Annals of Gastroenterology (2026) **39,** 40-47

Serum anti-integrin αvβ6 autoantibodies for diagnosis of primary sclerosing cholangitis: a systematic review and meta-analysis

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Abstract

Background Currently, there is no noninvasive serological marker for primary sclerosing cholangitis (PSC). Serum anti-integrin αvβ6 autoantibodies were recently suggested as potential diagnostic PSC biomarkers. We conducted a systematic review and meta-analysis to evaluate their diagnostic performance, the influence of concomitant inflammatory bowel disease (IBD), and differentiation from other cholestatic liver diseases.

Methods PubMed, Embase, Cochrane Library and Web of Science databases were systematically searched for studies assessing the diagnostic value of serum anti-αvβ6 autoantibodies in PSC. Pooled sensitivity, specificity, diagnostic odds ratio and area under the summary receiver operating characteristic curve (AUC) were calculated using a bivariate random-effects model. Subgroup analyses were performed based on IBD status and differentiation from other cholestatic liver diseases.

Results Four studies including 1294 subjects (398 PSC patients and 896 controls) were analyzed. The pooled sensitivity and specificity of anti-αvβ6 autoantibodies for PSC diagnosis were 62.3% and 87.3%, respectively (AUC: 0.76). The specificity increased to 96% (AUC: 0.86) in PSC without IBD, while it decreased to 71% (AUC: 0.67) in PSC with IBD. For the differentiation of PSC from other cholestatic liver diseases, anti-αvβ6 autoantibodies had pooled sensitivity 81% and specificity 95% (AUC: 0.90).

Conclusions Serum anti-αvβ6 autoantibodies exhibit moderate sensitivity and high specificity for PSC diagnosis, especially in differentiation from other cholestatic diseases. Their clinical utility as a noninvasive diagnostic biomarker is promising and warrants validation in larger, multicenter prospective studies to establish their role in routine clinical practice.

Keywords Primary sclerosing cholangitis, anti-integrin αvβ6 autoantibodies, diagnostic biomarker, inflammatory bowel disease

Ann Gastroenterol 2026; 39 (1): 40-47

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Trial Registration: This systematic review and meta-analysis was registered in PROSPERO (Registration ID: CRD420251067882)

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Received 28 September 2025; accepted 15 November 2025; published online 8 December 2025

DOI: https://doi.org/10.20524/aog.2026.1025

Introduction

Primary sclerosing cholangitis (PSC) is a progressive cholangiopathy that often leads to cirrhosis and liver failure [1,2]. Despite its clinical significance and frequent association with inflammatory bowel disease (IBD) [3], in particular ulcerative colitis (UC), its diagnosis relies primarily on imaging and histology, with no established diagnostic serological biomarkers [4].

Integrin αvβ6 is an epithelial-specific integrin that is implicated in tissue repair and the activation of transforming growth factor (TGF)-β [5-7]. Given its limited epithelial expression and its critical role in epithelial restitution and localized TGF-β activation, sustained biliary injury in PSC may lead to aberrant αvβ6 exposure or modification, rendering

it an autoantigenic target and triggering a loss of immune tolerance. Recent findings from the phase 2a INTEGRIS-PSC trial showed that bexotegrast, an oral dual αvβ6/αvβ1 inhibitor, stabilized fibrosis markers compared to placebo [8]. These results highlight the biological importance of αvβ6 in PSC.

Recent interest has focused on the potential role of anti-integrin αvβ6 autoantibodies as noninvasive biomarkers for PSC [9]. Elevated levels of anti-αvβ6 autoantibodies have been reported in UC and PSC, suggesting a possible link between autoimmunity against epithelial structures and the pathogenesis of these diseases [10]. In UC, serum αvβ6 autoantibodies exhibit high diagnostic performance, with a pooled sensitivity of 82%, specificity of 94%, and an area under the curve (AUC) of 0.96 [9]. However, their role in PSC diagnosis has only recently emerged and remains less systematically evaluated [10-13]. Furthermore, anti-αvβ6 positivity appears to vary with IBD status, potentially affecting diagnostic accuracy.

Given the growing evidence and the critical need for novel serological markers in PSC, we performed a systematic review and meta-analysis to assess the diagnostic performance of serum anti-integrin αvβ6 autoantibodies in patients with PSC. Our analysis also explored the potential influence of concomitant IBD on their diagnostic performance, as well as their role in the differentiation of PSC from other cholestatic liver diseases.

Materials and methods

Literature search

A systematic search of PubMed, Embase, the Cochrane Library, and Web of Science was performed up to April 4th, 2025. Search terms included combinations of "αvβ6", "integrin", "primary sclerosing cholangitis", "PSC", "autoantibodies" and "diagnosis". Additional relevant articles were identified by screening the references of selected studies. The search strategy and study selection followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [14] (Supplementary Table 1). The protocol was registered in PROSPERO under registration number CRD420251067882.

Study selection

Studies were considered eligible if they met the following criteria: (a) full papers evaluating serum anti-αvβ6 autoantibody positivity for PSC diagnosis; (b) inclusion of both a PSC patient group and a non-PSC control group for comparative analysis; and (c) availability of diagnostic performance data, including at least sensitivity and specificity. Exclusion criteria comprised case reports, narrative reviews, editorials, letters, and duplicate publications.

