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PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 86171

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

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03537165
Position: Editorial Board
Academic degree: PhD
Professional title: Associate Professor
Reviewer's Country/Territory: Croatia
Author's Country/Territory: China

Manuscript submission date: 2023-06-04

Reviewer chosen by: AI Technique

Reviewer accepted review: 2023-06-19 14:50

Reviewer performed review: 2023-06-19 15:30

Review time: 1 Hour

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation

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Scientific significance of the conclusion in this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No scientific significance
Language quality	[ ] Grade A: Priority publishing [ ] Grade B: Minor language polishing [Y] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [ ] Anonymous [Y] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

This article represents cross-sectional study which evaluates the clinical characteristics of early-stage primary biliary cholangitis (PBC). While a liver biopsy is often not required to make the diagnosis, the main advantage of the study is the existence of histological findings that indicate the stage of PBC. The study found a higher proportion of patients with negative findings of antimitochondrial antibodies and ALP than is described in the literature (36,59 vs 5% and 29,1% vs < 5%). How do the authors explain it? Is it the effect of the studied population? What diagnostic criteria were used in the study (histological findings?, positive AMHA findings? and/or ALP level >= 1.5 UNL)? Anti-centromere antibodies are present in approximately 15 percent of patients with PBC and such patients tend to have a worse outcome. How the authors explain the correlation of anti-centromere antibodies and severity of liver disease? The title, abstract, manuscript organization, discussion, tables and references are appropriate. Language requires significant polishing to achieve precision, clarity and grammatical correctness.

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Reviewer's code: 00028182
Position: Peer Reviewer
Academic degree: MD

Professional title: Associate Professor, Doctor

Reviewer's Country/Territory: Italy

Author's Country/Territory: China

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Review time: 67 Days and 3 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[Y] Grade A: Excellent [ ] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[Y] Grade A: Excellent [ ] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation

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Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

In this retrospective study, the authors explored the characteristics of patients in the early-stage PBC and found that in 82 patients with PBC confirmed by pathology serum levels of GGT as an indicator of cholestasis in the early diagnosis of PBC. They also found that when AMA and AMA-M2 are negative, the positivity rate of the ANA Centromere is the highest in the early-stage. In particular, they found that in early-stage (stage I+II) PBC patients, 50.00% of patients had normal ALT levels, and 37.50% had normal 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 ($P < 0.05$). In early-stage, 29.17% of patients had normal ALP levels. The rest of the patients had different degrees of elevated ALP; 6.25% had elevated ALP >5 times the upper limit of normal value. Moreover, γ-GGT was more robustly elevated, as 29.17% of patients had elevated γ-GGT levels of >10 times the upper limit of normal value. The ALP value comparison among the three groups was statistically significant ($P <0.05$). The detection rate of an antibody against the Cytoplasmic Speckled was the highest at 50.00%. The

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positivity rate for anti-sp100 antibodies was significantly higher in patients with stage IV PBC. When AMA and AMA-M2 were negative, the highest positivity rate (38.46%) was found for the ANA Centromere. They concluded that significantly elevated GGT levels with or without normal ALP levels and with ANA Centromere positivity（when AMA and AMA-M2 are negative) may indicate the possibility of early PBC. The study is of interest as it focused on the early stage of PBC and early diagnosis allows prompt treatment thus avoiding disease progression. However, the authors should further report additional informations. -Serological analysis: the authors considered positive a titter ≥1:100. However, autoantibody standardized positivity is at titer ≥ 1:40 or 1≥80. The authors therefore, should further specify the autoantibody procedure (commercial kit? in-house protocol?). -The most important finding of this study is the role af autoantibodies since geographical differences in autoantibodies prevalence and autoimmune disease features do exist and it is of major relevance to describe such a information. A comparison with previous studies demonstrating the diagnostic role of antinuclear antibodies as surrogate markers of AMA for the diagnosis of PBC, should be discussed, as previously reported (Antinuclear antibodies giving the 'multiple nuclear dots' or the 'rim-like/membranous' patterns: diagnostic accuracy for primary biliary cirrhosis. Aliment Pharmacol Ther. 2006 Dec;24(11-12):1575-83. doi: 10.1111/j.1365-2036.2006.03172.x.; Antinuclear antibodies as ancillary markers in primary biliary cirrhosis. Expert Rev Mol Diagn. 2012 Jan;12(1):65-74. doi: 10.1586/erm.11.82.) -Regarding the diagnostic role of anti-centromere, a previous study demonstrated also a prognostic role of such a autoantobody and should be recalled (Antibodies to SS-A/Ro-52kD and centromere in autoimmune liver disease: a clue to diagnosis and prognosis of primary biliary cirrhosis. Aliment Pharmacol Ther. 2007 Sep 15;26(6):831-8. doi: 10.1111/j.1365-2036.2007.03433.x.). -Lastly, autoantibodies to speckled proteins have been widely described as additional diagnostic markers of PBC, as

