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Diagnostic value of anti-hexokinase 1 and anti-kelch-like 12 antibodies in primary biliary cholangitis patients

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Abstract

Objectives: Anti-mitochondrial antibody (AMA) is not always present in patients with primary biliary cholangitis (PBC). We aimed to determine the additional value of anti-hexokinase 1 (anti-HK1) and anti-kelch-like 12 (anti-KLHL12) antibody in PBC and analyzed the biochemical and immunological parameters of 212 subjects, including PBC patients and healthy controls.
Methods: Serum anti-gp210 and sp100 antibodies were determined by an immunoblotting test (IBT). Enzyme-linked immunosorbent assay (ELISA) was employed to evaluate anti-HK1 and anti-KLHL12. The diagnostic value of anti-HK1 and anti-KLHL12 to PBC was analyzed by constructing a receiver operating characteristic (ROC) curve.
Results: ROC analyses didn't show a very good performance of serum anti-HK1 for PBC diagnosis; the AUC was 0.664 with a sensitivity of 53.3 % and a specificity of 79.2 %. Regarding anti-KLHL12, ROC analysis yielded an AUC of 0.626, with a sensitivity of 45.7 % and a specificity of 93.8 %. For AMA-negative PBC patients, the AUC increased to 0.790 for KLHL12, and 0.708 for HK1. AMA combined with anti-HK1 or anti-KLHL12 antibody significantly improved the diagnostic sensitivity of PBC from 82 to about 95 %, respectively. In AMA-negative PBC patients, the sensitivities for anti-HK1 (62.50 %) and anti-KLHL12 (75 %) antibodies were higher than for anti-gp210 (37.5 %) and anti-sp100 antibody (43.75 %). When these four antibodies were combined, the overall sensitivity increased to 87.5 %.
Conclusions: The determination of anti-HK1 and anti-KLHL12 facilitates the diagnosis of PBC, particularly in AMA-negative patients. Adding anti-HK1 and anti-KLHL12 antibodies to clinical detection enables early diagnosis and timely treatment, potentially improving patient prognosis.

Keywords: anti-hexokinase 1 antibody; anti-kelch-like 12 antibody; diagnosis; primary biliary cholangitis

Introduction

Primary biliary cholangitis (PBC), formerly known as primary biliary cirrhosis, is a prevalent autoimmune liver disease that predominantly affects middle-aged women [1]. This disease is characterized by a chronic immune-driven destruction of the small bile duct, resulting in histopathological evidence of granulomatous lymphocytic cholangitis [2]. Approximately 40 % of PBC patients are asymptomatic at presentation, with symptoms such as hepatomegaly, splenomegaly, fatigue, and pruritus often appearing at an advanced histological stage when the prognosis is poor [3]. However, even patients with fully developed liver cirrhosis may be free of symptoms. Previous studies have shown that early treatment with ursodeoxycholic acid (UDCA) was more effective for the maintenance of early-stage PBC [4], nearly 40 % of patients who received an early PBC diagnosis and promptly started UDCA treatment; and remained in the early stage even 20 years after diagnosis [5]. Thus, early diagnosis of PBC is of great clinical importance.

Anti-mitochondrial antibodies (AMA) represent the seroimmunological hallmark and diagnostic tool for PBC due to its high specificity and sensitivity. AMA positivity has been considered to be a serological biomarker for preclinical PBC, even in individuals without clinical or biochemical signs of cholestasis [6]. However, AMA were found to be absent in 10–40 % of PBC patients [7], and they are also present in other diseases [8–11]. Antibodies that target specific nuclear antigens associated with PBC, such as anti-gp210 and anti-sp100, exhibit higher specificity but lower sensitivity [12, 13]. Several PBC

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patients have been diagnosed without manifesting positivity to the aforementioned auto-antibodies [14, 15]. Two novel antibodies, anti-HK1, and anti-KLHL12, that target hexokinase-1 and Kelch-like 12 protein, respectively, have been discovered, and they appear to be highly prevalent and specific for PBC [16, 17]. Using the combination of anti-KLHL12 and anti-HK1 with other available serological biomarkers in AMA-negative individuals significantly improves the effectiveness of clinical detection and diagnosis [16]. Despite their availability, the application of these two novel antibodies remains limited in clinical practice, and there are few reports as to their relevance in the diagnosis of PBC in the Chinese population. Consequently, it is crucial to determine the importance of the serological measurement of anti-HK1 and anti-KLHL12 in the diagnosis of PBC, and we in this study therefore aimed to assess the diagnostic accuracy of anti-HK1 and anti-KLHL12 among Chinese PBC patients, especially AMA-negative patients.

