maximum likelihood (REML), implemented in R (v4.4.x; mada package). This approach jointly models logit sensitivity and false-positive rate, accounting for between-study heterogeneity and correlation.

In the overall PSC analysis, pooled sensitivity was 0.705 and specificity 0.894 (area under the curve receiver operating characteristic [AUROC]: 0.893); positive likelihood ratio [PLR] was 6.65 and negative likelihood ratio [NLR] 0.33. Between-study heterogeneity was substantial (standard deviation (SD) logit sensitivity: 1.462; SD logit false positive rate: 1.197), with strong negative correlation ($\rho \approx -0.97$), consistent with threshold variability (Supplementary Fig. 1,2).

All studies used data-derived thresholds based on healthy controls (mean +X SD). Three studies applied mean +3 SD [3-5], whereas 1 [6] used mean +2 SD, confirming threshold heterogeneity, handled within the hierarchical model.

In the predefined PSC plus inflammatory bowel disease (IBD) subgroup, 2 studies lacked IBD-only controls [3,5]; therefore, a hypothetical comparator was constructed using externally reported specificity (88%) [7] and a 1:1 case–control ratio, acknowledging assumptions introduced. Hierarchical analysis yielded sensitivity 0.831 (95%CI 0.418-0.971) and specificity 0.740 (95%CI 0.502-0.889), AUROC 0.835, PLR 3.20, and NLR 0.23, with substantial heterogeneity (Supplementary Fig. 3,4).

In PSC without IBD, specificity remained high (0.966) with PLR 14.04 (AUROC: 0.965). For PSC vs. other cholestatic diseases, sensitivity was 0.814 and specificity 0.959 (AUROC: 0.968; PLR: 19.85) (Supplementary Fig. 5-8).

Overall, hierarchical modelling confirms moderate sensitivity and high specificity, with strong rule-in performance in selected subgroups, reinforcing the conclusions of our work.

Authors' reply

Alexandra Argyrou[a], Stamatina Vogli[b], Stavros P. Papadakos[a], Antonios Chatzigeorgiou[c], Andreas Koutsoumpas[a], Jiannis Vlachogiannakos[a], George V. Papatheodoridis[a]

Medical School, National and Kapodistrian University of Athens, General Hospital of Athens "Laiko"; "Metaxa" Cancer Hospital, Piraeus, Medical School, National and Kapodistrian University of Athens, Greece

We sincerely thank Dr. Montero [1] for his thoughtful comments on the modeling strategy used in our meta-analysis of serum anti-integrin αvβ6 autoantibodies for primary sclerosing cholangitis (PSC) [2]. His emphasis on hierarchical diagnostic test accuracy (DTA) methodology contributes to interpreting our findings [1].

We reanalyzed the original 2×2 data using a hierarchical bivariate random-effects (Reitsma) model with restricted

References

1. Arredondo Montero J. Comments on modeling strategy and data handling in a meta-analysis of anti-integrin αvβ6 for primary sclerosing cholangitis. *Ann Gastroenterol* 2026;**39**:379-381.
2. Papadakos SP, Vogli S, Argyrou A, et al. Serum anti-integrin αvβ6 autoantibodies for diagnosis of primary sclerosing cholangitis: a systematic review and meta-analysis. *Ann Gastroenterol* 2026;**39**:40-47.
3. Yoshida H, Shiokawa M, Kuwada T, et al. Anti-integrin αvβ6 autoantibodies in patients with primary sclerosing cholangitis. *J Gastroenterol* 2023;**58**:778-789.
4. Bloemen H, Livanos AE, Martins A, et al. Anti-integrin αvβ6 autoantibodies are increased in primary sclerosing cholangitis patients with concomitant inflammatory bowel disease and correlate with liver disease severity. *Clin Gastroenterol Hepatol* 2025;**23**:1612-1622.
5. Yasuda M, Shiokawa M, Kuwada T, et al; Japan PSC Study Group (JPSCSG). Anti-integrin αvβ6 autoantibody in primary sclerosing cholangitis: a Japanese nationwide study. *J Gastroenterol* 2025;**60**:118-126.
6. Roth D, Düll MM, Horst LJ, et al. Integrin αVβ6: autoantigen and driver of epithelial remodeling in colon and bile ducts in primary sclerosing cholangitis and inflammatory bowel disease. *J Crohns*

Colitis 2025;**19**:jjae131.
7. Yang J, Huang MMC, Liang MMJ, Lei MMY. The diagnostic performance of serum αvβ6 autoantibodies for ulcerative colitis: a systematic review and meta-analysis. *Clin Res Hepatol Gastroenterol* 2024;**48**:102317.

