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META-ANALYSIS

Liu et al: Fecal SDC2 methylation for CRC

Fecal DNA SDC2 methylation test for colorectal cancer diagnosis: A systematic review and meta-analysis

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ABSTRACT

Fecal DNA methylation of the syndecan-2 *(SDC2)* gene is being explored as a noninvasive biomarker for colorectal cancer (CRC) detection. However, its diagnostic performance necessitates thorough evaluation. A systematic search of PubMed, Embase, and Web of Science was conducted to identify studies investigating fecal *SDC2* methylation (*mSDC2*) for CRC diagnosis. Eligible studies included adult CRC patients with histological confirmation and controls with either normal mucosa or benign colorectal lesions. Pooled sensitivity and specificity were synthesized using a Reitsma bivariate random-effects model, and summary receiver operating characteristic (SROC) curves with corresponding area under the curve (AUC) values were derived from this hierarchical model. Twenty-five studies encompassing 3,427 CRC patients, 3,267 individuals with benign lesions, and 5,372 with normal mucosa were included. For the comparison of CRC versus normal mucosa (24 studies), the pooled sensitivity and specificity were 0.86 (95% confidence interval [CI]: 0.82-0.89; I^2 = 88%) and 0.93 (95% CI: 0.90-0.95; I^2 = 95%), respectively. The pooled diagnostic odds ratio (DOR) was 81.73 (95% CI: 51.60-129.46), with an AUC of 0.95 (95% CI: 0.93-0.97). In the comparison against benign lesions (22 studies), the sensitivity was 0.85 (95% CI: 0.81-0.89; I^2 = 87%), specificity was 0.66 (95% CI: 0.59-0.71; I^2 = 91%), DOR was 11.10 (95% CI: 7.61-16.19), and AUC was 0.83 (95% CI: 0.80-0.86). Deeks' funnel plot asymmetry tests indicated no statistically significant publication bias (p = 0.48 and 0.54). In conclusion, fecal *mSDC2* testing demonstrates high diagnostic accuracy for CRC detection when compared to individuals with normal mucosa and moderate performance against benign colorectal lesions. These findings suggest that *mSDC2* may serve as a promising noninvasive biomarker to complement existing CRC screening methodologies.

Keywords: Syndecan-2, DNA methylation, stool, colorectal cancer, diagnosis.

INTRODUCTION

Colorectal cancer (CRC) is one of the most prevalent malignancies globally, representing a leading cause of cancer-related morbidity and mortality (1, 2). The prognosis of CRC is closely linked to the stage at diagnosis, with early-stage detection offering significantly improved survival outcomes (3, 4). Although colonoscopy remains the gold standard for early detection, its invasiveness, high cost, and limited accessibility reduce compliance in population-based screening programs (5, 6). Noninvasive approaches such as the fecal immunochemical test (FIT) and multi-target stool DNA (mt-sDNA) testing have been developed to improve participation rates (5, 6); however, their diagnostic performance remains suboptimal, particularly for early-stage disease and precancerous lesions (5, 6). Therefore, there is an urgent need for accurate, noninvasive biomarkers that can reliably identify CRC at an early stage (7, 8).

The *syndecan-2* (*SDC2*) gene, a member of the syndecan family of heparan sulfate proteoglycans, plays a key role in cell adhesion, proliferation, and migration (9, 10). Aberrant *SDC2* methylation (*mSDC2*) contributes to colorectal tumorigenesis by silencing tumor suppressor functions and promoting malignant transformation (10, 11). Detection of *mSDC2* in fecal DNA—most commonly via quantitative methylation-specific PCR (qMSP)—offers a promising strategy for noninvasive CRC screening (12). Fecal testing has the added advantages of being safe, convenient, and well accepted by patients (13). Previous meta-analyses evaluating the diagnostic value of *mSDC2*, both published in 2022 (14, 15), were limited by small sample sizes, inclusion of both fecal and non-fecal samples, lack of distinction between normal mucosa and benign colorectal lesions. In addition, accumulating studies have been published afterwards to evaluate the role of fecal *mSDC2* in early diagnosis of CRC (16-31). To address these gaps, we conducted an up-to-date meta-analysis focusing exclusively on fecal *mSDC2* testing for CRC diagnosis, separately summarizing its diagnostic performance against normal mucosa and benign colorectal lesions.

MATERIAL AND METHODS

This systematic review and meta-analysis was conducted in accordance with the (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) PRISMA guidelines (32, 33) and followed methodological recommendations provided in the

Cochrane Handbook (34) to ensure rigor in study design, data synthesis, and reporting. The protocol of the meta-analysis has been registered in PROSPERO with the ID: CRD420251112337.

Database search

To identify eligible studies, we conducted a systematic search of PubMed, Embase, and Web of Science using a combination of terms related to the biomarker ("*syndecan-2*" OR "*syndecan 2*" OR "*SDC2*"), anatomical site ("colon" OR "rectal" OR "rectum" OR "colorectal" OR "colorectum"), and disease condition ("cancer" OR "tumor" OR "neoplasms" OR "carcinoma" OR "adenocarcinoma" OR "malignancy"). No restrictions were placed on sample source or study outcomes at the search stage to maximize retrieval of relevant literature; however, only studies using fecal samples were eligible for inclusion according to the predefined selection criteria. The search was limited to human studies published as full-text articles in English, covering the period from database inception to May 31, 2025. Additionally, we manually screened the reference lists of relevant publications to identify further eligible studies. The complete search strategies for each database are provided in **Supplemental File 1**.

Study selection criteria

Studies were selected if they met the following criteria:

Population: Adult participants (≥18 years), including patients with histologically confirmed CRC and appropriate control groups (e.g., healthy individuals or patients with non-malignant colorectal diseases such as adenoma).

Index test: Studies evaluating *SDC2* gene methylation in fecal DNA samples using any valid detection method (e.g., qMSP or quantitative bisulfite next-generation sequencing [NGS] etc.).

Reference standard: Diagnosis of CRC must be confirmed by histopathological examination (either by samples from endoscopic or surgical resection), considered the gold standard.

Outcomes: Studies must provide sufficient data to construct a 2×2 contingency table (i.e., true positives, false positives, false negatives, and true negatives), allowing the calculation of diagnostic performance metrics (sensitivity, specificity, etc.).

Study design: Original clinical studies, including cross-sectional, case-control, or cohort designs (retrospective or prospective).

Language: Only studies published in English were included, consistent with the journal scope. However, potentially relevant non-English studies may have been missed.

Exclusion Criteria:

(1) Studies using non-fecal samples for *mSDC2* detection (e.g., blood, tissue, intestinal lavage fluid).

(2) Studies that did not report diagnostic performance specifically for CRC or did not provide extractable 2×2 data for CRC patients.

(3) Studies that evaluated multi-gene panels but did not report the individual performance of *mSDC2*.

(4) Experimental studies involving cell lines, animal models, or in vitro systems rather than clinical human samples.

(5) Non-original studies, such as reviews, meta-analyses, editorials, or conference abstracts.

If two studies included potentially overlapping patient populations, the one with the largest sample size was included in the meta-analysis.