Materials and methods

Participants

A total of 92 patients diagnosed with PBC, 31 patients with viral hepatitis B, 41 patients with autoimmune disease (21 cases of systemic lupus erythematosus (SLE) and 20 cases of primary Sjögren's Syndrome [pSS]), and 48 healthy controls were enrolled at the Sir Run Run Shaw Hospital, Hangzhou, China, between April 2019 and December 2022. PBC, viral hepatitis B, SLE, and pSS were diagnosed according to the appropriate corresponding criteria [18–20]. The PBC patients were diagnosed based on the criteria recommended by the European Association for the Study of Liver (EASL) [21]. Patients who were diagnosed with PBC met any two of the following three criteria: 1) serological biochemical indices indicating cholestasis, including alkaline phosphatase (ALP); 2) AMA-positivity; and 3) AMA-negativity, but with a liver biopsy that was consistent with PBC. This study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Hangzhou Sir Run Run Shaw Hospital (no. 20200522-18). In addition, all enrolled participants provided informed consent.

Serological determinations

AMA was determined by indirect immunofluorescence (Euroimmun, Lübeck, Germany) at a titer of 1:100, while serum anti-gp210 and sp100 antibodies were evaluated by immunoblot assay (Euroimmun). The concentrations of anti-HK1 and anti-KLHL12 were quantified using ELISA kits (Meimian, Jiangsu, China) according to the manufacturer's instructions.

Statistical analysis

Quantitative data are described using means and standard deviations, while categorical data are presented as numbers with percentages. Student's t or Mann–Whitney U tests were used to compare the differences in quantitative data, and Chi-squared or Fisher's exact test was used for qualitative data when appropriate. Correlations analysis was adopted to quantify the relationship between anti-HK1 and anti-KLHL12 concentrations and GLOBE risk score. Receiver operating characteristic (ROC) curves were constructed to assess the sensitivity and specificity for anti-HK1 and anti-KLHL12 as diagnostic biomarkers for PBC, and the area under the ROC curve (AUC) was calculated to evaluate the diagnostic performance of anti-HK1 and anti-KLHL12, with 95 % confidence intervals (95 % CI). We calculated the cutoff values for anti-HK1 and anti-KLHL12 concentrations using the Youden index. A p-value of <0.05 was considered to be statistically significant. We employed SPSS (version 22.0) and Graph Pad Prism 8 software for all statistical analyses.

Results

Patient characteristics

The demographic and clinicopathological characteristics of all enrolled patients are described in Table 1. The mean age of the 92 PBC patients was 55.5 ± 13.1 years, with a female-to-male ratio of 6.1:1. Notably, 76 of 92 patients exhibited AMA positivity, while 16 were diagnosed with AMA-negative PBC. There were significant differences ($p<0.05$) in ALT, AST, GGT, IgG, and IgM between AMA-positive and AMA-negative subgroups. Compared with healthy controls and non-PBC disease controls, PBC patients possessed higher levels of serological biochemical indices indicating cholestasis, including increase in alkaline phosphatase levels. Although we noted no difference in these indices between AMA-positive and AMA-negative PBC patients, the GLOBE score of AMA-negative PBC patients was much higher than that of AMA-positive PBC patients regardless of age (Table 2). As for clinical staging, a majority of patients were diagnosed with stage II/III/IV (stage II, 42.39 %; stage III, 35.87 %; stage IV, 20.65 %).

Anti-HK1 and anti-KLHL12 antibodies among PBC patients

Compared with healthy controls, PBC patients exhibited much higher concentrations of anti-HK1 and anti-KLHL12 antibodies, whether among AMA-positive or AMA-negative PBC patients ($p<0.05$ for all). We did not observe any differences in the levels of anti-HK1 and anti-KLHL12 antibodies between AMA-positive and AMA-negative PBC patients ($p=0.36$ for anti-HK1, $p=0.32$ for anti-KLHL12) (Figure 1). In addition, there was no significant association between anti-HK1 and anti-KLHL12 concentrations and GLOBE risk score ($p=0.39$ for anti-HK1 and $p=0.88$ for anti-KLHL12) (Table 3).

