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RECEIVED 12 March 2024

ACCEPTED 24 April 2024

PUBLISHED 13 May 2024

CITATION

Wang Q, Fang Y, Tan S, Li Z, Zheng R,
Ren Y, Jiang Y and Huang X (2024)
Diagnostic performance of volatile
organic compounds analysis and electronic
noses for detecting colorectal cancer: a
systematic review and meta-analysis.
Front. Oncol. 14:1397259.
doi: 10.3389/fonc.2024.1397259

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Diagnostic performance of volatile organic compounds analysis and electronic noses for detecting colorectal cancer: a systematic review and meta-analysis

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Introduction: The detection of Volatile Organic Compounds (VOCs) could provide a potential diagnostic modality for the early detection and surveillance of colorectal cancers. However, the overall diagnostic accuracy of the proposed tests remains uncertain.

Objective: This systematic review is to ascertain the diagnostic accuracy of using VOC analysis techniques and electronic noses (e-noses) as noninvasive diagnostic methods for colorectal cancer within the realm of clinical practice.

Methods: A systematic search was undertaken on PubMed, EMBASE, Web of Science, and the Cochrane Library to scrutinize pertinent studies published from their inception to September 1, 2023. Only studies conducted on human subjects were included. Meta-analysis was performed using a bivariate model to obtain summary estimates of sensitivity, specificity, and positive and negative likelihood ratios. The Quality Assessment of Diagnostic Accuracy Studies 2 tool was deployed for quality assessment. The protocol for this systematic review was registered in PROSPERO, and PRISMA guidelines were used for the identification, screening, eligibility, and selection process.

Results: This review encompassed 32 studies, 22 studies for VOC analysis and 9 studies for e-nose, one for both, with a total of 4688 subjects in the analysis. The pooled sensitivity and specificity of VOC analysis for CRC detection were 0.88 (95% CI, 0.83-0.92) and 0.85 (95% CI, 0.78-0.90), respectively. In the case of e-nose, the pooled sensitivity was 0.87 (95% CI, 0.83-0.90), and the pooled specificity was 0.78 (95% CI, 0.62-0.88). The area under the receiver operating characteristic analysis (ROC) curve for VOC analysis and e-noses were 0.93 (95% CI, 0.90-0.95) and 0.90 (95% CI, 0.87-0.92), respectively.

Conclusion: The outcomes of this review substantiate the commendable accuracy of VOC analysis and e-nose technology in detecting CRC. VOC analysis has a higher specificity than e-nose for the diagnosis of CRC and a sensitivity comparable to that of e-nose. However, numerous limitations, including a modest sample size, absence of standardized collection methods,

lack of external validation, and a notable risk of bias, were identified. Consequently, there exists an imperative need for expansive, multi-center clinical studies to elucidate the applicability and reproducibility of VOC analysis or e-nose in the noninvasive diagnosis of colorectal cancer.

Systematic review registration: <https://www.crd.york.ac.uk/prospero/#recordDetails>, identifier CRD42023398465.

KEYWORDS

volatile organic compounds, VOCs, electronic nose, E-nose, colorectal cancer, diagnosis

1 Introduction

Colorectal carcinoma (CRC) stands as a substantial global public health concern, with an estimated 1.93 million new cases and 0.93 million deaths in 2020 (1). CRC is known to develop from precursor lesions, in most cases adenomas, through the adenoma-carcinoma sequence (2) which can be diagnosed earlier through screening even in its early stages. Through standardized early diagnosis and treatment, the 5-year survival rate for early-stage CRC could exceed 90% (1). Fecal immunochemical test (FIT) and colonoscopy screening for colorectal cancer are pivotal tools for early diagnosis of colorectal cancer (3). However, the detection performance of FIT falls short, with a miss detection rate of 9–29% for CRC and 60–75% for advanced CRC (4). FIT-positive patients are recommended to undergo colonoscopy, but colonoscopy is painful, expensive, and invasive, with the risk of complications such as perforation and bleeding. So not all FIT-positive individuals undergo regular colonoscopy follow-up (5, 6). Therefore, there is an urgent need for convenient, non-invasive, reliable, simple, and cost-effective diagnostic methods to enhance early diagnosis and screening of colorectal cancer.