Data extraction and quality assessment

Data from eligible studies were extracted in a standardized format including: (a) baseline characteristics, including first author, year of publication, study design, geographic region, sex distribution, mean or median age, study groups, and the positivity threshold applied for serum anti-αvβ6 autoantibodies; and (b) diagnostic performance parameters, specifically the numbers of true positives (TP), false positives (FP), false negatives (FN), and true negatives (TN).

Methodological quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool, integrated within Review Manager (RevMan) version 5.4 (https://training.cochrane.org/online-learning/core-software/revman) [15]. QUADAS-2 comprises 4 domains: patient selection, index test, reference standard, and flow and timing. Each domain is evaluated for risk of bias, while the first 3 domains are also assessed for applicability concerns. Two independent reviewers (SV and AA) conducted the literature search, study selection, data extraction and risk of bias assessment. Any discrepancies were resolved through discussion with a third investigator (SP). Assessment of certainty in the body of evidence, using formal tools such as Grading of Recommendations, Assessment, Development and Evaluations (GRADE), was not performed, given the limited number of studies and the diagnostic nature of this review.

Statistical analysis

For each eligible study, a 2×2 contingency table was constructed, based on the reported values of TP, FP, FN, and TN. From these, pooled sensitivity, specificity and the summary receiver operating characteristic (SROC) curve were derived, along with the corresponding area under the SROC curve (AUC), using R software (version 4.4.2; R Foundation for Statistical Computing, Vienna, Austria). AUC values approaching 1 were interpreted as indicating higher diagnostic performance. Statistical significance was defined as a P-value <0.05. Heterogeneity among studies was assessed using the chi-squared (χ^2) test and the inconsistency index (I^2). Substantial

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Conflict of Interest: George V. Papatheodoridis has served as advisor for AbbVie, Astra Zeneca, Genesis, Gilead, GlaxoSmithKline, Janssen, Ipsen, Merck Sharp & Dohme, Novartis, Novo Nordisk, Roche, Takeda and Vir, as lecturer for AbbVie, Astra Zeneca, Gilead, GlaxoSmithKline, Janssen, Ipsen, Merck Sharp & Dohme, Novartis, Novo Nordisk and Roche and has received research grants from AbbVie, Gilead, Takeda, Vianex. The other authors declare no conflicts of interest

heterogeneity was defined as I^2>50% or P<0.01. In such cases, a bivariate random-effects model was applied to generate pooled estimates. Subgroup analyses were subsequently conducted to explore potential sources of heterogeneity. In view of the small number of included studies, assessment of publication bias (e.g., via funnel plots or Deeks' test) was not feasible. A leave-one-out sensitivity analysis was performed to evaluate the robustness of the pooled estimates.

Results

Literature search and study selection

A comprehensive literature search initially identified 236 articles. Following the exclusion of 141 duplicates and 91 studies deemed irrelevant based on title and abstract screening, 4 articles were retrieved for full-text review [10-13]. After thorough assessment, all 4 articles met the inclusion criteria and were deemed eligible for the current analysis. The detailed selection process is illustrated in Fig. 1. The 4 studies included 1294 subjects: 398 patients with PSC and 896 non-PSC controls. Of the 4 eligible studies, 1 was a retrospective case–control study [11], 1 was a multicenter retrospective cohort validation [13], 1 was a prospective observational cohort [10], and 1 was a cross-sectional cohort study [12]. All studies enrolled adult participants with PSC and appropriate control groups. Two studies [11,12] applied in-house enzyme-linked immunosorbent assays (ELISA), while another 2 studies [10,13] employed both in-house methods and a standardized commercial ELISA kit (Medical & Biological Laboratories Co., Ltd., Nagoya, Japan). The definition of seropositivity was consistent across studies, with all using the healthy control group mean plus 3 standard deviations as a threshold. In cases where age was reported separately for multiple subgroups, we calculated a weighted average of the group means to provide a single representative value per study. When standard deviations were not reported, they were not included in the pooled estimate. The baseline characteristics of the included studies are summarized in Table 1. Raw diagnostic data (TP, FN, FP, TN) from each study are presented in Supplementary Table 2.

Risk of bias and applicability assessment

Application of the QUADAS-2 tool indicated that the included studies exhibited a low risk of bias in the domains of

