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Authors' reply

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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 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.

References

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Conflict of Interest: None

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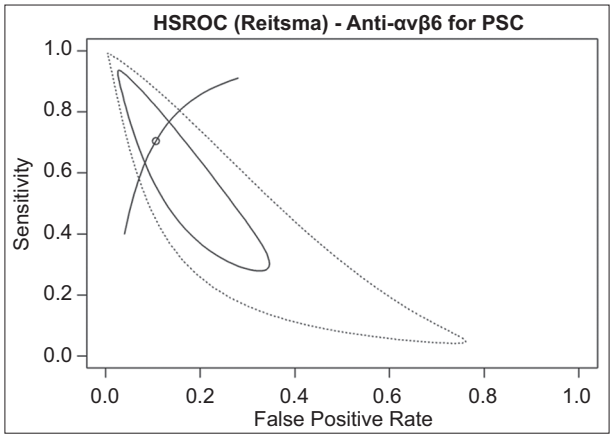
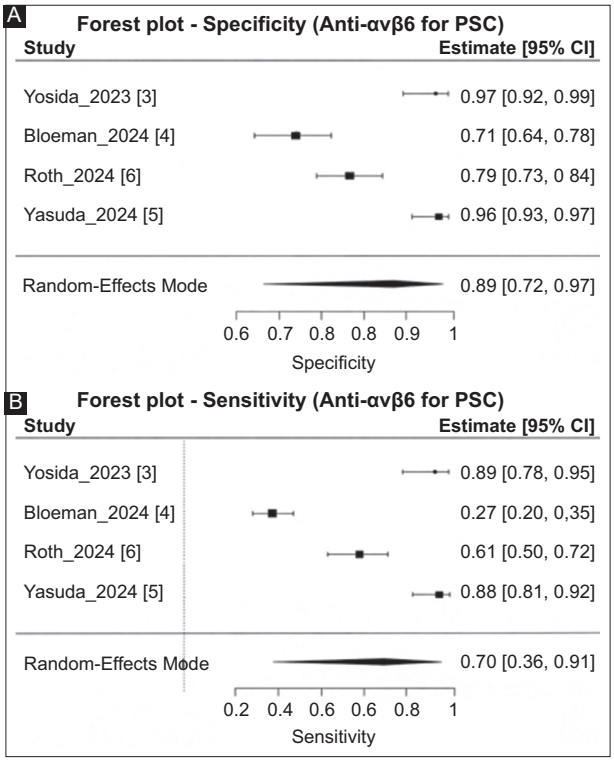
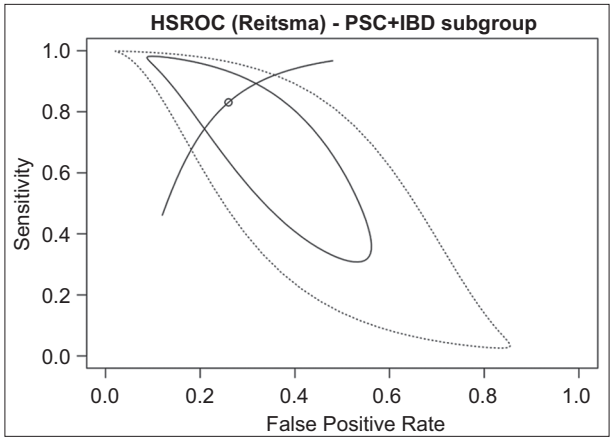
Supplementary material



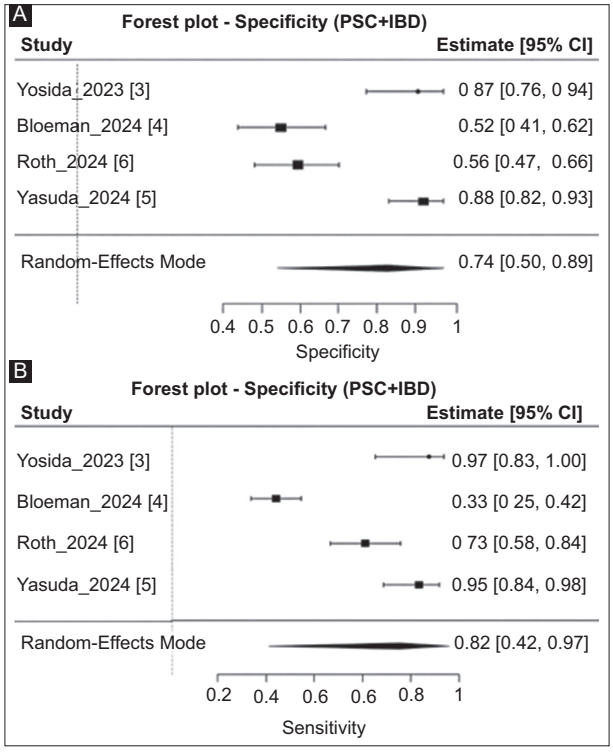
Supplementary Figure 1 Hierarchical summary receiver operating characteristic (HSROC) curve for serum anti-integrin αvβ6 autoantibodies in the diagnosis of primary sclerosing cholangitis (PSC)



