The accuracy of the anti-mitochondrial antibody and the M2 subtype test for diagnosis of primary biliary cirrhosis: a meta-analysis

Abstract: The aim of this study was to evaluate the diagnostic value of anti-mitochondrial antibodies (AMAs) and/or the M2 subtype (AMA-M2) in patients with primary biliary cirrhosis (PBC). AMA/AMA-M2 data were obtained by searching electronic databases. Studies showing AMA/AMA-M2 results in patients with PBC and control groups with other liver diseases or healthy livers were included. The quality of the involved studies was assessed using the QUADAS tool. The pooled sensitivity and specificity were calculated, and stratified analysis was performed according to possible heterogeneity sources. The pooled AMA (all methods) sensitivity and specificity were 84.5% (95% confidence interval (CI) 83.3%–85.6%) and 97.8% (95% CI 97.6%–98.0%), respectively. The positive and negative likelihood ratios were 25.201 (95% CI 17.583–36.118) and 0.162 (95% CI 0.131–0.199), respectively. The current evidence suggests that AMA and AMA-M2 show favorable accuracy for the diagnosis of PBC with high specificity and sensitivity. AMA is a better and more comprehensive marker than AMA-M2. The accuracy established in this meta-analysis is based on clinical studies using patient cohorts from different ethnicities.

Keywords: anti-mitochondrial antibody (AMA); anti-mitochondrial antibody/the M2 subtype (AMA-M2); diagnosis; meta-analysis; primary biliary cirrhosis.
in the diagnosis of PBC. Therefore, we conducted a meta-analysis and review of related literature.

Methods

Data sources and searches

Studies published in English or Chinese were identified through searches in PubMed (Medline), the Cochrane Library, the Chinese National Knowledge Infrastructure (CNKI), and Technology of Chongqing (VIP) using the following keywords: “Anti-mitochondrial Antibody”, “AMA,” “Autoantibody”, “Primary Biliary Cirrhosis”, “PBC” and “cholestatic liver diseases”. Two reviewers (Shiling Hu and Fengrong Zhao) independently performed the literature search. The search was performed without ethnicity or geographic region limits. Studies found were retrieved and examined carefully.

Study selection

We included literature if the studies met the following criteria: 1) assess the diagnostic accuracy of the AMA test on PBC with full-text articles; 2) present sensitivity and specificity or sufficient information to construct two-by-two tables; 3) for qualified studies with data published more than once, only articles with the largest sample size of patients were included; and 4) no duplicate data. The exclusion criteria were as follows: 1) case reports, letters, reviews, conferences, meta-analysis, and editorial articles; 2) overlapping data; and/or 3) not enough information or data were reported.

Data extraction and study quality assessment

The following data were independently extracted from each article by two investigators (Shiling Hu and Fengrong Zhao): name of the first author; year of publication; country of origin; ethnicity of the study population; control sources; PBC diagnosis criteria; antibody testing methods; antibody type; test results including true positive (TP), false-positive (FP), false-negative (FN), and true negative (TN); the sensitivity and specificity; and essential sample size. The quality assessment of diagnostic accuracy studies (QUADAS) tool was used to assess each studies’ quality, and studies were scored as “Yes (high quality)”, “No (low quality)”, or “Unclear”. We (Shiling Hu and Qingsong Wang) evaluated each article independently and discussed discrepancies when they were found.

Data analysis

Meta-analysis was performed using MetaDiSc, version 1.4 (Hospital Universitario Ramony Cajal, Madrid, Spain) and Review Manager 5.2 (Oxford, UK: The Cochran Collaboration). We calculated the sensitivity and specificity as well as the positive and negative likelihood ratios (LR±) for each study. The Q test and I² test were performed to examine whether variations were caused by heterogeneity or sampling errors (chance). Fixed-effects methods were used if the result of the Q test was not significant (p > 0.10 or I² < 50%) or the random-effects model was used. Subgroup analysis was performed to assess whether the threshold effect and heterogeneity among studies existed according to different measurement methods, autoantibody type, and ethnicities. The ethnicities used were Caucasians, Africans, South Americans and Asians. Summary receiver operator characteristic (SROC) curves, which show the relationship between sensitivity and 1-specificity, were constructed to summarize these results. Q* values, which show the point where sensitivity equals specificity, were calculated from the SROC curves. Finally, the funnel plot was used to assess publication bias.