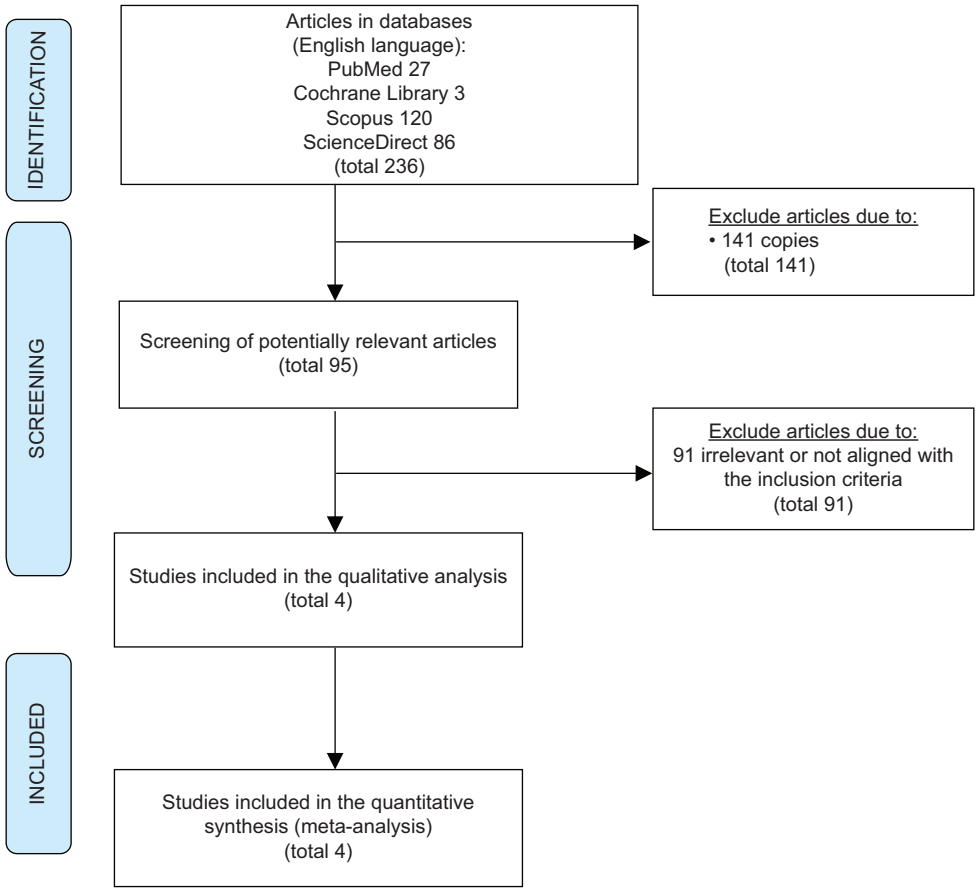

Figure 1 PRISMA flowchart illustrating the selection of eligible studies
PRISMA, preferred reporting items for systematic reviews and meta-analyses; PSC, primary sclerosing cholangitis

Table 1 Baseline characteristics of the studies included in the meta-analysis

First author, year [ref.]	Country/ Setting	Study design	Participants	Age[1], years (PSC/non-PSC)	Males, n (PSC/non-PSC)	Assay	Positivity threshold
Yoshida, 2023 [11]	Japan, single-center	Case–control (retrosp.)	55 PSC, 150 non-PSC (UC, other liver diseases, HC)	40/66	38/59	In-house ELISA in sera	Mean HC + 3 SD
Bloemen, 2024 [12]	USA, Portugal, multicenter registry (CALiD, 4 cohorts)	Cross-sectional cohort	137 PSC (76 PSC-UC, 33 PSC-CD, 28 PSC alone), 91 IBD, 69 HC	45 (33-57) / 54 (42-67)[2]	85/70	In-house ELISA in sera and plasma	Mean HC + 3 SD
Roth, 2024 [10]	Germany, multicenter	Prosp.	70 PSC-IBD, 228 non-PSC (IBD, other liver diseases, HC)	39/48	39/109	Commercial ELISA kit (MBL) + in-house ELISA in sera	Mean HC + 3 SD
Yasuda, 2024 [13]	Japan, multicenter registry	Retrosp.	136 PSC, 358 non-PSC (other liver diseases, HC)	28/67	87/177	Commercial ELISA kit (MBL) + in-house ELISA in sera	Mean HC + 3 SD

[1]Mean age is provided; in studies reporting age separately for multiple patient groups, a weighted average of means was calculated to present a single summary value. [2]Median (interquartile range)

PSC, primary sclerosing cholangitis; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; HC, healthy controls; SD, standard deviation; Prosp., Prospective; Retrosp., Retrospective; ELISA, enzyme-linked immunosorbent assay; MBL, Medical & Biological Laboratories Co., Ltd. Nagoya, Japan. "Anti-integrin αvβ6 ELISA Kit"

flow and timing, and an unclear risk of bias in the domains of reference standard and patient selection. One study [12] was judged to have a high risk of bias in the index test domain, due to the use of both serum and plasma for biomarker measurement without a clearly defined separation in the analytical process. Importantly, no major concerns regarding applicability were identified across the domains of patient selection, index test or reference standard (Fig. 2).

Meta-analysis: the diagnostic accuracy of serum αvβ6 autoantibodies for PSC

All 4 studies were included in the meta-analysis. Among the 1294 participants included across all studies, 398 (30.8%) were diagnosed with PSC. Substantial heterogeneity was observed among studies, with an I^2 value of 90% and P<0.001. Consequently, a random-effects model was applied for the meta-analysis. The pooled sensitivity of anti-integrin αvβ6 for the diagnosis of PSC was 62.3% (95% confidence interval [CI] 59.6-65.0%), whereas the pooled specificity was 87.3% (95%CI 86.6-88.0%) (Fig. 3A). A perfect inverse correlation between sensitivity and specificity was observed (Spearman's ρ=1.000, P<0.001), probably influenced by the small number of included studies. The pooled positive likelihood ratio (PLR) was 12.87 (95%CI -7.63 to 33.36), and the negative likelihood ratio (NLR) was 0.44 (95%CI -0.24 to 1.12). The implausible confidence intervals, which include negative values, suggest instability in these estimates and warrant cautious interpretation. The pooled diagnostic odds ratio (OR) was 21.35 (95%CI 0.11-3996.64). The SROC AUC was 0.76 (95%CI 0.41-1.00), indicating moderate overall diagnostic accuracy, although the wide confidence interval underscores the limitations posed by the small number of studies and the high degree of between-study variability (Fig. 3B).

