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Systematic Review and Meta-Analysis

Comparative Efficacy of Combined Serum Biomarkers and Clinical Variables for Endometriosis Diagnosis: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Endometriosis is a chronic condition affecting about one in ten women of reproductive age, resulting in reduced quality of life. Non-invasive diagnostic methods based on single serum biomarkers or isolated clinical parameters have shown limited reliability. Consequently, integrating serum biomarkers with clinical variables has been proposed as a more effective diagnostic approach. This study aimed to assess the diagnostic accuracy of combined serum biomarkers and clinical variables for endometriosis diagnosis.

Methods: A systematic review and meta-analysis were carried out in line with PRISMA recommendations. Literature synthesize were conducted across PubMed, Cochrane, ScienceDirect, Epistemonikos, Scopus, ProQuest, and EBSCO to February 2025. Eligible studies included diagnostic investigations that compared combined serum biomarker and clinical-variable models with serum biomarker or clinical-variable only reference standards. Study quality was evaluated using the QUADAS-2 tool. Pooled effect analysis was generated as odds ratios (ORs) using 95% confidence intervals (CI).

Results: Seventeen studies met eligibility criteria. Combined diagnostic models demonstrated significantly higher sensitivity (OR 2.64; 95% CI 1.54–4.53) but non-significant specificity (OR 1.03; 95% CI 0.43–2.49) compared with single diagnostic approaches. However, the area under the curve (AUC) analysis significantly improved in combined models (OR 1.46; 95% CI 1.10–1.93). Moderate to high heterogeneity with publication bias was observed across studies.

Conclusion: Combined serum biomarkers and clinical variables provide better diagnostic performance than single tests and support the use of non-invasive multimodal strategies prior to surgical confirmation. Further prospective validation is required to ensure consistency and clinical applicability.

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INTRODUCTION

Endometriosis is a long-term gynecological disorder defined by the growth of endometrial-like tissue outside the uterine cavity and affects an estimated 10% of women of reproductive age globally [1]. It is frequently accompanied by chronic pelvic pain, dysmenorrhea, dyspareunia, and infertility, leading to substantial impairment in physical functioning, mental health, and overall quality of life [2]. In addition to its clinical consequences, endometriosis imposes a considerable socioeconomic burden through increased healthcare utilization and reduced work productivity [3].

Accurate diagnosis of endometriosis remains a major clinical challenge. Laparoscopy with histopathological confirmation is currently regarded as the diagnostic reference standard; however, it is invasive, costly, and often performed

only after prolonged periods of unresolved symptoms [4]. Non-invasive alternatives, including imaging modalities and individual serum biomarkers such as cancer antigen 125 (CA-125), have demonstrated suboptimal diagnostic accuracy, particularly for early or minimal disease [5,6]. These limitations contribute to substantial diagnostic delays and inappropriate management.

Recent progress in translational research has prompted growing interest in identifying non-invasive diagnostic strategies that combine circulating biomarkers with clinical characteristics. Biomolecules associated with inflammation, angiogenesis, immune response, and hormonal regulation—including CA-125, cytokines, vascular endothelial growth factor (VEGF), and microRNAs—have been explored as potential indicators of disease presence [7,8]. At the same time, clinical parameters such as age, symptom patterns, menstrual features, and reproductive history have been incorporated into multivariable prediction models to enhance diagnostic performance [9].

Combining serum biomarkers with clinical variables offers a potentially superior approach compared with reliance on single diagnostic indicators. Several investigations have reported improved sensitivity and specificity when integrated models are applied [1,4]. Nevertheless, reported results differ substantially among studies due to heterogeneity in study populations, biomarker selection, analytical methods, and reference standards. As a result, the true diagnostic value and clinical applicability of these combined approaches remain unclear.

Given the urgent need for reliable non-invasive diagnostic tools, a systematic review with profound statistical analysis of existing evidence is needed. Therefore, this systematic review and meta-analysis aim to compare the diagnostic performance of combined serum biomarkers and clinical variables for detecting endometriosis. Key outcomes include sensitivity, specificity, and area under the receiver operating characteristic curve (AUC), with publication bias analysis. This study seeks to provide a comprehensive evidence base to guide future diagnostic strategies and support clinical decision-making in endometriosis care.

METHODS

We conducted a structured literature search in seven major databases (PubMed, Cochrane, ScienceDirect, Epistemonikos, Scopus, ProQuest, and EBSCO) for articles published up to February 2025. Keyword combinations using Boolean logic were applied according to the strategy presented in Table 1.

Study Eligibility Criteria

To standardize study selection, inclusion criteria were specified prior to the search process. Eligible studies were those that fulfill these criterias: 1) were published in a readable and interpretable language, 2) adopted an experimental design for diagnostic evaluation, 3) enrolled women with endometriosis established through laparoscopic assessment and histopathological confirmation as the reference standard, 4) assessed biomarker-based and/or clinical-variable–based diagnostic models, and 5) reported at least one outcome related to diagnostic accuracy, including sensitivity, specificity, or area under the curve (AUC).

Conversely, studies were excluded if they: 1) involved animal experiments or in vitro models, 2) were published in a language that could not be adequately interpreted or retrieved, and 3) had not undergone peer review. Study selection was performed independently by the reviewers, with disagreements resolved through discussion until a consensus was reached.

Outcome Measures

This study assesses the diagnostic performance of combined serum biomarkers and clinical variables for the diagnosis of endometriosis by synthesizing outcome data reported across eligible studies. The analysis emphasizes diagnostic outcomes, including sensitivity, specificity, and area under the receiver operating characteristic curve (AUC). All outcome data were obtained from the included studies according to reporting completeness. Data extraction for quantitative synthesis was conducted independently by three reviewers, and any inconsistencies were resolved through discussion to ensure data accuracy and methodological consistency.