Data collection and quality assessment

Two independent reviewers screened the literature, extracted data, and evaluated study quality using predefined criteria. Discrepancies were resolved through discussion to reach consensus. Extracted data included study characteristics (first author, publication year, country, and design), participant information (number and stage of CRC cases, control type, overall mean age, and sex distribution), details of fecal *mSDC2* testing, numbers of *mSDC2*-positive individuals in cases and controls, and the reference standard for CRC diagnosis. Study quality was assessed using the Quality Assessment Tool for Diagnostic Accuracy Studies (QUADAS-2) tool (35), with each study rated as having low, high, or unclear risk of bias across key domains based on risk sources and applicability.

Statistical methods

This meta-analysis separately summarized the diagnostic performance of fecal *mSDC2* for colorectal cancer (CRC), comparing it with controls having normal colonic mucosa and those with benign colorectal lesions. Sensitivity and specificity were jointly synthesized using a Reitsma bivariate random-effects model, which accounts for the correlation between paired outcomes and between-study heterogeneity. Positive and negative diagnostic likelihood ratios and diagnostic odds ratios were derived from the pooled sensitivity and specificity estimates. The diagnostic odds ratio (DOR), indicating the odds of a correct diagnosis relative to a misdiagnosis (36), was also calculated to reflect overall test accuracy. Discriminative performance was assessed using summary receiver operating characteristic (SROC) curves, and the corresponding AUCs were obtained from the hierarchical model, rather than by averaging study-level AUCs. When a study contained zero cells in the 2×2 contingency table, a continuity correction of 0.5 was applied to all four cells to allow model convergence. Summary sensitivity and specificity represent the model-implied operating point of the Reitsma bivariate random-effects model, based on thresholds reported in the original studies or, when not explicitly stated, the Youden index–optimized cutoff used by the study authors. Between-study heterogeneity was assessed using the Cochrane Q test ($p < 0.10$ considered significant) (34), and quantified with the I^2 statistic, with thresholds of <25%, 25–75%, and >75% indicating low, moderate, and substantial heterogeneity, respectively (37). Publication bias was examined using Deeks' funnel plot and asymmetry test (38). All statistical analyses were conducted using STATA software (Version 17.0; Stata Corporation, College Station, TX, USA), with $p < 0.05$ regarded as statistically significant.

RESULTS

Results of literature search

The initial database search yielded 461 studies as depicted in **Figure 1**, of which 296 remained after 165 duplicates were removed. Upon analyzing the titles and abstracts, a further 250 studies were excluded due to lack of relevance to the meta-analysis objective, leaving 46 studies undergoing full-text review. After a thorough review of

full texts, 21 out of the remaining studies were excluded for reasons detailed in **Figure 1**. Ultimately, 25 studies (16-31, 39-47) were included for the meta-analysis.

Study characteristics and quality assessment

The main characteristics of the 25 studies included in this meta-analysis are presented in **Table 1**. These studies were conducted in China (including Taiwan), Korea, and Thailand, and were published between 2017 and 2025. Most studies (20/25) adopted a prospective design (16, 18, 20-25, 27-30, 39, 40, 42-47), while five were retrospective (17, 19, 26, 31, 41). In total, data from 3,427 patients with CRC were included. The stage of CRC ranged from 0 to IV. The controls comprised individuals with normal mucosa, benign colorectal lesions (such as adenomas or hyperplastic polyps), or both. Overall, 5372 participants with normal mucosa and 3267 participants with benign colorectal lesions were included in this meta-analysis. Overall, the mean age of participants varied between 52.4 and 67.8 years, with the proportion of male participants ranging from 39.4% to 68.1%. In 24 studies, fecal *mSDC2* levels were evaluated using qMSP (16-23, 25-31, 39-47), while in the other study (24), the quantitative bisulfite NGS was used. The cutoff thresholds most commonly defined by receiver operating characteristic curve analysis or prespecified cycle-threshold values, although some studies did not report the methods to generate the cutoff thresholds (17-19, 24, 26-28, 30, 31, 45) or the threshold value (20, 24-26, 28, 39, 47). In addition, the methods for threshold determination and exact cutoff values were variably reported, limiting further stratified analyses by threshold definition. The reference standard for CRC diagnosis was histological confirmation via endoscopic or surgical biopsy across all studies.

Study quality was assessed using the QUADAS-2 tool, with results detailed in **Table 2**. Most studies were rated as having low risk of bias across all domains. However, five studies (17, 19, 26, 31, 41) were judged to have high risk of bias in the domain of patient selection due to retrospective design or unclear sampling methods. In addition, the domain of flow and timing was rated as unclear in eight studies (17, 18, 21, 24, 29, 31, 39, 44), largely due to insufficient reporting on the interval between index testing and reference standard confirmation. All other domains, including those related to applicability concerns, were judged as low risk in all of the studies.

Performance of fecal mSDC2 in detecting CRC versus normal mucosa

Based on pooled data from 24 studies (16-28, 30, 31, 39-47), fecal *mSDC2* demonstrated robust diagnostic performance for distinguishing CRC from individuals with normal colonic mucosa. The combined sensitivity and specificity were 0.86 (95% CI: 0.82–0.89; I^2 = 88%, **Figure 2A**) and 0.93 (95% CI: 0.90–0.95; I^2 = 95%, **Figure 2B**), respectively. The pooled positive and negative diagnostic likelihood ratios were 12.28 (95% CI: 8.39–18.01) and 0.15 (95% CI: 0.11–0.19), respectively, yielding a diagnostic odds ratio (DOR) of 81.73 (95% CI: 51.60–129.46). The area under the summary receiver operating characteristic curve (AUC) was 0.95 (95% CI: 0.93–0.97; **Figure 2C**), indicating excellent diagnostic accuracy.

Performance of fecal mSDC2 in detecting CRC versus benign lesions

Pooled results from 22 studies (16-20, 22, 23, 25-31, 39-43, 45-47) indicated that fecal *mSDC2* had acceptable diagnostic performance for differentiating CRC from benign colorectal lesions. The combined sensitivity was 0.85 (95% CI: 0.81–0.89; I^2= 87%, **Figure 3A**), and specificity was 0.66 (95% CI: 0.59–0.71; I^2 = 91%, **Figure 3B**). The pooled positive and negative diagnostic likelihood ratios were 2.48 (95% CI: 2.08–2.96) and 0.22 (95% CI: 0.17–0.29), respectively, yielding a diagnostic odds ratio (DOR) of 11.10 (95% CI: 7.61–16.19). The AUC was 0.83 (95% CI: 0.80–0.86; **Figure 3C**), supporting the moderate diagnostic accuracy of fecal *mSDC2* in distinguishing CRC from benign colorectal lesions.

Publication bias

The Deeks' funnel plots for the meta-analyses summarizing the performance of fecal *mSDC2* in detecting CRC versus normal mucosa and benign colorectal lesions are shown in **Figure 4A and 4B**, which did not suggest statistically significant publication bias (p = 0.48 and 0.54). However, these findings should be interpreted cautiously, given the limited power of the test in diagnostic accuracy meta-analyses.

