] Additionally, PBC-specific antibodies can be detected in various liver or non-liver diseases.[9–13]

For example, a study showed that 5.1% of 2,802 patients with drug-induced liver injury (DILI) tested positive for AMA-M2; however, their antibody titers decreased as their liver injury improved, with only a small number of patients ultimately developing PBC.[13] Weber *et al*. also reported that AMA and ANA were positive in 10% and 67% of patients with DILI.[12] However, not all studies provided detailed descriptions of the specific patterns of immunofluorescence, which are crucial for the diagnosis of PBC.[12,14] Furthermore, elevation of alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) can occur in numerous liver and non-liver diseases.[15–17] These findings underscore that even in patients with elevated ALP and/or GGT, the presence of PBC-specific antibodies does not automatically lead to the diagnosis of PBC. However, studies in this set-

ting remain limited.

Therefore, in this retrospective cohort study, we investigated the profiles of AMA, anti-sp100 antibodies, and anti-gp210 antibodies in patients with abnormal liver function tests and confirmed non-PBC diseases. Our investigation primarily focused on evaluating the changes in ALP and GGT levels following non-UDCA etiological treatment.

Methods

Patient enrollment

This was a retrospective study of patients who tested positive for PBC-specific antibodies at Beijing Friendship Hospital, Capital Medical University, Beijing, China, from February 2017 to May 2023.

Patients were included if they: Tested positive for AMA with a titer ≥1:80, or positive for AMA-M2, anti-gp210, or anti-sp100 with a level ≥25 U/mL; and had elevated ALP and/or GGT levels that could be explained by non-PBC diseases.

Patients were excluded if they met any of the following criteria: (1) Had a diagnosis of PBC; (2) Had been treated with ursodeoxycholic acid (UDCA); or (3) Had key baseline clinical data missing.

Collection of baseline data

Demographic and baseline data were retrieved from the electronic medical records. Biochemical data included alanine aminotransferase, aspartate aminotransferase, ALP, GGT, albumin, globulin, total bilirubin, immunoglobulin G, and immunoglobulin M. PBC-specific antibodies included AMA, AMA-M2, anti-sp100, and anti-gp210. Abdominal imaging and liver histology were collected when available. The reason for initiating the detection of PBC-specific antibodies was also carefully evaluated.

Diagnosis of non-PBC diseases

Metabolic-associated fatty liver disease (MAFLD): The detection of liver steatosis (by liver histology, non-invasive biomarkers, or imaging) together with the presence of at least one of three criteria: overweight or obesity, type 2 diabetes mellitus, or clinical evidence of metabolic dysfunction.[15]

DILI: A score of 6 or higher on the Roussel Uclaf Causality Assessment Method.[16]

Autoimmune hepatitis (AIH): A score of 7 or higher on the simplified scoring system for AIH proposed by the International Autoimmune Hepatitis Group.[18]

Alcoholic liver disease (ALD): A daily alcohol intake of ≥40 g/d for males and ≥20 g/d for females for over five years, or >80 g/d for over two weeks, along with the presence of hepatic steatosis detected by ultrasound and/or elevation in liver enzymes and serum bilirubin.[19]

Connective tissue diseases (CTDs) and other non-liver diseases were diagnosed by rheumatologists according to the relevant guidelines.[20–22]

Follow-up of enrolled patients

Follow-up data were obtained from electronic medical records and/or telephone interviews. The follow-up information included therapeutic modalities and liver biochemistries, focusing on the dynamic changes in ALP and GGT. Therapeutic information included whether patients received etiological treatments (targeting the causes of liver test abnormalities) or treatment with UDCA. Patients who received UDCA or did not receive etiological treatments were excluded.

Methods for autoantibody test and definitions of positive results

The AMA titer (dilution 1:80) was detected by indirect immunofluorescence (IIF) on HEp2 cells (Euroimmun, Inc), with titers ≥1:80 regarded as positive. The levels of AMA-M2, anti-gp210, and anti-sp100 were detected by enzyme-linked immunosorbent assay (ELISA) (Inova Diagnostics). Concentrations ≥25 U/mL were considered positive.