[a]First Department of Gastroenterology, Medical School, National and Kapodistrian University of Athens, General Hospital of Athens "Laiko", Athens, Greece (Alexandra Argyrou, Stavros P. Papadakos, Andreas Koutsoumpas, Jiannis Vlachogiannakos, George V. Papatheodoridis); [b]Department of Gastroenterology, "Metaxa" Cancer Hospital, Piraeus, Greece (Stamatina Vogli); [c]Laboratory of Physiology, Medical School, National and Kapodistrian University of Athens, Athens, Greece (Antonios Chatzigeorgiou)

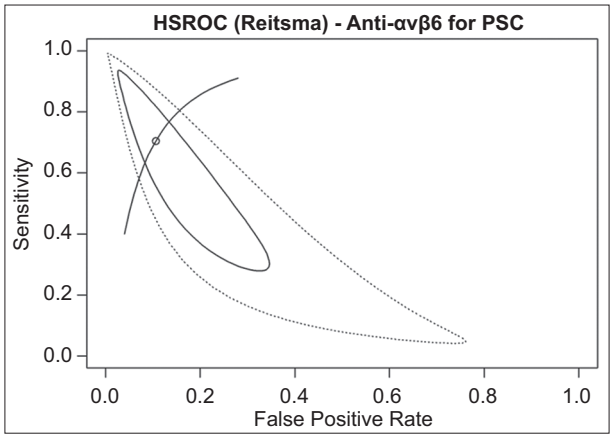
Conflict of Interest: None

Correspondence to: Prof. George V. Papatheodoridis, MD, PhD, 1st Department of Gastroenterology, Medical School of National and Kapodistrian University of Athens, General Hospital of Athens "Laiko", 17 Agiou Thoma street, 11527 Athens, Greece, e-mail: gepapath@med.uoa.gr

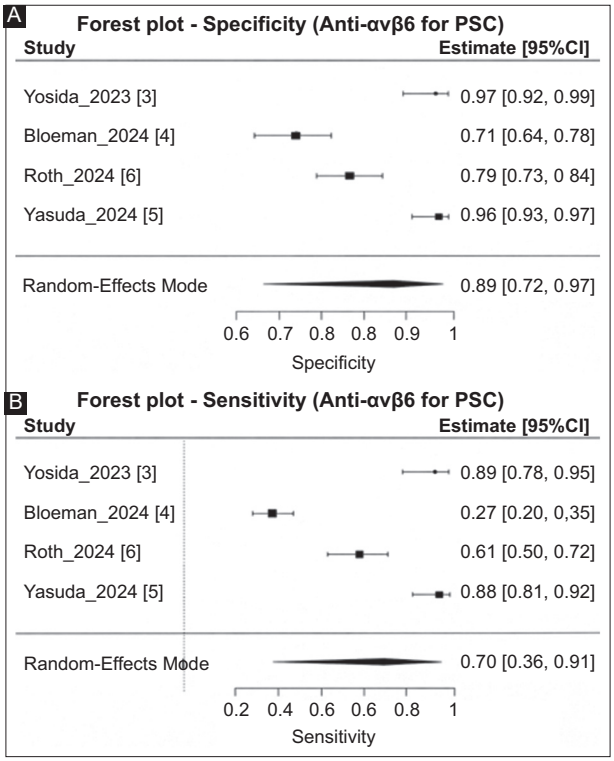
Received 5 March 2026; accepted 19 March 2026; published online 23 April 2026