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recently summarized (Autoantibodies to speckled protein family in primary biliary cholangitis. Allergy Asthma Clin Immunol. 2021 Mar 31;17(1):35. doi: 10.1186/s13223-021-00539-0). -reference 13 is related to hepatocellular carcinoma. Please modify if not appropriate. ere the authors aimed to explore the clinical characteristics of early-stage primary biliary cholangitis (PBC). They studied data of 82 patients with PBC confirmed by pathology 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. They found that in early-stage (stage I+II) PBC patients, 50.00% of patients had normal ALT levels, and 37.50% had normal 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 ($P < 0.05$). In early-stage, 29.17% of patients had normal ALP levels. The rest of the patients had different degrees of elevated ALP; 6.25% had elevated ALP >5 times the upper limit of normal value. Moreover, γ-GGT was more robustly elevated, as 29.17% of patients had elevated γ-GGT levels of >10 times the upper limit of normal value. The ALP value comparison among the three groups was statistically significant ($P <0.05$). With the progression of the disease, the levels of ALB and A/G tended to decrease, and the difference between the three groups was statistically significant ($P<0.05$). In early-stage patients, IgM and IgG levels were mildly elevated, and CHO levels were mildly elevated. However, there were no significant differences among the three groups. TG 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 AMA and AMA-M2 were detected at a high rate of 66.67% and 45.83%, 3 respectively. The detection rate of an antibody against the Cytoplasmic Speckled was the highest at 50.00%. The positivity rate for anti-sp100 antibodies was

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significantly higher in patients with stage IV PBC. When AMA and AMA-M2 were negative, the highest positivity rate (38.46%) was found for the ANA Centromere. They concluded that in early-stage PBC patients, ALT and AST levels were normal or mildly elevated, GGT and ALP levels were not elevated in parallel, GGT levels were more robustly elevated, and some ALP levels were normal. When AMA and AMA-M2 are negative, the positivity rate of the ANA Centromere is the highest. Therefore, in the clinic, significantly elevated GGT levels with or without normal ALP levels and with ANA Centromere positivity（when AMA and AMA-M2 are negative） may indicate the possibility of early PBC. The study has interesting findings, however, some additional informations are required. 1) Histology: how histology was assessed. Experienced pathologist? this is a very important point as early stage of PBC may be not particularly evident for not experienced pathologist. 2) serological markers / autoantibodies: the authors should recall and discuss the diagnostic role of the so-called PBBC-specific antinuclear antibodies in PBC patients who are AMA negative or low-titer of AMA as previously described in previous studies demonstrating the diagnostic accuracy of rim-like ANA and multiple nuclear dots ANA in a very large studies performed in more than 4000 patients (Antinuclear antibodies giving the 'multiple nuclear dots' or the 'rim-like/membranous' patterns: diagnostic accuracy for primary biliary cirrhosis. Aliment Pharmacol Ther. 2006 Dec;24(11-12):1575-83. doi: 10.1111/j.1365-2036.2006.03172.x.), as confirmed in other similar studies well-summarized in a comprehensive review (Antinuclear antibodies as ancillary markers in primary biliary cirrhosis. Expert Rev Mol Diagn. 2012 Jan;12(1):65-74. doi: 10.1586/erm.11.82.). 3) the diagnostic and prognostic role of anti-centromere antibodies has been previously demonstrated also in other geographical area and should be recalled as previously demonstrated (Antibodies to SS-A/Ro-52kD and centromere in autoimmune liver disease: a clue to diagnosis and prognosis of primary biliary cirrhosis.

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