Results

The characteristics of included studies

The search strategy retrieved 2851 potentially relevant studies. After reading titles and abstracts, 2586 citations were excluded according to the selection criteria. According to the inclusion criteria, 24 full-text studies [14–37] were included in this meta-analysis, and 241 studies were excluded: 188 articles had no direct link with the main subject; four of them were reviews; 47 were incomplete result data and two duplicated studies. Figure 1 illustrates the study selection procedure. These 24 case control studies included 2992 PBC cases and 18,467 other liver disease/healthy controls. The baseline characteristics of all included studies are summarized in Table 1.

Quality evaluation of literature

Most of the studies included in this meta-analysis had high quality with above seven satisfied items in 11 items using
QUADAS tool [38]. None of the studies satisfied all criteria of the quality checklist. Four studies satisfied nine items of 11 standard items, 10 studies satisfied eight items, five studies satisfied seven items, four studies satisfied six items and one study satisfied five items. Studies scored poorly on items regarding the reference standard independent of the index test and blinding of the index test results. The included articles’ qualities are shown in Figure 2.

Data synthesis and meta-analysis

The heterogeneity analysis showed less homogeneity (p=0.000, I²=79.7%), so the random-effects model was used to perform the meta-analysis. The positive and negative LRs were 25.201 (95% CI 17.583–36.118) and 0.162 (95% CI 0.131–0.199), respectively. The pooled sensitivity and specificity were 84.5% (95% CI 83.3%–85.6%) and 97.8% (95% CI 97.6%–98.0%), respectively. The pooled sensitivity, specificity, LR+, LR−, and diagnostic odds ratio (DOR) for AMA (all methods) and AMA-M2 are summarized in Table 2. The forest plot and SROC curve for AMA and AMA-M2 are shown in Figures 3 and 4. The Spearman’s correlation coefficient was found using the MetaDiSc. For AMA the Spearman’s correlation coefficient was 0.168 (p=0.479), whereas it was 0.093 (p=0.722) for AMA-M2. Meta-regression analysis showed that heterogeneity is related to ethnicity. Stratified analyses were performed; the results are summarized in Table 2.

Diagnostic accuracy of AMA/AMA-M2 detection in different ethnicities (subgroup analysis)

Seven studies reported data about Europeans [18, 25, 26, 30, 31, 34, 35], three about South Americans [21, 23, 37], 12 about Asians [14–17, 20, 22, 27–29, 32, 33, 36] and one about Africans [24]. Significant differences between the four ethnicities were found (Table 2).

Detection by different methods

AMA/AMA-M2 were measured using IIF in 20 studies [14, 17–22, 24, 25, 27–37], in 12 studies [16, 17, 21–26, 29, 30, 35, 36] with the ELISA method, in three studies [15, 22, 30] with the Western blot technique, and in one study [24] with the Dot blot technique. The sensitivities of AMA detected with IIF ranged from 43.8% to 100% (pooled Sen: 84.6%, 95% CI 83.1%–86.0%) whereas specificities ranged from 83.3% to 100% (pooled Spe: 98.4%, 95%
Table 1 Characteristics of studies included in the meta-analysis of the diagnosis of PBC using the AMA/AMA-M2 test.

