The diagnosis of primary biliary cholangitis (PBC) in patients with seropositive anti-mitochondrial antibody (AMA) but normal alkaline phosphatase (ALP) depends on a liver biopsy. We aimed to reveal potential serum biomarkers that could suggest the necessity of a liver biopsy in such patients. Retrospective analysis was performed. Subjects who were treatment naive with seropositive AMA but normal ALP and who underwent at least one liver biopsy between 2008 and 2020 were included in this study. Histologic biopsies were evaluated by two experienced pathologists blinded to the serum tests. A total of 115 patients who were treatment naive were included in this study. Of these, 77 patients (67%) exhibited histologic PBC features and nonspecific histologic features were found in the remaining 38 (33%) patients. Multivariate analysis suggested that baseline serum immunoglobulin M (IgM) >0.773 × upper limit of normal (ULN) (P < 0.001) and age >42 years (P = 0.002) were associated with the diagnosis of PBC through liver biopsies. A significant decrease in the median levels of gamma-glutamyl transpeptidase (GGT) and IgM was found in 54 patients with PBC who received ursodeoxycholic acid (UDCA). Conclusion: For patients who were treatment naive with seropositive AMA but normal ALP, baseline serum IgM >0.773 × ULN and age >42 years were the factors that strongly suggested a diagnosis of PBC. In these patients receiving UDCA, a dynamic monitoring of GGT and IgM might be helpful in evaluating therapeutic responses. (Hepatology Communications 2022;6:1403-1412).
with UDCA significantly improves the long-term prognosis of patients with PBC. However, the clinical decision-making process becomes much more complex for those with seropositive AMA but normal ALP. A definite diagnosis of PBC cannot be reached due to the lack of a typical cholestatic manifestation. An annual detection of liver biochemistry instead of a routine liver biopsy is recommended under such circumstances. Therefore, the diagnosis in such a population is usually vague. In fact, a study from 1986 suggested that a large proportion of these patients exhibited histologic features consistent with PBC, and recent data from Terziroli Beretta-Piccoli et al. confirmed this theory. The ambiguous diagnosis has directly prevented those patients with real PBC from benefitting from UDCA and other necessary treatment. In addition, ALP is a key index in the current criteria for evaluating the responses to UDCA, but ALP remains stable within the normal range in these patients. Therefore, no suitable criteria are available to evaluate the therapeutic responses in those patients who received UDCA treatment, which makes it difficult to distinguish patients who have refractory UDCA who need the second-line treatment. In recent years, a small number of studies have focused on patients with seropositive AMA and normal ALP. Sun et al. proposed that ALP >0.475 x upper limit of normal (ULN) may provide some clues to help diagnose this highly heterogeneous disease, whereas Terziroli Beretta-Piccoli et al. noted the potential role of serum gamma-glutamyl transferase (GGT) as a biomarker for PBC among patients who are seropositive for AMA alone. However, these indicators need to be further validated in different populations, and their capacities to evaluate responses to UDCA treatment remain unclear.

To further address these issues, we performed a study including 115 patients with seropositive AMA and normal ALP who were treatment naive and who had undergone a liver biopsy for a definite diagnosis. Our analysis showed that baseline serum IgM and age were potential indicators for PBC diagnosis. A significant decrease in IgM and GGT was found in 54 patients with PBC who received UDCA treatment. Adequate responses to UDCA were also confirmed by histologic evaluation in patients with multiple liver biopsies.

Patients and Methods

STUDY DESIGN

This was a retrospective cohort study. Patients were divided into patients with histologically confirmed PBC and patients with histologically unconfirmed PBC depending on whether their liver biopsies demonstrated histologic findings consistent with PBC or nonspecific changes, respectively. We compared the clinical characteristics between the groups and investigated whether any serum biomarker was predictive of PBC and indicative of a need for a liver biopsy. We also performed a subgroup analysis on patients who presented with advanced fibrosis at
baseline as well as assessed the therapeutic response to UDCA and prognosis of patients with PBC but with normal levels of ALP. The study design was approved by the ethics committee of the Xijing Hospital of the Air Force Military Medical University. Written informed consent was obtained from all participants.