DISCUSSION

This meta-analysis comprehensively evaluated the diagnostic performance of fecal *mSDC2* testing for CRC by synthesizing data from 25 studies including over 12,000 participants. Our findings indicate that fecal *mSDC2* demonstrates excellent

diagnostic accuracy for distinguishing CRC from individuals with normal colonic mucosa and moderate performance in differentiating CRC from those with benign colorectal lesions. By separately analyzing these two clinically relevant comparison groups, this study provides more granular insight into the utility of fecal *mSDC2* testing in real-world early screening and triaging strategies.

The role of *mSDC2* in CRC detection is mechanistically plausible. The *SDC2* gene encodes a transmembrane heparan sulfate proteoglycan that is involved in key biological processes such as cell proliferation, adhesion, and migration (48, 49). Aberrant methylation of the *SDC2* promoter region leads to transcriptional silencing, which disrupts normal epithelial cell behavior and promotes colorectal carcinogenesis (50, 51). *SDC2* hypermethylation has been observed in early-stage CRC as well as in advanced adenomas, making it a promising biomarker for early detection (11). Importantly, tumor-derived DNA is shed into the intestinal lumen and eventually expelled in feces, where methylated gene targets such as *mSDC2* can be captured and amplified using qMSP or similar technologies (52, 53). The noninvasive nature of stool-based collection, combined with the high specificity of methylation detection, underpins the clinical relevance of *mSDC2* as a CRC screening biomarker (54).

The present analysis highlights several clinically meaningful observations. First, fecal *mSDC2* shows excellent diagnostic efficacy when compared with normal mucosa, with pooled sensitivity and specificity exceeding 85% and 90%, respectively, and an AUC of 0.95. This level of performance compares favorably with widely used noninvasive tests such as FIT (55) and mt-sDNA (56). Second, when compared with benign lesions, including non-neoplastic polyps and inflammatory conditions, the specificity of *mSDC2* was moderate. This finding reflects the biological continuum between benign and malignant lesions and suggests that *mSDC2* may be less effective in distinguishing low-risk lesions from early-stage malignancies (57). Nevertheless, its strong sensitivity in both comparisons supports the utility of *mSDC2* testing in initial screening settings, particularly when used to prioritize individuals for further diagnostic evaluation such as colonoscopy. From a clinical perspective, the high pooled sensitivity observed in this meta-analysis suggests that fecal *mSDC2* testing could meaningfully increase post-test probability of CRC detection in screening settings, particularly when applied to populations with non-negligible baseline risk. However, the exact magnitude of post-test risk reduction depends on underlying disease prevalence, which varies across screening and clinical contexts. In addition,

although several included studies reported favorable detection rates in early-stage CRC, inconsistent reporting of stage-specific diagnostic data precluded pooled analyses by cancer stage. Future studies should provide stage-stratified accuracy estimates to better define the role of fecal mSDC2 in early detection and precancerous lesion interception.

Moderate to substantial heterogeneity was observed, which is common in diagnostic test accuracy meta-analyses. In this study, heterogeneity is primarily attributable to differences in assay thresholds, cutoff-determination strategies, and control group composition (normal mucosa versus benign lesions), rather than study design or overall study quality. Because cutoff definitions were variably reported and not standardized, formal threshold-based subgroup or meta-regression analyses were not methodologically reliable. In addition, sensitivity analyses excluding retrospective or high-risk-of-bias studies were not performed, as diagnostic accuracy estimates are largely determined by index test performance and reference standards rather than temporal study design, and such exclusions would substantially reduce sample size without meaningfully addressing the principal sources of heterogeneity. Importantly, the use of a hierarchical bivariate random-effects model allows robust estimation of pooled sensitivity, specificity, and AUC while appropriately accounting for between-study variability. Notably, several studies reported relatively higher *mSDC2* positivity among normal-mucosa controls—most prominently by Cheng et al. 2023 (16) and Liu et al. 2023 (17), in which positivity exceeded 30–50%, and to a lesser extent in Kim et al. 2024 (23) and Zhan et al. 2023 (20)—which likely contributed to between-study heterogeneity and attenuation of pooled specificity estimates; such findings may reflect differences in population risk profiles, assay thresholds, or background epigenetic alterations rather than true diagnostic failure.

Our meta-analysis has several notable strengths. It represents the most up-to-date and comprehensive synthesis of fecal *mSDC2* testing for CRC diagnosis, incorporating 25 studies with a relatively large sample size. Unlike previous meta-analyses, we restricted inclusion to studies that used fecal samples, excluded studies using tissue or plasma, and separately summarized diagnostic performance based on the nature of the control group—either benign lesions or normal mucosa. This approach allows for more clinically relevant interpretation. Furthermore, publication bias was not evident in either analysis, suggesting stability of our pooled results. However, several limitations should also be acknowledged. First, although most included studies were

prospective, five were retrospective in design, potentially introducing selection or recall bias (58). Second, the cutoff thresholds and platforms used for *mSDC2* detection varied across studies, which may have contributed to the moderate-to-high heterogeneity observed in sensitivity and specificity estimates. Future studies are needed to determine the optimal cutoff thresholds of fecal *mSDC2* testing for CRC diagnosis. Third, the stage distribution of CRC was inconsistently reported, precluding subgroup analysis of diagnostic accuracy by cancer stage. In addition, although benign colorectal lesions comprise a heterogeneous group, most included studies did not report diagnostic outcomes stratified by advanced versus non-advanced lesions, precluding separate analyses for high-risk precancerous neoplasia. Fourth, although we stratified analyses by control type, other patient-level factors such as age, sex, family history, or comorbidities could not be accounted for due to lack of individual participant data. In addition, the restriction to English-language publications may have introduced language bias, particularly given the substantial body of *SDC2* research from East Asia. Nevertheless, most large, high-quality diagnostic studies in this field are available in English. In addition, all included studies were conducted in Asian populations, reflecting the current geographic focus of fecal *mSDC2* research. While Deeks' funnel plot did not indicate significant asymmetry, publication bias assessment remains qualitative and exploratory, and the generalizability of findings to non-Asian populations requires further validation. Lastly, while fecal *mSDC2* is promising, formal head-to-head diagnostic accuracy comparisons with established screening tools (e.g., FIT and mt-sDNA) remain limited. However, comparative evidence with FIT is emerging from real-world/community screening studies in which both tests were applied within the same screening setting, providing preliminary context for relative performance (53); further standardized, prospective head-to-head evaluations are still warranted.