Table 1: Demographic and clinicopathologic characteristics of participants.

General information	ALL PBC	AMA+ PBC	AMA− PBC	HBV	SLE	SS	HC
Age, years	55.5 ± 13.1	54.5 ± 13.7	60.5 ± 8.6	53.1 ± 12.0	37.1 ± 11.8	57 ± 12.5	48.6 ± 7.5
Sex (male/female)	13/79	8/68	5/11	14/17	1/20	2/18	19/29
ALT, U/L	64.9 ± 156.6	45.1 ± 50.6	154.3 ± 346.1	27.9 ± 27	14.7 ± 5.5	36.5 ± 57.4	18.1 ± 7.8
AST, U/L	63 ± 149.4	45.3 ± 34.6	142.5 ± 340	28.2 ± 13.6	20.4 ± 7.4	33.8 ± 29.5	21.6 ± 4.8
ALP, U/L	160.8 ± 97.6	156.5 ± 101.4	179.9 ± 78.1	82.1 ± 42.7	59.2 ± 14.9	81.5 ± 43.6	66.8 ± 14.7
GGT, U/L	145.6 ± 176.2	137.7 ± 186.1	181.4 ± 120.6	31.7 ± 36.2	17.1 ± 6.6	31.8 ± 36.2	20.1 ± 11.5
ALB, g/L	40.7 ± 5.1	41.1 ± 4.9	39.2 ± 5.8	43.5 ± 4.5	38.5 ± 7.6	39.9 ± 4.5	43.9 ± 2.1
BIL, μmol/L	22 ± 27.5	20.4 ± 26.6	29.4 ± 31.4	17.1 ± 9.5	10.8 ± 7.7	13.4 ± 5.7	13 ± 3.5
PLT ($\times 10^9$/L)	189.1 ± 84.4	190.3 ± 85	184.1 ± 85	188.3 ± 55	184.4 ± 83	186.4 ± 51	211.2 ± 38
IgG, g/L	16.3 ± 5	15.6 ± 4.3	21 ± 6.9	–	13.6 ± 5	16.9 ± 4.7	–
IgM, g/L	2.9 ± 1.9	3.1 ± 2	1.4 ± 0.6	–	1.2 ± 0.7	1.1 ± 0.6	–

Table 2: Estimated GLOBE scores in AMA-positive and negative patients.

Age, years	Threshold value	AMA+ PBC	AMA− PBC
≤45	−0.52	−0.52	–
45–52	0.01	0.01	0.65
52–58	0.6	0.29	0.56
58–66	1.01	0.82	1.51
>66	1.69	1.51	1.58