STUDY POPULATION

We analyzed 115 patients who were treatment naive from Xijing Hospital of Digestive Diseases (Xi’an, Shanxi, China) between 2008 and 2020 and who 1) were seropositive for AMA, 2) had normal ALP levels at baseline, and 3) underwent at least one liver biopsy. Patients were excluded from our study if they had histories of UDCA use before enrollment or had evidence of concomitant liver disease (viral hepatitis, alcoholic hepatitis, drug-induced liver injury, Wilson’s disease, hemochromatosis, autoimmune hepatitis, hepatocellular carcinoma). All patients exhibited persistent normal ALP before liver biopsies. We took the latest levels of ALP and other liver biochemical indexes before liver biopsy as the baseline data in our analyses.

DATA COLLECTION AND ANALYSIS

We systematically collected clinical data at presentation and each follow-up. Data included general characteristics, clinical symptoms, serology results, and histologic findings. Liver biopsies were analyzed based on the METAVIR and Ludwig Symposium scoring systems for chronic hepatitis and PBC, respectively. Biopsy specimens were analyzed by two experienced pathologists who were blinded to the serologic findings. Hepatic deterioration was defined as the occurrence of a decompensatory event (such as ascites, hepatic encephalopathy, or variceal bleeding) and/or progression of the Child-Pugh grade by at least one level. Histologic remission was defined as a reduction of at least one grade in PBC staging.

STATISTICAL ANALYSIS

All statistical analyses were performed with SPSS version 26.0 (IBM). Continuous variables were described as mean and range, whereas categorical variables were expressed as median and range. Differences in proportions were assessed using the Fisher’s exact test, whereas the Mann-Whitney U test was used to analyze continuous non-normally distributed variables. We conducted a multivariate analysis for all variables with \( P < 0.05 \). Logistic regression analysis was used to identify independent predictors using a forward-selection process. The Kruskal-Wallis H test was used for comparison between multiple groups. Cut-off values were assessed through a receiver operating characteristic (ROC) analysis. A two-sided \( P < 0.05 \) was considered statistically significant.

Results

CLINICAL FEATURES OF PATIENTS WITH SEROPOSITIVE AMA BUT NORMAL ALP

The study flow chart is represented in Fig. 1. We examined 115 patients who were treatment naive. Seventy-seven of these patients were diagnosed with PBC by histology, and the remaining 38 patients who were seropositive for AMA alone served as controls. Their demographic characteristics are presented in Table 1. All 115 patients underwent ALP observation at least twice for a mean of 13.6 (range, 0.5-72.0) months before liver biopsy, and they all exhibited persistent normal ALP. The majority of patients were women (83.5%), and the average age was 50 (range, 21-72) years. The most common symptoms were fatigue (29.6%). Twenty-three patients who were found to be AMA positive through pedigree screening were included, and 11 of these were histologically confirmed as PBC with lower histologic stages and milder symptoms. This may suggest a better biochemical response and improved prognosis compared to patients with sporadic disease. More than a quarter of patients with PBC also had splenomegaly at presentation, suggesting a possible diagnostic delay. There were 16/115 (13.9%) with Sjogren’s syndrome, 7/115 (6.1%) with Hashimoto’s thyroiditis, 2/115 (1.7%) with scleroderma, and 2/115 (1.7%) with rheumatoid arthritis. Autoimmune diseases were found in 32.5% of the PBC cases and 5.3% of the non-PBC cases (\( P = 0.001 \)). It has been reported that the presence of autoimmune diseases is associated with increased likelihood of finding PBC on liver biopsy in a more
Among the 77 patients in the PBC group, 21 had a histologic stage of advanced fibrosis at presentation and were subclassified as the advanced-stage group; the remaining patients were classified as the early stage group with no signs of advanced fibrosis. Baseline clinical characteristics of these two subgroups are shown in Table 2. There were significant differences in symptoms, such as fatigue, between the subgroups. Four parameters were significantly associated with fibrosis stage at baseline, namely, total bilirubin (Tbil) \( (P < 0.001) \), albumin (ALB) \( (P = 0.008) \), platelet (PLT) \( (P = 0.001) \), and IgG \( (P = 0.006) \) levels.

The inclusion of Tbil, ALB, and PLT levels in the multifactorial analysis showed that serum Tbil levels (odds ratio [OR], 6.75; 95% confidence interval [CI], 1.60–28.49; \( P = 0.009 \)) and serum ALB levels (OR, 0.82; 95% CI, 0.70–0.95; \( P = 0.007 \)) at baseline were associated with advanced fibrosis. Compared to the early stage group, the advanced-stage group had more advanced PBC and liver fibrosis staging (both \( P < 0.001 \)).