Table 1. Literature Search Terms for Included Studies

Database	Keywords
PubMed	#1 "endometriosis" [MeSH Terms] #2 ("endometriosis"[Title/Abstract]) #3 #1 OR #2 #4 "biomarkers" [MeSH Terms] #5 ("serum biomarker"[Title/Abstract]) OR ("biomarkers"[Title/Abstract]) OR ("CA-125"[Title/Abstract]) OR ("interleukin"[Title/Abstract]) OR ("VEGF"[Title/Abstract]) OR ("microRNA"[Title/Abstract]) #6 #4 OR #5 #7 "clinical variables" [MeSH Terms] #8 ("clinical variables"[Title/Abstract]) OR ("clinical characteristics"[Title/Abstract]) OR ("clinical parameters"[Title/Abstract]) OR ("symptoms"[Title/Abstract]) OR ("risk factors"[Title/Abstract]) #9 #7 OR #8 #10 "diagnosis" [MeSH Terms] #11 ("diagnosis"[Title/Abstract]) OR ("diagnostic accuracy"[Title/Abstract]) OR ("predictive model"[Title/Abstract]) OR ("diagnostic model"[Title/Abstract]) OR ("sensitivity and specificity"[Title/Abstract]) #12 #10 OR #11 #13 #3 AND #6 AND #9 AND #12 #14 Filters: Humans; English
Epistemonikos	("endometriosis") AND ("serum biomarker" OR "biomarkers" OR "CA-125" OR "interleukin" OR "VEGF" OR "microRNA") AND ("clinical variables" OR "clinical characteristics" OR "clinical parameters" OR "symptoms" OR "risk factors") AND ("diagnosis" OR "diagnostic accuracy" OR "predictive model" OR "diagnostic model")
Scopus	("endometriosis") AND ("serum biomarker" OR "biomarkers" OR "CA-125" OR "interleukin" OR "VEGF" OR "microRNA") AND ("clinical variables" OR "clinical characteristics" OR "clinical parameters" OR "symptoms" OR "risk factors") AND ("diagnosis" OR "diagnostic accuracy" OR "predictive model" OR "diagnostic model")
ScienceDirect	("endometriosis") AND ("serum biomarker" OR "biomarkers" OR "CA-125" OR "interleukin" OR "VEGF" OR "microRNA") AND ("clinical variables" OR "clinical characteristics" OR "clinical parameters" OR "symptoms" OR "risk factors") AND ("diagnosis" OR "diagnostic accuracy" OR "predictive model" OR "diagnostic model")
EBSCO	("endometriosis") AND ("serum biomarker" OR "biomarkers" OR "CA-125" OR "interleukin" OR "VEGF" OR "microRNA") AND ("clinical variables" OR "clinical characteristics" OR "clinical parameters" OR "symptoms" OR "risk factors") AND ("diagnosis" OR "diagnostic accuracy" OR "predictive model" OR "diagnostic model")
Cochrane	("endometriosis") AND ("serum biomarker" OR "biomarkers" OR "CA-125" OR "interleukin" OR "VEGF" OR "microRNA") AND ("clinical variables" OR "clinical characteristics" OR "clinical parameters" OR "symptoms" OR "risk factors") AND ("diagnosis" OR "diagnostic accuracy" OR "predictive model" OR "diagnostic model")
ProQuest	#1 mesh.Exact("endometriosis") #2 noft("serum biomarker" OR "biomarkers" OR "CA-125" OR "interleukin" OR "VEGF" OR "microRNA") #3 noft("clinical variables" OR "clinical characteristics" OR "clinical parameters" OR "symptoms" OR "risk factors") #4 noft("diagnosis" OR "diagnostic accuracy" OR "predictive model" OR "diagnostic model") #5 noft("clinical study" OR "observational study" OR "diagnostic study") #6 #1 AND #2 AND #3 AND #4 AND #5

Quality Assessment

Assessment of bias for the included non-randomized studies was conducted using the QUADAS-2 framework. The resulting evaluations were systematically recorded in the "bias" section of a Microsoft Excel 2021 spreadsheet and

subsequently uploaded to the ROBVIS platform to create a visual overview presented as a traffic light and summary plot [11,12].

Statistical Analysis

Meta-analyses were conducted using RStudio with the "meta" package (RStudio Team, 2020) to estimate pooled effects by comparing intervention and control groups alongside "mada" to conduct diagnostic statistical analysis. A 95% confidence interval (CI) was applied for both continuous and dichotomous outcomes. Between-study heterogeneity was assessed using the I^2 statistic, with thresholds of 0%, 25%, 50%, and 75% indicating no, low, moderate, and high heterogeneity, respectively. Forest plots were constructed to display pooled effect estimates and interstudy comparisons for all evaluated outcomes. Publication bias was examined through funnel plot visualization

RESULTS

Study Selection and Identification

After removing duplicates and screening abstracts, 17 articles were reviewed in full text. Seventeen studies met the inclusion criteria and were included in the meta-analysis (Figure 1). Three studies were excluded due to irrelevance or insufficient data, and two were removed because their outcomes did not match the study objectives.

Demography and Clinical Characteristics of The Included Studies

The demography and clinical characteristics of each study were presented in Supplementary Data 1.

Risk of Bias Assessment for Included Studies

Sixteen clinical trials were assessed for methodological quality using the QUADAS 2.0

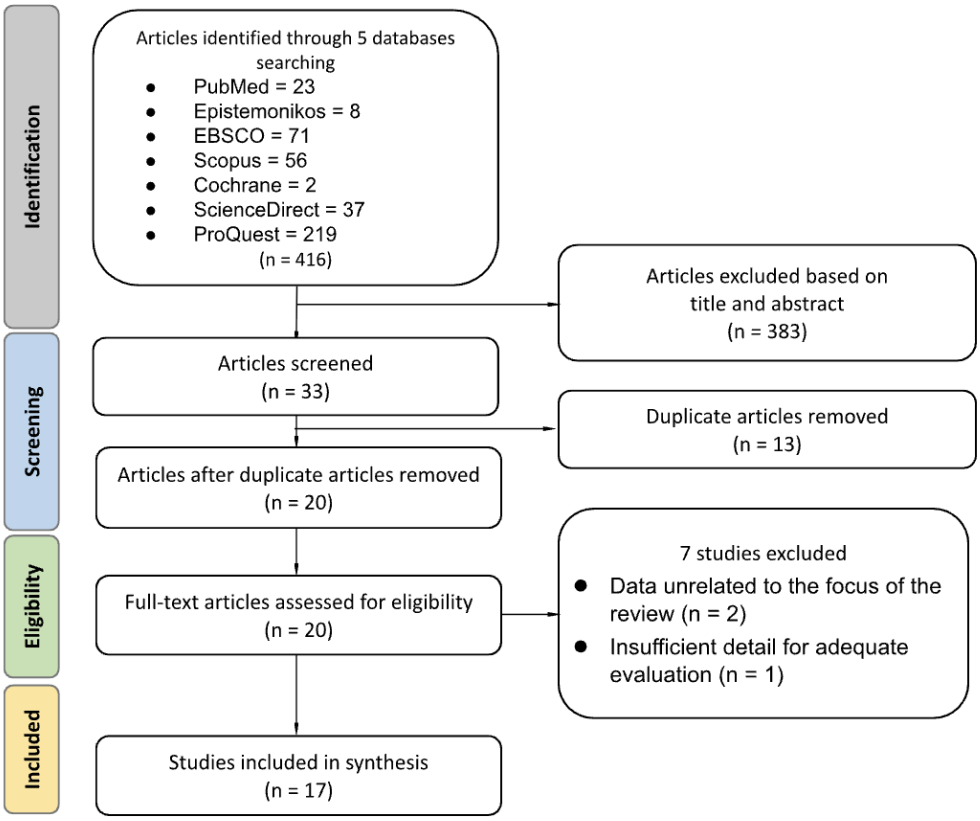


Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart for study identification and selection.

tool for diagnostic studies. The overall assessment for the 17 studies was that they were of low risk of bias [12]. Therefore, the methodological quality of the included studies was generally high, with most studies demonstrating a low risk of bias across all QUADAS-2 domains (D1–D4). In particular, all studies were rated as low risk in patient selection (D1) and index test (D2), indicating appropriate sampling strategies and consistent, unbiased application and interpretation of the index tests in Suplemetary Data 2.

