Letter to the Editor

Testing strategies for anti-mitochondrial M2 antibodies

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Optimal testing strategies for incidental anti-mitochondrial M2 antibody-positive patients

Ilkay Ergenc[1], Busra Gozaydinoglu[1], Caglayan Keklikkiran[2], Yusuf Yilmaz[1,34]

[1]Department of Gastroenterology, Marmara University School of Medicine, Istanbul, Turkiye; [2]Institute of Gastroenterology, Marmara University, Istanbul, Turkiye; [3]Department of Gastroenterology, Recep Tayyip Erdogan University School of Medicine, Rize, Turkiye; [4]Department of Gastroenterology, Recep Tayyip Erdogan University Rize Training and Research Hospital, Rize, Turkiye

Dear Editor,

We carefully considered the letter entitled "Optimal testing strategies for incidental anti-mitochondrial M2 antibody-positive patients." We sincerely appreciate the authors' insights and the thoughtful review of our paper, "The risk of development of primary biliary cholangitis among incidental antimitochondrial M2 antibody-positive patients".[1,2] We wish to offer clarification on the issues raised in the letter.

First and foremost, it is crucial to underscore that we utilized well-recognized international PBC diagnostic criteria to establish diagnoses. These criteria entail the presence of at least 2 out of 3 key indicators: persistent elevation of alkaline phosphatase (ALP), the existence of anti-mitochondrial antibodies (AMA) or other PBC-specific autoantibodies in case AMA is negative, and histologic evidence of nonsuppurative destructive cholangitis alongside destruction of interlobular bile ducts.[3,4] Both the EASL and AASLD guidelines do not recommend routine TE for diagnosing PBC. However, these guidelines advocate for the utilization of TE to risk-stratify and/or monitor patients with PBC, with a suggested threshold of 9.6 kPa. In our study design, we employed TE to gain further insights into risk stratification and disease severity. Although we extended invitations to all participants for TE, we were only able to perform the test on patients who consented to participate in their appointments. Nonetheless, we do not believe that the absence of TE in a subgroup of patients eventually diagnosed with PBC weakens the diagnostic certainty. We consider the TE measurements of the 11 patients with a definitive diagnosis of PBC to bolster our results. Among these patients, two exhibited F4 fibrosis (28.4 kPA and 30.6 kPA), one had F2 fibrosis (9.3 kPA), while five showed F1 fibrosis (ranging between 6.2 and 8.0 kPA).

The second concern raised addresses the calculation of sensitivity and specificity for AMA-M2 IIF. It is important to note that our study exclusively focused on AMA-M2 positive individuals, and we did not include any AMA-M2 negative cases as per the study design. This design choice precluded the calculation of a traditional sensitivity/specificity table. To recap the study design, we retrospectively screened all Immunoblot (IB) panel test results, which revealed a 1.03% positivity rate. Our aim was to include 95 individuals with positive AMA-M2 antibodies and without an established PBC diagnosis up to the study timing (Table 1 in the original article).

Notably, Emsell-Needham and Khan provided valuable insights in their letter. They disclosed that the positivity of the mitochondrial M2/M4/M9 immunoblot assay did not confer any additional utility to the routine analysis of immunofluorescence positivity on mouse liver/kidney/stomach tissue in 51 samples derived from retrospective analysis of immunoblot results between 2014–2021. Their findings constitute a significant contribution to the current literature regarding the additional value of IB testing in the presence of immunofluorescence.

On the other hand, the unique design of our study underscored the significance of incidental positivity of AMA-M2. It is crucial to reiterate that the AMA-M2 positive patient cohort in our study comprised individuals with highly suspicious or diagnosed autoimmune/inflammatory disorders, particularly within rheumatologic and neurologic autoimmune populations, as detailed in the article. EASL recommends following up patients who are AMA positive with normal serum liver tests with annual biochemical reassessment for the presence of liver disease. This recommendation serves as a reference point to determine the follow-up needs and methods in incidental AMA-M2 cases. We concur with Emsell-Needham and Khan that follow-up testing strategies should be tailored to the cohort of patients based on risk stratification.

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Corresponding author: Ilkay Ergenc; Marmara Universitesi Tip Fakultesi, Gastroenteroloji Anabilim Dalı, Istanbul, Turkiye
Phone: +90 537 663 70 95; **e-mail:** ergencilkay@gmail.com

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Author's Reply

Dear Editor,

We thank Ergenc I et al. for clarifying the issues we raised in the letter, but Table 2 in the original article mentions 21 of 48 patients to be AMA-M2 positive,[1] and we used this premise to consider 27 patients to be negative, which was the basis for our sensitivity and specificity calculations in the correspondence (Fig. 1).[2] The authors indeed also report the same in the original report that 'twenty-seven individuals had negative AMA-IIF serology,' so our observations were accurate, unless these were from a different cohort altogether. They further report that 'two AMA-IIF-negative and ANA-positive patients were diagnosed with PBC.' So, overall, 17 of 48 patients (35%) had developed PBC during the 27-month follow-up period.

We agree that neither TE nor liver biopsy can be considered 'routine' tests for the diagnosis of PBC in AMA-positive individuals and especially more problematic in patients with normal alkaline phosphatase levels, even though immunoblots are highly sensitive and specific. We would, therefore, need a pragmatic approach to such patients but have a low threshold of more regular follow-ups in those with other autoimmune/inflammatory disorders.

Sujoy Khan,[1] Kristina Emsell Needham[2]
[1]Department of Immunology and Allergy, Castle Hill Hospital, Hull University Teaching Hospitals NHS Trust, UK
[2]Immunology Laboratory, Scarborough Hull York Pathology Services (SHYPS), Hull Royal Infirmary, Hull, UK
e-mail: sujoykhan@gmail.com

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