Despite these limitations, the findings of this study have relevant clinical implications. Fecal *mSDC2* testing may serve as a complementary tool to existing CRC screening modalities, particularly for individuals at average risk or those unwilling or unable to undergo colonoscopy. Its high specificity and sensitivity against normal mucosa make it attractive for initial screening in asymptomatic populations, while the moderate performance against benign lesions suggests it may also play a role in risk stratification among patients with detected polyps. From a public health perspective,

implementing such a noninvasive and cost-effective tool could enhance screening uptake and reduce the burden of CRC-related mortality through earlier detection (59). Future research should aim to standardize *mSDC2* detection protocols, including optimal methylation thresholds and target sequences, to improve comparability across studies. Additionally, large-scale prospective screening trials are warranted to assess the performance of fecal *mSDC2* in average-risk populations and to evaluate its additive value when combined with other noninvasive tests. Studies focusing on longitudinal monitoring of methylation markers may also offer insight into the utility of *mSDC2* for surveillance in high-risk groups or post-polypectomy follow-up. Finally, economic evaluations are needed to establish cost-effectiveness and feasibility of integrating *mSDC2* testing into routine screening programs.

CONCLUSION

In conclusion, this meta-analysis indicates that fecal *mSDC2* testing shows good diagnostic performance for detecting CRC, particularly when compared with individuals with normal mucosa, and moderate discriminative ability in distinguishing CRC from benign colorectal lesions. These findings suggest that fecal *mSDC2* may serve as a promising noninvasive biomarker to complement existing CRC screening strategies. However, given the substantial heterogeneity, limited comparative data with established screening tests, and the predominance of evidence from Asian populations, further large-scale, prospective, and geographically diverse studies—including stage-specific and head-to-head evaluations—are warranted to better define its clinical role.

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TABLES AND FIGURES WITH LEGENDS

Table 1. Characteristics of the included studies

Study	Country	Design	CRC stage	No. of patients with CRC	Control characteristics	No. of subjects with benign colorectal lesions	No. of subjects with normal colonic mucosa	Mean age (years)	Men (%)	Methods for fecal mSDC2 evaluation	Methods for determination of cutoff of mSDC2	Cutoff values of mSDC2	No. of fecal mSDC2 (+) in CRC patients	No. of fecal mSDC2 (+) controls with benign lesions	No. of fecal mSDC2 (+) controls with normal mucosa	Reference test
Oh 2017	Korea	P	Stages I–IV	50	Both benign lesions (adenomatous polyps) and healthy mucosa	21	22	60.6	60.2	qMSP	ROC curve analysis	Ct ≤ 40	45	7	2	Endoscopic or surgical histology
Niu 2017	China	P	Stages I–IV	196	Both benign lesions (adenomas ≥1 cm) and healthy mucosa	122	179	59.3	54.4	qMSP	ROC curve analysis	NR	159	71	12	Endoscopic histology
Han 2019	Korea	R	Stages 0–	245	Both benign lesions	44	245	60.5	52.5	qMSP	Pre-specified	Ct ≤ 40	221	12	24	Endoscopic or surgical histology

			IV		(advanced adenomas ≥1 cm, non-advanced adenomas <1 cm, hyperplastic/other polyps) and healthy mucosa					based on prior pilot study results					
Sun 2019	China	P	Stages I–IV	105	Both benign (adenoma; hyperplastic polyps) and healthy mucosa	26	102	NR	53	qMSP	Assay's analytical detection limit	Ct ≤ 42	72	10	9	Endoscopic histology
Wang 2020	China	P	Stages I–IV	359	Both benign (advanced adenoma) and healthy mucosa	38	512	54.1	51.3	qMSP	Cutoff selected to maximize sensitivity and minimize the false positive rate	Ct ≤ 38	301	16	14	Endoscopic histology
Su 2021	Taiwan (China)	P	Stages 0–IV	62	Healthy mucosa only	0	76	58.3	50.5	qMSP	Cutoffs selected balance	Ct ≤ 39	48	0	9	Endoscopic histology

											overall sensitivity and specificity					
Zhang 2021	China	P	Stages I–IV	61	Both benign (adenoma) and healthy mucosa	16	53	54.5	58.5	qMSP	NR	Ct ≤ 38	47	11	1	Endoscopic or surgical histology
Dai 2022	China	P	Stages 0–IV	244	Benign (advanced adenomas; small polyp) and healthy mucosa	98	187	55.6	52.9	qMSP	ROC curve analysis	Ct ≤ 40	204	42	9	Endoscopic or surgical histology
Ma 2022	China	P	Stages 0–IV	102	Benign (advanced adenoma; non-advanced adenomas; colitis) and healthy mucosa	107	130	61	49	qMSP	ROC curve analysis	NR	89	31	7	Endoscopic or surgical histology
Li 2023a	China	P	Stages I–IV	30	Healthy mucosa only	0	30	52.4	51.7	qMSP	ROC curve analysis	Ct ≤ 38	28	0	3	Endoscopic or surgical histology
Liu 2023	China	R	Stages I–	263	Both benign (adenoma/poly	512	445	NR	61.2	qMSP	NR	Ct ≤ 38	220	195	140	Endoscopic or surgical histology

			IV		ps) and healthy mucosa										
Xu 2023	China	P	Stages I–IV	42	Benign (advanced adenoma) and healthy mucosa	302	1345	60	48.1	qMSP	NR	Ct ≤ 38.5	39	106	94	Endoscopic histology
Cheng 2023	China	P	Stages I–III	50	Benign (advanced adenoma) and healthy mucosa	50	50	58.9	57.3	qMSP	ROC curve analysis	Ct ≤ 38	49	18	25	Endoscopic histology
Zeng 2023	China	R	Stages 0–IV	150	Benign (advanced adenoma) and healthy mucosa	23	275	NR	68	qMSP	NR	Ct ≤ 38	119	7	21	Endoscopic histology
Li 2023b	China	P	Stages 0–IV	105	Both benign (adenoma/polyps) and healthy mucosa	158	100	54.3	59.2	qMSP	ROC curve analysis	Ct ≤ 38	86	52	1	Endoscopic histology
Zhan 2023	China	P	Stages 0–IV	445	Both benign lesions (adenomas, non-neoplastic GI diseases) and healthy mucosa	472	62	NR	62.9	qMSP	ROC curve analysis	NR	310	78	7	Endoscopic histology

Kim 2024	Korea	P	Stages 0–IV	20	Both benign lesions (advanced adenomas) and healthy mucosa	73	384	67.8	49.6	qMSP	ROC curve analysis	Ct ≤ 40	19	35	71	Endoscopic histology
Lohsiriwat 2024	Thailand	P	NR	47	Both benign lesions (advanced adenomas, non-advanced adenomas) and healthy mucosa	60	150	62.1	39.4	qMSP	ROC curve analysis	NR	43	11	11	Endoscopic histology
Liu 2024	China	P	Stages I–IV	83	Healthy mucosa only	0	98	60	65.1	quantitative bisulfite NGS	NR	NR	76	0	0	Endoscopic or surgical histology
Long 2024	China	R	Stages 0–IV	138	Both benign (advanced adenoma/polyps) and healthy mucosa	62	28	57.8	53.2	qMSP	NR	NR	102	13	2	Endoscopic histology
Zhang 2024	China	P	Stages I–IV	403	Both benign (advanced or non-advanced adenomas) and	219	210	60.9	61.6	qMSP	NR	NR	371	82	12	Endoscopic histology

					healthy mucosa										
Zhao 2024	China	P	Stages I–IV	26	Only benign lesions (adenoma, hyperplastic polyps, etc.)	382	0	NR	40.6	qMSP	ROC curve analysis	Ct ≤ 39	22	118	0	Endoscopic histology
Zou 2024	China	P	Stages I–IV	116	Benign (adenoma) and healthy mucosa	31	44	59.8	57.6	qMSP	NR	Ct ≤ 38	85	12	1	Endoscopic histology
Luo 2024	China	P	Stages 0–IV	16	Benign lesions (adenoma, hyperplastic polyps, etc.) and healthy mucosa	404	615	52	48.5	qMSP	NR	Ct ≤ 38	14	46	27	Endoscopic histology
Liu 2025	China	R	Stages I–IV	69	Benign (adenoma) and healthy mucosa	47	30	64	68.1	qMSP	NR	Ct ≤ 38	68	28	2	Endoscopic histology

Abbreviations: CRC: Colorectal cancer; CT: Cycle threshold; NR: Not reported; P: Prospective; R: Retrospective; qMSP: Quantitative methylation-specific PCR; NGS: Next-generation sequencing; mSDC2: Methylated syndecan-2.