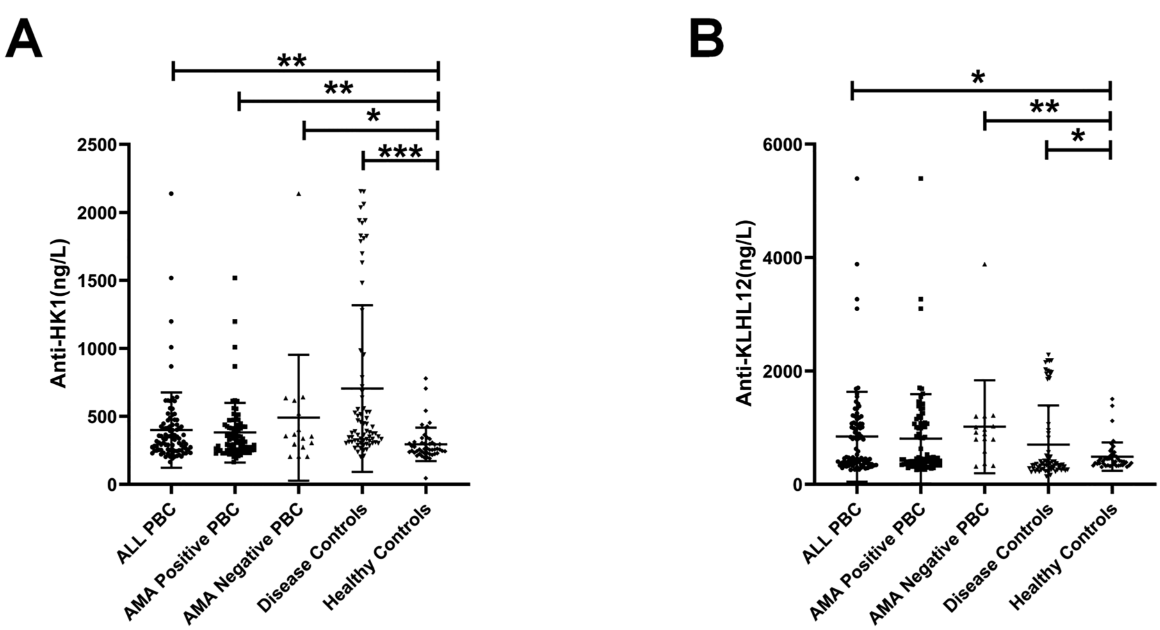

Figure 1: Expression levels of (A) anti-HK and (B) anti-KLHL12 in each group. *p<0.01, **p<0.05, ***p<0.001.

Table 3: The expression of two antibodies in GLOBE score for low- and high-risk patients.

GLOBE score risk	n	Antibody-expression level M (P25, P75)		p-Value	
		Anti-HK1	Anti-KLHL12	Anti-HK1	Anti-KLHL12
Low risk	43	311.4 (247.9, 423.2)	582.5 (344.1, 1,067.1)	0.390	0.882
High risk	31	331.3 (255.4, 473.4)	466.8 (352.6, 1,085.9)		

ROC analysis of anti-HK1 and anti-KLHL12 alone

The ROC curves for anti-HK1 and anti-KLHL12 autoantibodies are illustrated in Figure 2. ROC analyses showed an acceptable performance of serum anti-HK1 in PBC diagnosis, with an AUC was 0.664, a sensitivity of 53.3 %, and a specificity of 79.2 %; with 311.1 ng/mL as the optimal cutoff value. ROC analysis of anti-KLHL12 yielded an AUC of 0.626, with a sensitivity of 45.7 % and specificity of 93.8 %; and with 774.4 ng/mL as the optimal cutoff value. However, the effect was more robust with respect to the diagnosis of AMA-negative PBC patients, as the AUC increased to 0.790 for KLHL12 and 0.708 for HK1.

Combined analysis for multiple auto-antibodies

The analysis for the combination of multiple auto-antibodies is depicted in Figure 3, with the results showing that the addition of anti-HK1 or anti-KLHL12 to AMA or anti-gp210/sp100 significantly improved diagnostic efficacy. For example, the diagnostic sensitivity using the combination of AMA with anti-HK1 or anti-KLHL12 increased to 93.48 % (specificity 79.16 %) and 95.65 % (specificity 93.75 %) from 82.61 % (specificity 95.83 %) relative to using AMA alone, respectively. And the sensitivity using anti-gp210/sp100 plus anti-HK1/KLHL12 actually attained 87.5 % (specificity 79.16 %) in AMA-negative PBC patients. When the specificity was set to 95 %, the sensitivity of AMA combined with anti-HK1 or KLHL12 increased from 82.61

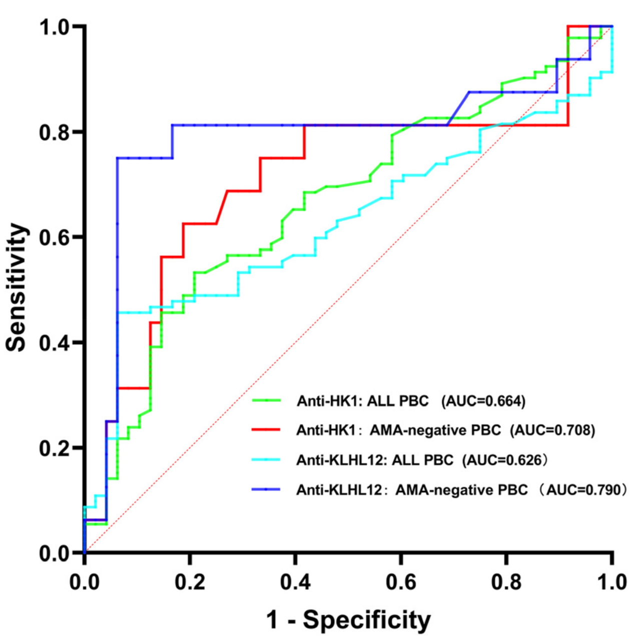

Figure 2: ROC curves for anti-HK1 and anti-KLHL12.

to 86.96 %. Meanwhile, in AMA negative patients, the sensitivity of anti-gp210/sp100 combined with anti-HK1/KLHL12 reached to 81.25 %. In addition, the global sensitivity for all PBC (AMA– and AMA+) selecting for all the markers is 96.74 % at a specificity of 95 %.

