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The *WJG* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports, Index Medicus, MEDLINE, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJG* as 4.3; Quartile category: Q2. The *WJG*'s CiteScore for 2021 is 8.3.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Ying-Yi Yuan*; Production Department Director: *Xu Guo*; Editorial Office Director: *Jia-Ru Fan*.

NAME OF JOURNAL

World Journal of Gastroenterology

ISSN

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

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PUBLICATION DATE

September 14, 2023

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PUBLISHING PARTNER

Pancreatic Cancer Institute, Fudan University

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<https://www.wjgnet.com/bpg/gerinfo/204>

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<https://www.wjgnet.com/bpg/GerInfo/288>

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<https://www.wjgnet.com/bpg/GerInfo/310>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

PUBLISHING PARTNER'S OFFICIAL WEBSITE

<https://www.shca.org.cn/>

Retrospective Study

Role of biochemical markers and autoantibodies in diagnosis of early-stage primary biliary cholangitis

Yu-Jin Zhu, Jing Li, Yong-Gang Liu, Yong Jiang, Xiao-Jing Cheng, Xu Han, Chun-Yan Wang, Jia Li

Specialty type: Gastroenterology and hepatology**Provenance and peer review:**

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind**Peer-review report's scientific quality classification**Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0**P-Reviewer:** Filipic Kanizaj T, Croatia; Granito A, Italy**Received:** June 4, 2023**Peer-review started:** June 4, 2023**First decision:** June 21, 2023**Revised:** July 15, 2023**Accepted:** August 25, 2023**Article in press:** August 25, 2023**Published online:** September 14, 2023**Yu-Jin Zhu, Jing Li**, Graduate School, Tianjin Medical University, Tianjin 300041, China**Yong-Gang Liu**, Department of Pathology, Clinical School of the Second People's Hospital, Tianjin 300110, China**Yong Jiang**, Department of Gastroenterology, The Second Hospital of Tianjin Medical University, Tianjin 300211, China**Xiao-Jing Cheng, Xu Han, Chun-Yan Wang, Jia Li**, Department of Gastroenterology, Clinical School of the Second People's Hospital, Tianjin 300110, China**Corresponding author:** Chun-Yan Wang, Doctor, Chief Doctor, Department of Gastroenterology, Clinical School of the Second People's Hospital, No. 7 Sudi South Road, Nankai District, Tianjin 300110, China. wangchunyan123@tmu.edu.cn**Abstract****BACKGROUND**

Primary biliary cholangitis (PBC) is a chronic progressive autoimmune cholestatic disease. The main target organ of PBC is the liver, and nonsuppurative inflammation of the small intrahepatic bile ducts may eventually develop into cirrhosis or liver fibrosis.

AIM

To explore the clinical characteristics of early-stage PBC, identify PBC in the early clinical stage, and promptly treat and monitor PBC.

METHODS

The data of 82 patients with PBC confirmed by pathology at Tianjin Second People's Hospital from January 2013 to November 2021 were collected, and the patients were divided into stage I, stage II, stage III, and stage IV according to the pathological stage. The general data, serum biochemistry, immunoglobulins, and autoimmune antibodies of patients in each stage were retrospectively analyzed.

RESULTS

In early-stage (stages I + II) PBC patients, 50.0% of patients had normal alanine aminotransferase (ALT) levels, and 37.5% had normal aspartate aminotransferase (AST) levels. For the remaining patients, the ALT and AST levels were mildly elevated; all of these patients had levels of < 3 times the upper limit of normal

values. The AST levels were significantly different among the three groups (stages I + II *vs* stage III *vs* stage IV, $P < 0.05$). In the early stage, 29.2% of patients had normal alkaline phosphatase (ALP) levels. The remaining patients had different degrees of ALP elevation; 6.3% had ALP levels > 5 times the upper limit of normal value. Moreover, γ -glutamyl transferase (GGT) was more robustly elevated, as 29.2% of patients had GGT levels of > 10 times the upper limit of normal value. The ALP values among the three groups were significantly different ($P < 0.05$). In early stage, the jaundice index did not increase significantly, but it gradually increased with disease progression. However, the above indicators were significantly different ($P < 0.05$) between the early-stage group and the stage IV group. With the progression of the disease, the levels of albumin and albumin/globulin ratio tended to decrease, and the difference among the three groups was statistically significant ($P < 0.05$). In early-stage patients, IgM and IgG levels as well as cholesterol levels were mildly elevated, but there were no significant differences among the three groups. Triglyceride levels were normal in the early-stage group, and the differences among the three groups were statistically significant ($P < 0.05$). The early detection rates of anti-mitochondria antibody (AMA) and AMA-M2 were 66.7% and 45.8%, respectively. The positive rate of anti-sp100 antibodies was significantly higher in patients with stage IV PBC. When AMA and AMA-M2 were negative, in the early stage, the highest autoantibody was anti-nuclear antibody (ANA) (92.3%), and in all ANA patterns, the highest was ANA centromere (38.5%).