Table 2. Evaluation of study quality using the QUADAS-2 scale

	Risk of bias				Applicability concerns		
Study	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Oh 2017	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Niu 2017	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk
Han 2019	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Sun 2019	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Wang 2020	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Su 2021	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk
Zhang 2021	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Dai 2022	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Ma 2022	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Li 2023a	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk
Liu 2023	High risk	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk
Xu 2023	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk
Cheng 2023	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Zeng 2023	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Li 2023b	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Zhan 2023	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Kim 2024	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Lohsiriwat 2024	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Liu 2024	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk
Long 2024	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Zhang 2024	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Zhao 2024	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk
Zou 2024	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Luo 2024	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Liu 2025	High risk	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk

Abbreviation: QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies 2.

.

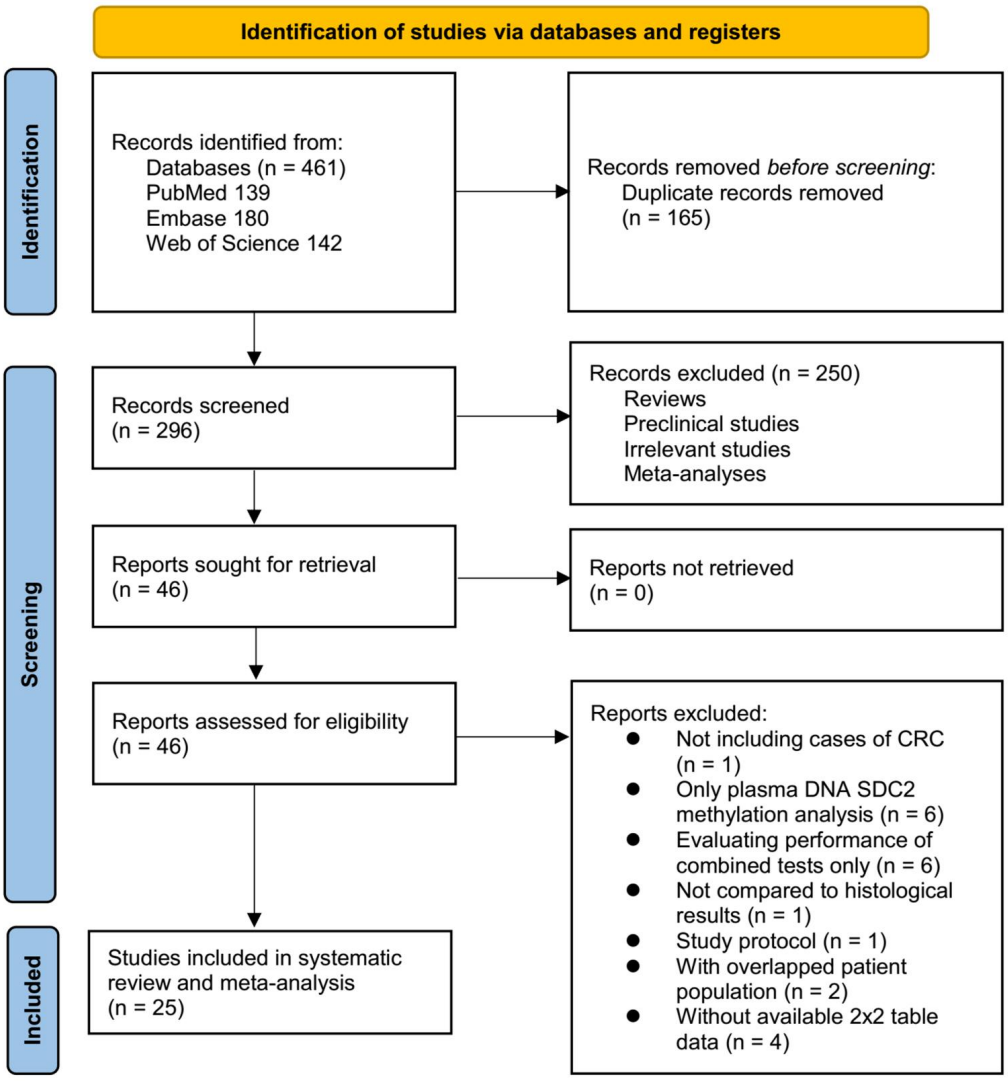
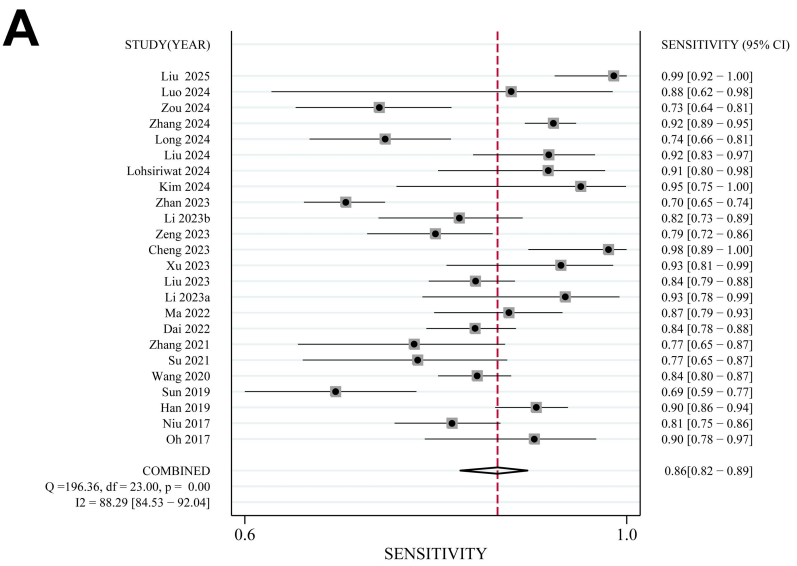
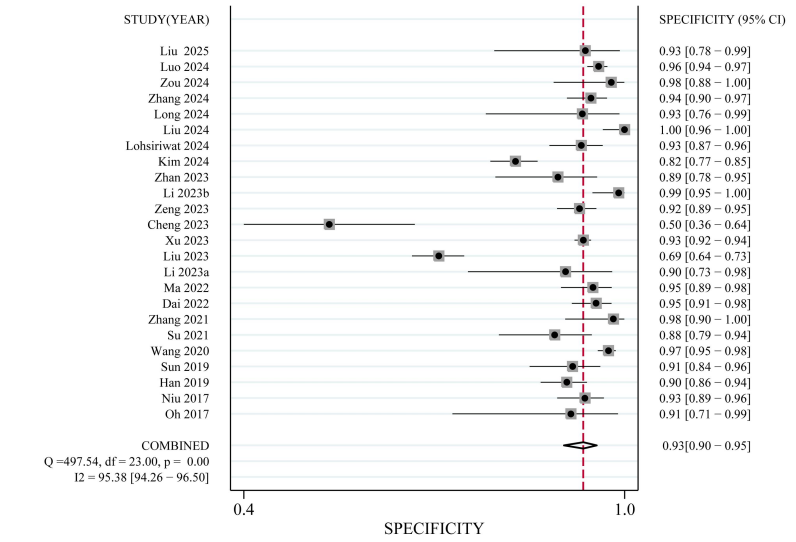