**Clinical Conditions Require a Liver Biopsy**

A univariate analysis identified seven parameters that were significantly different at baseline between the groups, including age \( (P = 0.002) \), ALP \( (P = 0.007) \), GGT \( (P < 0.001) \), alanine aminotransferase (ALT) \( (P = 0.011) \), aspartate aminotransferase (AST) \( (P = 0.002) \), IgM \( (P < 0.001) \), and autoimmune diseases \( (P = 0.001) \). Complete results are shown in Table 1. All variables showing \( P < 0.05 \) were selected for multivariate analysis. Serum IgM (OR, 29.58; 95% CI, 6.22–140.75; \( P < 0.001 \)) and age (OR, 1.09; 95% CI, 1.03–1.12; \( P = 0.001 \)) at baseline were associated with histologic findings consistent with PBC. We further examined serum IgM levels and age through an ROC analysis, which demonstrated areas under the curve of 0.810 and 0.676, respectively (Fig. 2). The optimal threshold for baseline serum IgM and age were 0.773 \( \times \) ULN and 42 years, respectively. Serum IgM was 78% sensitive and 76% specific in diagnosing PBC; positive and negative predictive values were 87% and 63%, respectively, whereas age was 91% sensitive and 47% specific.
UDCA was administered to 74 of the 77 patients in the PBC group. Among the 74 patients, 54 were followed up regularly for more than a year; of these, 45 had elevated GGT levels before UDCA therapy. During treatment, GGT levels showed improvement in 44 patients of whom 32 were completely normal. Nine of 54 patients with normal GGT levels at baseline showed a reduction of GGT levels after UDCA treatment. Median levels of GGT decreased significantly after 1 year of treatment (2.22 × ULN vs. 0.69 × ULN, \( P < 0.001 \)). Together with serum IgM levels, data on treatment were fully available for 54 patients of whom 35 had elevated IgM levels before UDCA therapy. During treatment, IgM levels showed improvement in 34 patients of whom 17 were completely normal. Eighteen of 54 patients with normal IgM levels at baseline showed a reduction of IgM levels on UDCA. Median levels of IgM decreased significantly after 1 year of treatment (1.15 × ULN vs. 0.89 × ULN, \( P = 0.003 \)). Two of 54 patients treated with UDCA suffered from increased IgM levels that remained unabated thereafter. One patient demonstrated a serum IgM level >1.54 × ULN. He was the only patient who did not show any improvement in GGT levels after UDCA therapy and progressed to compensated liver cirrhosis in year 4 of follow-up. Another patient with an IgM >2.10 × ULN was disappeared in the third year of follow-up with Tbil levels of 4.01 × ULN.

Thirteen patients with reduced GGT and IgM levels during UDCA treatment underwent at least two liver biopsies at a mean interval of 42 (range, 12-78)
No histologic progression was observed in 12 patients; 8 of them exhibited histologic remission. The above data suggest that dynamic changes in serum IgM and GGT levels may serve as potential indicators for a biochemical response to treatment. Median IgM and GGT levels before and after treatment are shown in Fig. 3.

Of the 54 patients, 14 were in the advanced-stage group and 40 were in the early stage group. The overall median follow-up time was not different between patients with and without advanced fibrosis (39 vs. 36 months, \( P = 0.961 \)). Compared to the early stage group, patients with advanced fibrosis reported significantly higher prevalence of hepatic deterioration at the end of the study (28.6% vs. 2.5%; \( P = 0.013 \)). We also evaluated the predictive values of the Mayo, GLOBE, and United Kingdom (UK)-PBC risk-scoring models.15-17 There were significant differences between the two groups in Mayo, GLOBE, and UK-PBC scores (\( P < 0.001 \), \( P < 0.001 \), and \( P = 0.014 \), respectively) (Table 2), implying patients with advanced fibrosis progressed more quickly to liver transplantation or death.
Discussion

We examined the liver specimens of 115 patients who were treatment naive and who were seropositive for AMA but had normal levels of ALP. Seventy-seven of these patients had histologic findings of PBC. This was consistent with data from earlier studies\(^8 to \(^{10,18}\) that claimed more than half of patients who were seropositive for AMA alone exhibited classic histologic signs of PBC. These phenomena suggest that most of those with seropositive AMA and normal ALP were probable patients with PBC, and a liver biopsy should be one of the options in the clinical decision-making process to help in the diagnosis and treatment-initiation timing.