CONCLUSION

In early-stage PBC patients, ALT and AST levels are normal or mildly elevated, GGT and ALP levels are not elevated in parallel, GGT levels are more robustly elevated, and ALP levels are normal in some patients. When AMA and AMA-M2 are negative, ANA especially ANA centromere positivity suggests the possibility of early PBC. Therefore, in the clinic, significantly elevated GGT levels with or without normal ALP levels and with ANA (particularly ANA centromere) positivity (when AMA and AMA-M2 are negative) may indicate the possibility of early PBC.

Key Words: Primary biliary cholangitis; Early stage; Biochemical makers; Autoantibodies; Pathology

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Core Tip: This is a retrospective study of the characteristics of early-stage primary biliary cholangitis (PBC) patients, in which we found the suggestive role of γ -glutamyl transferase as an indicator of cholestasis in the early diagnosis of PBC. We also found that when anti-mitochondria antibody (AMA) and AMA-M2 were negative, positivity for anti-nuclear antibody (ANA) especially ANA centromere indicates early-stage PBC.

Citation: Zhu YJ, Li J, Liu YG, Jiang Y, Cheng XJ, Han X, Wang CY, Li J. Role of biochemical markers and autoantibodies in diagnosis of early-stage primary biliary cholangitis. *World J Gastroenterol* 2023; 29(34): 5075-5081

URL: <https://www.wjgnet.com/1007-9327/full/v29/i34/5075.htm>

DOI: <https://dx.doi.org/10.3748/wjg.v29.i34.5075>

INTRODUCTION

Primary biliary cholangitis (PBC) is a chronic progressive autoimmune cholestatic disease. The main target organ of PBC is the liver, and nonsuppurative inflammation of the small intrahepatic bile ducts may eventually develop into cirrhosis or liver fibrosis[1]. Currently, patients who are diagnosed and treated early respond well to ursodeoxycholic acid (UDCA) and have an estimated survival rate similar to that of the general population. Based on this, we retrospectively analyzed the data of patients with PBC in our hospital, aiming to analyze the biochemical parameters and autoimmune antibody characteristics of patients with early PBC to help identify early-stage PBC, actively treat this condition, and delay disease progression.

MATERIALS AND METHODS

Study design and sample collection

This retrospective observational study was conducted at the Clinical School of the Second People's Hospital. Patients were included if they met the following criteria: (1) Confirmed PBC (detected by "APASL clinical practice guidance: The diagnosis and management of patients with primary biliary cholangitis"). The diagnosis of PBC can be established when two or more of the following three criteria are met: (a) Biochemical evidence of cholestasis based mainly on the elevation of alkaline phosphatase (ALP) and gamma glutamyl transferase (GGT) with the exclusion of extrahepatic biliary

obstruction by imaging studies; (b) presence of anti-mitochondria antibody (AMA) or other PBC-specific anti-nuclear antibodies (ANAs) including anti-sp100 or anti-gp210; and (c) histologic evidence of non-suppurative destructive cholangitis mainly affecting the interlobular bile ducts; (2) underwent liver pathology biopsy and had a clear pathological stage; (3) initially diagnosed with PBC; and (4) were not previously treated with UDCA. Exclusion was based on the following criteria: (1) Various liver tumors; (2) other autoimmune diseases; (3) alcoholic liver disease, nonalcoholic fatty liver disease, and drug-induced liver injury; (4) active viral hepatitis; (5) obstructive cholestasis; (6) repeated liver biopsy; (7) incomplete information; (8) no defined pathological stage; (9) long-term application of UDCA; and (10) rejected liver biopsy (Figure 1).

Serological analysis

For the detection of ANA, a Hep-2 kit was used, according to standard indirect immunofluorescence (IIF) protocols. Each serum sample was investigated at a starting dilution of 1:100 and titrated to zero positive; samples with positive IIF at a titer $\geq 1:100$ were deemed positive. Line immunoassay was used to detect AMA (M2), anti-sp100, and anti-gp210. According to Hep-2 cell patterns, ANAs were divided into nuclear (including homogeneous, cytoplasmic speckled, nucleolar, centromere, discrete, and nuclear) and cytoplasmic (including fibrillar, cytoplasmic speckled, and reticular)[2]. Pathology readings were performed by two experienced pathologists and at least one chief pathologist.