<table>
<thead>
<tr>
<th>Author</th>
<th>Time</th>
<th>Country</th>
<th>Criteria</th>
<th>Methods</th>
<th>Type</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
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<tr>
<td>Imura-Kumada S [16]</td>
<td>2012</td>
<td>Japan</td>
<td>–</td>
<td>ELISA</td>
<td>AMA-M2</td>
<td>22</td>
<td>15</td>
<td>0</td>
<td>188</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ELISA</td>
<td>AMA-M2</td>
<td>173</td>
<td>20</td>
<td>25</td>
<td>65</td>
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<tr>
<td>Cavazzana I [18]</td>
<td>2011</td>
<td>Italy</td>
<td>EASL</td>
<td>IIF</td>
<td>AMA</td>
<td>14</td>
<td>5</td>
<td>9</td>
<td>173</td>
</tr>
<tr>
<td>Liu HY [20]</td>
<td>2010</td>
<td>China</td>
<td>EASL</td>
<td>IIF</td>
<td>AMA</td>
<td>4</td>
<td>31</td>
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<td></td>
<td>ELISA</td>
<td>AMA-M2</td>
<td>173</td>
<td>20</td>
<td>25</td>
<td>65</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>WB</td>
<td>AMA-M2</td>
<td>74</td>
<td>0</td>
<td>5</td>
<td>51</td>
</tr>
<tr>
<td>Bargou I [24]</td>
<td>2008</td>
<td>Tunisia</td>
<td>–</td>
<td>IIF</td>
<td>AMA-M2</td>
<td>54</td>
<td>0</td>
<td>1</td>
<td>51</td>
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<tr>
<td>Oertelt S [26]</td>
<td>2007</td>
<td>Italy</td>
<td>–</td>
<td>ELISA</td>
<td>AMA-M2</td>
<td>84</td>
<td>0</td>
<td>19</td>
<td>111</td>
</tr>
<tr>
<td>Yao DK [27]</td>
<td>2005</td>
<td>China</td>
<td>AASLD 2000</td>
<td>IIF</td>
<td>AMA-M2</td>
<td>75</td>
<td>3</td>
<td>3</td>
<td>52</td>
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<tr>
<td>Yan HP [28]</td>
<td>2005</td>
<td>China</td>
<td>AASLD 2000</td>
<td>IIF</td>
<td>AMA-M2</td>
<td>52</td>
<td>84</td>
<td>0</td>
<td>2864</td>
</tr>
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<td>Liu YM [29]</td>
<td>2004</td>
<td>China</td>
<td>AASLD 2000</td>
<td>IIF</td>
<td>AMA-M2</td>
<td>5</td>
<td>10</td>
<td>0</td>
<td>454</td>
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<tr>
<td>Muratori P [30]</td>
<td>2004</td>
<td>Italy</td>
<td>–</td>
<td>ELISA</td>
<td>AMA-M2</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>464</td>
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<td>Romero-Gómez M [31]</td>
<td>2004</td>
<td>Spain</td>
<td>–</td>
<td>IIF</td>
<td>AMA-M2</td>
<td>91</td>
<td>7</td>
<td>36</td>
<td>259</td>
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<td>Sakugawa H [32]</td>
<td>2003</td>
<td>Japan</td>
<td>–</td>
<td>IIF</td>
<td>AMA-M2</td>
<td>95</td>
<td>4</td>
<td>41</td>
<td>34</td>
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<td>Jong-Hon K [33]</td>
<td>2001</td>
<td>Japan</td>
<td>–</td>
<td>IIF</td>
<td>AMA-M2</td>
<td>6</td>
<td>4</td>
<td>1</td>
<td>111</td>
</tr>
<tr>
<td>Bandin O [34]</td>
<td>1996</td>
<td>France</td>
<td>–</td>
<td>IIF</td>
<td>AMA-M2</td>
<td>49</td>
<td>0</td>
<td>14</td>
<td>291</td>
</tr>
<tr>
<td>Lee WM [37]</td>
<td>1983</td>
<td>Carolina</td>
<td>–</td>
<td>IIF</td>
<td>AMA-M2</td>
<td>16</td>
<td>7</td>
<td>0</td>
<td>97</td>
</tr>
</tbody>
</table>

*aThe substrate is rat kidney/stomach/liver sections; bMIT3-based ELISA; cThe antigen source is unknown; dUS et al.: US, Canada, UK, Greece, Italy, Japan; eAnti-PDC ELISA; fAnti-M2-3E ELISA. AASLD, the American Association for the Study of Liver Diseases; AMA/AMA-M2, anti-mitochondrial antibody/the M2 subtype; EASL, European Association for the Study of the Liver; ELISA, enzyme-linked immunosorbent assay; IIF, indirect immunofluorescence; WB, Western blot.

