Response to letter: Optimal testing strategies for incidental anti-mitochondrial M2 antibody-positive patients

Ilkay Ergenc[1] (ORCID iD: 0000-0003-1539-501X)

Busra Gozaydınoglu[1] (ORCID iD: 0000-0002-4471-799X)

Caglayan Keklikkiran[4] (ORCID iD: 0000-0001-6304-5554)

Yusuf Yilmaz [1,2,3] (ORCID iD: 0000-0003-4518-5283)

[1]Department of Gastroenterology, School of Medicine, Marmara University, İstanbul, Turkiye

[2]Institute of Gastroenterology, Marmara University, Istanbul, Turkiye

[3]Department of Gastroenterology, Faculty of Medicine, Recep Tayyip Erdoğan University, Rize, Turkiye

[4]Clinic of Gastroenterology, Recep Tayyip Erdoğan University Rize Research and Training Hospital, Rize, Turkiye

Corresponding author: Ilkay Ergenc, MD

Marmara University School of Medicine**,** Department of Gastroenterology

Fevzi Çakmak, Muhsin Yazıcıoğlu Cd No: 10, 34899 Pendik/İstanbul, Turkey

E-mail: ergencilkay@gmail.com

Phone: +90537-663-7095

Dear Editor,

We have 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 clarify 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 include the presence of at least two out of three 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 transient elastography (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 indirect immunofluorescence (IIF). It is important to note that our study focused exclusively on AMA-M2 positive individuals, and we did not include any AMA-M2 negative cases as per the study design. This 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).

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 a retrospective analysis of immunoblot results between 2014-2021. Their findings are 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.

References

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