Statistical analysis

The data were analyzed with SPSS 25.0 software. Normally distributed data were analyzed by ANOVA and are expressed as the mean \pm SD. Nonnormally distributed data were analyzed by the rank sum test and are expressed as medians and ranges. Count data are expressed as the number of subjects and percentages and were compared using the chi-square test. A difference was considered statistically significant at $P < 0.05$.

RESULTS

Comparison of general information among different groups

The age distribution of PBC patients ranged from 33-71 years, with an average age of 53.7 ± 8.9 years. The mean age in the three stage groups (stages I + II, stage III, and stage IV) was 52.4 ± 9.2 years, 57.7 ± 7.3 years, and 51.5 ± 8.7 years, respectively. The 82 patients with PBC were predominantly female (68/82), and the number of females in the three stage groups was 38, 20 and 10, respectively. There were no statistically significant differences in the mean age or sex proportion among the groups ($P > 0.05$).

In early-stage patients ($n = 48$), 18 (37.5%) patients did not have significant symptoms. The major symptoms of patients were gastrointestinal symptoms (including abdominal discomfort, pain, bloating, and nausea), fatigue, yellow urine, and pruritus.

Comparison of biochemical and immunological indicators among the three groups

The alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were normal or mildly increased in the early-stage PBC patients, and an increasing trend with the progression of the pathological stage was observed. Furthermore, the AST levels were significantly different among the three groups ($P < 0.05$). There were significant differences in total bilirubin (TBIL), direct bilirubin (DBIL), and total bile acid (TBA) levels among the three groups of PBC patients ($P < 0.05$), and the difference between the early stage group and stage IV group was statistically significant ($P = 0.002, 0.003, \text{ and } 0.009$, respectively). With pathological progression, a decreasing trend for albumin and albumin/globulin levels was observed, and there were statistically significant differences among the three groups and between the early stage group and stage IV group ($P = 0.005 \text{ and } 0.001$, respectively). ALP and GGT levels were trending toward an increase. While 29.2% of patients had normal ALP levels, the remaining patients had different degrees of elevation. For 6.3% of the patients, the ALP levels were elevated to > 5 times the upper limit of normal value. The elevation in GGT levels was more robust, as 29.2% of patients had elevated GGT levels of > 10 times the upper limit of normal value. The difference of ALP levels among the three groups was statistically significant ($P < 0.05$), and there was a statistically significant difference between the early stage group and stage IV group ($P = 0.006$). Triglyceride levels gradually decreased with the progression of the disease, and the differences among the different groups were statistically significant ($P < 0.05$). Cholesterol (CHO) levels showed an increasing tendency. CHO levels gradually increased but were not significantly different among the three groups. IgG, IgA, and IgM all showed an increasing trend with disease progression. IgG and IgM were predominantly elevated, while IgA and complement (C)3 and C4 were normal in the early stage. The IgA levels were significantly different among the three groups ($P < 0.05$) (Table 1).

Autoantibody levels in different groups of patients with PBC

The positive rates of AMA, AMA-M2, anti-sp100, and anti-gp210 were 52 (63.4%), 40 (48.8%), 16 (19.5%), and 13 (15.9%), respectively. The positive rate of ANA was 62 (75.6%). Cytoplasmic speckled pattern had the highest rate of 48.8%, and this was followed by nuclear pattern at 23.2% and centromere pattern at 15.9%. The positive rate of AMA-M2 significantly differed among the three groups ($P = 0.045$), but the remaining autoantibodies were not significantly different ($P > 0.05$). In early-stage PBC patients, 32 patients were positive for AMA, 22 positive for AMA-M2, 8 positive for anti-sp100, and 9 positive for anti-gp210 (Table 2). Thirty-four patients were positive for ANA, of which 24 had cytoplasmic speckled pattern, 10 had nuclear pattern, and 6 had centromere pattern (Table 3).