CI 98.2%–98.6%). The sensitivities of AMA-M2 by ELISA methods ranged from 72.9% to 100% (pooled Sen: 83.2%, 95% CI 80.8%–85.3%) and specificity values ranging from 76.5% to 100% (pooled Spe: 95.3%, 95% CI 94.5%–96.0%). Sensitivities and specificities by Western blot ranged from 85.0% to 94.9% (pooled Sen: 88.3%, 95% CI 83.5%–92.1%) and 84.8% to 100% (pooled Spe: 91.7%, 95% CI 89.3%–93.8%), respectively. The pooled sensitivity, specificity, LR+, LR−, and DOR values for AMA and AMA-M2 found through the different methods are summarized in Table 2.

**Discussion**

PBC is an organ-specific autoimmune disease and is the most common of all autoimmune liver diseases (ALD). It mainly affects middle-aged women and is characterized by damage to biliary epithelial cells, cholestasis, and liver cirrhosis and failure. Estimates of PBC incidence and prevalence are quite different in different geographic areas and range from 2.7 to 32.2 and/or 16–492 per million, respectively. The reported number keeps rising due to the improvement of diagnosis methods [20, 39–41].
patients may present with symptoms such as fatigue, pruritus, and/or jaundice, but most of them are asymptomatic. Some may present with complications of portal hypertension such as ascites, hypersplenism, hepatic encephalopathy, esophageal variceal bleeding, and gastrointestinal bleeding [3]. Unexpectedly, hepatocellular carcinoma (HCC) had a relatively high prevalence in PBC [42]. The early and accurate diagnosis of PBC in clinical practice is important. PBC diagnosis is based on established criteria including cholestatic liver tests, a positive AMA test, and histopathologic evidence. PBC is grouped into four histologic stages; however, the liver is not affected symmetrically, and a single biopsy might demonstrate the presence of all four stages at the same time [3]. Furthermore, liver biopsies pose a small but significant risk of fatal hemorrhage. Consequently, serum-specific biomarkers for the non-invasive diagnosis of PBC are vital for clinical applications.

In this study, pooled AMA (all methods) sensitivity and specificity were 84.5% and 97.8%, respectively.

Table 2: Stratified analyses of the included studies about ethnicities, methods, and types.