Statistical analysis

Categorical variables were summarized by counts and percentages. Continuous variables were expressed as medians or interquartile ranges. The Chi-square test and Mann-Whitney U test were used to analyze differences and compare variables between groups. A p-value of <0.05 was considered statistically significant (two-sided). All statistical analyses were conducted using SPSS Version 26.0.

Results

Baseline characteristics of the study population

We reviewed 206 patients who tested positive for PBC-specific antibodies and had elevated ALP and/or GGT levels due to other identifiable causes (Fig. 1). Among them, 51 patients were excluded due to their intake of UDCA or not receiving etiological treatments. Finally, a total of 155 patients were enrolled in this study, including 100 patients with non-PBC liver diseases and 55 patients with non-liver diseases.

The diagnostic information for the non-PBC liver diseases and non-liver diseases is shown in Figure 2. Among the non-PBC liver diseases, the most prevalent were MAFLD (n = 36), followed by DILI (n = 35), AIH (n = 9), viral hepatitis (n = 7), and ALD (n = 5). For non-liver diseases, CTDs (n = 28) were the most frequent. Liver biopsy results were available for 27 patients, including 10 with MAFLD, nine with AIH, four with DILI, two with porto-sinusoidal vascular disorder/idiopathic non-cirrhotic portal hypertension, one with viral hepatitis, and one with hepatocellular carcinoma.

The demographic and baseline characteristics of patients with non-PBC liver diseases and non-liver diseases are summarized in Table 1. Not surprisingly, the levels of alanine aminotransferase, aspartate aminotransferase, GGT, and total bilirubin in patients with non-PBC liver diseases were significantly higher than those in patients with non-liver diseases (all $p < 0.01$). However, there was no statistically significant difference in ALP levels between the two groups.

The dynamic change in liver biochemistry after etiological treatment

A total of 141 patients completed follow-up with a median follow-up duration of 15.9 (4.7–25.6) months. Four patients died from their underlying diseases (two with liver diseases and two with non-liver diseases).

Without UDCA treatment, improvements in ALP and/or GGT levels were observed in 85.1% (120/141) of patients who received etiological treatment. As shown in Figure 3, the levels of both ALP and GGT decreased significantly in patients with DILI, AIH, and CTD. In patients with MAFLD, both ALP and GGT levels decreased, but only the GGT level reached statistical significance. Notably, both ALP and GGT levels normalized in 51.8% (73/141) of patients, including 49 patients with non-PBC liver diseases (21 DILI, 12 MAFLD, six AIH, four viral hepatitis, and six other liver diseases) and 24 patients with non-liver diseases, as shown in Figure 4.