To optimize the diagnostic value of liver biopsies, we investigated a series of serum parameters. Our cohort did not indicate that ALP was a potential biomarker among patients with elevated AMA but normal ALP. This was inconsistent with the study by Sun et al.,\(^{10}\) which proposed that ALP $>$ 0.475 × ULN increased the likelihood of liver biopsy findings consistent with PBC. This may be due to many factors, such as differences in demographic or geographic characteristics. In contrast, our study found that baseline serum IgM $>$ 0.773 × ULN was a potential indicator for histologic findings indicative of PBC. Of relevance, Berdichevski et al.\(^{19}\) reported that a liver biopsy should be performed to rule out PBC among patients who are seropositive for AMA alone but have significantly elevated serum IgM levels. Data from a large-scale study revealed that 1 of 6 patients who were seropositive for AMA but had normal ALP levels developed PBC within 5 years,\(^{20}\) indicating the time-dependent nature of the disease. Our study also found that age $>$ 42 years may be associated with an increased risk for histologic findings of PBC on liver biopsy.

Balanced sensitivity, specificity, positive-predictive values, and negative-predictive values were found when IgM $>$ 0.773 × ULN was met. When combined with age $>$ 42 years, specificity and positive-predictive values could be further increased. Therefore, IgM $>$ 0.773 × ULN might be used as an important indicator for liver biopsy, particularly in patients over 42 years. The therapeutic response for PBC is currently evaluated based on dynamic changes in serum ALP and bilirubin levels; however, it is unclear whether the same criteria could be applied to patients with elevated AMA but normal ALP levels. A recent study observed a significant decline in median GGT levels before and after UDCA treatment, suggesting that GGT could be used as a potential indicator of therapeutic success. Reportedly, serum IgM levels decreased in parallel with liver biochemical parameters after UDCA treatment in patients with PBC.\(^{21,22}\)

We therefore speculate that the dynamic changes in IgM levels to treatment may reflect disease activity. Here, we found a sustained and significant decrease in median IgM levels during the same time period. In this way, serum IgM levels might be helpful in evaluating therapeutic responses. Hence, close follow-up

\[ \text{Fig. 2. ROC curves in patients with seropositive AMA but normal ALP levels. (A) IgM levels; (B) age. Abbreviations: AUC, area under the curve; FPR, false-positive rate; TPR, true-positive rate.} \]
serum IgM levels of patients with seropositive AMA but normal ALP, together with GGT, is essential for evaluation of treatment response, early identification of patients with refractory UDCA, and timely addition of second-line drugs. Recently, Takano et al.\(^\text{23}\) reported that serum IgM levels may be a useful predictor for cirrhosis-related symptoms and liver-related events in patients with PBC with refractory UDCA therapy. Our study showed that a patient with serum IgM \(>1.54 \times \text{ULN}\) progressed to compensated liver cirrhosis in year 4 of follow-up with an absence of other clear etiologies of disease progression. This suggested that a high titer of serum IgM levels may be a prognostic biomarker among patients with PBC who are seropositive for AMA alone. Another patient with an IgM \(>2.10 \times \text{ULN}\) was disappeared in the third year of follow-up with TBil levels of 4.01 \(\times \text{ULN}\). These patients should be monitored more closely because they may have poorer prognoses and require treatment adjustment in the near future.

In contrast with previous studies wherein the majority of patients presented with mild disease, 21 patients in our study presented with a histologic stage of advanced fibrosis at baseline, including 9 with stage 4 disease. This may be because Chinese patients tend to seek medical advice later in the illness course when they are more symptomatic, particularly with fatigue and/or pruritus. In contrast, patients in the West may undergo early screening as part of a routine pre-employment medical examination. Our findings showed a development compared to previous papers in that our study systematically described the clinical characteristics of such patients.\(^{8-10,17}\) Further follow-up will continue for these patients to provide new references for clinical practice.

Our study had some limitations. First, it was a single-center retrospective design. Second, only 13 patients with posttreatment liver biopsies were included in this study. These biopsies provided us with important information of disease progression.