<table>
<thead>
<tr>
<th>Subtype</th>
<th>DOR</th>
<th>95% CI</th>
<th>Sen</th>
<th>95% CI</th>
<th>Spe</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled sensitivity</td>
<td>Pooled specificity</td>
<td>Pooled LR+</td>
<td>pooled LR−</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMAa</td>
<td>191.65</td>
<td>120.13–305.75</td>
<td>0.845</td>
<td>0.833–0.856</td>
<td>0.978</td>
<td>0.976–0.980</td>
</tr>
<tr>
<td>AMA-M2b</td>
<td>180.59</td>
<td>81.569–399.81</td>
<td>0.843</td>
<td>0.823–0.862</td>
<td>0.948</td>
<td>0.940–0.955</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>European</td>
<td>206.82</td>
<td>87.530–488.69</td>
<td>0.815</td>
<td>0.792–0.836</td>
<td>0.972</td>
<td>0.966–0.978</td>
</tr>
<tr>
<td>South American</td>
<td>37.843</td>
<td>11.775–121.62</td>
<td>0.758</td>
<td>0.701–0.809</td>
<td>0.960</td>
<td>0.949–0.968</td>
</tr>
<tr>
<td>Asians</td>
<td>295.84</td>
<td>135.03–648.13</td>
<td>0.887</td>
<td>0.868–0.904</td>
<td>0.983</td>
<td>0.981–0.985</td>
</tr>
<tr>
<td>China</td>
<td>247.77</td>
<td>101.42–605.27</td>
<td>0.888</td>
<td>0.868–0.906</td>
<td>0.984</td>
<td>0.982–0.986</td>
</tr>
<tr>
<td>Japan</td>
<td>555.67</td>
<td>161.30–1914.30</td>
<td>0.879</td>
<td>0.808–0.931</td>
<td>0.966</td>
<td>0.951–0.977</td>
</tr>
<tr>
<td>African</td>
<td>534.75</td>
<td>73.724–3878.73</td>
<td>0.939</td>
<td>0.891–0.971</td>
<td>0.974</td>
<td>0.934–0.993</td>
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<tr>
<td>Methods</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>ELISAc</td>
<td>171.89</td>
<td>67.904–435.13</td>
<td>0.832</td>
<td>0.808–0.853</td>
<td>0.953</td>
<td>0.945–0.960</td>
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<tr>
<td>MIT3d</td>
<td>151.31</td>
<td>31.415–728.78</td>
<td>0.797</td>
<td>0.763–0.829</td>
<td>0.950</td>
<td>0.938–0.961</td>
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<td>Others%</td>
<td>214.91</td>
<td>57.775–799.39</td>
<td>0.872</td>
<td>0.840–0.899</td>
<td>0.955</td>
<td>0.944–0.965</td>
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<tr>
<td>IIFf</td>
<td>212.15</td>
<td>118.75–379.03</td>
<td>0.846</td>
<td>0.831–0.860</td>
<td>0.984</td>
<td>0.982–0.986</td>
</tr>
<tr>
<td>WBg</td>
<td>171.71</td>
<td>25.383–1161.6</td>
<td>0.883</td>
<td>0.835–0.921</td>
<td>0.917</td>
<td>0.893–0.938</td>
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<tr>
<td>Dot blot</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Only one study</strong></td>
<td></td>
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</tr>
</tbody>
</table>

*aAll methods; 1The detection methods are ELISA, WB and Dot blot; 2AMA-M2 is measured using ELISA; 3MIT3-based ELISA; 4The antigen sources are anti-PDC, anti-M2-3E or unknown; 5AMA is measured using IIF; 6AMA-M2 is measured using WB. AMA, anti-mitochondrial antibody; AMA-M2, the M2 subtype; CI, confidence interval; DOR, diagnostic odds ratio; ELISA, enzyme-linked immunosorbent assay; IIF, indirect immunofluorescence; LR±, positive/negative likelihood ratio; Sen, sensitivity; Spe, specificity; WB, Western blot.*
Through meta-analysis, pooled sensitivity and specificity of the AMA-M2 subtype (the detection methods are ELISA, WB and Dot blot: Sen=84.3%, Spe=94.8%) for PBC diagnosis was not as good as total AMA (all methods: Sen=84.5%, Spe=97.8%), which indicates that total AMA is a better and more comprehensive marker for PBC diagnosis. Both IIF for AMA and ELISA for AMA-M2 showed high specificity above 90% and relatively low sensitivity above 80%. As to the different antigen sources of ELISA kits, our results demonstrate that the sensitivity of MIT3-based ELISA (Sen=79.7%) is not good enough. The anti-M2E ELISA improves the diagnostic accuracy compared with those of anti-MIT3 ELISA and conventional anti-PDC ELISA [43]. Compared with IIF and ELISA, the Western blot has the highest sensitivity (88.3%) but low specificity (91.7%). However, a small number of patients have PBC without testing positive for AMA; these patients are often diagnosed with AMA-negative PBC. AMA-negative PBC patients, a subgroup of patients with undetectable AMA using routine methods, have analogous clinical courses as well as serum biochemical and hepatic histological features to AMA-positive patients [44–47]; these patients’ diagnosis is challenging. Interestingly, most of these patients have higher frequencies of positive rates for anti-nuclear antibodies (ANAs) and anti-smooth muscle antibodies (ASMAs) [48–57]. A meta-analysis conducted by Huang et al. showed that sensitivity and specificity in GP210 detection in a Chinese population with PBC were 0.34 and 0.98 [58]. The prevalence of SP100 in PBC is about 20%, and it appears highly specific (94%) for a PBC diagnosis [34]. However, of 15 patients with PBC who do not have detectable AMA, seven patients have ANA with a nuclear rim pattern [32]. ANA directs against the nuclear pore membrane GP210 or the nuclear protein SP100 and is highly specific for and correlated with PBC prognosis; it can be used as a useful supplement for diagnosis, especially in AMA-negative PBC patients [59–64].