At the end of the follow-up, 48.2% (68/141) of patients

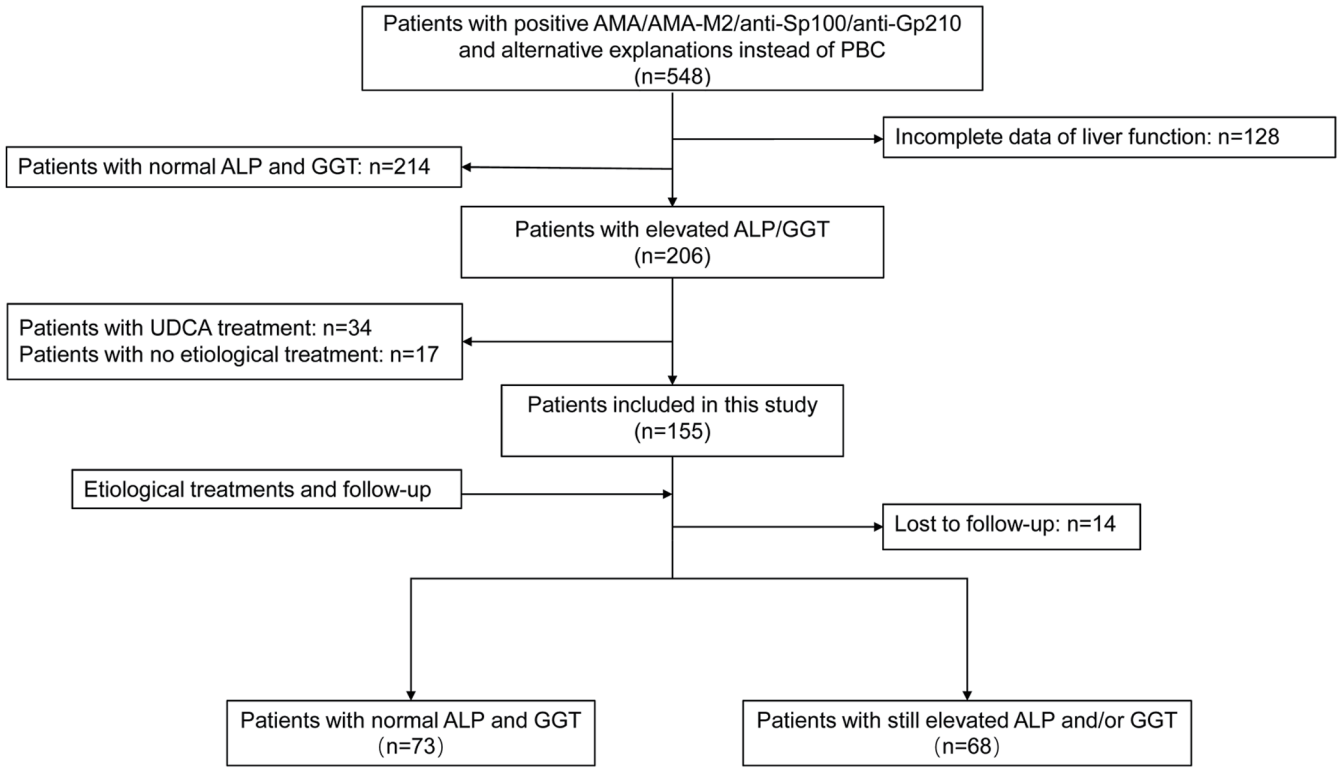

Fig. 1. The flowchart of the study. AMA, anti-mitochondrial autoantibody; AMA-M2, anti-mitochondrial M2 antibody; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; UDCA, ursodeoxycholic acid.

still had elevated levels of ALP and/or GGT. Among them, 45 patients had non-PBC liver diseases, while 23 had non-liver diseases. Notably, 55 out of the 68 patients only exhibited elevated levels of GGT but normal ALP levels after etiological treatments. Eleven out of the 68 patients had liver histological changes not consistent with PBC.

However, we observed that the levels of ALP and/or GGT were higher than baseline after etiological treatment in patients with MAFLD (n = 13) and CTD (n = 5). Furthermore, four out of the 13 patients with MAFLD underwent liver biopsy at baseline, and none of them met the diagnosis of PBC.

Discussion

In this study, we observed the presence of PBC-specific antibodies and elevated ALP and/or GGT levels in patients with a range of conditions, including both non-PBC liver diseases and non-liver diseases. Importantly, without the use of UDCA therapy, treatment targeting the primary diseases led to sig-