Table 1 Clinical and laboratory data of patients with primary biliary cholangitis

	Early-stage (stages I + II; n = 48)	Stage III (n = 22)	Stage IV (n = 12)	P value
ALT	53.5 (29.5-124.5)	54.0 (30.0-127.6)	80.0 (42.8-127.4)	0.639
AST	53.5 (34.0-97.3) ^a	68.5 (39.6-114.1)	112.2 (81.1-136.3)	0.009
TBA	9.0 (3.6-36.4) ^a	18.0 (7.0-45.1)	28.2 (18.0-111.5)	0.011
TBIL	15.4 (11.2-27.8) ^a	16.7 (13.7-24.2) ^a	61.2 (28.1-114.3)	0.002
DBIL	5.2 (3.7-16.0) ^a	8.7 (2.5-12.4) ^a	42.3 (15.8-67.3)	0.003
ALB	42.1 (38.3-44.8) ^a	39.3 (36.5-42.5)	35.8 (30.5-41.0)	0.005
A/G	1.2 (1.1-1.4) ^a	1.0 (0.9-1.3)	0.9 (0.7-1.1)	0.001
ALP	200.4 (117.8-414.0) ^a	292.5 (162.0-421.3)	463.5 (329.6-770.5)	0.008
GGT	289.0 (133.0-668.8)	532.0 (326.5-764.3)	336.5 (264.0-648.0)	0.070
CHO	5.8 (4.6-6.9)	6.2 (5.1-7.5)	6.8 (4.9-7.0)	0.509
TG	1.3 (1.0-1.8)	1.6 (1.2-2.1) ^a	1.1 (0.8-1.5)	0.019
IgG	16.7 ± 4.6	17.6 ± 6.7	20.6 ± 7.9	0.056
IgA	2.9 (2.1-3.3)	3.5 (2.5-4.7)	3.4 (2.4-4.4)	0.031
IgM	3.4 (1.8-5.1)	3.7 (2.1-5.0)	3.7 (1.9-6.8)	0.967
C3	1.4 (1.2-1.6)	1.6 (1.3-1.8)	1.2 (1.0-1.7)	0.126
C4	0.2 (0.2-0.3)	0.2 (0.2-0.3)	0.2 (0.2-0.3)	0.963

^a*P* < 0.05 indicates statistically significant difference compared to stage IV.

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TBA: Total bile acid; ALP: Alkaline phosphatase; GGT: γ -glutamyl transferase; ALB: Albumin; A/G: Albumin/globulin; TBIL: Total bilirubin, DBIL: Direct bilirubin; CHO: Cholesterol; TG: Triglycerides; IgG: Immunoglobulin G; IgM: Immunoglobulin M; IgA: Immunoglobulin A; C3: Complement 3; C4: Complement 4.

Table 2 Autoantibody positive rate in patients with early-stage primary biliary cholangitis

Autoantibody	AMA	AMA-M2	Anti-sp100	Anti-gp210	Anti-SSA/Ro52	Anti-SSA/Ro60	ANA
<i>n</i>	32	22	8	9	8	2	34
%	66.7	45.8	16.7	18.8	16.7	4.2	70.8

AMA: Anti-mitochondria antibody; ANA: Anti-nuclear antibody.

Table 3 Anti-nuclear antibody subtype positive rate in patients with early-stage primary biliary cholangitis

ANA	Cytoplasmic speckled	Fibrillar	Reticular	Discrete	Homogeneous	Centromere	Nuclear speckled	Nucleolar	Nuclear
<i>n</i>	24	2	6	7	1	6	5	0	10
%	50	4.2	12.5	14.6	2.1	12.5	10.4	0	20.8

ANA: Anti-nuclear antibody.

Analysis of other autoantibodies detected when AMA and AMA-M2 are negative

There were 25 PBC patients negative for both AMA and AMA-M2. These included 13 patients in the early stage, 6 patients in stage III, and 6 patients in stage IV. The autoantibody positive rates among the three groups were not significantly different (*P* > 0.05). In early-stage AMA- and AMA-M2-negative patients, the positive rate was highest for ANA (92.3%), followed by anti-SSA/RO52 (23.1%) and anti-sp100 (15.3%). In all ANA patterns, the highest was ANA centromere (38.5%).

