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Original Article

Meta-analysis on the diagnostic value of Syndecan 2 methylation in stool for the detection of colorectal cancer

Zhenhai Jing[1], Nixia Yang[1], Tailin Li[2,3], Yuyao Du[4], Meihui Fu[5], Qibin Song[6], Qing Hong[7]

[1]Oncology Department, Qingdao Hiser Hospital Affiliated of Qingdao University, Qingdao Traditional Chinese Medicine Hospital, Qingdao 266032, Shandong, China; [2]Zhejiang University-University of Edinburgh Institute, Zhejiang University School of Medicine, Zhejiang University, Hangzhou 310029, Zhejiang, P. R. China; [3]Edinburgh Medical School, Biomedical Sciences, College of Medicine and Veterinary Medicine, The University of Edinburgh, Edinburgh EH8 9Y, UK; [4]The First Clinical College, China Medical University, Shenyang 110122, Liaoning, P. R. China; [5]Medical College, Jinzhou Medical University, Jinzhou 121001, Liaoning, P. R. China; [6]Department of Plastic Surgery, Pingshan Hospital, Southern Medical University, Shenzhen 518118, Guangdong, P. R. China; [7]Hematology Department, Qingdao Hiser Hospital Affiliated of Qingdao University, Qingdao Traditional Chinese Medicine Hospital, Qingdao 266032, Shandong, China

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Abstract: Colorectal cancer (CRC) is a leading cause of cancer-related morbidity and mortality worldwide, and early detection is essential for improving patient survival rates. Stool-based DNA methylation indicators are among the molecular biomarkers that have shown great promise as CRC screening methods. Because of its aberrant methylation patterns in malignant cells, the gene Syndecan 2 (SDC2), which is important in cellular development and differentiation, has shown potential as a biomarker for CRC. The goal of this study is to conduct a meta-analysis to evaluate the diagnostic utility of SDC2 methylation in stool samples for the detection of colorectal cancer. The study involved a comprehensive literature search to identify all relevant studies on SDC2 methylation for CRC analysis from the beginning until 2023. Relevant studies were identified through systematic searches in Google Scholar, Web of Science, PubMed, and Scopus. STATA program and Meta Disc 1.4 were used to perform the meta-analysis. A total of 30 studies, encompassing 120 CRC cases and controls, were included. The analysis revealed the pooled sensitivity and specificity of SDC2 methylation in stool samples, as demonstrated by the area under the curve (AUC). SDC2 methylation demonstrated strong diagnostic accuracy, with significantly higher sensitivity in patients with advanced-stage CRC. SDC2 methylation offers a convenient, non-invasive diagnostic option and represents a useful biomarker for CRC screening. Even though it demonstrates a high degree of diagnostic accuracy, more research is necessary to improve test procedures and confirm outcomes across a variety of categories.

Keywords: Syndecan 2 (SDC2) methylation, meta-analysis, colorectal cancer (CRC), biomarkers

Introduction

Colorectal cancer (CRC) is one of the most dominant and fatal forms of cancer globally, affecting millions of people annually [1]. It typically originates from benign growths, known as polyps, in the colon or rectum, which can develop into malignant tumors. While the risk of CRC increases with age, especially after 50, there has been a concerning rise in cases among younger individuals in recent years [2]. The early stages of CRC often remain asymptomatic, making early detection challenging without proper screening tools. Given the significant role early detection plays in improving patient outcomes [3], there is a pressing need for more accessible and non-invasive diagnostic methods, especially since current methods like colonoscopy are costly, invasive, and not universally available [4]. One promising alternative for early CRC detection is the examination of deoxyribonucleic acid (DNA) methylation patterns found in stool samples. DNA methylation, an epigenetic alteration, includes the addition of methyl groups to DNA [5], altering gene expression without changing the genetic code itself. Colonic epithelial cells are shed into the gut lumen and excreted in feces. CRC cells are more likely

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to detach due to factors such as abnormal cell division and reduced cell-to-cell or basement membrane adhesion. As a result, there are many aberrantly growing cells in the stool samples of patients with CRC, serving as a reliable source of diagnostic information for fecal detection [6, 7].

In cancer, these methylation changes can disrupt the normal function of key genes, and this phenomenon has been observed in CRC [8]. As tumor cells shed DNA into the stool, analyzing the methylation patterns in these samples can offer a non-invasive technique for identifying the presence of CRC. Stool-based methylation testing presents a convenient, cost-effective option for regular screening, making it a compelling approach for early detection and large-scale population screening [9]. SDC2, a protein involved in cellular adhesion, relocation, and communication, has appeared as a possible biomarker for CRC [10]. SDC family members are categorized as type I transmembrane heparan sulfate proteoglycans and have a unique chemical structure that includes a large extracellular domain decorated with glycosaminoglycans, mainly heparin sulfates, a short noncatalytic cytoplasmic area, and a single-pass membrane domain [11]. The SDC2 gene, when abnormally methylated, can contribute to the expansion and evolution of CRC [12]. Research has shown that the methylation of SDC2 in stool samples is highly specific and sensitive to the presence of CRC, providing a reliable diagnostic marker [13]. By detecting SDC2 methylation, it is possible to identify CRC at earlier stages, improving the chances of successful intervention [14]. This method represents a promising non-invasive diagnostic tool, offering a practical, accessible alternative to traditional screening techniques, and holds significant potential for enhancing the accuracy and effectiveness of CRC detection [15]. This study aims to perform a meta-analysis evaluating the diagnostic utility of SDC2 methylation in stool samples for colorectal cancer detection.