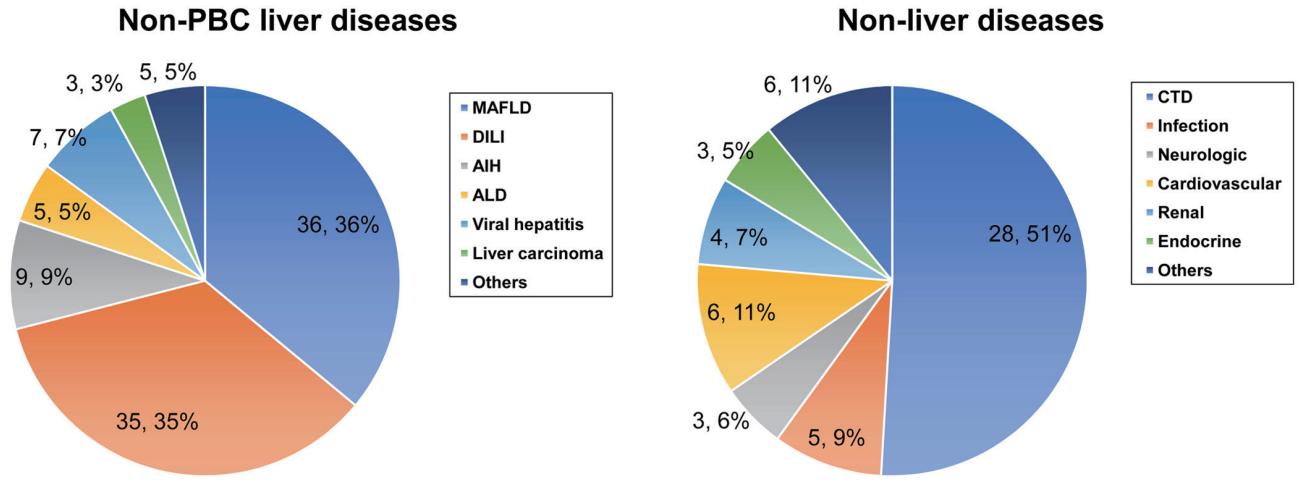

Fig. 2. The categorization of non-PBC liver diseases and non-liver diseases of the whole cohort at baseline. MAFLD, metabolic associated fatty liver disease; DILI, drug-induced liver injury; AIH, autoimmune hepatitis; ALD, alcoholic liver disease; CTD, connective tissue disease.

Table 1. Demographic and baseline characteristics of the patients

Characteristics	Non-PBC liver diseases	Non-liver diseases	*p*
Number of cases, n (%)	100 (64.52%)	55 (35.48%)	0.076
Female, n (%)	67 (66.33%)	47 (85.45%)	0.014
Age at baseline, years	58 (44–67)	63 (53–68)	0.076
ALT, ×ULN	2.22 (0.96–3.90)	0.65 (0.38–1.28)	<0.001**
AST, ×ULN	1.69 (0.92–4.44)	0.77 (0.59–1.39)	<0.001**
ALP, ×ULN	0.80 (0.66–1.01)	0.76 (0.66–1.24)	0.834
GGT, ×ULN	1.96 (1.40–3.71)	1.38 (1.13–1.98)	0.001*
ALB, g/L	40.20 (35.40–43.80)	38.90 (33.10–41.20)	0.025*
GLO, g/L	31.10 (28.13–34.93)	33.00 (28.70–37.80)	0.096
TBIL, umol/L	15.58 (12.53–26.63)	12.08 (9.41–15.88)	<0.001**
IgG, mg/dL	1,455.00 (1,210.00–1,827.50)	1,470.00 (1,260.00–1,970.00)	0.554
IgM, mg/dL	112.50 (75.00–164.75)	127.00 (78.60–222.00)	0.178
AMA-M2, U/mL	27.23 (7.52–52.32)	28.49 (7.84–82.25)	0.309
Anti-sp100, U/mL	14.50 (3.70–48.07)	3.97 (2.39–31.92)	0.031*
Anti-gp210, U/mL	1.77 (1.40–2.49)	2.14 (1.21–4.63)	0.379
AMA (1:80), n	11	8	0.530
AMA (1:160), n	9	16	
AMA (1:320), n	9	9	
AMA (1:640), n	1	1	

Levels of significance: *$p < 0.05$; **$p < 0.001$. ALB, albumin; ALT, alanine aminotransferase; ALP, alkaline phosphatase; AMA, anti-mitochondrial autoantibody; AMA-M2, anti-mitochondrial M2 antibody; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; GLO, globulin; IgG, immunoglobulin G; IgM, immunoglobulin M; TBIL, total bilirubin; ULN, upper limit of normal.