The analysis of Volatile organic compounds (VOCs) has been applied as a novel and promising diagnostic technique for exploration of non-invasive colorectal neoplasia biomarker. VOCs constitute the by-products of biochemical processes within the human body and typically mirror metabolic states (7, 8). Pathological conditions precipitate aberrant metabolic processes, resulting in a marked increase in VOC production (9). Investigations into cancer-related VOCs have explored various matrices, including breath, blood, urine, saliva, and feces (10–13). Many studies have demonstrated that the applicability of VOC analysis could be used in cancer diagnosis (14–20).

The electronic nose (e-nose) emerges as an instrument equipped with a suite of sensors endowed with specificity and an adept pattern recognition system capable of discerning both simple and complex odors (21). As a relatively recent development, the e-nose has become widely accepted for detecting diseases, owing to its

portability, expeditious, cost-effective, and user-friendly diagnostic capabilities, rendering it particularly suited for routine clinical applications. Multiple researchers (22–24) have substantiated the commendable diagnostic accuracy of available e-nose technologies across diverse indications. Notably, van Keulen et al. (25) analyzed exhaled breath from patients with CRC and advanced adenomas (AAs), proving that the Aeonose electronic nose can distinguish CRC and AAs from controls. Additionally, de Meij et al. (26) reported an e-nose sensitivity of 0.85 and a specificity of 0.87 in CRC detection.

Our article aims to systematically review published studies on VOC analysis and e-nose technology concerning colorectal cancer (CRC) detection. Furthermore, we aim to compare their diagnostic performance, with the aspiration of offering a valuable reference for the application of diagnostic techniques in CRC diagnosis.

2 Methods

2.1 Registration

This systematic review has been registered with PROSPERO, under registration number CRD42023398465. The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines were adhered to in both the identification and reporting phases of this review (27).

2.2 Search strategy

A comprehensive literature search encompassing PubMed, Embase, Cochrane Library, and Web of Science was conducted from inception up to September 1, 2023. This search, void of language or data publication restrictions, utilized keywords such as “Volatile Organic Compounds,” “VOCs,” “electronic nose,” “e-nose,” “Colorectal neoplasms,” and “diagnosis” or “diagnostic” as search strategy terms. A detailed search strategy is provided in the [Supplement](#).

2.3 Study selection

A total of 192 articles were retrieved. The eligibility of each article was assessed through a meticulous examination of titles and abstracts by two independent reviewers (Y.F. and S.Y.T.). Inclusion criteria were as follows: (1) studies conducted on adult subjects; (2) studies involving colorectal patients; and (3) studies that identified evaluating the diagnostic accuracy of using VOC analysis or e-nose technology. Exclusion criteria encompassed: (1) studies lacking information on the number of cases, controls, sensitivity, and specificity; and (2) studies published as review articles or case reports. Discrepancies between reviewers were resolved through consensus or, if necessary, with the involvement of a third investigator (Q.L.W.). A total of 32 articles met the inclusion criteria and were subsequently included in this systematic review.

2.4 Data collection process

The data extraction and tabulation process from the selected studies was undertaken by two reviewers (S.Y.T. and R.Y.Z.). Tables 1, 2 summarized basic study characteristics, including authorship, country and year of publication, study type, detection medium, analysis method, sample size, CRC stage, statistical analysis methodology, sampler, sensitivity, specificity, and the area under the curve (AUC), as well as accuracy.

2.5 Quality assessment

The Quality Assessment of Diagnostic Studies 2 tool (QUADAS-2) (56) was conducted to assess the quality of the included studies. This evaluation encompassed four domains: patient selection, index test, reference standard, and patient flow and timing. Ratings were assigned as “low risk,” “unclear,” or “high risk”. The assessment was conducted independently by two investigators (Y.F.J. and Z.H.L.), and any disparities were resolved through the involvement of a third investigator (X.P.H.). The complete QUADAS-2 version can be found in Supplement.

2.6 Statistical analysis

This meta-analysis was performed by a bivariate model to obtain summary estimates of sensitivity, specificity, and positive and negative likelihood ratios. The Deeks funnel plot asymmetry test was employed to discern publication bias (57). A two-sided $P < 0.10$ was deemed statistically significant. Statistical heterogeneity was evaluated among pooled studies using I^2 index. STATA software (version 16 SE; Stata Corporation, College Station, TX, USA) was used to aggregate analysis and the statistical package MIDAS was used for bivariate meta-analysis and summary receiving operate characteristic (SROC) curve calculation with 95% confidence region. Subgroup analyses were performed by Open Meta-Analyst software to explore sources of heterogeneity based on the characteristics of the included articles.

