



# Editorial on: large-scale characterization study of patients with antimitochondrial antibodies but non-established primary biliary cholangitis

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Primary biliary cholangitis (PBC) is an autoimmune disease of the liver characterized by destruction of the interlobular bile ducts, leading ultimately to an increased risk for cirrhosis, and its consequent complications, such as portal hypertension and increased risk for liver cancer (1). PBC is an important cause of morbidity and mortality in Western society. Diagnosis of PBC relies on the finding of cholestatic biomarker elevation and the presence of antimitochondrial antibodies (AMA); a highly-specific auto antibody present in more than 95% of patients with PBC (2).

The presence of AMA without clinical and/or biochemical evidence of PBC has been previously reported, and this often represents a clinical dilemma. It is widespread practice that healthcare providers test for the presence of AMA in patients with abnormal liver function tests, particularly elevated serum alkaline phosphatase (ALP). Mattalia *et al.* (3) investigated the prevalence of AMA in an Italian cohort of 1,530 people; only 9 (0.6%) tested positive for AMA. Follow-up of 8 subjects after a period of 8–14 months confirmed AMA reactivity; however, none of these subjects developed PBC during the follow-up period. In a similar fashion, Chen *et al.* (4) reported an AMA-positivity prevalence of 0.7% (133/19,012) among healthy Chinese residents who received routine medical examinations in Xuhui District of Shanghai; 25 subjects in the AMA-positive group were diagnosed with PBC. Mitchison *et al.* (5) reported 29 patients with positive AMA, detected during screening for other autoimmune diseases, and normal

liver function tests, including ALP and bilirubin. Twenty-four patients (83%) had liver biopsies either diagnostic of or compatible with PBC. Of the 16 patients who had been followed for a mean of 8.7 years (range, 4–13 years), 5 patients developed symptoms suggestive of PBC, and 11 patients developed elevation of ALP. Later, Metcalf *et al.* (6) reported a 10-year follow-up of this cohort; 22 (76%) developed symptoms of PBC, and 24 (83%) had persistent cholestasis.

What is the clinical significance (if any) of presence of AMA when there is no clinical, biochemical, or histological evidence of PBC? Should we worry about it? Do subjects who test positive for AMA but don't exhibit symptoms or signs of liver disease or biochemical evidence of PBC need to be monitored? And if yes, who, how, for how long, and how often? Do such patients need to be treated with ursodeoxycholic acid (UDCA)?

We read with great interest the paper reported by Dahlqvist *et al.* (*Hepatology* 2017; 65:152-163). In their fascinating study (7), they report the clinical outcomes' data collected from a nation-wide registry of 63 French immunology laboratories and healthcare providers on 1,318 patients (with 1,367 positive AMA tests), of whom 229 subjects had positive AMA test with non-established PBC, and follow-up data available for 92 patients. Of the 229 subjects who had positive AMA and non-established PBC, 179 (78%) were female, 31/130 (24%) had a history of autoimmune disease, and 9/143 (6%) had PBC-

specific antinuclear antibodies (ANAs). The most frequent autoimmune diseases were systemic lupus erythematosus (n=18), followed by Sjogren's syndrome (n=14), and autoimmune hepatitis (n=10). In 12% of cases, AMAs were found in patients with nonautoimmune liver diseases (chronic hepatitis C, n=8, and alcoholic liver disease, n=8).

Follow-up data was available for 92 patients (mean follow-up of 4 years; and range: 0.5–7.3 years). Eighteen percent (17/92) of patients died during the follow-up period; none of the patients died from autoimmune liver diseases, including PBC. Ten percent (9/92) of patients developed PBC during the follow-up period, with a reported 5-year PBC incidence rate of 16%. The majority were women (89%), and the median age at PBC diagnosis was 62 years.

This is an important study and highlights the long-awaited outcomes' data related to patients who have positive AMA without clinical/biochemical/histological evidence of PBC. The study also reports the very low liver-related mortality in this group of patients, which in turn questions the frequent testing for the presence of AMA in subjects in the absence of clinical and/or biochemical evidence of PBC. Perhaps the most striking and unexpected finding of this study is the high mortality in this group of patients irrespective of PBC development. What is even more interesting is that more half of the deaths in this group were cancer-related, which raises an important question and that is if the finding positive AMA is associated with increased cancer-mortality, irrespective of the development of PBC? The risk factor(s) for development of PBC in patients who test positive for AMA but without evidence of PBC remains a mystery.

The reported prevalence of AMA positivity in healthy individuals has varied, ranging between 0.07% and 9.9% (3,8-11). Dahlqvist *et al.* (7) reported a 2.5% prevalence of AMA positivity in their cohort. The differences in the reported prevalence of AMA positivity may be attributed to the techniques used for detecting AMA. Muratori *et al.* (12) assessed the sensitivity and specificity of Western immunoblot with bovine sub-mitochondrial particles, indirect immunofluorescence (IF) on rat tissue sections and Hep-2 cells, and two ELISAs with AMA-specific recombinant proteins for detecting AMA in 127 patients with PBC. They found that the Western immunoblot detects AMA significantly more often than IF on Hep-2 cells (85% *vs.* 72%) or rodent tissue (85% *vs.* 71%), whereas both ELISAs were only slightly less sensitive than the Western immunoblot technique (81% *vs.* 78%). These data highlight

the differences in the sensitivities of laboratory techniques used for detecting AMA, which should be accounted for when examining the prevalence of AMA and PBC.

In conclusion, this study reports the long-term outcomes of patients who have tested positive for AMA with non-established PBC. Only a small portion of patients will eventually develop PBC. The mortality in this group of patients is higher than in the healthy population. Future studies are needed to clarify the role of AMA on patients' outcomes and to identify the risk factors for development PBC in AMA-positive patients with non-established PBC.

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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