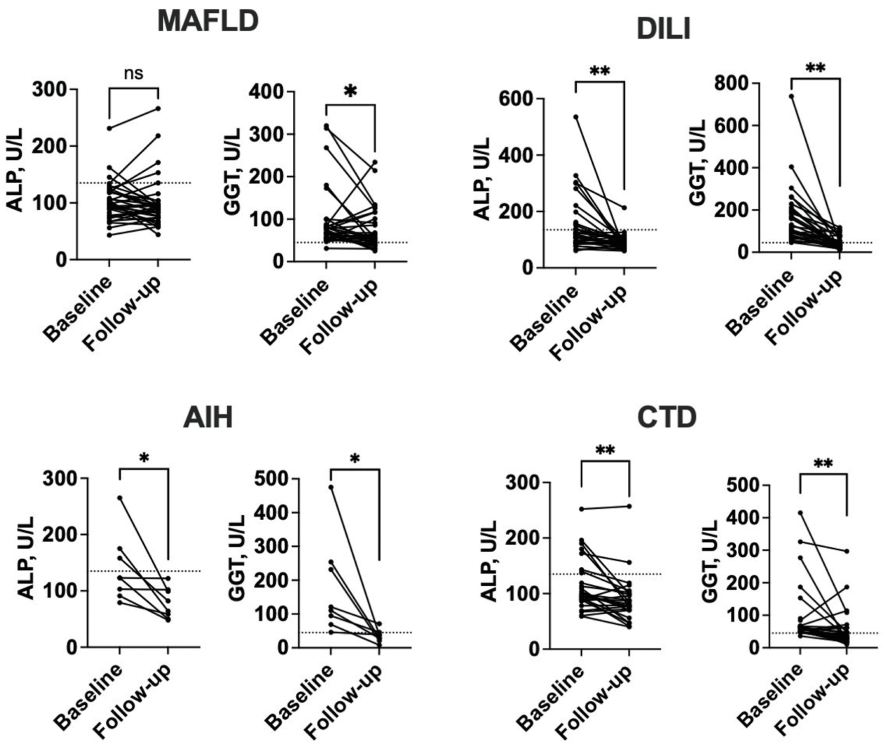

Fig. 3. The level of ALP and GGT in patients with MAFLD, DILI, AIH, and CTD at baseline and follow-up. Levels of significance: *$p < 0.05$; **$p < 0.001$. The dotted line refers to the upper limit of normal (ULN) for ALP or GGT. MAFLD, metabolic associated fatty liver disease; DILI, drug-induced liver injury; AIH, autoimmune hepatitis; CTD, connective tissue disease; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase.

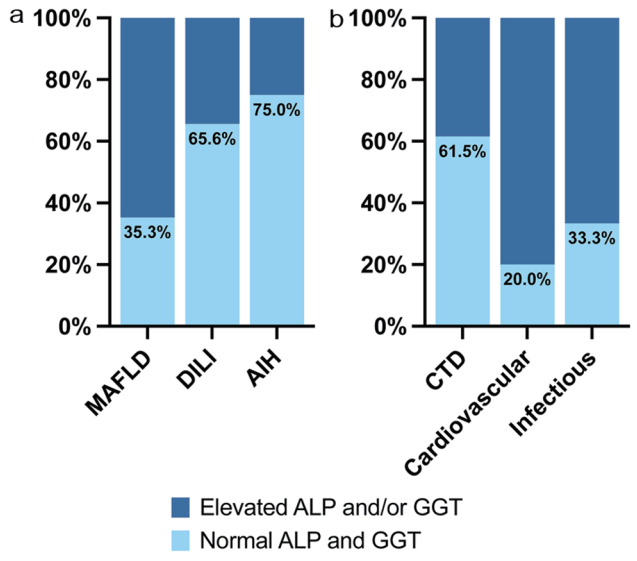

Fig. 4. The proportion of patients with elevated ALP and/or GGT and with normalized ALP and GGT at follow-up in the most frequent non-PBC diseases. Non-PBC liver diseases; (b) Non-liver diseases. MAFLD, metabolic associated fatty liver disease; DILI, drug-induced liver injury; AIH, autoimmune hepatitis; CTD, connective tissue disease; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase.