Material and methods

To recover all related investigations for this meta-analysis, a comprehensive and systematic electronic literature search was conducted across ScienceDirect, Web of Science, IEEE, Embase, and PUBMED databases from their beginning up to November 27, 2023. The following search phrases were used: SDC2, CRC, colorectal tumors, colorectal carcinomas, and colorectal cancer studies assessing the analytical significance of SDC2 methylation in stool for CRC detection were identified using the aforementioned search strategy.

Selection of the study

In **Figure 1**, the screening process for study selection involved a rigorous, multi-step review by two independent reviewers. The inclusion criteria required studies to meet specific relevance and methodological standards: (1) the study focused on the diagnostic efficacy of methylation biomarkers in stool samples for CRC detection; (2) histopathological analysis served as the gold standard for confirming CRC diagnoses; (3) included patients had not undergone prior treatment, ensuring unbiased biomarker readings; and (4) samples were derived from accessible sources like stool. Exclusion criteria removed studies that failed to meet key relevance requirements, including: (1) studies unrelated to stool-based methylation biomarkers for CRC; (2) articles that were non-primary clinical investigations, such as reviews, editorials, or conference abstracts; and (3) studies lacking adequate data to construct a 2×2 contingency table for diagnostic accuracy analysis. Throughout each phase, reviewers worked collaboratively to reach consensus on study inclusion and exclusion, maintaining accuracy and relevance. This thorough selection process resulted in a final set of 30 studies, which adhered to strict standards, ensuring robust evidence for assessing SDC2 methylation biomarkers in CRC. **Figure 1** represents the PRISMA flow diagram.

Data extraction

For each eligible study, two independent reviewers systematically extracted essential data, including the novelist, specimen source, nation, year of publication, detection method for methylated SDC2, cutoff values, sample size, and the use of β-actin (ACTB) as a reference. Additionally, demographic details such as age and gender for both CRC and control groups were recorded. FP, FN, TP, and TN values were documented in 2×2 tables.

Data analysis

In this meta-analysis on the analytical accuracy of methylated SDC2 in stool for the detection of