Discussion

The timely diagnosis of PBC can delay the progression of the disease and liver decompensation. The GLOBE score is an internationally relevant and validated risk assessment tool, able to accurately stratify PBC patients to high and low risk (https://www.globalpbc.com/globe). We herein first demonstrated that the GLOBE score of AMA-negative PBC patients in our study was much higher than that for AMA-positive patients regardless of age, suggesting that AMA-negative PBC patients reflected a relatively poor prognosis due to delayed diagnosis caused by AMA-negativity. A serological biomarker for early detection of PBC would be vital to its early diagnosis. Anti-HK1 and anti-KLHL12 antibodies were first found by high-density human recombinant protein microarrays in 2015, and showing excellent diagnostic value among Caucasians [16]. There are few reports as to their relevance in the diagnosis of PBC in the Chinese population. In the present study, we ascertained the levels of two novel auto-antibodies (anti-HK1 and anti-KLHL12) in PBC patients and further explored their diagnostic value.

Anti-HK1 and anti-KLHL12 antibodies in all PBC patients were statistically higher in the present study than those of healthy controls, and ROC analysis revealed that the AUCs for anti-HK1 and anti-KLHL12 were similar to those shown by Liu et al. [11] in a Chinese population, but it's lower than Norman's study [16]. Until now, we did not find any data of these two antibodies in Japan or Korea PBC patients, more research should be conducted to verify whether this difference was caused by ethnicities. Overlap in autoantibody presence in autoimmune diseases also occurs. Interestingly, in our study, these two antibodies showed a high positive rate in SS patients. This phenomenon may have been influenced by sample size, or the fact that anti-HK1 and anti-KLHL12 also play a specific role in SS. Previous study has also reported the presence of anti-KLHL12 in SS [22]. In such situation, more information such as detailed consultation and other determinations are needed to differentiate diagnosis. Our study is just a preliminary study, next we will investigate whether these two antibodies play a certain role in the pathogenesis of autoimmune diseases.

For the diagnosis of AMA-negative PBC patients, the performance was even better, as the AUC increased to 0.790 for anti-KLHL12 and 0.708 for anti-HK1. The combination of anti-HK1 and anti-KLHL12 antibodies in addition to