Little difference was found in sensitivity in our stratified analyses of ethnicities. The sensitivity is highest in Africans (93.9%), followed by in Asians (88.7%), then in Europeans (81.5%) and lowest in South Americans (75.8%). Different geographical area and selecting cases according to genetic and environmental factors could explain the discrepancy [65, 66]. As in the majority of autoimmune diseases, PBC is likely to be genetically complex. The role of genetic factors in PBC is strongly supported by the 63% concordance rate in monozygotic twins; this rate is second only to celiac disease, which is the highest reported in autoimmunity [67]. Over the past few years, a number of genes, such as cytotoxic T-lymphocyte antigen-4 (CTLA-4) [68], HLA DRB1*08 [69], tumor necrosis factor-α (TNF-α) [70], and programmed cell-death 1 (PDCD1) [71, 72], have been significantly associated with PBC susceptibility.

Heterogeneity is a latent problem when interpreting results in meta-analysis. On one hand, the Spearman’s correlation coefficient indicates that no heterogeneity from threshold effects arises when differences in sensitivities and specificities occur due to different cut-offs or thresholds used in different studies to define positive or negative test results. On the other hand, the pooled DOR

Figure 3 The SROC curve of the AMA/AMA-M2 test for the diagnosis of PBC.
Sample size is indicated by the size of the square. The regression SROC curve indicates the overall diagnostic accuracy. (A) The SROC curves for all data sets about AMA (all methods). (B) The SROC curves for all data sets about AMA-M2. AUC, area under curve; Q*, index; SE, standard error; SROC curve, summary receiver operator curve.
was used to discuss the heterogeneity caused by non-threshold effects. We found that the DOR of each study did not distribute along a straight line with the pooled DOR in the forest plots. Meanwhile, the Q* (199.63, \( p = 0.0000 \)) implied a non-threshold effect in the analysis. Different ethnicities, measurement methods, or autoantibody types may contribute to heterogeneity sources. We performed a meta-regression analysis to assess the contribution of the factors above and found that ethnicities and autoantibody types were the sources of heterogeneity. Next, the sub-group analysis was performed.

Similar to other meta-analyses of diagnostic tests, the limitations of our work should be considered. First, we did not compare the sensitivity and specificity of \( \text{AMA} \)/\( \text{AMA-M2} \) using a combination of \( \text{AMA}/\text{AMA-M2} \) and GP210 and/or SP100 due to a lack of data. Second, we did not compare the sensitivity and specificity of the source of reagents in ELISA due to a lack of documents. Last, only one study was included the Dot blot method, and we could not assess the utility.

In conclusion, despite the limitations mentioned above, the current evidence suggests that \( \text{AMA} \) and \( \text{AMA-M2} \) are

![Forest plot of the sensitivity and specificity of AMA-IIF (AMA*) and AMA-M2 (AMA-M2**) in the diagnosis of PBC. Only the first author of each study is given. Sensitivity and specificity given with CIs. AMA*: AMA is measured using IIF. AMA-M2**: The detection methods are ELISA, WB and Dot blot. CI, confidence interval.](image-url)
favorable serum markers with high specificities and relative moderate sensitivities for PBC diagnosis. However, determining PBC diagnoses and prognoses remains challenging. In order to decrease the misdiagnosis rate, a combination of AMA/AMA-M2 and the GP210 and/or SP100 antibodies may be necessary in clinical applications.

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Conflict of interest statement

Authors’ conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article. Research support played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

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Honorarium: None declared.

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