DOI: https://doi.org/10.20524/aog.2026.1061

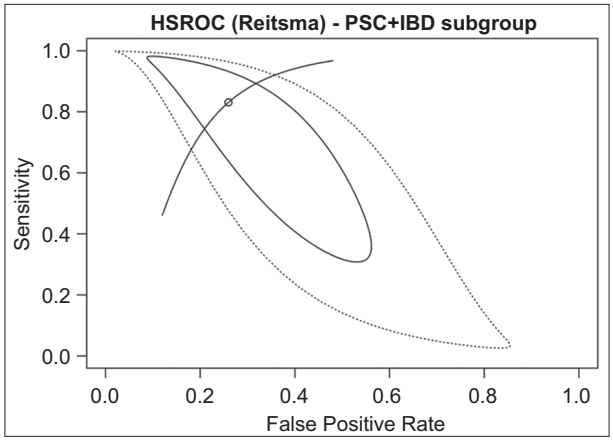
Supplementary material



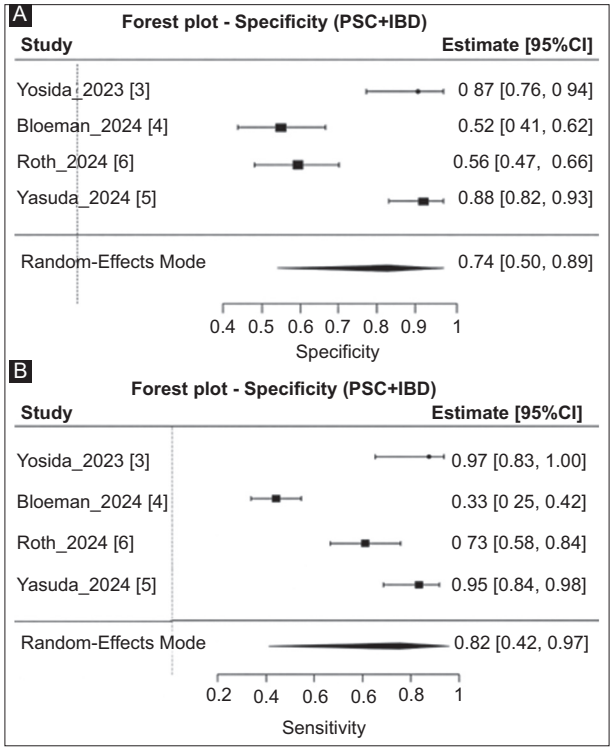
Supplementary Figure 1 Hierarchical summary receiver operating characteristic (HSROC) curve for serum anti-integrin αvβ6 autoantibodies in the diagnosis of primary sclerosing cholangitis (PSC)



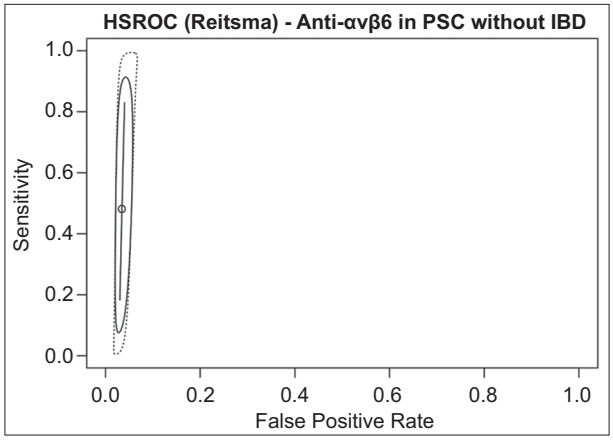
Supplementary Figure 2 Forest plots of diagnostic accuracy for serum anti-integrin αvβ6 autoantibodies in primary sclerosing cholangitis (PSC). (A) Forest plot of study-specific and pooled specificity estimates. (B) Forest plot of study-specific and pooled sensitivity estimates



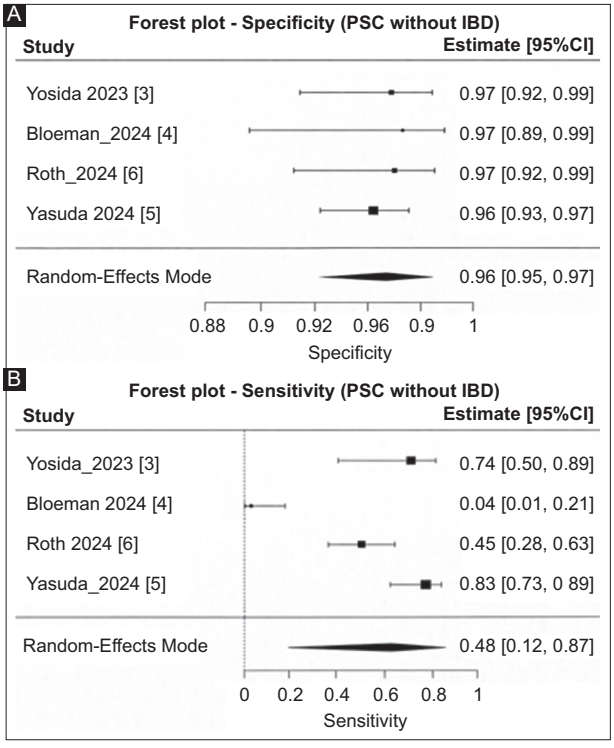
Supplementary Figure 3 Hierarchical summary receiver operating characteristic (HSROC) curve for serum anti–integrin αvβ6 autoantibodies in the primary sclerosing cholangitis (PSC) with concomitant inflammatory bowel disease (IBD) subgroup