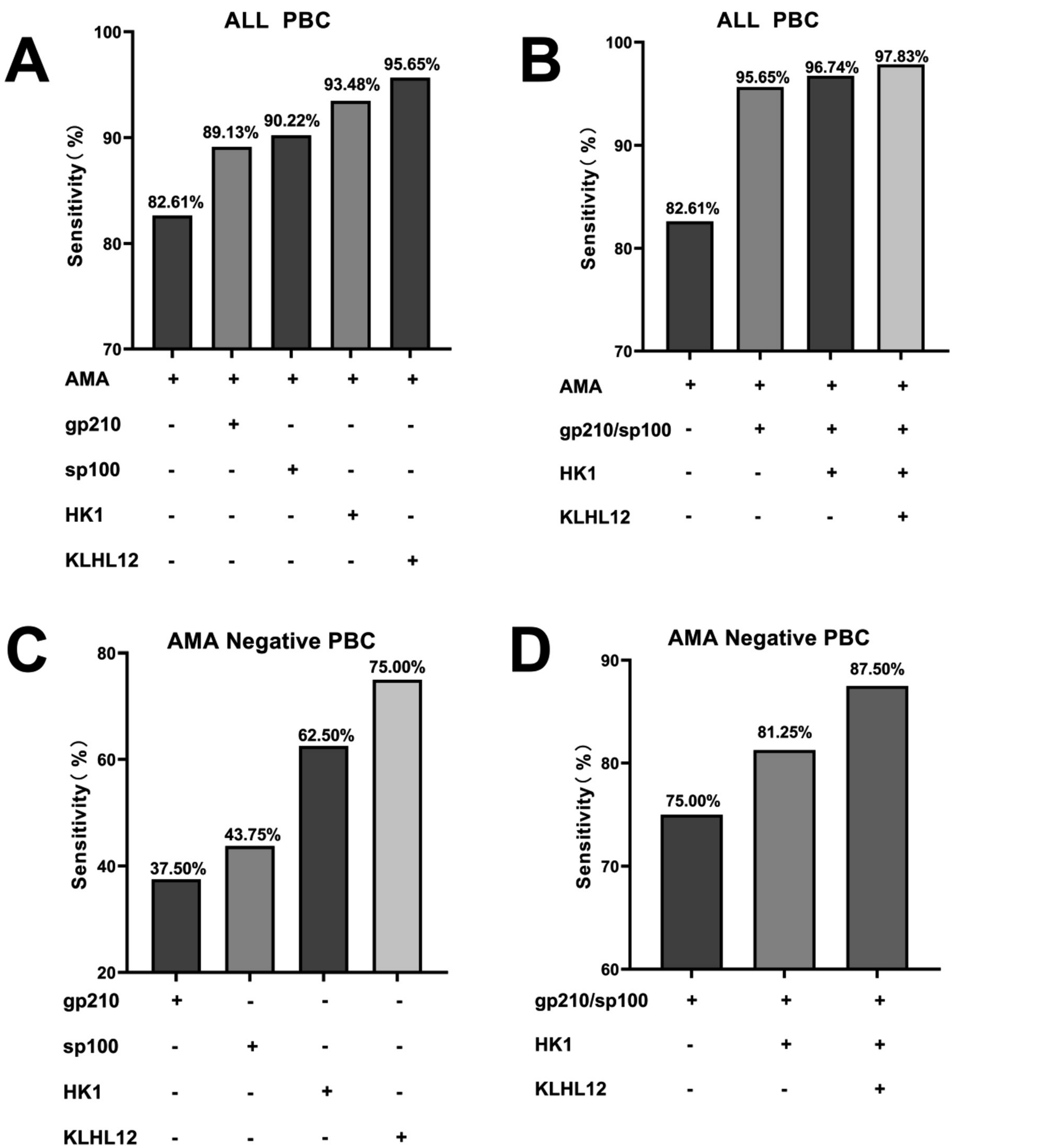

Figure 3: Combined analysis of multiple indicators. (A) Sensitivity of all PBC patients (n=92) detected by AMA combined with a single antibody. (B) Sensitivity of all PBC patients (n=92) detected by AMA combined with multiple antibodies. (C) Sensitivity of single auto-antibody in AMA-negative PBC patients (n=16). (D) Sensitivity of AMA-negative PBC patients (n=16) by combining multiple auto-antibodies.

conventional markers in AMA-negative PBC patients then significantly improved the overall diagnostic sensitivity from about 40 to 87.5 %. The inclusion of these antibodies in routine testing may facilitate the recognition of AMA-negative PBC patients by reducing the serological gap in AMA-negative patients and the frequency of liver biopsy.

Previous study has also shown that these novel antibodies remained rather steady during the development of disease, but that HK1 antibodies were associated with unfavorable outcomes [23]. However, in our study, there was no significant association between anti-HK1 or anti-KLHL12 concentrations and GLOBE risk score, suggesting that these two antibodies may not be acceptable for monitoring disease progression. The value of adopting the anti-HK1 and anti-KLHL12 antibody in differentiating clinical stage and prognosis, requires additional study.

There were some limitations to our study. First, the study was conducted at a single center. Current studies on anti-HK1 and anti-KLHL12 antibodies are primarily performed in Europe and the United States; therefore, it is of practical significance to conduct multi-center clinical studies in Asia and other regions, as we may find differences in the expression and pathogenesis of HK1 and KLHL12 in different ethnicities and races. Second, our sample size was small, potentially causing certain bias. The mechanism(s) underlying the production of these two antibodies remains unclear; thus, it would be of great clinical significance to further assess the role of HK1 and KLHL12 in autoimmune diseases.

In conclusion, anti-HK1 and anti-KLHL12 constitute two promising biomarkers that may hasten the diagnosis of PBC in AMA-negative patients, resulting in prompt initiation of effective treatment and thereby improving the prognosis of patients with PBC.

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Research ethics: The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and approved by the Ethics Committee of Hangzhou Sir Run Run Shaw Hospital (no. 20200522-18).
Informed consent: Informed consent was obtained from individuals included in this study, or their legal guardians or wards.
Author contributions: The authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Competing interests: The authors state no conflict of interest.
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Data availability: The raw data can be obtained on request from the corresponding author.

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