Figure 1. Flowchart illustrating the study screening and identification process


A
STUDY(YEAR)
SENSITIVITY (95% CI)
Liu 2025 0.99 [0.92 − 1.00]
Luo 2024 0.88 [0.62 − 0.98]
Zou 2024 0.73 [0.64 − 0.81]
Zhang 2024 0.92 [0.89 − 0.95]
Long 2024 0.74 [0.66 − 0.81]
Liu 2024 0.92 [0.83 − 0.97]
Lohsiriwat 2024 0.91 [0.80 − 0.98]
Kim 2024 0.95 [0.75 − 1.00]
Zhan 2023 0.70 [0.65 − 0.74]
Li 2023b 0.82 [0.73 − 0.89]
Zeng 2023 0.79 [0.72 − 0.86]
Cheng 2023 0.98 [0.89 − 1.00]
Xu 2023 0.93 [0.81 − 0.99]
Liu 2023 0.84 [0.79 − 0.88]
Li 2023a 0.93 [0.78 − 0.99]
Ma 2022 0.87 [0.79 − 0.93]
Dai 2022 0.84 [0.78 − 0.88]
Zhang 2021 0.77 [0.65 − 0.87]
Su 2021 0.77 [0.65 − 0.87]
Wang 2020 0.84 [0.80 − 0.87]
Sun 2019 0.69 [0.59 − 0.77]
Han 2019 0.90 [0.86 − 0.94]
Niu 2017 0.81 [0.75 − 0.86]
Oh 2017 0.90 [0.78 − 0.97]
COMBINED 0.86[0.82 − 0.89]
Q =196.36, df = 23.00, p = 0.00
I2 = 88.29 [84.53 − 92.04]
0.6
1.0
SENSITIVITY


B
STUDY(YEAR)
SPECIFICITY (95% CI)
Liu 2025 0.93 [0.78 − 0.99]
Luo 2024 0.96 [0.94 − 0.97]
Zou 2024 0.98 [0.88 − 1.00]
Zhang 2024 0.94 [0.90 − 0.97]
Long 2024 0.93 [0.76 − 0.99]
Liu 2024 1.00 [0.96 − 1.00]
Lohsiriwat 2024 0.93 [0.87 − 0.96]
Kim 2024 0.82 [0.77 − 0.85]
Zhan 2023 0.89 [0.78 − 0.95]
Li 2023b 0.99 [0.95 − 1.00]
Zeng 2023 0.92 [0.89 − 0.95]
Cheng 2023 0.50 [0.36 − 0.64]
Xu 2023 0.93 [0.92 − 0.94]
Liu 2023 0.69 [0.64 − 0.73]
Li 2023a 0.90 [0.73 − 0.98]
Ma 2022 0.95 [0.89 − 0.98]
Dai 2022 0.95 [0.91 − 0.98]
Zhang 2021 0.98 [0.90 − 1.00]
Su 2021 0.88 [0.79 − 0.94]
Wang 2020 0.97 [0.95 − 0.98]
Sun 2019 0.91 [0.84 − 0.96]
Han 2019 0.90 [0.86 − 0.94]
Niu 2017 0.93 [0.89 − 0.96]
Oh 2017 0.91 [0.71 − 0.99]
COMBINED 0.93[0.90 − 0.95]
Q =497.54, df = 23.00, p = 0.00
I2 = 95.38 [94.26 − 96.50]
0.4
1.0
SPECIFICITY

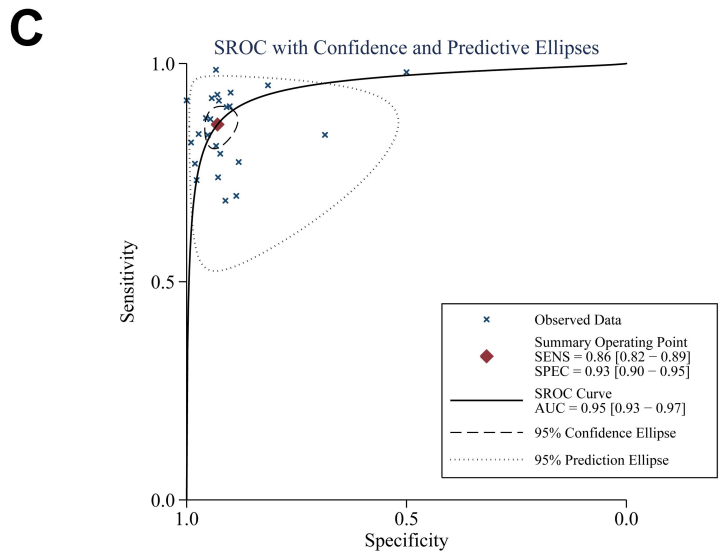
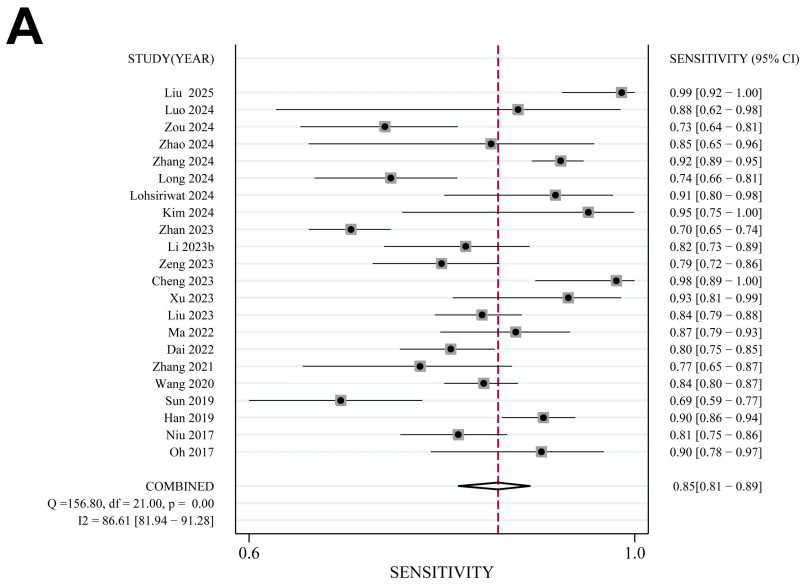
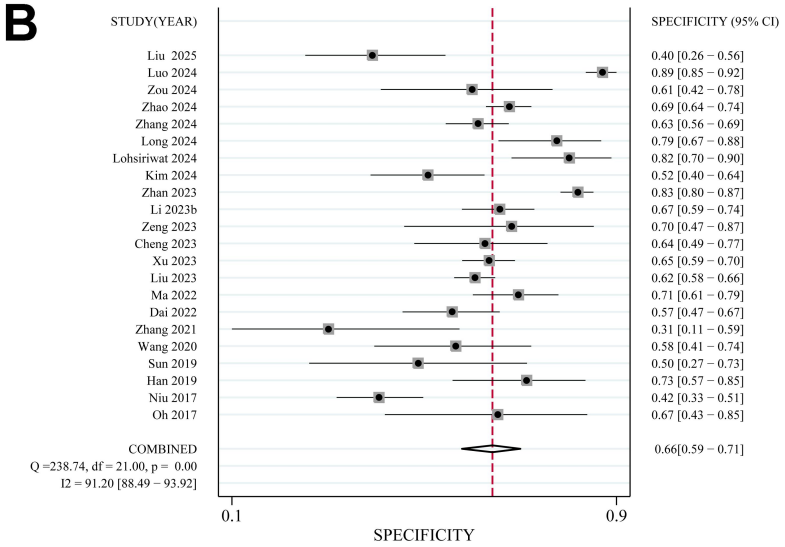