Subgroup analyses

A predefined subgroup analysis was conducted to evaluate the diagnostic performance of anti-integrin αvβ6 specifically in patients with concomitant PSC and IBD (PSC+IBD). In 2 studies [11,13] that did not include IBD-only controls, a hypothetical control group was constructed based on values reported in a recent meta-analysis of serum αvβ6 autoantibodies for UC [9], in which the specificity against non-IBD controls was 88%. For consistency, a 1:1 ratio of PSC+IBD patients to IBD-only controls was assumed. The numbers of FP and TN were then imputed using the reported specificity. In this subgroup, the pooled sensitivity of anti-αvβ6 was 63% (95%CI 57-69%) and the pooled specificity was 71% (95%CI 66-75%) (Fig. 4A). The pooled PLR was 2.19 (95%CI 1.82-2.63), and the NLR was 0.51 (95%CI 0.43-0.61). The diagnostic OR was estimated at 4.26 (95%CI 3.02-6.00). The SROC AUC was 0.67 (95%CI 0.63-0.71), indicating modest diagnostic performance in this subgroup. Notably, the heterogeneity across studies was low, with an estimated I^2 of 11%. The raw diagnostic data used for this analysis are presented in Supplementary Table 3.

A separate subgroup analysis was conducted to assess the diagnostic performance of anti-integrin αvβ6 in patients with PSC without concomitant IBD. In this analysis, the comparator group consisted of individuals without PSC and without IBD, thereby minimizing potential confounding effects related to

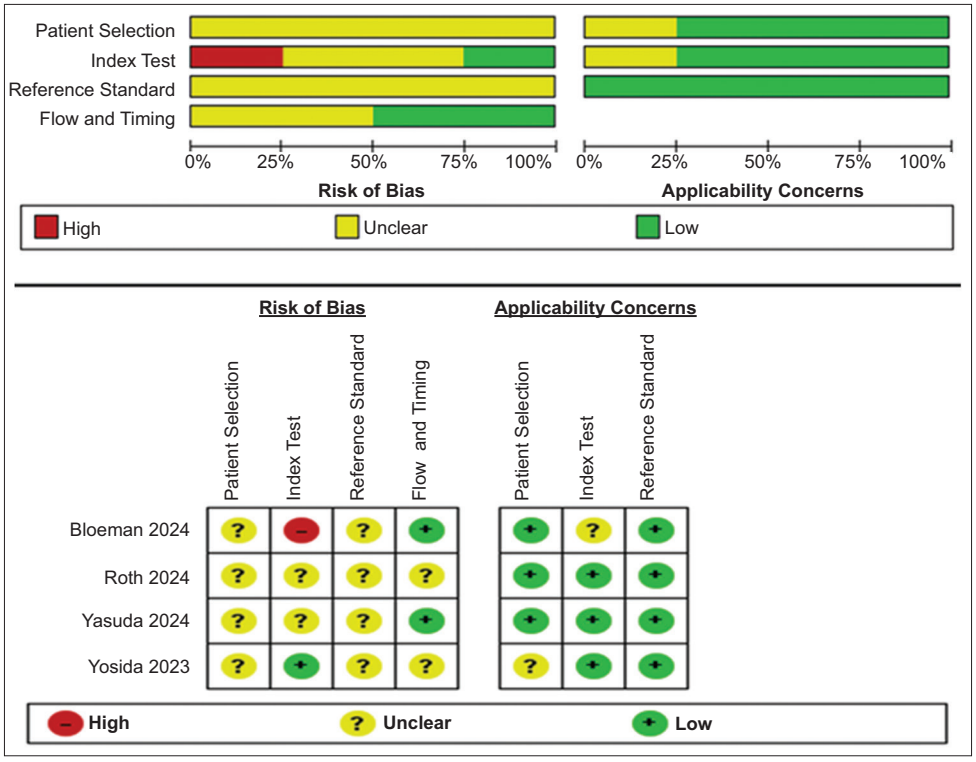

Figure 2 Graph and concerns summary for QUADAS-2 risk of bias and applicability concerns
QUADAS-2, quality assessment of diagnostic accuracy studies-2