Minor concerns were identified in a small subset of studies. Flow and timing (D4) was the most frequently affected domain, with studies such as Turgut et al., 2019 and Guo et al., 2022 rated as having some concerns, likely due to unclear or inconsistent intervals between index and reference tests or incomplete participant follow-up. Additionally, Moustafa et al., 2020 showed some concerns in the reference standard domain (D3), suggesting potential limitations in the validity or application generalization of the reference standard. No study was judged to have a high risk of bias in any domain (Figure 2).

Diagnostic Performance Analysis of Combined versus Single (Serum Biomarker/Clinical Variable Only) in Diagnosing Endometriosis

A double-arm meta-analysis was performed for each diagnostic outcome, including sensitivity, specificity, and AUC.

Sensitivity Analysis

A total of seventeen diagnostic studies were included in this meta-analysis, analyzing the sensitivity of the diagnostic approach, comprising 3,187 participants combined for experimental and control groups (Figure 3). The pooled analysis demonstrated a significantly higher diagnostic performance for the combined biomarker and clinical variable approach compared with the control, with an overall odds ratio (OR) of 2.64 (95% CI: 1.54 to 4.53). However, substantial heterogeneity was observed among the included studies (I^2 = 88.5%, τ^2 = 1.0508, $p < 0.0001$), suggesting considerable variability in study characteristics consistent with the scattered points found in the funnel plot (Figure 4). Therefore, subgroup analysis was done.

Specificity Analysis

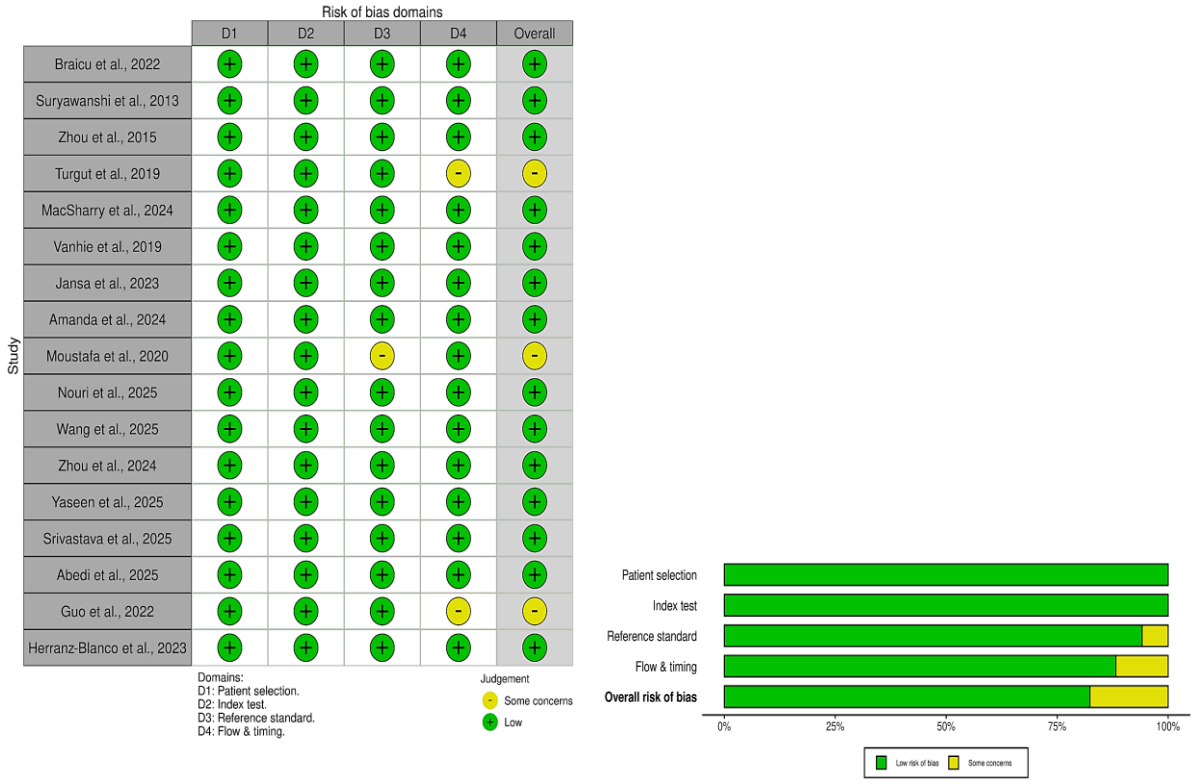


Figure 2. Risk of bias summary for diagnostic studies assessed using the QUADAS-2 tool. Green indicates low risk of bias, yellow indicates some concerns, and red indicates high risk of bias.

The forest plot shows the pooled OR of the specificity in diagnosing endometriosis comparing the experimental and control groups across 13 included studies. Individual study effect sizes vary substantially, with ORs ranging from 0.02 to 17.07, indicating marked between-study variability. Several studies favored the experimental group (OR < 1), while others favored the control group (OR > 1). Using a random-effects model, the overall pooled effect estimate was OR = 1.03 (95% CI: 0.43–2.49), suggesting no statistically significant difference in specificity rates between groups, while the pooled effect slightly supports a higher specificity of the combined group. Substantial heterogeneity was observed among studies (I^2 = 95.4%, τ^2 = 2.6364, p < 0.0001), indicating considerable inconsistency in effect estimates across trials as pictured in the funnel plot in Figure 6. Therefore, subgroup analysis was done.

Area Under the Curve (AUC) Analysis

The forest plot summarizes the OR of the outcome across 11 included studies comparing the experimental and control groups. Using a random-effects model, the pooled effect estimate was OR = 1.46 (95% CI: 1.10–1.93), demonstrating a statistically significant difference between groups. Moderate heterogeneity was observed among the included studies (I^2 = 57.0%, τ^2 = 0.0840, p = 0.0098), suggesting some variability in effect sizes across trials but acceptable consistency for pooled analysis and visually depicted in the funnel plot (Figure 8).

Diagnostics Analysis

The probability-modifying plot based on the Reitsma model demonstrated that the diagnostic test provides a moderate increase in post-test probability following a positive result and a meaningful reduction following a negative result. With a positive likelihood ratio (PLR) of 3.79, a positive test result moderately increases the likelihood of disease presence. Conversely, the negative likelihood ratio (NLR) of 0.23 indicates that a negative test result substantially reduces the probability of disease. Overall, these findings suggest that the test is more effective in ruling out disease than definitively confirming it, as depicted in Figure 9.

The summary receiver operating characteristic (SROC) curve demonstrated an area under the curve (AUC) of 0.868, indicating good overall diagnostic accuracy. This suggests that the test has a strong ability to discriminate between patients with and without the condition. The position of the SROC curve closer to the upper left corner further supports its high diagnostic performance, reflecting a favorable balance between sensitivity and specificity across the included studies (Figure 10).