nificant improvements or even normalization of ALP and/or GGT levels in most of these patients.

ELISA was employed to detect AMA-M2, anti-sp100, and anti-gp210 antibodies, and IIF was employed to detect AMA in our study. These different detection methods may also have an impact on the research results. The detection methods for AMA and ANA primarily include IIF, ELISA, and immunoblotting, each with its own advantages and disadvantages. A previous report found that 11%, 8%, and 17% of patients with PBC who were negative for AMA by IIF actually reacted against pMIT3 (a triple AMA recombinant antigen), gp210, and sp100 by ELISA, respectively.[23] In another study involving 108 patients with histology-proven PBC, the ELISA method demonstrated higher specificity and sensitivity for detecting sp100 than IIF (99% vs. 98%, and 44% vs. 34%, respectively).[24] Therefore, different detection methods can be adopted to reduce missed diagnoses, misdiagnoses, and unnecessary liver biopsies.[25]

Although AMA serves as a specific biomarker for PBC, ANA also plays an important role in the diagnosis of PBC, especially in AMA-negative cases. Indeed, in a study involving over 4,000 sera from both liver and non-liver patients with autoimmune and non-autoimmune diseases, immunofluorescence revealed that the rim-like membranous patterns (including gp210, lamin B receptor, and nucleoporin p62) and multiple nuclear dot patterns (including sp100 and the promyelocytic leukemia protein) had high PBC specificity, particularly in AMA-negative PBC cases.[25,26] Similarly, by using IIF, Granito *et al*. also identified sp140 (a nucleolar antigen) as a highly specific new autoantigen for PBC, but no specific clinical features have been linked to anti-sp140.[27] Furthermore, as an autoimmune liver disease, PBC can overlap with rheumatic diseases, resulting in positive serum antibodies against extractable nuclear antigens. The most prevalent antibody against extractable nuclear antigens reactivity in PBC is anti-SSA/Ro-52kD, which was found to be positive by immunoblotting in 28% of PBC patients. This reactivity predicts more advanced histological stages, and higher levels of serum bilirubin and immunoglobulin M.[28] Additionally, the anti-centromere antibody was detected by immunoblotting in 28% of patients with PBC, although it was not associated with specific biochemical or histological features. Therefore, for patients with suspected PBC, a more detailed exploration of antibody types can enhance diagnostic accuracy and provide insights into clinical manifestations and prognosis.

Our current study demonstrated the presence of PBC-specific antibodies across various intrahepatic and extrahepatic diseases, especially in MAFLD, DILI, AIH, and CTDs, which further corroborates our previous findings.[9] In line with these results, O'Brien *et al*. demonstrated that 11.9% of patients with AIH were AMA-positive during a median follow-up of eight years.[29] Similarly, Neuschwander-Tetri BA *et al*. reported AMA positivity in 4% of MAFLD patients without histological evidence of PBC.[30] Additionally, the prevalence of AMA in patients with DILI ranged from 3.22% to 10%, with titers decreasing as liver damage improved.[13,31] All the evidence suggests that the specific clinical scenario needs to be considered when interpreting the clinical significance of so-called PBC-specific autoantibodies.