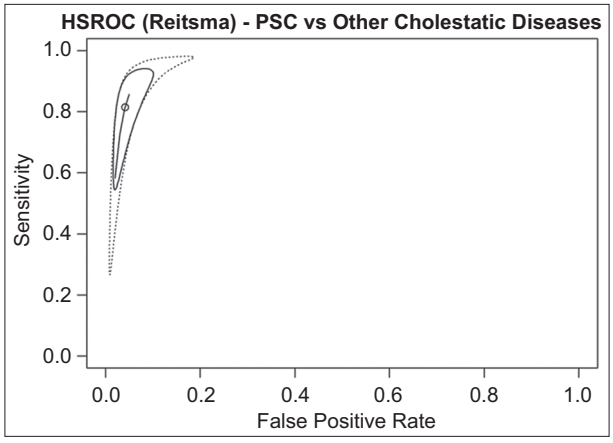
Supplementary Figure 4 Forest plots of diagnostic accuracy for serum anti-integrin αvβ6 autoantibodies in the primary sclerosing cholangitis (PSC) with concomitant inflammatory bowel disease (IBD) subgroup. (A) Forest plot of study-specific and pooled specificity estimates. (B) Forest plot of study-specific and pooled sensitivity estimates



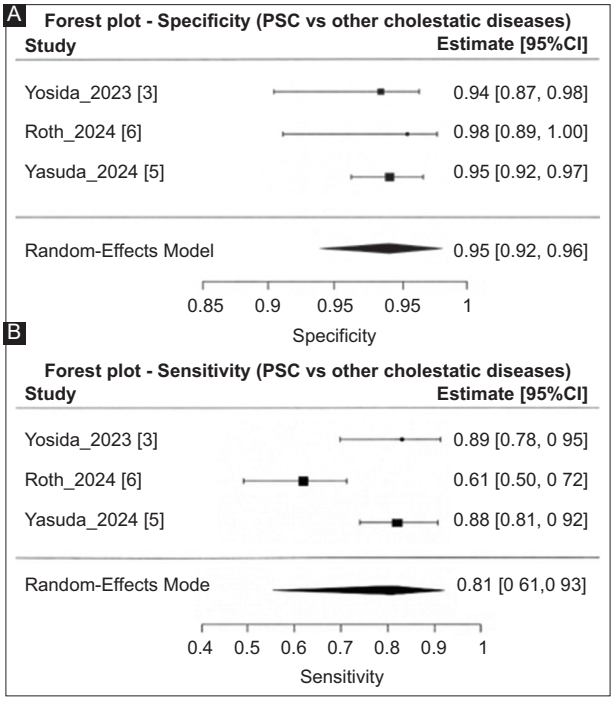
Supplementary Figure 5 Hierarchical summary receiver operating characteristic (HSROC) curve for serum anti-integrin αvβ6 autoantibodies in patients with primary sclerosing cholangitis (PSC) without concomitant inflammatory bowel disease (IBD)



Supplementary Figure 6 Forest plots of diagnostic accuracy for serum anti-integrin αvβ6 autoantibodies in patients with primary sclerosing cholangitis (PSC) without concomitant inflammatory bowel disease (IBD), (A) Forest plot of study-specific and pooled specificity estimates, (B) Forest plot of study-specific and pooled sensitivity estimates



Supplementary Figure 7 Hierarchical summary receiver operating characteristic (HSROC) curve for serum anti-integrin αvβ6 autoantibodies distinguishing primary sclerosing cholangitis (PSC) from other cholestatic liver diseases



Supplementary Figure 8 Forest plots of diagnostic accuracy for serum anti-integrin αvβ6 autoantibodies in distinguishing primary sclerosing cholangitis (PSC) from other cholestatic liver diseases. (A) Forest plot of study-specific and pooled specificity estimates. (B) Forest plot of study-specific and pooled sensitivity estimates