Deeks' funnel plot asymmetry test showed no evidence of publication bias (p = 0.981) as pictured in Figure 11, suggesting that there was no significant small-study effect and that the included studies were symmetrically distributed around the pooled diagnostic effect. This finding indicates that the overall results of the meta-analysis are unlikely to be influenced by selective reporting or publication bias, thereby supporting the robustness and reliability of the pooled diagnostic accuracy estimates.

DISCUSSION

Mechanisms and Current Guidelines for Endometriosis Diagnosis

Endometriosis is a chronic inflammatory condition defined by the presence of endometrial-like tissue outside the uterine cavity, with an underlying pathophysiology that involves estrogen-dependent lesion growth, immune dysregulation, neuroangiogenesis, and inflammatory mediator release. This contributes to both lesion persistence and heightened pain sensitivity. Aberrant estrogen signaling also promotes lesion proliferation and survival. It increases the production of pro-inflammatory cytokines and activation of peripheral and central pain pathways. These mechanisms explain the heterogeneous clinical manifestations [5,6].

Laparoscopy with histopathological confirmation has been regarded as the diagnostic gold standard for endometriosis [5]. However, contemporary guidelines increasingly advocate for a noninvasive, structured diagnostic approach to reduce delays and avoid unnecessary surgery. This approach integrates comprehensive clinical history, targeted physical examination, and advanced imaging modalities. Imaging plays a crucial role in identifying ovarian endometriomas

and deep infiltrating endometriosis, while also mapping of disease extent [13,14].

To support standardized assessment and treatment planning, classification systems such as the revised American Society for Reproductive Medicine (rASRM) are widely utilized for more accurate staging of disease severity and anatomical involvement. Clinical diagnosis must account for the broad spectrum of symptom presentations and disease phenotypes, emphasizing early recognition to mitigate the substantial diagnostic delays that frequently extend over several years [5,14,15].

Current guidelines recommend individualized management strategies that prioritize medical therapy as first-line treatment for pain control, reserving surgical intervention for refractory symptoms, complications, or infertility-related indications [14,15]. Assisted reproductive technologies are advised for selected patients with infertility, while multidisciplinary care involving gynecologists, radiologists, pain specialists, and fertility experts is encouraged to address the complex clinical needs of affected women [15].

Diagnostic Performance of Combined Serum Biomarkers and Clinical Variables for Endometriosis Diagnosis

Our findings demonstrate significant evidence supporting the superior diagnostic performance of combined serum biomarkers and clinical variables compared with single diagnostic approaches for endometriosis. The pooled analysis of sensitivity indicates that the combined diagnostic strategy achieves higher sensitivity across studies, reflecting an overall improvement in identifying true endometriosis cases. Although individual study estimates have variabilities, the direction of effect consistently favored combined models over single biomarkers or clinical variables alone, highlighting the clinical advantage of integrative diagnostic approaches in heterogeneous patient populations.

In terms of diagnostic accuracy, the pooled specificity analysis revealed a non-statistically significant improvement for combined diagnostic methods, suggesting no improvement in rate of false-positive diagnoses. This is particularly relevant in clinical settings, where overdiagnosis may lead to unnecessary invasive procedures or prolonged hormonal treatment. The moderate heterogeneity observed across studies likely reflects differences in biomarker panels, patient selection, and disease stage distribution.

Further analysis showed that pooled area under the receiver operating characteristic curve (AUC) demonstrated that combined serum biomarkers and clinical variables provide significantly higher diagnostic performance compared with single-parameter models. The higher AUC values indicate improved balance between sensitivity and specificity, supporting the concept that multifactorial diagnostic algorithms more accurately capture the complex pathophysiology of endometriosis than isolated markers. This aligns with the understanding that endometriosis is driven by the combination of inflammatory, hormonal, and immunological mechanisms, which are unlikely to be adequately represented by a single biomarker.

Investigations integrating inflammatory markers such as interleukins and CA-125 with clinical features, such as dysmenorrhea severity, infertility history, and imaging findings, consistently reported superior predictive performance compared with standalone tests. These findings suggest that combined diagnostic frameworks may serve as practical noninvasive tools for early detection, particularly in resource-limited or pre-surgical settings where laparoscopy is not immediately feasible [16,17,36,37].

Moreover, serum biomarkers reflect systemic inflammatory and angiogenic activity, while clinical variables capture symptom expression and disease phenotype. Their integration therefore provides a more comprehensive representation of disease presence and severity, which may explain the observed increase in diagnostic yield [18,38,39,40].

Despite these encouraging results, a subset of studies demonstrated non-significant differences with some heterogeneities in diagnostic performance. This variability may be influenced by differences in biomarker selection, assay platforms, study populations, and reference standards.

Overall, this meta-analysis supports the growing role of combined serum biomarkers and clinical variables as a promising noninvasive diagnostic strategy for endometriosis. By achieving higher sensitivity, specificity, and AUC compared with single diagnostic components, combined models offer a clinically meaningful improvement in case detection and diagnostic precision. These findings align with current guideline trends favoring noninvasive and algorithm-based diagnosis prior to surgical confirmation.

Strengths and Limitations

This systematic review and meta-analysis is among the first to quantitatively assess the diagnostic performance of combined serum biomarkers and clinical variables for endometriosis using pooled sensitivity, specificity, and AUC estimates, to the authors' knowledge. Multiple diagnostic studies with high and acceptable variabilities provide clinically relevant evidence supporting nonsurgical, multimodal diagnostic strategies. Standardized meta-analytic methods and risk of bias assessment strengthen the reliability of the findings, creating a strong evidence-based medicine approach.

However, several limitations should be considered. Heterogeneity was observed in some parameters, likely due to variability in biomarker selection, assay methods, clinical variabilities, and disease stage distribution. Not to mention the differences in diagnostic thresholds, model construction, and individual study approach. Variation in surgical and pathological practices as the gold standard or reference in analysis may have also introduced verification bias. Moreover, publication bias might arise from restricted data availability precluded detailed subgroup analyses, and the inclusion of only accessible-language and indexed studies.

CONCLUSION

Combined serum biomarkers and clinical variables demonstrate improved sensitivity compared with single-parameter approaches; however, extreme heterogeneity, methodological variability, and lack of standardized diagnostic thresholds limit immediate clinical applicability. Rigorous prospective validation using standardized multivariable prediction frameworks is required before implementation in routine clinical practice.

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CONFLICT OF INTEREST

No conflicts of interest, whether financial or personal, were identified that could have impacted the design, execution, or interpretation of this research. The corresponding author affirms that all authors have no competing interests to disclose.

Availability of Data and Materials

All data generated and analyzed in this systematic review and meta-analysis were obtained from previously published clinical trials retrieved from major scientific databases. The datasets supporting the findings of this study are available from the corresponding author upon reasonable request.