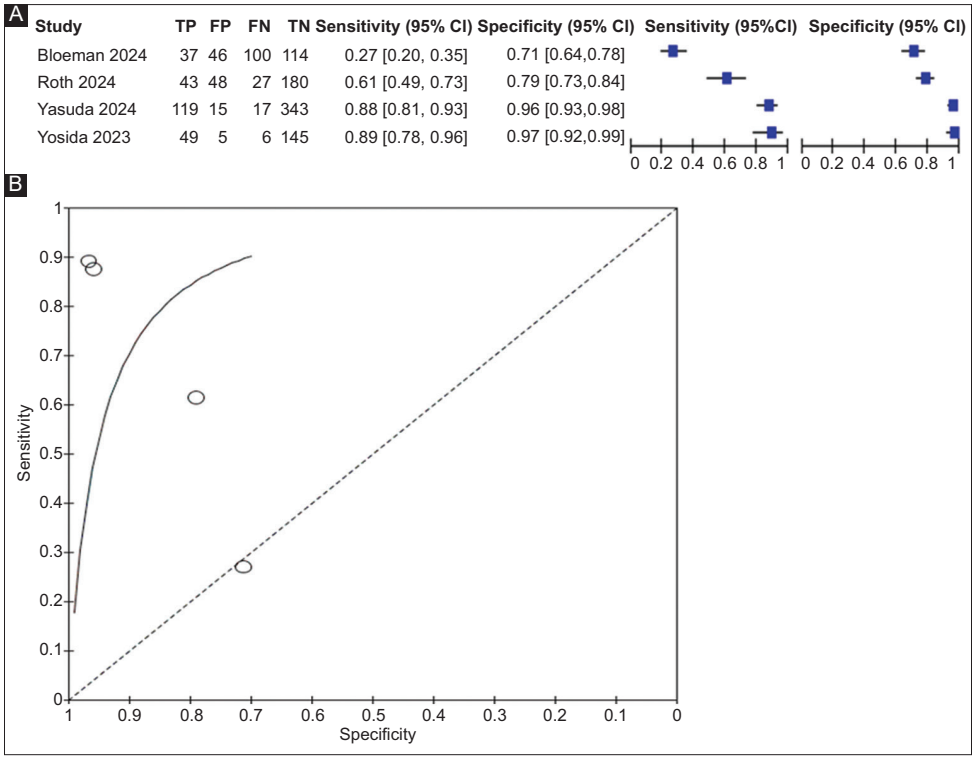

Figure 3 Diagnostic accuracy of serum anti-integrin αvβ6 autoantibodies for PSC: (A) Forest plot showing pooled sensitivity (62.3%) and specificity (87.3%) across 4 eligible studies, based on a bivariate random-effects model (B) Summary receiver operating characteristic (SROC) curve demonstrating an area under the curve (AUC) of 0.76, indicating moderate overall diagnostic performance
PSC, primary sclerosing cholangitis; CI, confidence interval; SROC, summary receiver operating characteristic; AUC, area under the curve

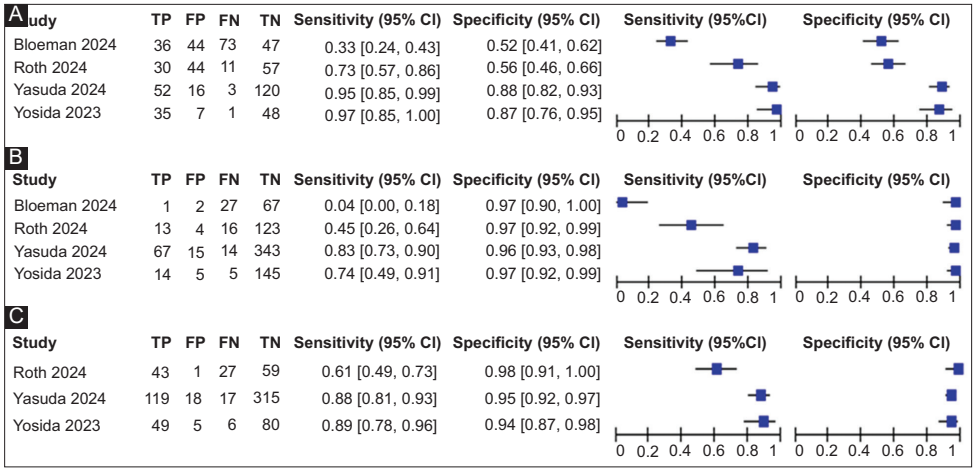

Figure 4 Subgroup diagnostic performance of serum anti-integrin αvβ6 autoantibodies: (A) In PSC patients with concomitant IBD, diagnostic sensitivity and specificity were 63% and 71%, respectively (AUC 0.67); (B) In PSC patients without IBD, specificity increased to 96%, with an AUC of 0.86; (C) For distinguishing PSC from other cholestatic liver diseases, pooled sensitivity and specificity were 81% and 95%, respectively, with an AUC of 0.90, indicating excellent discriminatory accuracy

PSC, primary sclerosing cholangitis; IBD, inflammatory bowel disease; PLR, positive likelihood ratio; NLR, negative likelihood ratio; PBC, primary biliary cholangitis

IBD. The diagnostic counts from each included study for this PSC-only subgroup are provided in Supplementary Table 4. In the PSC-only subgroup, the pooled sensitivity of anti-αvβ6 was 61% (95%CI 53-68%), while the pooled specificity was notably high at 96% (95%CI 95-97%) (Fig. 4B). The pooled PLR was 16.38 (95%CI 11.01-24.39), indicating a strong increase in post-test probability following a positive result. The NLR was 0.41 (95%CI 0.34-0.50). The diagnostic OR was 39.96 (95%CI 24.10–66.26) and the SROC AUC was 0.86 (95%CI 0.83-0.89), indicating good overall diagnostic accuracy. Heterogeneity across studies was minimal, with an estimated I^2 of 5%.