3 Results

3.1 Study selection

The literature search strategy yielded an initial pool of 192 articles. Following review, 110 articles were excluded based on title and abstract screening. Subsequently, 59 full-text articles, with a total of 4688 subjects underwent scrutiny against the inclusion criteria. Ultimately, 32 studies fulfilled the inclusion criteria for this review. The selection process of the studies is shown in the PRISMA diagram-Figure 1.

3.2 Study characteristics

All thirty-two studies included in this review were published in English (7, 25, 26, 28–55, 58). Among them, 22 studies employed VOC analysis for the diagnosis of colorectal cancer (7, 28–46, 48, 49), 9 studies utilized e-nose technology (25, 26, 50–55, 58), and one study used both VOC analysis and e-nose (47). In the VOC studies, 10 studies used breath samples (7, 28–30, 38, 39, 41–43, 49), 6 studies used urine samples (32, 37, 44–46, 48), 5 studies used fecal samples (31, 33, 35, 36, 40), and one study used salivary sample (34). Most studies used MS-based techniques, principally GC-MS (n=7), TD-GC-MS (n=4), FAIM (n=4), and SIFT-MS (n=2). In E-nose studies, 5 studies used breath samples (25, 50–52, 58), two studies used urine samples (53, 54), and two studies used fecal samples (26, 55). One study used both VOC analysis and e-nose technology in testing urine samples (47). The most commonly used e-noses were Aeonose (n=3), PEN3 (n=2), and WOLF (n=2). All studies were prospective, 25 were case-control studies, and 7 employed cross-sectional studies. Logistic regression analysis (LRA) and partial least squares discriminant analysis (PLS-DA) emerged as the most frequently reported analytical methods. Other reported analytical methods encompassed artificial neural network (ANN), support vector machine (SVM), linear discriminant analysis (LDA), random forest (RF), probabilistic neural network (PNN), discriminant function analysis (DFA), and neural network (NN). The majority of studies were conducted in hospital settings, with 29 studies in Europe, two in Asia, and one with an undisclosed location. Tables 1, 2 provides an overview of the fundamental characteristics of the studies.

3.3 Risk of bias

The quality appraisal of all incorporated literature was conducted according to the QUADAS-2 scale through Review Manager 5.4 software. The results of the risk of bias assessment are visually presented in Figures 2A, B.

In the aggregate, a few studies exhibited a high risk of bias. Concerning ‘patient selection’ seven studies (32, 34, 39, 42, 46, 53, 54) (21.9%) incurred a high risk of bias. The primary contributor to this high risk pertained to the absence of a detailed description of the sampling process and the implementation of a case-control study design. Regarding the ‘index test’ while most studies employed reference diagnostic tests to delineate the definition of a positive

TABLE 1 Basic characteristics and outcomes of VOC studies in the analysis.

Study	year	country	Type of Study	Detection medium	Analysis method	No of CRC patients	No of controls	Stage of CRC	Statistical method	Sampler	Sensitivity, %	Specificity, %	AUC, %	Accuracy, %
Altomare et al. (28)	2013	Italy	case-control	breath	GC-MS	37	41 (healthy)	I/II:19 III/IV:18	PNN	Tedlar bag	86	83	85.2	85
Altomare et al. (29)	2015	Italy	case-control	breath	TD-GC-MS	48	55 (healthy)	I/II:28 III/IV:20	PNN	Tedlar bag	100	97.72	100	98.75
Altomare et al. (30)	2020	Italy	case-control	breath	GC-MS	83	90 (non-cancer)	I/II:38 III/IV:42	LRA	ReCIVA	90	93	97.9	NR
Alustiza et al. (31)	2023	Spain	case-control	feces	TD-GC-MS	24	32(healthy) 24 (Adenomas)	I/II:7 III/IV:17	ANOVA	plastic container	83	82	85	NR
Arasaradnam et al. (32)	2014	UK	case-control	urine	FAIMS	83	50 (healthy)	NR	FDA	ATLAS sampler	88	60	NR	NR
Batty et al. (33)	2015	UK	case-control	feces	SIFT-MS	31	31 (healthy)	NR	PLS-DA	Nalophan sampler	72	78	NR	75
Bel'skaya et al. (34)	2020	Russia	case-control	salivary	capillary GS	18	16 (noncancer)	I/II:25 III/IV:38	CRT	NR	92.3	100	NR	NR
Bond et al. (35)	2019	UK	case-control	feces	GC-MS	21	60 (non-cancer)	NR	PLS-DA, LRA	OdoReader box	87.9	84.6	82	NR
Bosch et al. (36)	2020	Netherlands	case-control	feces	GC-IMS	14	227 (healthy)	AA:24	LRA, RF, SVM,NN	NR	100	100	96.1	NR
Boulind et al. (37)	2022	UK	cross-sectional	urine	GC-MS	558 (suspected)	NR	NR	ANN	NR	87.8	88.2	89.6	NR
Cheng et al. (38)	2022	Netherlands	cross-sectional	breath	TD-GC-TOF-MS	30	84 (negative colonoscopy)	AA:138	RF	Tedlar bag	80	70	NR	NR
Depalma et al. (39)	2014	Italy	case-control	breath	TD-GC-MS	15	15 (healthy)	NR	LDA	Tedlar bag	96.5	100	NR	NR
Ishibe et al. (40)	2018	Japan	case-control	feces	GC-MS	30	26 (healthy)	NR	PLS-DA	Tedlar bag	90	57.7	NR	75
Leja et al. (41)	2015	NR	case-control	breath	GC-MS	71	131 (healthy)	NR	NR	NR	85	90	NR	88
Lena et al. (42)	2012	Italy	case-control	breath	TD-GC-MS	34	36 (healthy)	NR	SVM	Tedlar bag	83	88	94.4	80