REFERENCES

1. Saunders P, Horne A. Endometriosis: Etiology, pathobiology, and therapeutic prospects. Cell. 2021; 184(11):2807–24. https://doi.org/10.1016/j.cell.2021.04.041
2. Horne A, Missmer S. Pathophysiology, diagnosis, and management of endometriosis. BMJ. 2022; 379:e070750. https://doi.org/10.1136/bmj-2022-070750
3. Smolarz B, Szyłło K, Romanowicz H. Endometriosis: Epidemiology, classification, pathogenesis, treatment and genetics. Int J Mol Sci. 2021; 22(19):10554. https://doi.org/10.3390/ijms221910554
4. Arafah M, Rashid S, Akhtar M. Endometriosis: A comprehensive review. Adv Anat Pathol. 2020; 27(6):376–88. https://doi.org/10.1097/PAP.0000000000000288
5. Chapron C, Marcellin L, Borghese B, Santulli P. Rethinking mechanisms, diagnosis and management of endometriosis. Nat Rev

Endocrinol. 2019; 15(11):666–82. https://doi.org/10.1038/s41574-019-0245-z

6. Saunders P, Horne A. Endometriosis: Etiology, pathobiology, and therapeutic prospects. Cell. 2021 Jun 10;184(11):2807–24. https://doi.org/10.1016/j.cell.2021.04.041
7. De Araújo Medeiros Santos C, De Souza A, Neta A, Freire L, Sarmento A, Medeiros K, et al. Exosomal microRNAs as epigenetic biomarkers for endometriosis: A systematic review and bioinformatics analysis. Int J Mol Sci. 2025;26(10):4564. https://doi.org/10.3390/ijms26104564
8. Nisenblat V, Bossuyt P, Shaikh R, Farquhar C, Jordan V, Scheffers C, et al. Blood biomarkers for the non-invasive diagnosis of endometriosis. Cochrane Database Syst Rev. 2016;(5):CD012179. https://doi.org/10.1002/14651858.CD012179
9. Pant A, Moar K, Arora T, Maurya P. Biomarkers of endometriosis. Clin Chim Acta. 2023; 546:117563. https://doi.org/10.1016/j.cca.2023.117563
10. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021; 372:n71.
11. McGuinness LA, Higgins JPT. Risk-of-bias visualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. Res Synth Methods. 2021; 12(1):55–61.
12. Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: A revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011; 155(8):529–36.
13. Agarwal S, Chapron C, Giudice L, Laufer M, Leyland N, Missmer S, et al. Clinical diagnosis of endometriosis: A call to action. Am J Obstet Gynecol. 2019; 220(4):354.e1–354.e12. https://doi.org/10.1016/j.ajog.2018.12.039
14. Singh S, Allaire C, Al-Nourhji O, Bougie O, Bridge-Cook P, Duigenan S, et al. Guideline No. 449: Diagnosis and impact of endometriosis—A Canadian guideline. J Obstet Gynaecol Can. 2024; 46(5):102450. https://doi.org/10.1016/j.jogc.2024.102450
15. Moïse A, Dzeitova M, De Landsheere L, Nisolle M, Brichant G. Endometriosis and infertility: Gynecological examination practical guide. J Clin Med. 2025; 14(6):1904. https://doi.org/10.3390/jcm14061904
16. Herranz-Blanco B, Daoud E, Viganò P, García-Velasco J, Colli E. Development and validation of an endometriosis diagnostic method based on serum biomarkers and clinical variables. Biomolecules. 2023; 13(7):1052. https://doi.org/10.3390/biom13071052
17. Nisenblat V, Bossuyt P, Shaikh R, Farquhar C, Jordan V, Scheffers C, et al. Blood biomarkers for the non-invasive diagnosis of endometriosis. Cochrane Database Syst Rev. 2016;(5):CD012179. https://doi.org/10.1002/14651858.CD012179
18. Schoeman E, Bringans S, Peters K, Casey T, Andronis C, Chen L, et al. Identification of plasma protein biomarkers for endometriosis and the development of statistical models for disease diagnosis. Hum Reprod. 2024;40(1):eae278. https://doi.org/10.1093/humrep/deae278
19. Braicu EI, Krause CL, Torsten U, Mecke H, Richter R, Hellmeyer L, et al. HE4 as a serum biomarker for the diagnosis of pelvic masses: a prospective, multicenter study in 965 patients. BMC Cancer. 2022;22(1). doi:10.1186/s12885-022-09887-5 PubMed PMID: 35907794.
20. Suryawanshi S, Vlad AM, Lin HM, Mantia-Smaldone G, Laskey R, Lee M, et al. Plasma MicroRNAs as novel biomarkers for endometriosis and endometriosis-associated ovarian cancer. Clinical Cancer Research. 2013;19(5):1213–24. doi:10.1158/1078-0432.CCR-12-2726 PubMed PMID: 23362326.
21. Zhou Y, Liu G, Yuan L, Qiao Y, Chen Q. Evaluating systemic immune-inflammation indices as predictive markers for endometriosis diagnosis: A retrospective observational study. J Reprod Immunol. 2025;167. doi:10.1016/j.jri.2024.104416 PubMed PMID: 39662241.