Subsequently, we conducted a subgroup analysis to evaluate the diagnostic performance of serum anti-integrin αvβ6 autoantibodies in distinguishing PSC from other cholestatic liver diseases. This analysis included a total of 478 patients with non-PSC cholestatic conditions, specifically: 149 cases of cholangiocarcinoma, 109 with IgG4-related sclerosing cholangitis, 173 with primary biliary cholangitis, 23 with secondary cholangiopathies, and 24 with metabolic dysfunction-associated steatotic liver disease, derived from 3 eligible studies [10,11,13]. Patients with autoimmune hepatitis-PSC variant were classified in the PSC group. The diagnostic 2×2 data used for this subgroup comparison are detailed in Supplementary Table 5. The pooled sensitivity of anti-αvβ6 in discriminating PSC from other cholestatic diseases was 81% (95%CI 76-85%), and the pooled specificity was 95% (95%CI 93-97%) (Fig. 4C). The PLR was 16.10 (95%CI 10.85-23.89), while the NLR was 0.20 (95%CI 0.16-0.26). The diagnostic OR was 79.83 (95%CI 47.77-133.39). The SROC AUC was 0.90 (95%CI 0.87-0.92), reflecting excellent overall diagnostic accuracy. Notably, between-study heterogeneity was minimal, with an I^2 estimate of 3%. A comparative summary of all subgroup diagnostic metrics is presented in Supplementary Table 6.

Sensitivity analysis

To assess the robustness of the pooled diagnostic estimates, a leave-one-out sensitivity analysis was performed by sequentially excluding each study and recalculating the pooled sensitivity and specificity. The results demonstrated moderate variability, particularly in sensitivity estimates. When the study of Yoshida *et al* was excluded [11], sensitivity decreased to 0.58 and specificity remained stable at 0.85. The exclusion of the study by Bloemen *et al* [12] resulted in an increase in sensitivity to 0.81, with specificity improving to 0.91. Removing the study of Roth *et al* [10] yielded a sensitivity of 0.62 and specificity of 0.90, whereas the exclusion of Yasuda *et al* [13] led to the lowest sensitivity (0.49) and specificity of 0.82. These findings suggest that the studies of Bloemen *et al* and Yasuda *et al* [12,13] have the greatest influence on the overall sensitivity estimate, highlighting potential heterogeneity in diagnostic performance across studies. The above findings are briefly summarized in Table 2.

Discussion

In this systematic review and meta-analysis, we evaluated the diagnostic performance of serum anti-integrin αvβ6 autoantibodies for the diagnosis of PSC. Four studies comprising 1294 subjects were included [10-13]. Pooled sensitivity was 62.3% and specificity 87.3%, with an SROC AUC of 0.76, indicating moderate accuracy. Subgroup analyses revealed important clinical insights: in PSC patients without IBD, specificity rose to 96% and AUC to 0.86, suggesting strong diagnostic utility in this subgroup. Conversely, in PSC patients with IBD, the diagnostic performance declined (specificity 71% and AUC to 0.67), potentially reflecting shared

Table 2 Impact of individual studies on sensitivity, specificity and area under the summary receiver operating characteristic curve (AUC)

Excluded study, year [ref.]	Sensitivity (95%CI)	Specificity (95%CI)	AUC (95%CI)
Yoshida, 2023 [11]	0.58 (0.53-0.63)	0.85 (0.83-0.88)	0.74 (0.71-0.77)
Bloemen, 2024 [12]	0.81 (0.76-0.85)	0.91 (0.88-0.93)	0.87 (0.84-0.89)
Roth, 2024 [10]	0.62 (0.57-0.68)	0.90 (0.88-0.92)	0.80 (0.77-0.82)
Yasuda, 2024 [13]	0.49 (0.43-0.55)	0.82 (0.78-0.85)	(0.64-0.71)

CI, confidence interval

immunopathology between PSC and IBD. Notably, serum anti-αvβ6 autoantibodies demonstrated excellent performance in differentiating PSC from other cholestatic liver diseases, with a pooled sensitivity of 81%, specificity of 95%, and an AUC of 0.90. Sensitivity analysis highlighted moderate variability across studies: the exclusion of Bloemen *et al* improved sensitivity and specificity [12], while the removal of Yasuda *et al* reduced both metrics [13], emphasizing the heterogeneity in study populations and assay methodologies.