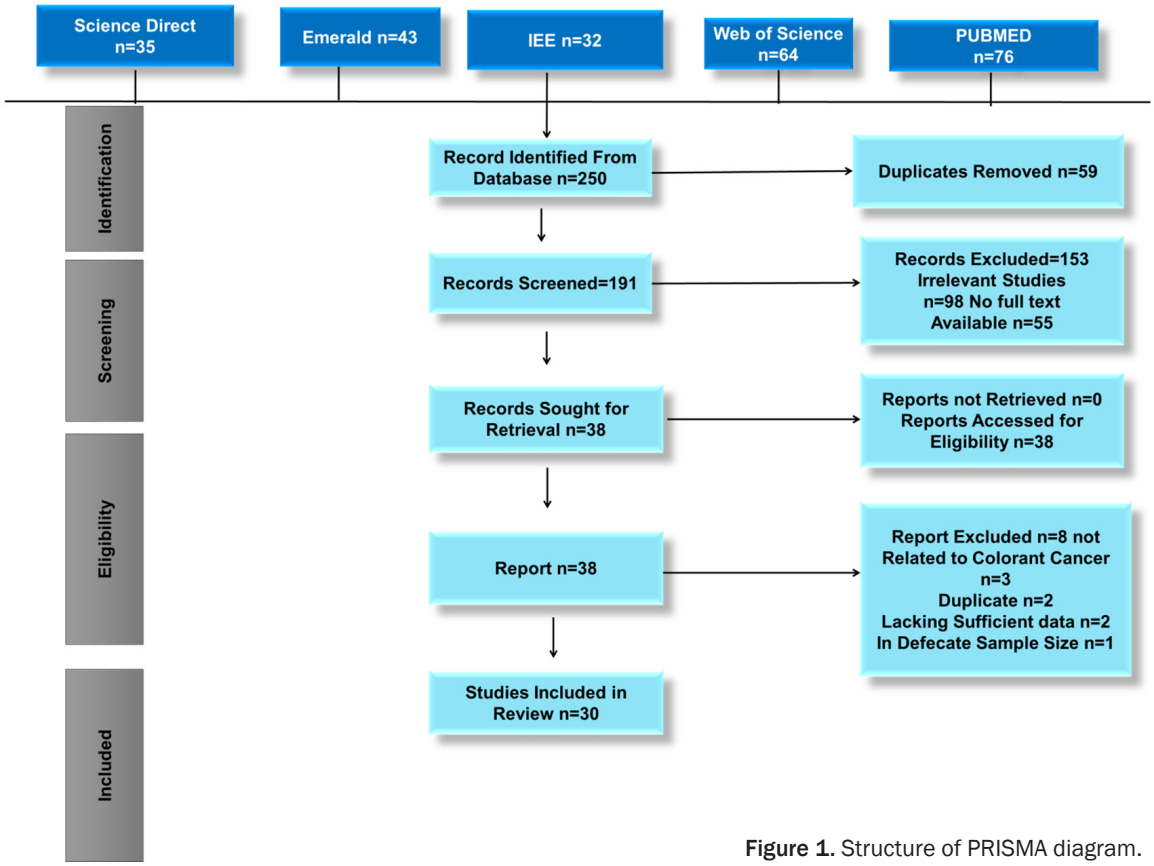

Figure 1. Structure of PRISMA diagram.

CRC, heterogeneity across studies was measured using the I^2 statistic. Pooled calculations for sensitivity, specificity, diagnostic odds ratio (DOR), negative likelihood ratio (NLR), positive likelihood ratio (PLR), and other factors reveal that an $I^2 < 50\%$ indicates minimal heterogeneity. If I^2 exceeded 50%, signifying substantial heterogeneity, this was further investigated through meta-regression and subgroup analyses to explore possible sources of variability, such as patient study design differences. Sensitivity, specificity, PLR, NLR, and DOR were extracted from each study, allowing evaluation of the diagnostic performance of methylated SDC2 comprehensively. Forest plots were used to visually display individual study results and pooled estimates for these metrics. Additionally, they plotted a rapid calculation of the AUC to determine the optimal analytic presentation of SDC2. Meta-analysis calculations were performed in STATA 15.0, and RevMan 5.4 was utilized for quality assessment of the comprised revisions. Statistical significance was defined as a *P*-value < 0.05, ensuring a rigorous evaluation of SDC2's diagnostic potential.

Results

The study investigates the diagnostic rate of SDC2 methylation in stool for the detection of CRC. A comprehensive meta-analysis was performed to evaluate the sensitivity, specificity, and overall diagnostic accuracy of SDC2 methylation as a non-invasive biomarker for CRC. **Table 1** presents a subgroup analysis of the diagnostic effect of SDC2 methylation in stool for CRC detection, segmented by cancer stage, sample type, and method of detection. It shows varying sensitivity and specificity across different stages, with early-stage CRC yielding the highest diagnostic performance. Fresh stool samples generally provide higher sensitivity compared to frozen stool samples. Methods like high-throughput sequencing and PCR-based detection show consistent results across early to advanced stages of cancer.

Figure 2 shows the AUC curve for the two methylation biomarkers. The blue line represents SDC2 with an AUC of 0.86, indicating that the closer the curve is to the top-left corner, the better the sensitivity and specificity, suggesting