22. Turgut A, Hocaoglu M, Ozdamar O, Usta A, Gunay T, Akdeniz E. Could hematologic parameters be useful biomarkers for the diagnosis of endometriosis? Bratislava Medical Journal. 2019;120(12):912–8. doi:10.4149/BLL_2019_153 PubMed PMID: 31855050.
23. MacSharry J, Kovács Z, Xie Y, Adamczyk B, Walsh C, Reidy F, et al. Endometriosis specific vaginal microbiota links to urine and serum N-glycome. Sci Rep. 2024;14(1). doi:10.1038/s41598-024-76125-2 PubMed PMID: 39455640.
24. Vanhie A, Dorien O, Peterse D, Beckers A, Cuéllar A, Fassbender A, et al. Plasma miRNAs as biomarkers for endometriosis. Human Reproduction. 2019;34(9):1650–60. doi:10.1093/humrep/dez116 PubMed PMID: 31411334.
25. Janša V, Pušić Novak M, Ban Frangez H, Rizner TL. TGFBI as a candidate biomarker for non-invasive diagnosis of early-stage endometriosis. Human Reproduction. 2023;38(7):1284–96. doi:10.1093/humrep/dead091 PubMed PMID: 37187159.
26. Riski Amanda C, Asmarinah, Hestiantoro A, Tulandi T, Febriyeni. Gene expression of aromatase, SF-1, and HSD17B2 in menstrual blood as noninvasive diagnostic biomarkers for endometriosis. European Journal of Obstetrics and Gynecology and Reproductive Biology. 2024;301:95–101. doi:10.1016/j.ejogrb.2024.07.061 PubMed PMID: 39116481.
27. Moustafa S, Burn M, Mamillapalli R, Nematian S, Flores V, Taylor HS. Accurate diagnosis of endometriosis using serum microRNAs. Am J Obstet Gynecol. 2020;223(4):557.e1-557.e11. doi:10.1016/j.ajog.2020.02.050 PubMed PMID: 32165186.
28. Nouri B, Talebian N, Kharaz L, Falah Tafti M. Diagnostic Value of Serum Cancer Antigen 125, Carcinoembryonic Antigen, Cancer Antigen 19-9, Anti Müllerian Hormone, White Blood Cell Count, Platelet Count, and Neutrophil to Lymphocyte Ratio in Endometriosis: A Retrospective Study. Int J Fertil Steril. 2025;19(3):259–63. doi:10.22074/ijfs.2024.2010957.1534
29. Wang Y, Qiu Z, Yao Y, Tan J, Che X. Integrating Thyroid Autoantibodies With CA125 Enhances Diagnostic Precision for Ovarian Endometriosis: A Retrospective Study of 885 Patients. Journal of Obstetrics and Gynaecology Research. 2025;51(10). doi:10.1111/jog.70111 PubMed PMID: 41093444.
30. Raouf Yaseen B, mohammed A jasim, Abdulhussein Salman S, Abd Alredha RD. Integrative analysis of inflammatory biomarkers and clinical features in endometriosis: insights into pain severity anddiagnostic utility. Anaesthesia, Pain and Intensive Care. 2025;29(4):276–82. doi:10.35975/apic.v29i4.2812
31. Srivastava A, Mallik R, Sharma LK, Rani A, Gupta A, Tiwari M, et al. Diagnostic utility of Synuclein gamma (SNCG) and b-cell Lymphoma 6 (BCL6) as potential non-invasive dual biomarkers for endometriosis. European Journal of Obstetrics and Gynecology and Reproductive Biology. 2025;315. doi:10.1016/j.ejogrb.2025.114778 PubMed PMID: 41160950.
32. Abedi RF, Mohammed AJ, Chyad A, Alredha RDA, Abbas GA, Haddawi KH. A Validated Serum Biomarker Signature for the Noninvasive Diagnosis of Endometriosis. Precis Nanomed. 2025;8(4):1645–58. doi:10.33218/001c.153841
33. Guo C, Zhang C. Platelet-to-Lymphocyte Ratio and CA125 Level as a Combined Biomarker for Diagnosing Endometriosis and Predicting Pelvic Adhesion Severity. Front Oncol. 2022;12. doi:10.3389/fonc.2022.896152
34. Herranz-Blanco B, Daoud E, Viganò P, García-Velasco JA, Colli E. Development and Validation of an Endometriosis Diagnostic Method Based on Serum Biomarkers and Clinical Variables. Biomolecules. 2023;13(7). doi:10.3390/biom13071052 PubMed PMID: 37509088.
35. Herranz-Blanco B, Daoud E, Viganò P, García-Velasco JA, Colli E. Development and Validation of an Endometriosis Diagnostic Method Based on Serum Biomarkers and

Clinical Variables. Biomolecules. 2023;13(7). doi:10.3390/biom13071052 PubMed PMID: 37509088.

36. Signorile PG, Baldi A. Serum biomarker for diagnosis of endometriosis. Journal of Cellular Physiology. 2014;229(11):1731-5.
37. Coutinho LM, Ferreira MC, Rocha AL, Carneiro MM, Reis FM. New biomarkers in endometriosis. Advances in clinical chemistry. 2019;89:59-77.
38. Irungu S, Mavrelos D, Worthington J, Blyuss O, Saridogan E, Timms JF. Discovery of non-invasive biomarkers for the diagnosis of endometriosis. Clinical Proteomics. 2019;16(1):14.
39. Ozhan E, Kokcu A, Yanik K, Gunaydin M. Investigation of diagnostic potentials of nine different biomarkers in endometriosis. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2014;178:128-33.
40. Kokot I, Piwowar A, Jędryka M, Sołkiewicz K, Kratz EM. Diagnostic significance of selected serum inflammatory markers in women with advanced endometriosis. International journal of molecular sciences. 2021;22(5):2295

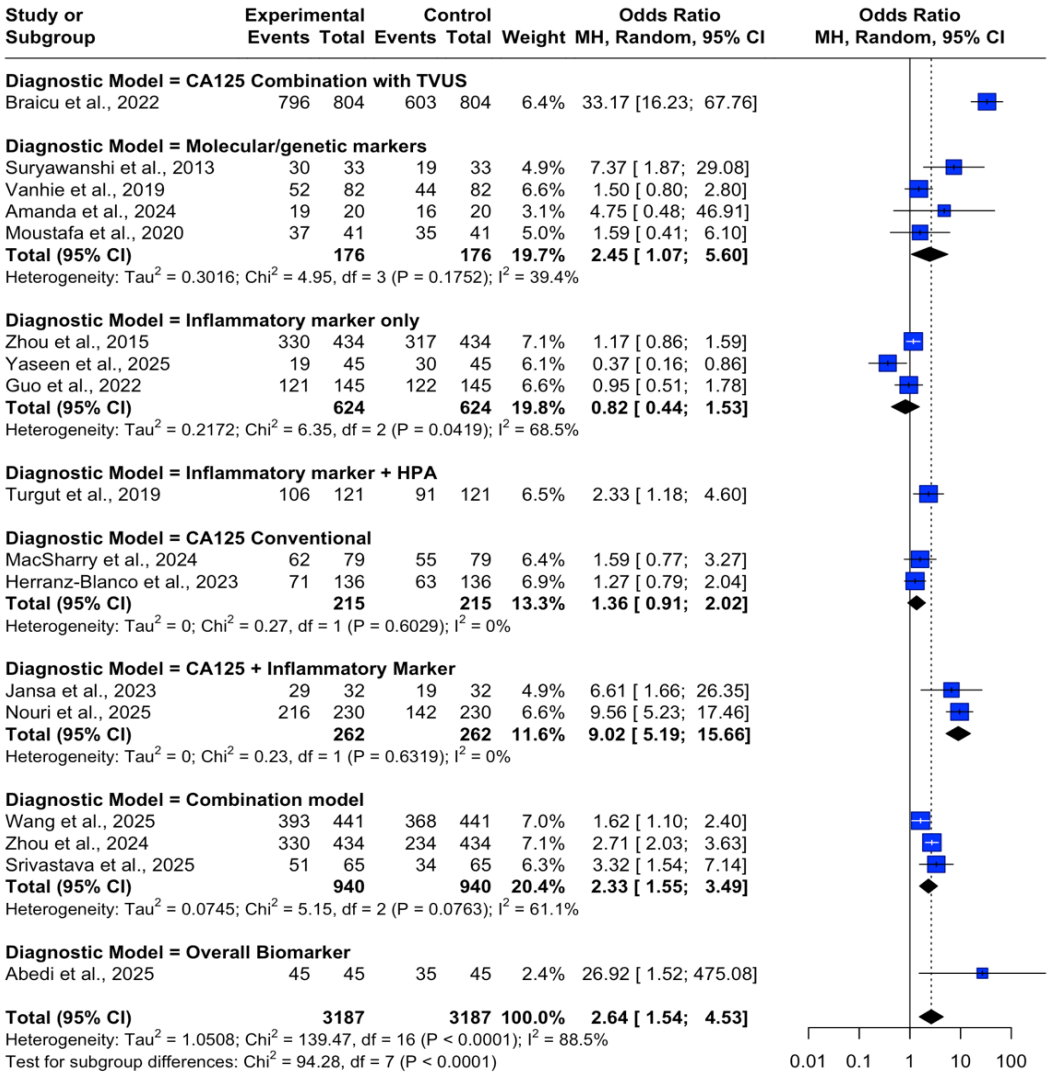


Figure 3. Forest plot illustrating the sensitivity of combined diagnostic models compared with single approaches (serum biomarker or clinical variable alone) for the detection of endometriosis. Blue squares represent individual study effect estimates, with horizontal lines indicating 95% confidence intervals. The area of each square corresponds to the study weight, and the black diamond denotes the pooled effect estimate.