Overall, these findings suggest that serum anti-αvβ6 autoantibodies hold promise as highly specific, noninvasive diagnostic biomarkers for PSC, particularly in patients without IBD, and are effective in distinguishing PSC from other cholestatic disorders, while underlining the need for context-specific interpretation. The clinical importance of αvβ6 integrin in PSC is further highlighted by the recent findings from the INTEGRIS-PSC phase 2a trial [8]. Bexotegrast, an oral dual inhibitor of αvβ6 and αvβ1 integrins, demonstrated favorable safety and tolerability over 12 weeks in patients with PSC, with no serious drug-related adverse events. Notably, the agent stabilized serum markers of fibrosis (e.g., ELF score and PRO-C3 levels) and prevented the deterioration of hepatobiliary excretory function compared to placebo, providing mechanistic proof that αvβ6-mediated TGF-β activation is critically involved in PSC fibrogenesis [8]. Selective blockade of αv-integrins restricts local activation of latent TGF-β, thereby attenuating profibrogenic signaling within epithelial–mesenchymal niches where αvβ6 and αvβ1 are engaged. Bexotegrast, a dual αvβ6/αvβ1 inhibitor, has also shown exploratory antifibrotic activity in the randomized INTEGRIS-IPF trial—stabilizing forced vital capacity, improving quantitative fibrosis imaging, and reducing circulating ITGB6 and PRO-C3—further supporting the therapeutic relevance of this pathway [16]. Consequently, the high specificity of anti-αvβ6 autoantibodies for PSC, particularly in the absence of IBD, not only may reflect an immunological epiphenomenon, but may also signal pathogenic engagement of the αvβ6-TGF-β axis.

In UC, serum anti-αvβ6 autoantibodies demonstrated excellent diagnostic performance, as shown by Yang *et al* [9], with a pooled sensitivity of 82%, specificity of 94%, and an AUC of 0.96, highlighting their potential utility as noninvasive biomarkers for diagnosis, disease monitoring, and prognostic assessment. Clinically, they could be used as a noninvasive diagnostic tool to distinguish UC from healthy individuals (specificity 96%), non-IBD controls (88% specificity) and Crohn's disease (80% specificity) [17-20]. Additionally, higher titers of these autoantibodies were associated with active disease states and adverse outcomes, such as the need for biologic therapy, hospitalizations and surgery [17,19,21,22]. Therefore, Yang *et al* propose that αvβ6 autoantibodies could not only aid the early diagnosis of UC, but also potentially serve as a marker of disease activity and prognosis [9]. However, they caution that these autoantibodies are not entirely specific to UC, as high positivity rates have also been observed in PSC. In the context of PSC, if validated in larger prospective cohorts, anti-αvβ6 autoantibody testing could assist in earlier diagnosis, risk stratification and noninvasive disease monitoring, potentially complementing imaging-based evaluation.

Several limitations must be considered when interpreting our findings. First, the small number of included studies (n=4) limits the statistical power and generalizability of our findings. Second, although all used ELISA for anti-αvβ6 measurement, variations in assay platforms and the use of non-commercial kits may affect diagnostic accuracy. Third, despite applying a consistent positivity threshold (mean + 3 standard deviations of healthy controls), Yoshida *et al* and Bloemen *et al* used slightly different optical density cutoffs [11,12], while the latter investigators included both serum and plasma, increasing variability. These factors probably contributed to the heterogeneity, especially in sensitivity estimates, possibly because of differences in study design, populations and IBD prevalence. Subgroup and sensitivity analyses could not fully resolve this. Moreover, in 2 of the 4 included studies [11,13], a hypothetical IBD-only control group was generated using data from a published meta-analysis, providing an indirect rather than observed estimate, and thus representing a methodological limitation of the PSC+IBD subgroup analysis.

In conclusion, this meta-analysis underscores the potential of serum anti-αvβ6 autoantibodies as highly specific, noninvasive biomarkers for PSC, especially in PSC patients without IBD, and for the differentiation of PSC from other cholestatic diseases. Their potential clinical utility as noninvasive diagnostic biomarkers, for a disease without any other noninvasive biomarker, is noteworthy and deserves further evaluation. Ongoing studies, including INTEGRIS-PSC, may further clarify their clinical and therapeutic utility.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Code availability

The R code used for the statistical analysis is available upon request.

Summary Box

What is already known:

- Primary sclerosing cholangitis (PSC) lacks validated noninvasive serological biomarkers for diagnosis
- Autoantibodies against integrin αvβ6 have been reported in patients with ulcerative colitis and in some studies of PSC
- Previous individual studies have suggested a potential diagnostic role of anti-αvβ6 autoantibodies, but with heterogeneous assays and inconsistent results

What the new findings are:

- This is the first systematic review and meta-analysis to synthesize all available data on anti-αvβ6 autoantibodies for PSC diagnosis
- Anti-αvβ6 autoantibodies show moderate sensitivity and high specificity, particularly in PSC patients without inflammatory bowel disease
- The antibodies discriminate PSC from other cholestatic liver diseases with high accuracy