(Continued)

TABLE 1 Continued

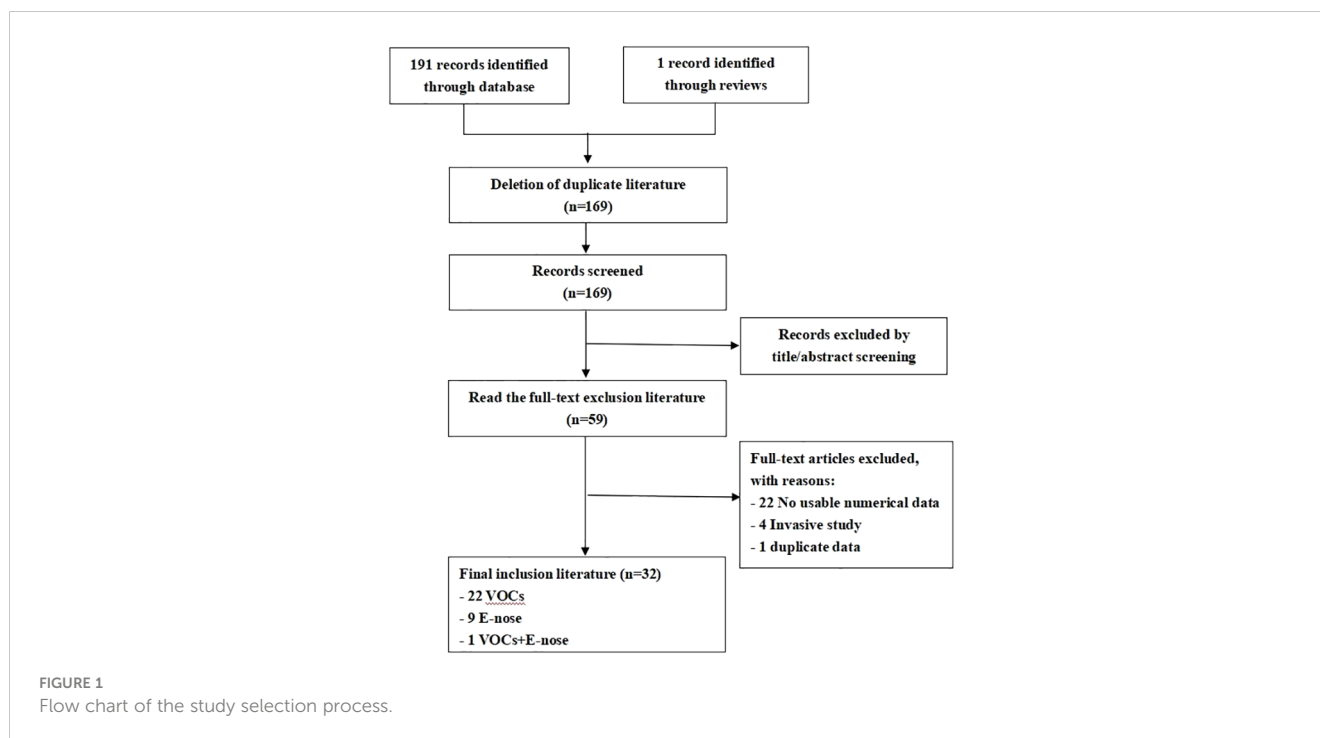
Study	year	country	Type of Study	Detection medium	Analysis method	No of CRC patients	No of controls	Stage of CRC	Statistical method	Sampler	Sensitivity, %	Specificity, %	AUC, %	Accuracy, %
Markar et al. (43)	2019	UK	case-control	breath	SIFT-MS	50	100 (healthy)	NR	LRA	NR	96	76	NR	NR
McFarlane et al. (44)	2019	UK	case-control	urine	FAIMS	56	82 (non-cancer)	NR	RF	NR	69	69	72	NR
Mozdiak et al. (45)	2019	UK	cross-sectional	urine	FAIMS and GC-IMS	163 (positive FOBT)	NR	NR	SLR, GPC	NR	100	100	98	NR
Politi et al. (7)	2021	Italy	case-control	breath	IMR-MS	52	45 (healthy)	NR	LRA	NR	96	93	NR	NR
Psutka et al. (46)	2017	JAPAN	case-control	urine	FAIMS	139	78 (healthy)	NR	PCA	NR	67.4	82.1	NR	NR
Tyagi et al. (47)	2021	UK	case-control	urine	GC-TOF-MS	58	38 (healthy)	I/II:24 III/IV:34	RF, NN	NR	86	81	93	NR
Widlak et al. (48)	2018	UK	cross-sectional	urine	FAIMS	562 (Completed colonoscopy)	NR	NR	PCA	NR	63	63	NR	NR
Zambrana et al. (49)	2012	Spain	case-control	breath	GC-MS	38	43 (healthy)	NR	NR	NR	87.06	76.85	NR	NR