C
SROC with Confidence and Predictive Ellipses
1.0
0.5
0.0
Sensitivity
1.0
0.5
0.0
Specificity
Observed Data
Summary Operating Point
SENS = 0.86 [0.82 − 0.89]
SPEC = 0.93 [0.90 − 0.95]
SROC Curve
AUC = 0.95 [0.93 − 0.97]
95% Confidence Ellipse
95% Prediction Ellipse

Figure 2. Forest plots and summarized ROC curve illustrating the diagnostic performance of fecal *mSDC2* for detecting CRC versus normal colonic mucosa across 24 studies. (A) Forest plot of pooled sensitivity: 0.86 (95% CI: 0.82–0.89; I^2 = 88%). **(B)** Forest plot of pooled specificity: 0.93 (95% CI: 0.90–0.95; I^2 = 95%). **(C)** Summarized ROC curve with AUC = 0.95 (95% CI: 0.93–0.97). The x-axis for the summarized ROC curve is presented with specificity on a reversed scale (1.0 → 0.0), corresponding to plotting 1−specificity (false-positive rate) on a forward scale.
Abbreviation: CRC: Colorectal cancer.


A
STUDY(YEAR)
SENSITIVITY (95% CI)
Liu 2025 0.99 [0.92 − 1.00]
Luo 2024 0.88 [0.62 − 0.98]
Zou 2024 0.73 [0.64 − 0.81]
Zhao 2024 0.85 [0.65 − 0.96]
Zhang 2024 0.92 [0.89 − 0.95]
Long 2024 0.74 [0.66 − 0.81]
Lohsiriwat 2024 0.91 [0.80 − 0.98]
Kim 2024 0.95 [0.75 − 1.00]
Zhan 2023 0.70 [0.65 − 0.74]
Li 2023b 0.82 [0.73 − 0.89]
Zeng 2023 0.79 [0.72 − 0.86]
Cheng 2023 0.98 [0.89 − 1.00]
Xu 2023 0.93 [0.81 − 0.99]
Liu 2023 0.84 [0.79 − 0.88]
Ma 2022 0.87 [0.79 − 0.93]
Dai 2022 0.80 [0.75 − 0.85]
Zhang 2021 0.77 [0.65 − 0.87]
Wang 2020 0.84 [0.80 − 0.87]
Sun 2019 0.69 [0.59 − 0.77]
Han 2019 0.90 [0.86 − 0.94]
Niu 2017 0.81 [0.75 − 0.86]
Oh 2017 0.90 [0.78 − 0.97]
COMBINED 0.85[0.81 − 0.89]
Q =156.80, df = 21.00, p = 0.00
I2 = 86.61 [81.94 − 91.28]
0.6
1.0
SENSITIVITY


B
STUDY(YEAR)
SPECIFICITY (95% CI)
Liu 2025 0.40 [0.26 − 0.56]
Luo 2024 0.89 [0.85 − 0.92]
Zou 2024 0.61 [0.42 − 0.78]
Zhao 2024 0.69 [0.64 − 0.74]
Zhang 2024 0.63 [0.56 − 0.69]
Long 2024 0.79 [0.67 − 0.88]
Lohsiriwat 2024 0.82 [0.70 − 0.90]
Kim 2024 0.52 [0.40 − 0.64]
Zhan 2023 0.83 [0.80 − 0.87]
Li 2023b 0.67 [0.59 − 0.74]
Zeng 2023 0.70 [0.47 − 0.87]
Cheng 2023 0.64 [0.49 − 0.77]
Xu 2023 0.65 [0.59 − 0.70]
Liu 2023 0.62 [0.58 − 0.66]
Ma 2022 0.71 [0.61 − 0.79]
Dai 2022 0.57 [0.47 − 0.67]
Zhang 2021 0.31 [0.11 − 0.59]
Wang 2020 0.58 [0.41 − 0.74]
Sun 2019 0.50 [0.27 − 0.73]
Han 2019 0.73 [0.57 − 0.85]
Niu 2017 0.42 [0.33 − 0.51]
Oh 2017 0.67 [0.43 − 0.85]
COMBINED 0.66[0.59 − 0.71]
Q =238.74, df = 21.00, p = 0.00
I2 = 91.20 [88.49 − 93.92]
0.1
0.9
SPECIFICITY

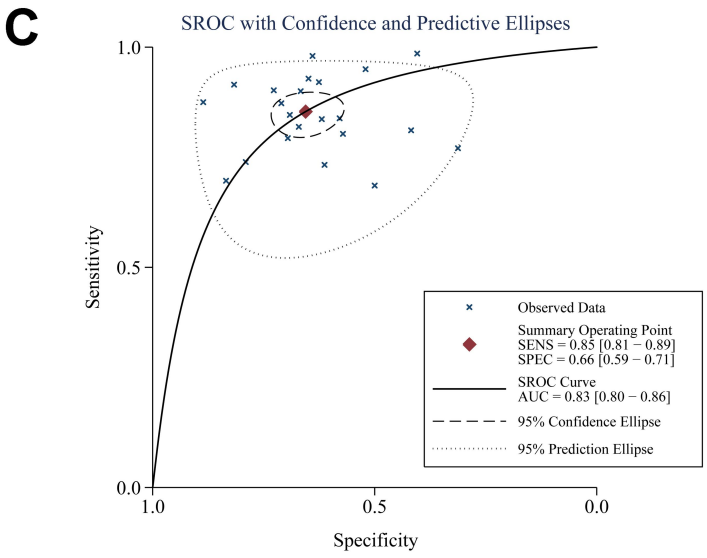

C
SROC with Confidence and Predictive Ellipses
1.0
0.5
0.0
Sensitivity
1.0
0.5
0.0
Specificity
Observed Data
Summary Operating Point
SENS = 0.85 [0.81 − 0.89]
SPEC = 0.66 [0.59 − 0.71]
SROC Curve
AUC = 0.83 [0.80 − 0.86]
95% Confidence Ellipse
95% Prediction Ellipse