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Supplementary material

Supplementary Table 1 PRISMA 2020 checklist for integrin αvβ6 meta-analysis

Section and Topic	Item #	Checklist item	Location in manuscript
Title	1	Identify the report as a systematic review	Title page
Abstract	2	See the PRISMA 2020 for Abstracts checklist	Abstract
Rationale	3	Describe the rationale for the review in the context of existing knowledge	Introduction, Paragraphs 1-3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses	Introduction, final paragraph
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses	Methods > Study Selection
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted	Methods > Literature Search
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used	Methods > Literature Search
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process	Methods > Study Selection
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process	Methods > Data Extraction and Quality Assessment
Data items	10	10a: List and define all outcomes for which data were sought. 10b: List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information	Methods > Data Extraction and Quality Assessment
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool (s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process	Methods > Data Extraction and Quality Assessment
Effect measures	12	Specify for each outcome the effect measure (s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results	Methods > Statistical Analysis
Synthesis methods	13	13a-f: Describe methods for synthesis, including data preparation, tabulation, synthesis model, heterogeneity assessment, and sensitivity analyses	Methods > Statistical Analysis
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases)	Methods > Statistical Analysis (mention: not feasible)
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome	Not performed
Study selection	16	16a-b: Describe the results of the search and study selection process, including flow diagram and exclusions	Results > Literature search and study selection; Supplementary Figure 1
Study characteristics	17	Cite each included study and present its characteristics	Results > Table 1; Supplementary Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study	Results > Risk of Bias and Applicability Assessment; Supplementary Figure 2
Results of individual studies	19	For all outcomes, present summary statistics and effect estimates with precision for each study	Results > Meta-analysis section and Table 1
Results of syntheses	20	20a-d: Summarise characteristics, meta-analysis results, heterogeneity analyses, and sensitivity analyses	Results > Meta-analysis and Subgroup Analyses

(*Contd...*)

Supplementary Table 1 (*Continued*)

Section and Topic	Item #	Checklist item	Location in manuscript
Reporting biases	21	Present assessments of risk of bias due to missing results (reporting biases) for each synthesis	Explained in Methods)
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed	Not performed
Discussion	23	23a-d: General interpretation, limitations of evidence and process, implications for practice/research	Discussion
Registration and protocol	24	24a-c: Registration number, protocol availability, and amendments	Methods>Literature Search (PROSPERO registration)
Support	25	Describe sources of financial or non-financial support and role of funders	Declarations > Funding
Competing interests	26	Declare any competing interests of review authors	Declarations > Competing Interests
Availability of data, code and other materials	27	Report availability of data, code, and materials used in the review	Available upon request

PRISMA, preferred reporting items for systematic reviews and meta-analyses; PROSPERO, international prospective register of systematic reviews

Supplementary Table 2 Diagnostic counts (TP, FN, FP, TN) from each study assessing serum anti-αvβ6 autoantibodies in PSC

First author, year [ref.]	TP	FN	FP	TN
Yoshida, 2023 [11]	49	6	5	145
Bloemen, 2024 [12]	37	100	46	114
Roth, 2024 [10]	43	27	48	180
Yasuda, 2024 [13]	119	17	15	343

TP, true positives; FP, false positives; FN, false negatives; TN, true negatives; PSC, primary sclerosing cholangitis; IBD, inflammatory bowel disease

Supplementary Table 3 Diagnostic data from the subgroup analysis of PSC patients with concomitant inflammatory bowel disease (PSC+IBD)

First author, year [ref.]	TP	FN	FP	TN
Yoshida, 2023 [11]	35	1	7	48
Bloemen, 2024 [12]	36	73	44	47
Roth, 2024 [10]	30	11	44	57
Yasuda, 2024 [13]	52	3	16	120

TP, true positives; FP, false positives; FN, false negatives; TN, true negatives; PSC, primary sclerosing cholangitis; IBD, inflammatory bowel disease

Supplementary Table 4 Diagnostic data from the subgroup analysis of PSC patients without concomitant IBD (PSC-only subgroup)

First author, year [ref.]	TP	FN	FP	TN
Yoshida, 2023 [11]	14	5	5	145
Bloemen, 2024 [12]	1	27	2	67
Roth, 2024 [10]	13	16	4	123
Yasuda, 2024 [13]	67	14	15	343

TP, true positives; FP, false positives; FN, false negatives; TN, true negatives; PSC, primary sclerosing cholangitis; IBD, inflammatory bowel disease

Supplementary Table 5 Diagnostic data from the subgroup analysis comparing PSC with other cholestatic liver diseases

First author, year [ref.]	TP	FN	FP	TN
Yoshida, 2023 [11]	49	6	5	80
Bloemen, 2024 [12]	43	27	1	59
Roth, 2024 [10]	119	17	18	315

TP, true positives; FP, false positives; FN, false negatives; TN, true negatives; PSC, primary sclerosing cholangitis; IBD, inflammatory bowel disease

Supplementary Table 6 Subgroup diagnostic performance of serum anti-αvβ6 autoantibodies in PSC

Subgroup	Sensitivity (95%CI)	Specificity (95%CI)	AUC (95%CI)	PLR (95%CI)	NLR (95%CI)	Diagnostic OR (95%CI)
PSC with IBD	63% (57-69%)	71% (66-75%)	0.67 (0.63-0.71)	2.19 (1.82-2.63)	0.51 (0.43-0.61)	4.26 (3.02-6.00)
PSC without IBD	61% (53-68%)	96% (95-97%)	0.86 (0.83-0.89)	16.38 (11.01-24.39)	0.41 (0.34-0.50)	39.96 (24.10-66.26)
PSC vs. other cholestatic diseases	81% (76-85%)	95% (93-97%)	0.90 (0.87-0.92)	16.10 (10.85-23.89)	0.20 (0.16-0.26)	79.83 (47.77-133.39)

PSC, primary sclerosing cholangitis; IBD, inflammatory bowel disease; AUC, area under the curve; PLR, positive likelihood ratio; NLR, negative likelihood ratio; OR, odds ratio; CI, confidence interval; SROC, summary receiver operating characteristic