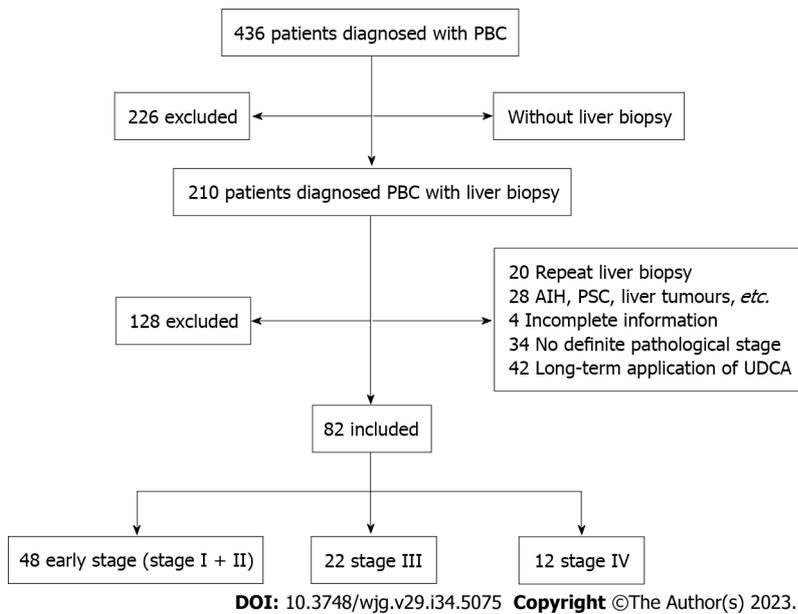


Figure 1 Participant flow in the study. AIH: Autoimmune hepatitis; PSC: Primary sclerosing cholangitis; PBC: Primary biliary cholangitis; UDCA: Ursodeoxycholic acid.

DISCUSSION

PBC occurs mainly in middle-aged women, and the common clinical presentations are fatigue, splenomegaly, jaundice, and pruritus[1]. PBC may take 10-15 years to develop from the onset of illness to the symptomatic stage. Early diagnosis and treatment can improve the survival and quality of life of patients. In the early stage of PBC, patients have no obvious symptoms, but most patients have liver fibrosis or cirrhosis when they are diagnosed. Therefore, to improve PBC patient prognosis, early diagnosis and treatment are essential.

In this study, we found that GGT levels were significantly elevated in early-stage patients (29.2% of patients had elevated levels of > 10 times the upper limit of normal value) and tended to increase with the progression of illness. A study from Switzerland found elevated GGT levels in 15 of 24 PBC patients with normal ALP levels and liver biopsy results, and GGT levels were elevated in 13 patients who had early Nakanura stage histology. These findings suggest that elevated GGT levels have potential diagnostic value in PBC patients with normal ALP levels[3]. Reportedly, elevated GGT levels are closely related to the inflammation caused by fat deposition[4]. GGT is a key factor in maintaining the activity of reduced glutathione (GSH), which is an important antioxidant in the body. GGT is also involved in the production of GSH, which plays a cytoprotective role in inflammation and when an inflammatory response occurs[5]. In contrast to the levels of GGT, the levels of the cholestasis indicator ALP are not significantly elevated, and some PBC patients have normal ALP levels. Elevated ALP levels may be due to increased intracapillary pressure or to bile acids dissolving ALP from the lipid membrane into the blood[6]. A study of 67 patients with normal ALP levels and AMA positivity who underwent liver puncture biopsies found that 55 of these cases had pathology consistent with characteristic PBC presentation. Of these 55 patients, 50 were in the early stage[7]. In our study, we found that the elevation of GGT levels was more pronounced in patients with early-stage disease, which may be related to early chronic inflammation, excessive GSH depletion, and a compensatory increase in GGT.

We found that most patients had normal or mildly elevated ALT and AST levels in the early stage, and these levels increased with disease progression. These findings suggest that the degree of hepatocellular damage gradually increases. Alternatively, TBA, TBIL, and DBIL levels were not significantly elevated in the early stage but gradually increased with disease progression. In stage IV, TBIL and DBIL levels were significantly elevated, and DBIL levels were robustly elevated. This may be due to most of the hepatic parenchyma being damaged. In this study, IgM levels were predominantly elevated in early-stage PBC patients, which is consistent with previous studies[8]. A rise in IgM levels may be caused by a strong IgM secretory capacity and cellular autophagy[9].

AMA and AMA-M2 may be detectable in serum when patients are symptom-free and liver tests are normal, and they are highly specific autoantibodies for PBC. In recent years, with the development of detection methods, anti-sp100 and anti-gp210 have already been identified as PBC-specific autoantibodies. In a retrospective study of 4371 patients from Italy, the specificity of anti-sp100 and anti-gp210 for PBC was confirmed, especially in AMA-negative patients[10]. However, the reported positive rates vary widely across regions. The differences in antibody positive rates among regions could be due to different patient selection criteria and differences in technical and genetic backgrounds. In our study, the autoantibody rates of all patients were as follows: AMA, 63.4%; AMA-M2, 48.8%; and anti-gp210, 15.9%. These rates are lower than those reported in previous studies[11,12]. We found that the positive rate of anti-sp100 was 19.5%, and the positive rate of ANA was 75.6%. These rates are higher than those in other reports. One possible explanation for this is that our study did not adopt random sampling, but only patients with PBC confirmed by liver biopsy were included. This may be the main reason why the autoantibody positive rates in this study are lower than those in other