More importantly, we found that treatment targeting primary diseases resulted in improved ALP and/or GGT levels in most of the patients with non-PBC liver diseases or non-liver diseases. Notably, non-UDCA interventions for primary diseases led to the normalization of ALP and GGT levels in nearly half of the patients with non-PBC disease. This subset of patients, initially presenting with PBC-specific antibody positivity and elevated cholestatic biochemistry, would conventionally meet the diagnostic criteria for PBC. However, after treatment of the primary disease, exclusion of PBC became feasible as their liver biochemistry improved or normalized even without UDCA therapy. This result adds further evidence that the presence of so-called PBC-specific autoantibodies cannot guarantee the correctness of the diagnosis of PBC, even in patients with cholestatic biochemistry. Therefore, in cases with abnormal liver function tests and positive PBC-specific antibodies, rather than immediately starting UDCA therapy, competing etiologies should be carefully searched for and treated if feasible.

We also found that 68 patients did not achieve complete normalization of either ALP or GGT during follow-up. Among them, 55 patients exhibited isolated elevation of GGT following treatment targeting primary diseases. Notably, none of the 11 patients with persistently elevated GGT exhibited PBC characteristics on liver histology. This is not surprising, since GGT elevation can be observed in various liver diseases such as DILI, ALD, and MAFLD, as well as in cardiovascular diseases, cancers, and endocrine diseases.[32–35] Thus, these observations emphasize the need for a more comprehensive differential diagnosis and more aggressive etiological treatment when feasible.

Of note, our study observed a further increase in the level of ALP and/or GGT after treatment targeting primary diseases in some cases, especially in patients with MAFLD. The co-existence of PBC and MAFLD has been reported,[36,37] with the prevalence of positive AMA in MAFLD patients ranging from 1% to 4%.[30,38,39] Additionally, over three-quarters of PBC patients may present with dyslipidemia due to cholestasis,[40] although the degree of hepatic steatosis is comparatively lower in PBC patients than in those with CHB, CHC, and MAFLD.[41,42] Therefore, distinguishing PBC from MAFLD can be tricky since they share certain clinical characteristics, and not all AMA-positive patients with MAFLD will develop PBC. A liver biopsy or close monitoring is required to promptly identify the development of PBC in this specific setting.

Our study had several limitations. Firstly, it was a single-

center study with a relatively small number of patients. Secondly, the prevalence of histological PBC may be underestimated due to the limited number of patients who underwent liver biopsy. Thirdly, being a retrospective study, it was difficult to assess the persistence of PBC-specific antibodies in all patients. However, we did observe a decrease in antibody titers to normal levels in some patients as liver function tests improved. Also, in our study, IIF was used for AMA detection, which could result in false-positive results due to the multi-organ origins of AMA. However, most patients were positive for AMA with high titers, which may partially compensate for the limitations of this detection method.

In conclusion, patients with positive PBC-specific antibodies and elevated ALP and GGT levels may present with non-PBC liver diseases and non-liver diseases. Careful searching and proper treatment of the underlying etiology can improve or even normalize their cholestatic biochemistry profiles.

Funding

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Conflict of interest

JJ has been an Executive Associate Editor of *Journal of Clinical and Translational Hepatology* since 2013, HY has been an Editorial Board Member of *Journal of Clinical and Translational Hepatology* since 2021. The other authors have no conflict of interests related to this publication.

Author contributions

Study design (XZ, TL, WD, JJ), performance of experiments (XZ, TL), analysis and interpretation of data (XZ, TL), manuscript writing (XZ, TL), critical revision (WD, JJ, YW, XO, XZ, HY), technical or material support (SL, SC, BL, ZL, YW, XO, XZ, HY). All authors have made significant contributions to this study and have approved the final version and publication of the manuscript.

Ethical statement

The study protocol was approved by the Ethics Committee of Beijing Friendship Hospital, Capital Medical University (Ethic no: BFH20231219003), adhered to the principles outlined in the Declaration of Helsinki. Verbal informed consent was obtained from all participants.

Data sharing statement

Data supporting the findings of this study are available from the corresponding authors upon reasonable request.

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