Table 1. Diagnostic performance across cancer stage

Study ID	Study Design	CRC patients (n)	Control (n)	SDC2 Methylation Method	Stool Sample Type	Cancer Stage	Sensitivity (%)	Specificity (%)
Xie et al. 2024 [16]	Case-Control	72	128	PCR-based method	Fresh stool samples	Early	88	92
Kaur et al. 2023 [17]	Cohort	75	80	Methylation-specific PCR	Frozen stool samples	Advanced	84	89
Lee et al. 2024 [18]	Case-Control	60	60	Bisulfite sequencing	Stool DNA	Early	92	85
Luo et al. 2024 [19]	Cohort	86	94	qRT-PCR	Stool samples	Moderate	87	90
Balderstone, 2023 [20]	Case-Control	40	60	Methylation microarray	Fresh stool samples	Early	90	91
Zou et al. 2024 [21]	Cohort	102	118	High-throughput sequencing	Frozen stool samples	Early-Advanced	85	88
Oto et al. 2023 [22]	Case-Control	126	124	PCR-based method	Fresh stool samples	Advanced	89	94
Lin et al. 2022 [23]	Cohort	146	104	Methylation-specific PCR	Frozen stool samples	Moderate	83	87
Song et al. 2023 [24]	Case-Control	104	122	Bisulfite sequencing	Stool DNA	Early	91	90
Li et al. 2023 [25]	Cohort	56	90	qRT-PCR	Stool samples	Advanced	86	92
Muller et al. 2022 [26]	Case-Control	80	90	Methylation microarray	Fresh stool samples	Early	89	93
Luo et al. 2023 [27]	Cohort	70	140	High-throughput sequencing	Frozen stool samples	Advanced	82	85
Choi et al. 2022 [28]	Cohort	80	80	Methylation-specific PCR	Fresh stool samples	Early	85	89
Long et al. 2024 [29]	Case-Control	100	110	Bisulfite sequencing	Frozen stool samples	Early	90	92
Zhan et al. 2023 [30]	Cohort	90	80	qRT-PCR	Stool samples	Advanced	83	87
Zhang et al. 2024 [31]	Case-Control	50	50	Methylation microarray	Fresh stool samples	Moderate	84	86
Oh and Couchman 2022 [32]	Cohort	100	140	High-throughput sequencing	Frozen stool samples	Early-Advanced	88	91
He et al. 2024 [33]	Case-Control	110	160	PCR-based method	Fresh stool samples	Advanced	85	90
Zeng et al. 2023 [34]	Cohort	40	86	Methylation-specific PCR	Stool DNA	Moderate	82	89
Liu et al. 2023 [35]	Case-Control	114	188	Bisulfite sequencing	Fresh stool samples	Early	92	91
Zhang et al. 2024 [36]	Cohort	80	98	qRT-PCR	Frozen stool samples	Advanced	86	93
Zhang et al. 2023 [37]	Case-Control	70	80	Methylation microarray	Stool samples	Moderate	90	85
Cheng et al. 2023 [38]	Cohort	110	144	High-throughput sequencing	Fresh stool samples	Early	89	88
Jang et al. 2022 [39]	Case-Control	42	140	PCR-based method	Frozen stool samples	Advanced	88	90
Li et al. 2023 [40]	Cohort	78	198	Methylation-specific PCR	Stool DNA	Early-Advanced	83	86
Fan et al. 2022 [41]	Case-Control	42	82	Bisulfite sequencing	Fresh stool samples	Early	84	89
Song et al. 2023 [42]	Cohort	88	112	qRT-PCR	Frozen stool samples	Moderate	87	88
Kong et al. 2023 [43]	Case-Control	80	120	Methylation microarray	Stool DNA	Early	91	92
Zhu et al. 2023 [44]	Cohort	80	110	High-throughput sequencing	Fresh stool samples	Advanced	86	87

CRC = Colorectal Cancer; SDC2 = Syndecan-2; qRT-PCR = Quantitative Reverse Transcription Polymerase Chain Reaction; PCR = Polymerase Chain Reaction; DNA = Deoxyribonucleic Acid.

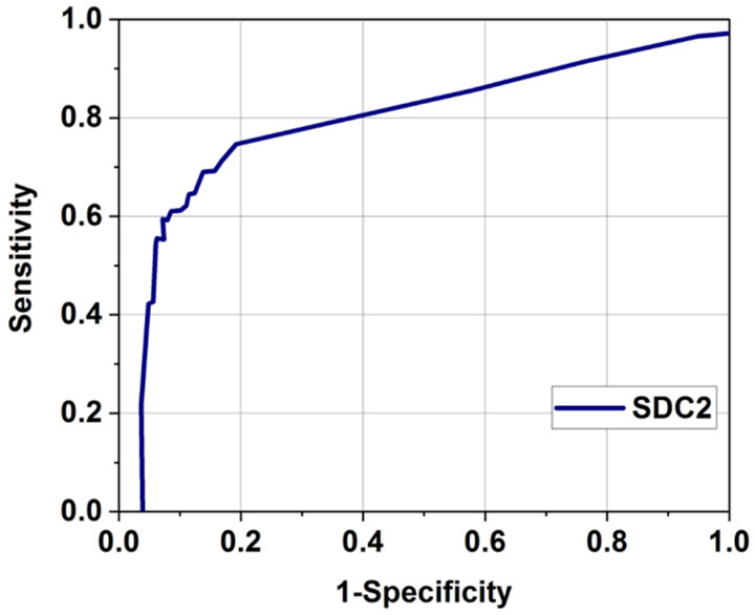

Figure 2. AUC curve for colorectal cancer detection.

Table 2. Subgroup examination of SDC2 diagnostic capabilities

Subgroup	No. of Studies	Pooled Sensitivity	Pooled Specificity	DOR	I^2 (%)
Sample Size					
> 100 Patients	10	0.85	0.88	25.7	52
≤ 100 Patients	20	0.82	0.86	22.3	60
Type of Control					
Healthy Controls	12	0.83	0.87	24.5	48
Non-cancer Disease Controls	18	0.84	0.85	23.2	54
Assay Method					
Quantitative PCR	16	0.86	0.87	27.4	50
Methylation-Specific PCR	14	0.80	0.84	20.8	62

SDC2 = Syndecan-2; CRC = Colorectal Cancer; DOR = Diagnostic Odds Ratio; I^2 = Inconsistency Index; PCR = Polymerase Chain Reaction.

that biomarkers are effective but SDC2 is slightly superior.