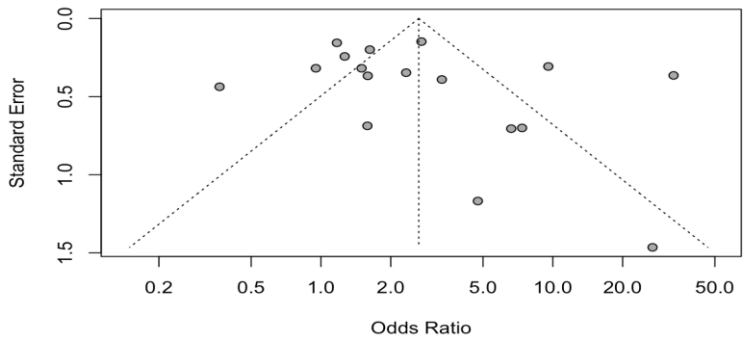


Figure 4. Funnel plot illustrating the difference regarding sensitivity in diagnosing endometriosis, showing the relationship between study size and reported effect estimates. The vertical axis represents trial size, whereas the horizontal axis corresponds to the effect size.

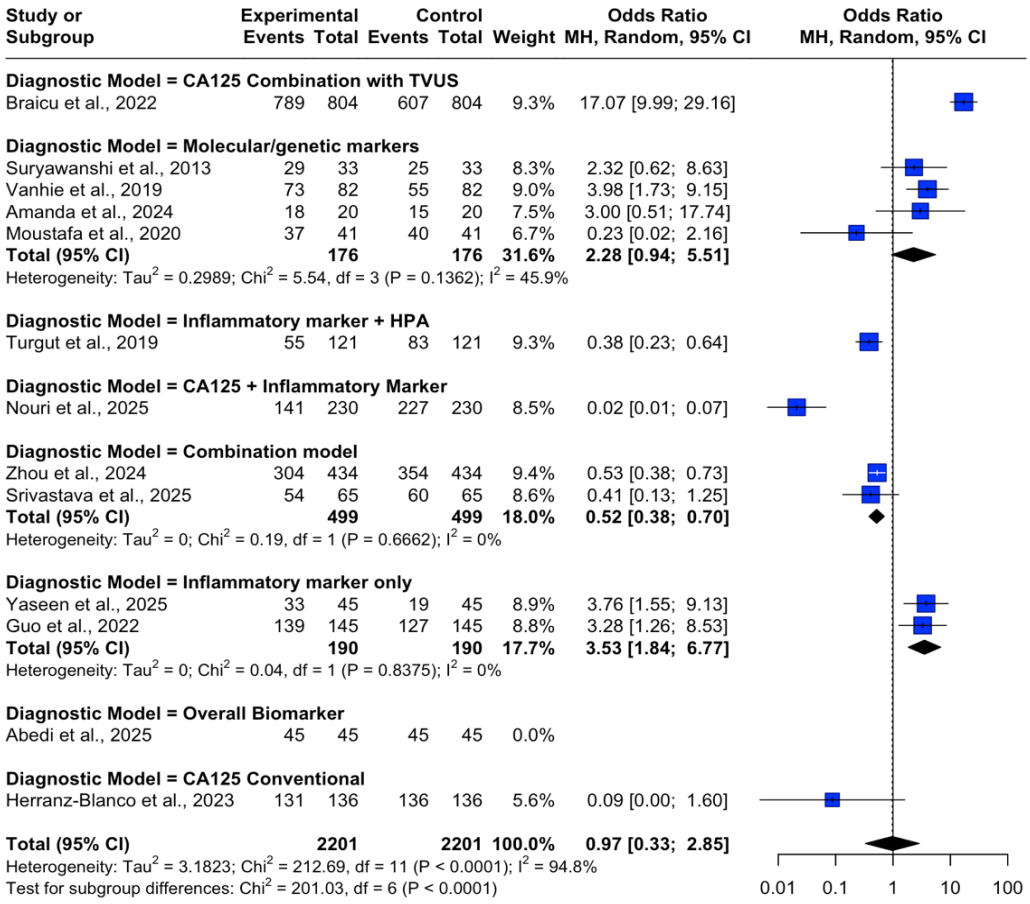


Figure 5. Forest plot illustrating the specificity of combined diagnostic models compared with single approaches for the detection of endometriosis. Blue squares represent individual study effect estimates, with horizontal lines indicating 95% confidence intervals. The area of each square corresponds to the study weight, and the black diamond denotes the pooled effect estimate.

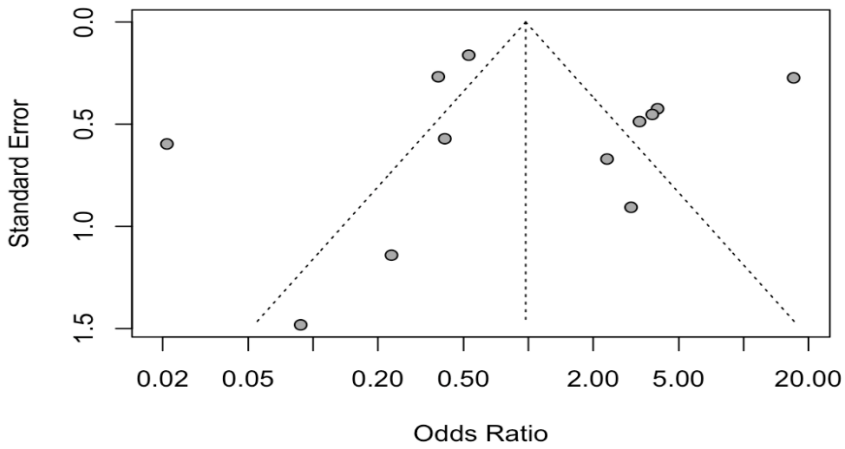


Figure 6. Funnel plot illustrating the difference in the specificity in diagnosing endometriosis, showing the relationship between study size and reported effect estimates. The vertical axis represents trial size, whereas the horizontal axis corresponds to the effect size.