studies. The positive rates of AMA, AMA-M2, and anti-gp210 in early-stage patients with PBC were 66.7%, 45.8%, and 18.8%, respectively, which were similar to the rates of all PBC patients. The positive rate of anti-sp100 was significantly higher in stage IV PBC patients.

The number of AMA- and AMA-M2-negative PBC patients was 25, of which 13 (86.7%) were in the early stage. In early-stage AMA- and AMA-M2-negative patients, the positive rate of ANA was highest (92.3%). In all ANA patterns, the highest was ANA centromere (38.5%), which decreased with the progression of the disease. However, there were no significant differences in this parameter among the three groups ($P > 0.05$). In this article, we summarized available data on the characteristics of ANA patterns. We should be aware of the possibility of unexplained elevations in serum markers for cholestasis in AMA(M2)-negative patients, but ANA, especially centromere pattern, was positive in early-stage patients. Although those ANAs are not specific for PBC diagnostic purposes, they can still be used as auxiliary markers to reduce the rate of missed diagnoses when AMA(M2) is negative. A previous study reported that ANA centromere was almost exclusively limited to PBC patients. Thus, this antibody can still be used as an auxiliary marker to reduce the rate of missed diagnoses when AMA(M2) is negative[12].

CONCLUSION

In summary, in early-stage PBC patients, ALT and AST levels are normal or mildly elevated, GGT and ALP levels are not elevated in parallel, GGT levels are more robustly elevated, and ALP levels are normal in some patients. When AMA and AMA-M2 are negative, ANA (especially ANA centromere) positivity suggests the possibility of early PBC. Therefore, in the clinic, significantly elevated GGT levels with or without normal ALP levels and with ANA (particularly ANA centromere) positivity (when AMA and AMA-M2 are negative) may indicate the possibility of early PBC.

This study is a retrospective study with limited inclusion. Thus, it adopted nonrandom sampling with some bias. Further studies should be conducted in the future to expand the sample size and to follow up on the prognosis of patients with early-stage PBC after treatment with UDCA.

ARTICLE HIGHLIGHTS

Research background

The long course and insidious symptoms of primary biliary cholangitis (PBC) make it difficult to diagnose in the early stage.

Research motivation

To analyze clinical features and autoantibodies in patients with early-stage PBC.

Research objectives

To improve the diagnosis rates of early-stage PBC.

Research methods

We included 82 patients with PBC diagnosed by liver pathology with clear pathologic stage and divided them into three groups to compare their laboratory parameters and autoantibody positivity.

Research results

In early-stage PBC patients, alanine aminotransferase and aspartate aminotransferase levels were normal or mildly elevated, gamma glutamyl transferase (GGT) and alkaline phosphatase (ALP) levels were not elevated in parallel, GGT levels were more robustly elevated, and ALP levels were normal in some patients. When anti-mitochondria antibody (AMA) and AMA-M2 were negative, anti-nuclear antibody (ANA) (especially ANA centromere) positivity suggests the possibility of early-stage PBC.

Research conclusions

We found that GGT is elevated significantly and earlier in the early-stage PBC group. ANA and associated-ANA subtypes can be used as second-line markers for the diagnosis of early-stage PBC (particularly when specific autoantibodies are negative).

Research perspectives

We hope that this study will increase the rates of diagnosis of early-stage PBC by clinicians.

FOOTNOTES

Author contributions: Zhu YJ wrote the manuscript; Zhu YJ, Cheng XJ, and Han X contributed to data collation; Zhu YJ and Li J

contributed to statistical analysis; Liu YG contributed to liver pathology reading; Jiang Y, Wang CY, and Li J contributed to manuscript revision; Wang CY and Li J contributed to research supervision; Wang CY contributed to project design.

Institutional review board statement: The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the local Ethics Committee (Clinical School of the Second People's Hospital of Tianjin).

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: All authors have no conflict of interest to disclose.

Data sharing statement: The data underlying this article can be available in this article and in its online supplementary material or from the first author.

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Country/Territory of origin: China

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S-Editor: Yan JP

L-Editor: Wang TQ

P-Editor: Yan JP

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