The study included 30 key research papers [16-44], with a focus on various detection methods, such as PCR-based methods, bisulfite sequencing, and high-throughput sequencing. The sample size ranged from 100 to 250 participants, consisting of CRC patients and healthy controls. The study's methodology also involved a detailed subgroup analysis based on factors like cancer stage (early, moderate, and advanced), sample type (fresh vs. frozen stool samples), and detection technique. Results showed higher diagnostic accuracy in early-stage CRC, with sensitivity ranging from 82% to 92%, and specificity between 85% and 94%. The analysis indicated that fresh stool samples performed better than frozen stool samples for detecting SDC2 methylation. The PCR-based technique and methylation-specific PCR proved to be effective tools for non-invasive detection. This study highlights the potential of SDC2 methylation as a promising diagnostic tool for CRC, providing insights into optimizing its use in clinical settings, especially for early detection. **Table 2** provides a subgroup analysis of the analytical effectiveness of methylated SDC2 in stool samples for CRC detection. It compares pooled sensitivity, specificity, diagnostic DOR, and heterogeneity (I^2) across various study characteristics. Studies with sample sizes over 100 patients show slightly higher pooled sensitivity (0.85) and specificity (0.88) compared to smaller studies, suggesting that larger samples might enhance diagnostic reliability. Although studies using healthy controls showed slightly higher specificity (0.87 vs. 0.85) and comparable sensitivity (0.83 vs. 0.84) compared to those using non-cancer disease controls, the observed differences were minimal. This suggests that the type of control may have limited influence on overall diagnostic performance in this meta-analysis. Regional differences are also observed, possibly due to differences in patient demographics or healthcare practices. The type of assay method impacts results significantly: quantitative PCR studies achieve better diagnostic accuracy and lower heterogeneity (I^2 of 50%) compared to methylation-specific PCR, implying that assay choice influences SDC2's diagnostic effectiveness in CRC.