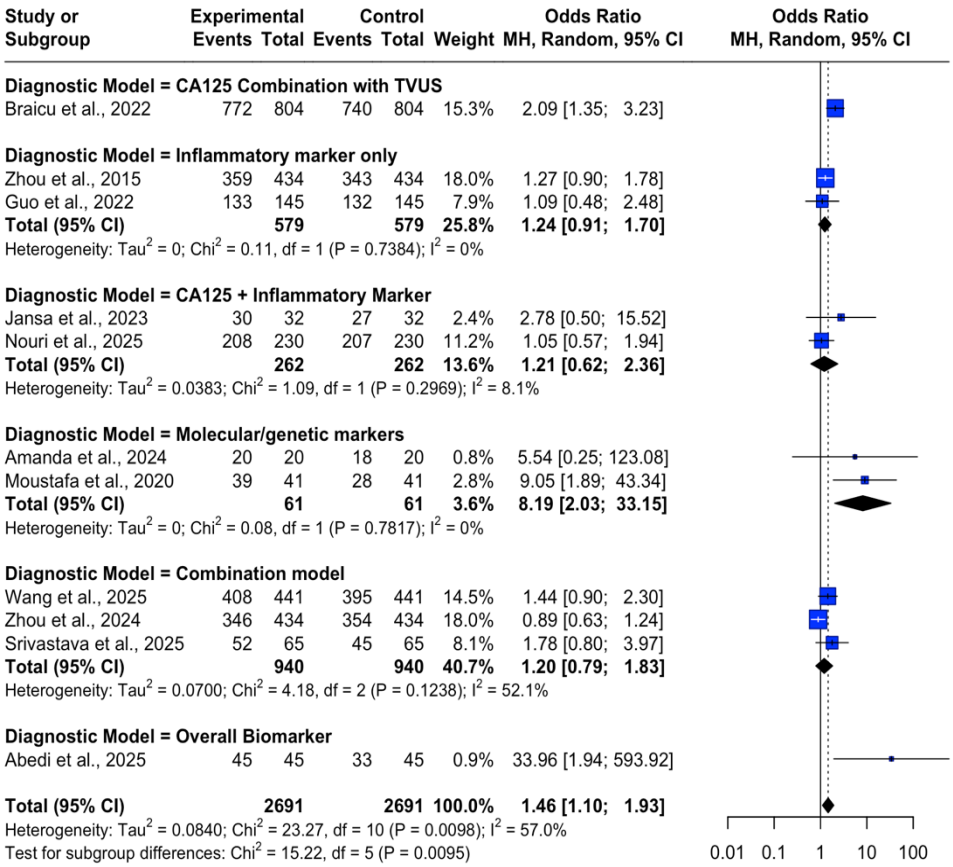


Figure 7. Forest plot showing the effect of AUC in two different diagnostic arms (combined and single). Each square represents the effect size of an individual study, with horizontal lines showing the 95% confidence interval. The diamond represents the pooled standardized mean difference estimate.

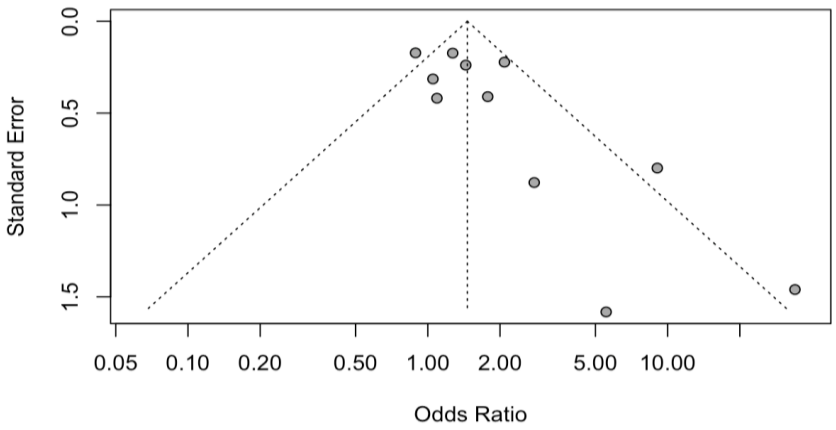


Figure 8. Funnel plot of the AUC difference on diagnostic approach for endometriosis as a graphical representation of the size of trials plotted against the effect size they report. The vertical axis represents the study size, while the horizontal scale represents the effect estimates

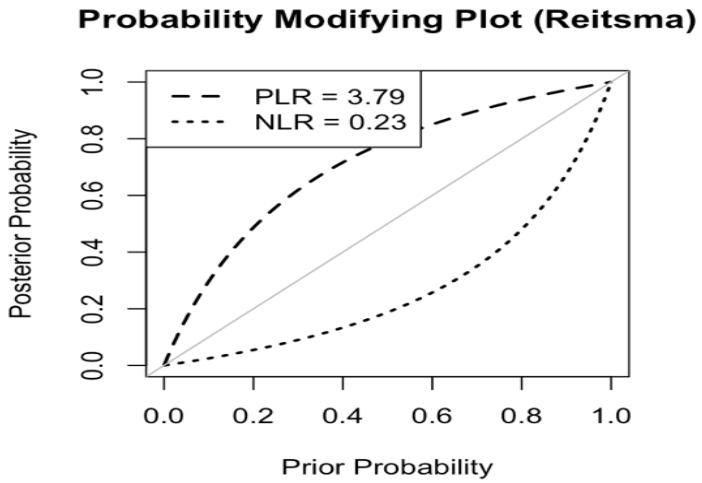


Figure 9. Probability Modifying Plot (Reitsma) on diagnostic approach for endometriosis.

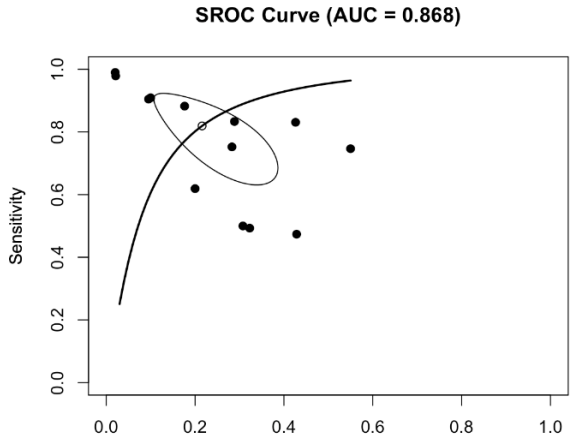


Figure 10. SROC Curve on diagnostic approach for endometriosis showing AUC of the included studies.

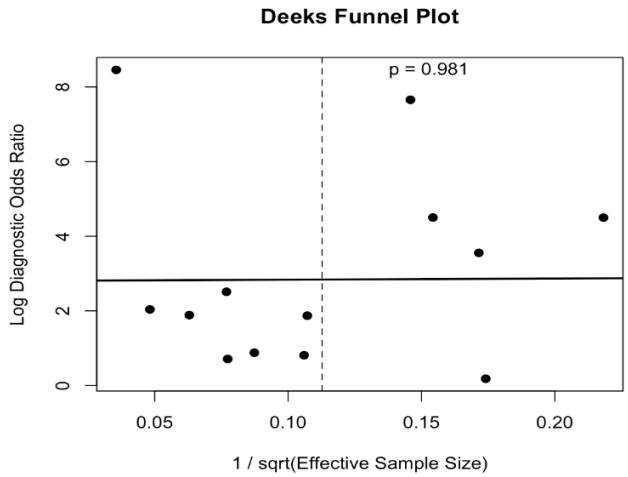


Figure 11. Deeks Funnel Plot/Asymmetry Test showing the publication bias of the analyzed studies.