JHEP|Reports

Reply to: "Challenges in the diagnosis and management of AIH-PBC syndrome"

To the Editor:

We appreciate the valuable feedback from our esteemed colleagues on our recent publication regarding the diagnostic criteria and long-term outcomes in autoimmune hepatitis–primary biliary cholangitis (AIH-PBC) variant syndrome.[1] Gerussi *et al.* emphasize the challenges that studying the clinical phenotype of AIH-PBC variant syndrome bring, and we gladly respond to some of the helpful comments given.[2]

Indeed, the use of the Paris criteria for AIH-PBC variant syndrome is a subject of debate.[3,4] Despite their high specificity, the high cut-offs for both aminotransferases and IgG may underestimate the prevalence of the syndrome, *i.e.* exclude patients with milder presentations of either AIH, PBC or both disease entities. Our results suggest that this is indeed the case, with 76% of patients treated with the combination therapy of ursodeoxycholic acid (UDCA) and immunosuppressive therapy, yet not meeting the commonly used diagnostic criteria. Nonetheless, this group of patients still reaches similar long-term outcomes. We agree with the authors that within a spectrum of disease, the Paris criteria may only encompass a subgroup of patients with PBC and more hepatitis or with AIH and more cholestasis, suggesting that many patients outside the Paris criteria may also benefit from combined treatment with UDCA and immunosuppression.

We acknowledge that including histological data from the select group of patients with PBC and significantly elevated IgG and aminotransferases could have enhanced our data. A liver biopsy should be considered in patients with unexplained cholestasis after serological testing has been performed,[5] especially if a diagnosis of AIH has been made, but also in cases with PBC with significant elevation of IgG and aminotransferases. Antimitochondrial antibodies (AMA) were tested in all 74 patients in this subgroup, with 71 patients (96%) being AMA positive. In 51 patients a liver biopsy was performed, however, only data on the Ludwig score was available for these biopsies. If more liver biopsies would have been performed in these 74 patients and more data on the severity of portal and lobular inflammation was available in these patients, this could have given more insight into potential features of both PBC and AIH being present. Consequently, with a liver biopsy, these patients might have had a stronger diagnosis of AIH-PBC variant syndrome, not fulfilling the Paris criteria, and they might have benefitted from combination therapy with both UDCA and immunosuppression, instead of only UDCA.

As stated in the discussion of our manuscript, the study design was limited by its retrospective nature. We agree with Gerussi *et al.* that complete data on the use of second-line PBC therapy would have strengthened our conclusion regarding the higher mortality rate in patients with PBC and elevated IgG and aminotransferases. These patients were treated only with UDCA, since no second-line therapies were available during the timeframe of this study. With emerging novel therapies, future studies should ascertain adequate documentation on different treatment regimens prescribed to patients. When correcting for cirrhosis at diagnosis, and when correcting for age, the difference in liver transplantation-free survival of these patients compared to AIH-PBC was not significant anymore. This suggests that there may be different confounders responsible for the significantly worse prognosis in PBC with elevated IgG and aminotransferases next to the lack of prescribed immunosuppression or, as Gerussi *et al.* suggest, second-line anti-cholestatic therapy might have also benefitted these patients.

Finally, we would like to express our gratitude to the authors for highlighting the ongoing international Delphi process regarding standardization of nomenclature, diagnostic criteria and therapeutic strategies in patients with AIH-PBC variant syndrome. As participating core group members delegated from the IAIHG (International Autoimmune Hepatitis Group), we fully endorse this initiative from the ERN-RARE LIVER network, the IAIHG and the Global PBC study group, and we fully agree with the aim of improving long-term outcomes for this group of patients.

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Authors' contributions

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Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the author(s) used ChatGPT in order to improve language and readability. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2024.101248.

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