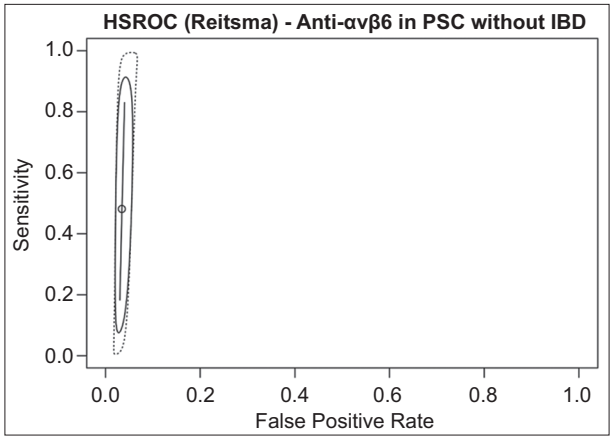
Supplementary Figure 2 Forest plots of diagnostic accuracy for serum anti-integrin αvβ6 autoantibodies in primary sclerosing cholangitis (PSC). (A) Forest plot of study-specific and pooled specificity estimates. (B) Forest plot of study-specific and pooled sensitivity estimates



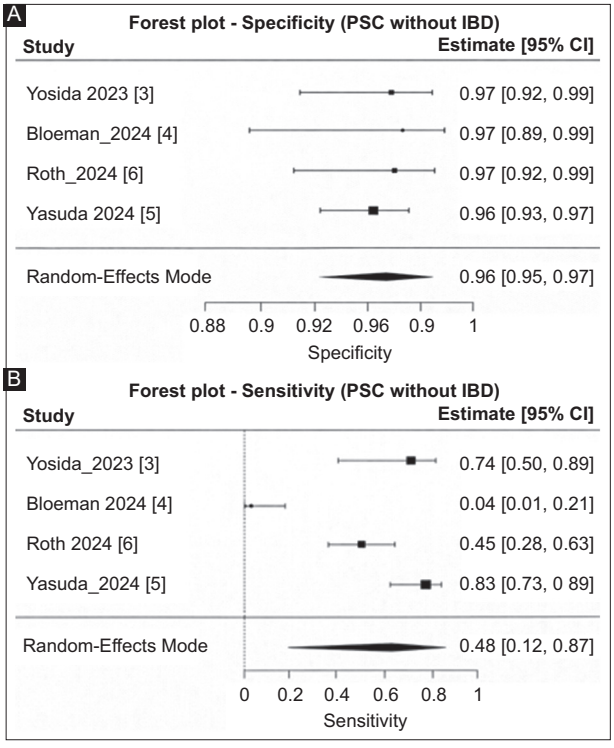
Supplementary Figure 3 Hierarchical summary receiver operating characteristic (HSROC) curve for serum anti–integrin αvβ6 autoantibodies in the primary sclerosing cholangitis (PSC) with concomitant inflammatory bowel disease (IBD) subgroup



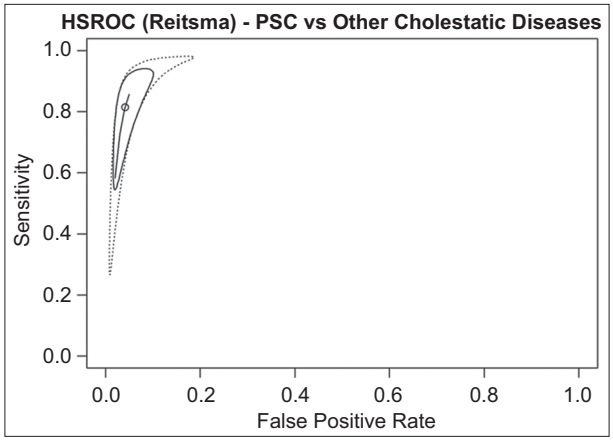
Supplementary Figure 4 Forest plots of diagnostic accuracy for serum anti-integrin αvβ6 autoantibodies in the primary sclerosing cholangitis (PSC) with concomitant inflammatory bowel disease (IBD) subgroup. (A) Forest plot of study-specific and pooled specificity estimates. (B) Forest plot of study-specific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



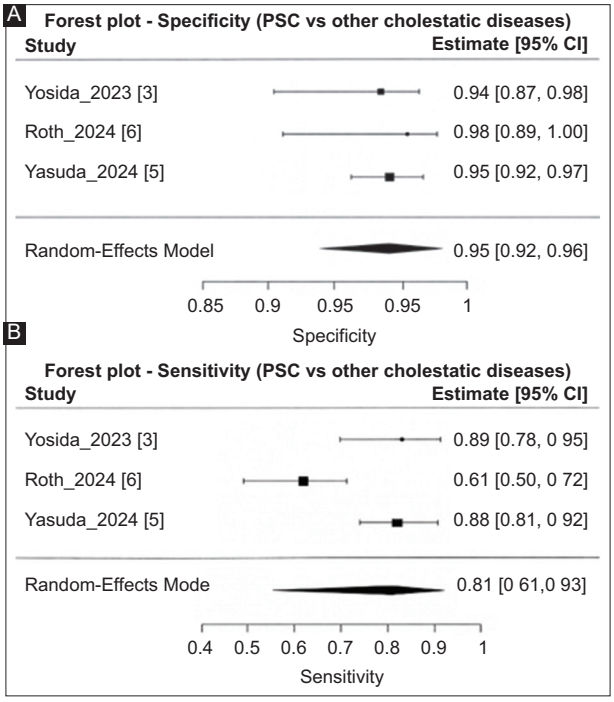
Supplementary Figure 5 Hierarchical summary receiver operating characteristic (HSROC) curve for serum anti-integrin αvβ6 autoantibodies in patients with primary sclerosing cholangitis (PSC) without concomitant inflammatory bowel disease (IBD)



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