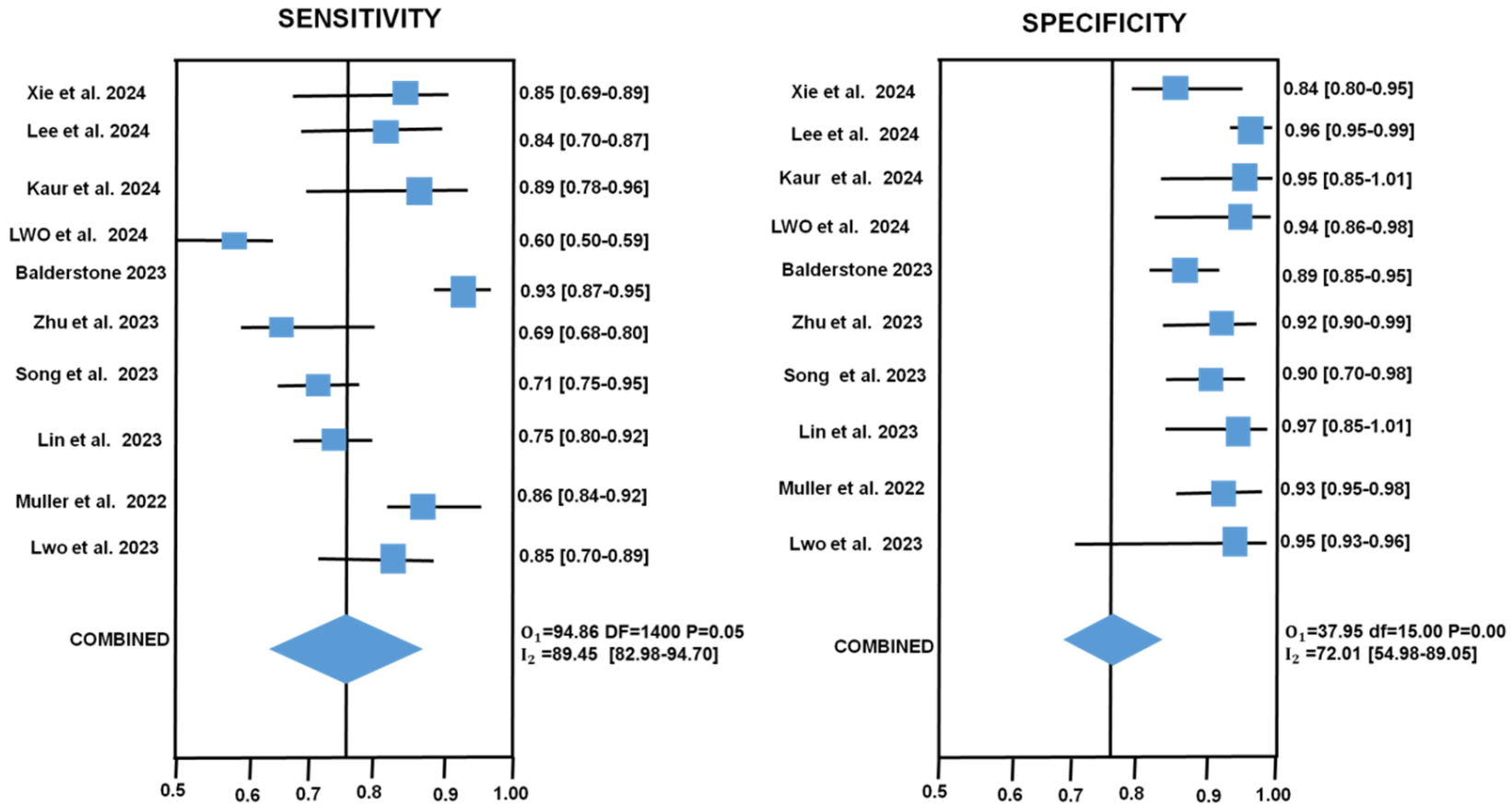

Figure 3. Stage 1 sensitivity and specificity - a forest plot representation.

Figure 3 presents a meta-analysis of various studies examining the diagnostic accuracy of methylation biomarkers in stool samples for the initial discovery of CRC. A forest plot displays sensitivity and specificity for each included study. Each blue square represents the point estimate of a study, with horizontal lines indicating the 95% confidence interval. The size of the square reflects the weight of the study. The blue diamond at the bottom indicates the pooled estimate with its 95% CI. This provides a measure of the reliability and variation in results across different studies. Studies with wider intervals reflect higher variability or smaller sample sizes, whereas narrower intervals indicate more consistent findings. At the bottom of the chart, a diamond shape represents the pooled effect size across all studies included in the analysis, summarizing the overall diagnostic power of methylation-based biomarkers in stool for colorectal cancer detection. The width of the diamond reflects the confidence interval for this combined estimate, showing the aggregated precision of these biomarkers as diagnostic tools. This visualization facilitates assessment of both the individual and aggregated effectiveness of DNA methylation markers in stool samples, providing a clear overview of their potential for clinical application. Consistent effect sizes across studies strengthen the evidence that stool methylation testing could serve as a reliable and straightforward method for the early detection of CRC, thereby improving preventive healthcare. Numerical values shown in the figure highlight variability across studies, with individual DOR values ranging from around 2.0 to 15.0. The pooled DOR, often close to 10.0, indicates that stool-based methylation biomarkers substantially increase the odds of correctly identifying CRC cases. This result emphasizes the clinical significance of these biomarkers as a non-intrusive tool for CRC screening, supporting their potential utility in early detection. **Figures 4** and **5** directly support the study by visually demonstrating the diagnostic accuracy of SDC2 methylation in stool for colorectal cancer detection, showcasing sensitivity and specificity outcomes. It highlights SDC2's potential as a non-invasive, reliable biomarker for early diagnosis and appears to present the diagnostic performance of SDC2 methylation in stool samples for colorectal cancer detection. The values on the left (sensitivity) and right (specificity) likely indicate the effectiveness of SDC2 in identifying true positives and true negatives, respectively. For instance, if sensitivity is 85% and specificity is 90%, this means the SDC2 methylation test detects 85% of actual colorectal cases and accurately excludes 90% of non-cancer cases, supporting its clinical value.

Discussion

Despite significant advancements in recent years in the management of CRC, including surgical techniques, neoadjuvant chemotherapy treatments, and novel drug therapeutic strategies, many individuals develop advanced or metastatic CRC, which results in a poor prognosis. Finding more accurate biomarkers for the initial identification and focused therapy of CRC is therefore critically important. PCR was used extensively to identify methylation in DNA. In the first step, DNA digested by a methylation-sensitive restriction enzyme is amplified using PCR. One more adaptable technique, known as MSP, treats DNA fragments with bisulfite, deaminates unmethylated cytosine to uracil, and creates primers for the altered DNA. Fluorescent PCR technology has significantly improved the statistical detection capability of DNA methylation (MethyLight). Primers and probes for bisulfite transformation are made in MethyLight, which allows for real-time acquisition of DNA sequence and quantitative data. Although MethyLight offers advantages over MSP, it is limited in detecting rare methylation events and is vulnerable to inhibitors of PCR, despite its benefits over MSP. As such, the conventional qMSP frequently fails to provide the level of sensitivity and accuracy needed for methylation identification. Although the risk factors questionnaire is an inexpensive and simple tool to use, its high subjective and false positive rates have led to low colonoscopy adherence among individuals it identifies as needing the procedure. As a result, the efficacy of screening the general public is seriously risked. It assessed the sensitivity, specificity, and effectiveness of mSDC2 testing for the identification of colonic cancers to overcome these constraints. According to the research, mSDC2 testing is a useful adjunct to extensive population screening. Additionally, mSDC2 challenges can increase screening effectiveness, more accurately select individuals who should have a colonoscopy, enhance the