### Table 3. Histologic Findings from at Least Two Liver Biopsies in Patients with PBC Who Were ALP Normal and AMA Positive and Treated with UDCA

| Patient | Time | PBC Stage | Inflammation | Fibrosis | ALP×ULN | GGT×ULN | ALT×ULN | AST×ULN | TBIL×ULN | IgM×ULN |
|---------|------|-----------|--------------|----------|---------|---------|---------|---------|---------|---------|
| 5       | 1    | 2         | 2            | 2        | 0.92    | 1.20    | 0.78    | 1.00    | 0.71    | 0.80    |
| 2       | 2    | 1         | 1            | 1        | 1.34    | 1.18    | 0.76    | 0.94    | 0.65    | 0.68    |
| 9       | 1    | 2         | 2            | 2        | 0.93    | 5.51    | 1.84    | 1.60    | 0.78    | 1.48    |
| 8       | 1    | 2         | 1            | 2        | 0.30    | 0.69    | 0.44    | 0.66    | 0.32    | 0.63    |
| 12      | 1    | 2         | 2            | 2        | 0.67    | 1.29    | 4.31    | 3.31    | 0.85    | 0.30    |
| 16      | 1    | 1         | 1            | 1        | 0.39    | 0.27    | 0.24    | 0.54    | 0.83    | 0.24    |
| 21      | 1    | 2         | 1            | 2        | 0.93    | 7.04    | 3.02    | 2.74    | 0.42    | 1.50    |
| 1       | 1    | 1         | 1            | 1        | 0.30    | 0.71    | 0.44    | 0.49    | 0.35    | 0.41    |
| 22      | 1    | 2         | 2            | 2        | 0.75    | 1.16    | 0.31    | 0.69    | 0.43    | 0.72    |
| 25      | 1    | 2         | 2            | 2        | 0.56    | 2.42    | 1.80    | 1.86    | 0.59    | 1.18    |
| 26      | 1    | 2         | 2            | 2        | 0.65    | 0.93    | 0.80    | 0.69    | 0.33    | 1.11    |
| 31      | 1    | 3         | 3            | 3        | 0.56    | 1.47    | 0.44    | 0.60    | 0.93    | 0.45    |
| 2       | 2    | 2         | 2            | 2        | 0.41    | 0.42    | 0.27    | 0.51    | 0.66    | 0.40    |
| 34      | 1    | 2         | 2            | 2        | 0.67    | 1.91    | 1.09    | 1.09    | 0.30    | 1.19    |
| 45      | 1    | 3         | 3            | 3        | 0.40    | 0.69    | 0.11    | 0.43    | 1.00    | 0.44    |
| 104     | 1    | 2         | 3            | 2        | 0.67    | 2.76    | 2.35    | 3.49    | 0.96    | 1.76    |
| 115     | 1    | 4         | 3            | 4        | 0.73    | 8.56    | 2.60    | 1.51    | 0.89    | 1.21    |
| 2       | 2    | 4         | 2            | 4        | 0.60    | 1.24    | 0.31    | 0.77    | 0.78    | 0.89    |
and treatment responses, and more biopsies might be considered in other patients to generate more reliable clinical evidence for managing such patients.

In conclusion, serum IgM is an extremely important clinical indicator that should be noted in patients who are treatment naive with seropositive AMA but normal ALP. In the course of consultation, clinicians should comprehensively consider various clinical features of patients, especially baseline IgM level and age. IgM >0.773 × ULN and age >42 years increased the likelihood of liver biopsy findings being consistent with PBC. In these patients, dynamic detection of IgM and GGT levels was helpful in evaluating therapeutic responses of UDCA. Clinicians should screen appropriate patients for biopsy and initiate treatment to prevent disease progression.