Figure 3. Forest plots and summarized ROC curve illustrating the diagnostic performance of fecal *mSDC2* in distinguishing CRC from benign colorectal lesions across 22 studies. (A) Forest plot of pooled sensitivity: 0.85 (95% CI: 0.81–0.89; $I^2 = 87\%$). **(B)** Forest plot of pooled specificity: 0.66 (95% CI: 0.59–0.71; $I^2 = 91\%$). **(C)** Summarized ROC curve with AUC = 0.83 (95% CI: 0.80–0.86). The x-axis for the summarized ROC curve is presented with specificity on a reversed scale (1.0 → 0.0), corresponding to plotting 1−specificity (false-positive rate) on a forward scale. **Abbreviation**: CRC: Colorectal cancer.

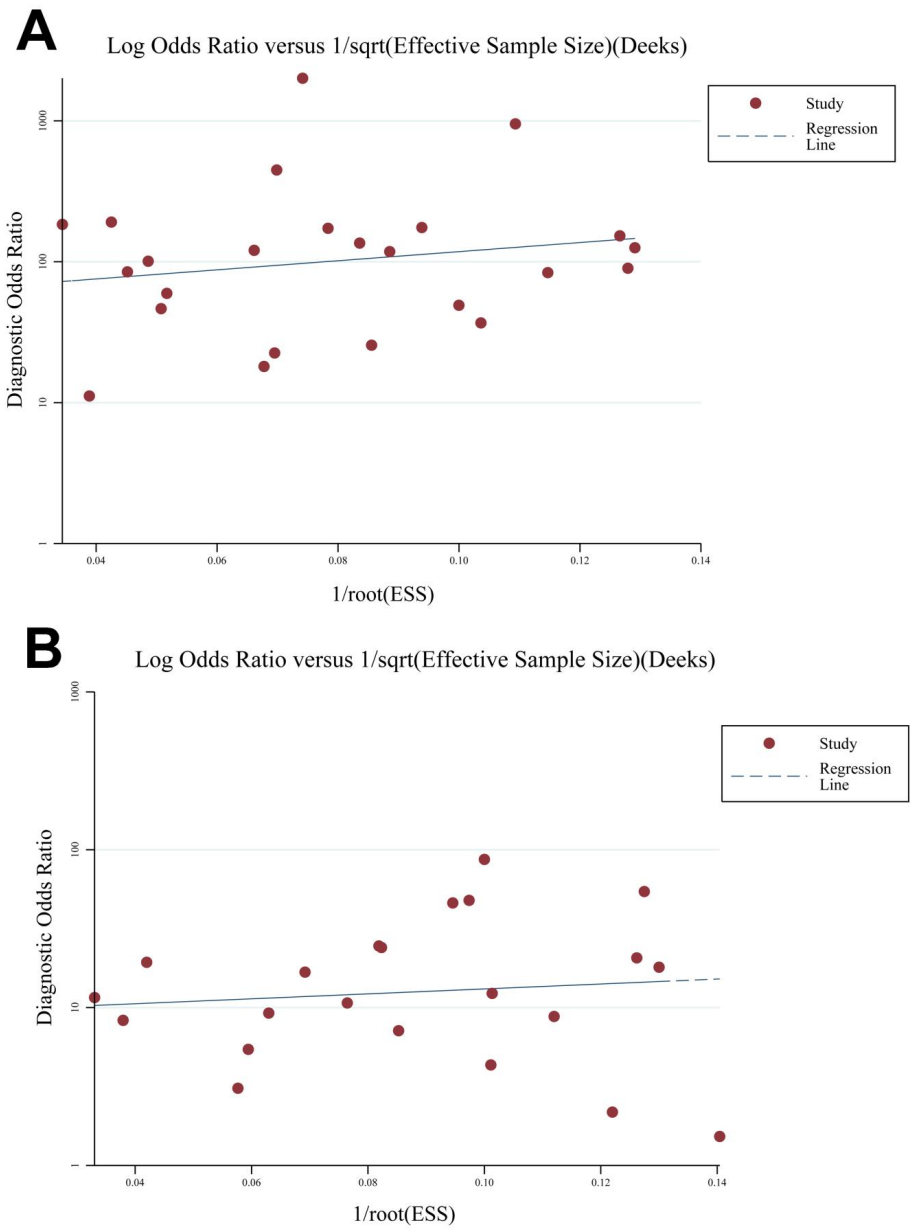


Figure 4. Deeks' funnel plots assessing potential publication bias in the diagnostic accuracy meta-analyses of fecal *mSDC2*. (A) Deeks' funnel plot for studies comparing CRC versus normal colonic mucosa ($p = 0.48$). **(B)** Deeks' funnel plot for studies comparing CRC versus benign colorectal lesions ($p = 0.54$).

Abbreviation: CRC: Colorectal cancer.

SUPPLEMENTAL DATA

Supplemental file 1. Detailed search strategy for each database

PubMed

("syndecan-2"[Mesh] OR "syndecan-2"[tiab] OR "syndecan 2"[tiab] OR "SDC2"[tiab]) AND ("colorectal neoplasms"[Mesh] OR "colorectal"[tiab] OR "colorectum"[tiab] OR "colon"[tiab] OR "rectal"[tiab] OR "rectum"[tiab]) AND ("neoplasms"[Mesh] OR "carcinoma"[tiab] OR "cancer"[tiab] OR "tumor"[tiab] OR "malignancy"[tiab] OR "adenocarcinoma"[tiab])

Filters: Humans, English, Publication date from inception to 2025/05/31

Embase

('syndecan 2'/exp OR 'syndecan-2':ti,ab OR 'syndecan 2':ti,ab OR sdc2:ti,ab) AND ('colorectal tumor'/exp OR colorectal:ti,ab OR colorectum:ti,ab OR colon:ti,ab OR rectal:ti,ab OR rectum:ti,ab) AND ('neoplasm'/exp OR carcinoma:ti,ab OR cancer:ti,ab OR tumor:ti,ab OR malignancy:ti,ab OR adenocarcinoma:ti,ab)

Limits: Human, English, Publication date from inception to 2025/05/31

Web of Science

TS=("syndecan-2" OR "syndecan 2" OR "SDC2") AND TS=("colorectal" OR "colorectum" OR "colon" OR "rectal" OR "rectum") AND TS=("neoplasms" OR "carcinoma" OR "cancer" OR "tumor" OR "malignancy" OR "adenocarcinoma")

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