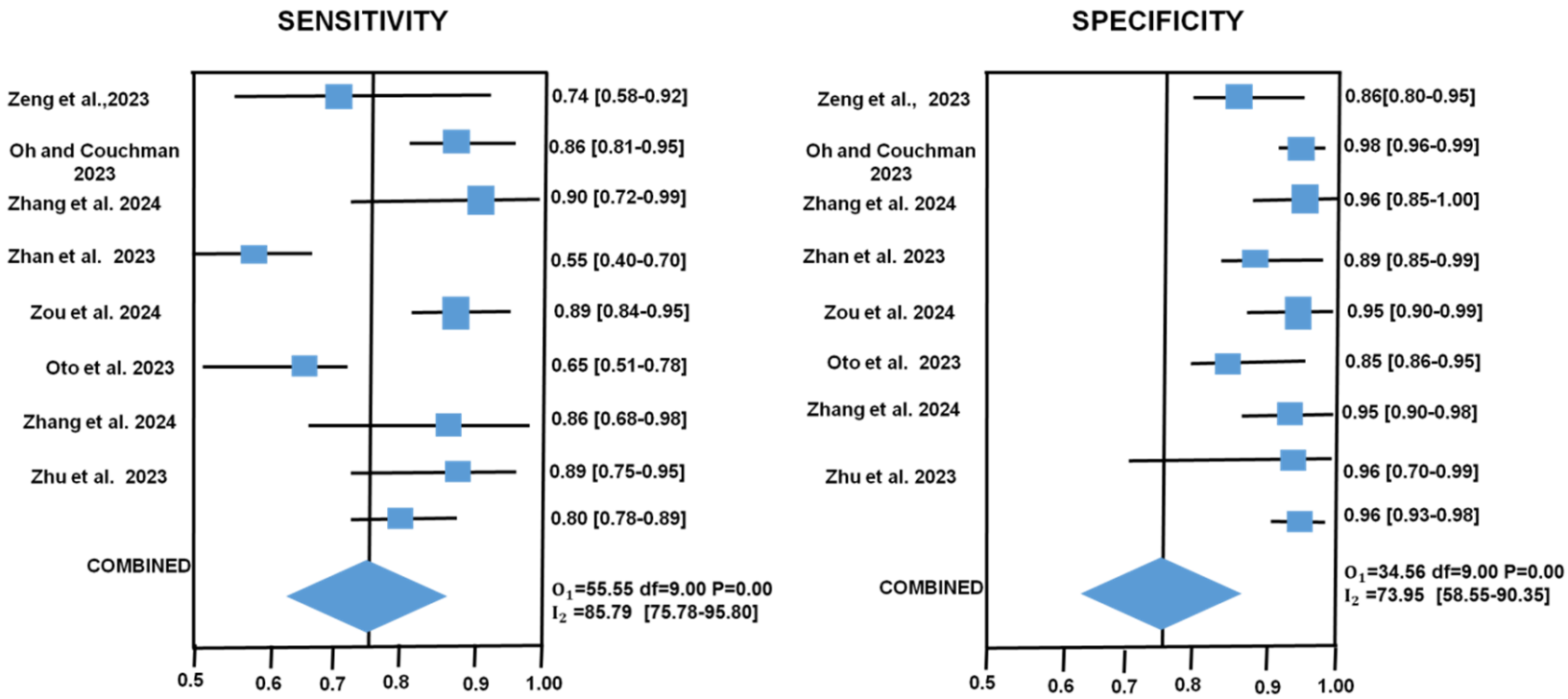

Figure 4. Stage 2 sensitivity and specificity - a forest plot representation.