REFERENCES

1) Lindor KD, Gershwin ME, Poupon R, Kaplan M, Bergasa NV, Heathcote EJ; American Association for Study of Liver Diseases. Primary biliary cirrhosis. Hepatology 2009;50:291-308.
2) Beuers U, Gershwin ME, Gish RG, Invernizzi P, Jones DE, Lindor K, et al. Changing nomenclature for PBC: from ‘cirrhosis’ to ‘cholangitis’. Hepatology 2015;62:1620-1622.
3) Lleo A, Liao J, Invernizzi P, Zhao M, Bernuzzi F, Ma LE, et al. Immunoglobulin M levels inversely correlate with CD40 ligand promoter methylation in patients with primary biliary cirrhosis. Hepatology 2012;55:153-160.
4) Lindor KD, Bowlds CL, Boyer J, Levy C, Mayo M. Primary Biliary Cholangitis: 2018 practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2019;69:394-419.
5) Parés A, Caballeria L, Rodés J. Excellent long-term survival in patients with primary biliary cirrhosis and biochemical response to ursodeoxycholic acid. Gastroenterology 2006;130:715-720.
6) Corpechot C, Abenavoli L, Rabahi N, Chretien Y, Andreani T, Johanet C, et al. Biochemical response to ursodeoxycholic acid and long-term prognosis in primary biliary cirrhosis. Hepatology 2008;48:871-877.
7) European Association for the Study of the Liver. EASL clinical practice guidelines: the diagnosis and management of patients with primary biliary cholangitis. J Hepatol 2017;67:145-172.
8) Mitchison HC, Bassendine MF, Hendrick A, Bennett MK, Bird G, Watson AJ, et al. Positive antimitochondrial antibody but normal alkaline phosphatase: is this primary biliary cirrhosis? Hepatology 1986;6:1279-1284.
9) Terzoli Rol Beretta-Piccoli B, Stimmimann G, Mertens J, Semela D, Zen Y, Mazzucchelli L, et al; Swiss PBC Cohort Study Group. Primary biliary cholangitis with normal alkaline phosphatase: A neglected clinical entity challenging current guidelines. J Autoimmun 2021;116:102578.
10) Sun C, Xiao X, Yan Li, Sheng Li, Wang Q, Jiang P, et al. Histologically proven AMA positive primary biliary cholangitis but normal serum alkaline phosphatase: is alkaline phosphatase truly a surrogate marker? J Autoimmun 2019;99:33-38.
11) Brind AM, Bray GP, Portmann BC, Williams R. Prevalence and pattern of familial disease in primary biliary cirrhosis. Gut 1995;36:615-617.
12) Lazaridis KN, Juran BD, Boe GM, Slusser JP, de Andrade M, Homburger HA, et al. Increased prevalence of antimitochondrial antibodies in first-degree relatives of patients with primary biliary cirrhosis. Hepatology 2007;46:785-792.
13) Gershwin ME, Selmi C, Warman HJ, Gold EB, Watnik M, Utts J, et al.; USA PBC Epidemiology Group. Risk factors and comorbidities in primary biliary cirrhosis: a controlled interview-based study of 1032 patients. Hepatology 2005;42:1194-1202.
14) Efe C, Torgutalp M, Henriksson I, Alalkim F, Lytvynk E, Trivedi H, et al. Extrahepatic autoimmune diseases in primary biliary cholangitis: prevalence and significance for clinical presentation and disease outcome. J Gastroenterol Hepatol 2021;63:936-942.
15) Dickson ER, Grambsch PM, Fleming TR, Fisher LD, Langworthy A. Prognosis in primary biliary cirrhosis: model for decision making. Hepatology 1989;10:1-7.
16) Lammers WJ, Hirschfield GM, Corpechot C, Nevens F, Lindor KD, Janssen HLA, et al.; Global PBC Study Group. Development and validation of a scoring system to predict outcomes of patients with primary biliary cirrhosis receiving ursodeoxycholic acid therapy. Gastroenterology 2015;149:1804-1812.e4.
17) Carbone M, Sharp SJ, Flack S, Poximadas D, Spies K, Adgey C, et al.; UK-PBC Consilium. The UK-PBC risk scores: derivation and validation of a scoring system for long-term prediction of end-stage liver disease in primary biliary cholangitis. Hepatology 2016;63:930-950.
18) Mitchal JV, Mitchison HC, Palmer JM, Jones DE, Bassendine MF, James OF. Natural history of early primary biliary cirrhosis. Lancet 1996;348:1399-1402.
19) Berdichevski T, Cohen-Ezra O, Pappo O, Ben-Ari Z. Positive antimitochondrial antibody but normal serum alkaline phosphatase: is alkaline phosphatase truly a surrogate marker? J Autoimmun 2019;99:33-38.
20) Dahlqvist G, Gaouar F, Carrat F, Meurisse S, Chazouilleres O, Poupon R, et al.; French network of Immunology Laboratory. Large-scale characterization study of patients with antimitochondrial antibodies but nonestablished primary biliary cholangitis. Hepatology 2017;65:152-163.
21) Poupon RE, Eschewege E, Poupon R. Ursodeoxycholic acid for the treatment of primary biliary cirrhosis. Interim analysis of a
22) Kikuchi K, Hsu W, Hosoya N, Moritoki Y, Kajiyama Y, Kawai T, et al. Ursodeoxycholic acid reduces CpG-induced IgM production in patients with primary biliary cirrhosis. Hepatol Res 2009;39:448-454.
23) Takano K, Sacki C, Oikawa T, Hidaka A, Mizuno Y, Ishida J, et al. IgM response is a prognostic biomarker of primary biliary cholangitis treated with ursodeoxycholic acid and bezafibrate. J Gastroenterol Hepatol 2020;35:663-672.

Supporting Information
Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep4.1907/suppinfo.