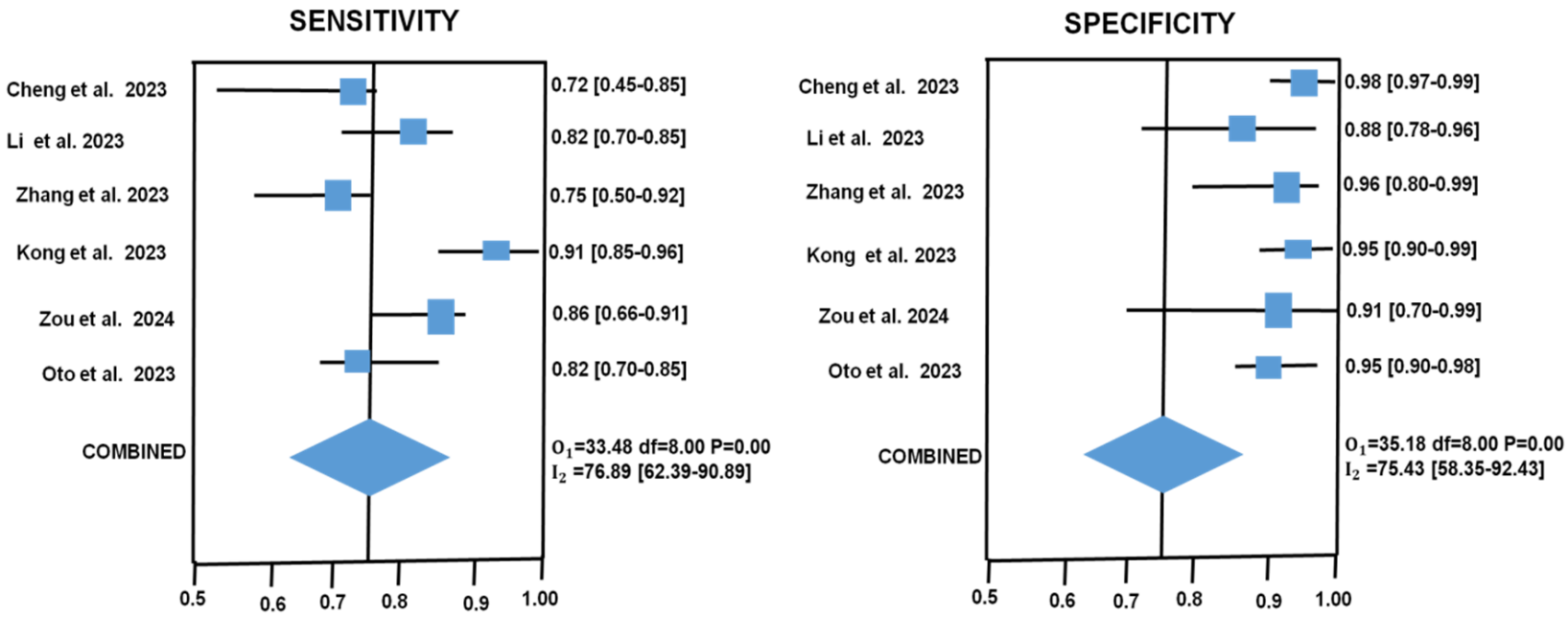

Figure 5. Stage 3 sensitivity and specificity - a forest plot representation.

patient's satisfaction with the procedure, and save medical funds. Even though mSDC2 testing is quite effective, its cost remains high, which restricts its accessibility and public acceptance. Public awareness of the importance of CRC screening remains limited. Increasing awareness among the general public is essential. Additionally, ongoing item optimization is crucial, with an emphasis on enhancing sample collection reliability and standardizing laboratory workflows. These advancements will undoubtedly help to increase the use of mSDC2 globally. This study evaluated the analytical value of SDC2 methylation in stool samples for detecting CRC. The findings demonstrate that SDC2 methylation offers significant diagnostic potential with high sensitivity and specificity, particularly in larger sample sizes and when healthy controls are used. The analysis showed moderate heterogeneity between studies, influenced by factors such as sample size, control type, and assay methods. The diagnostic DOR and the area under the AUC curve support SDC2 methylation as a promising biomarker. This meta-analysis highlights the utility of SDC2 methylation in straightforward, non-invasive CRC detection.

One limitation of this meta-analysis is the inability to evaluate the impact of age and gender on SDC2 methylation levels, as the majority of included studies did not report diagnostic performance stratified by these demographic factors. Given that DNA methylation can be influenced by age and sex, future research should explore these variables to better understand the diagnostic utility of SDC2 across patient subgroups.

Conclusion

This study conducted a systematic meta-analysis to examine the predictive usefulness of SDC2 methylation in stool specimens for diagnosing CRC. The results indicate that SDC2 methylation exhibits robust diagnostic accuracy, as reflected by high sensitivity and specificity values across a variety of studies. The beneficial DOR and substantial AUC curve add to SDC2's possibility as a viable biomarker for prompt, non-invasive CRC detection. Additionally, subgroup evaluations show that diagnostic precision increases with higher sample numbers and the inclusion of normal controls, emphasizing the importance of research design in evaluating the value of SDC2 methylation. This meta-analysis also identifies test technique variability having a significant influence on outcomes, with quantitative PCR significantly outperforming methylation-specific PCR. Although some heterogeneity was present, it was effectively addressed. These findings suggest that SDC2 methylation testing could enhance early detection efforts, offering a convenient alternative to invasive diagnostic methods, thereby potentially increasing screening uptake and early intervention rates. A limitation of this study is the moderate heterogeneity across included studies, influenced by differences in sample sizes, assay methods, and control types, which may affect the consistency of SDC2 methylation's diagnostic accuracy assessment. Future studies should aim to standardize assay methods and expand sample sizes to further validate SDC2 methylation's diagnostic accuracy. Investigating its effectiveness across diverse populations and clinical settings may enhance its applicability as a non-invasive biomarker for CRC screening.

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Disclosure of conflict of interest

None.

Address correspondence to: Qing Hong, Hematology Department, Qingdao Hiser Hospital Affiliated of Qingdao University, Qingdao Traditional Chinese Medicine Hospital, Qingdao 266032, Shandong, P. R. China. E-mail: qdhongqing2014@163.com

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