AA, advanced adenomas; ANN, artificial neural network; CRC, colorectal cancer; CRT, Classification and Regression Tree; FDA, Fisher Discriminant Analysis; FOBT, fecal occult blood testing; GPC, Gaussian process classifier; LDA, linear discriminant analysis; LRA, logistic regression analysis; NR, Not reported; NN, Neural Network; PCA, Principal Component Analysis, PLS-DA, partial least squares discriminant analysis; PNN, Probabilistic Neural Network; RF, Random Forest; SLR, Sparse Logistic Regression, SVM, support vector machine.

TABLE 2 Basic characteristics and outcomes of e-nose studies in the analysis.

source	year	country	Type of Study	Detection medium	E-Nose type	NO of CRC patients	No of controls	Stage of CRC	Statistical method	Sampler	Sensitivity, %	Specificity, %	AUC, %	Accuracy, %
Amal et al. (14)	2015	Latvia	case-control	breath	Prototype: 6 nanomaterial sensors (GNP and SWCNTs)	65	122 (healthy)	AA:22	DFA	NR	85	94	NR	91
Altomare et al. (50)	2016	Italy	case-control	breath	PEN3:10 MOS	15	15 (healthy)	I/II:1 III/IV:14	PNN	Tedlar bag	93.3	10	NR	37.78
de Meij et al. (26)	2014	Netherlands	case-control	feces	Cyranose 320:32 conducting polymer sensors	40	57 (healthy)	AA:60	CDA	BD box	85	87	NR	92
Steenhuis et al. (51)	2020	Netherlands	cross-sectional	breath	Aeonose:3 MOS	62	NR	I/II:25 III/IV:37	ANN	NR	88	75	NR	NR
Tyagi et al. (47)	2021	UK	case-control	urine	PEN3:10 MOS	58	38 (healthy)	I/II:24 III/IV:34	RF, NN	NR	91	55	81	NR
van de Goor et al. (52)	2017	Netherlands	case-control	breath	Aeonose:3 MOS	28	100 (HNSCC)	NR	ANN	NR	79	81	NR	81
van Keulen et al. (25)	2019	Netherlands	cross-sectional	breath	Aeonose:3 MOS	447t (colonoscopy patients)	NR	NR	ANN	NR	95	64	74	84
Westenbrink et al. (53)	2015	UK	case-control	urine	WOLF:13 electro-chemical sensors	39	18 (healthy)	NR	LDA	NR	92	77	NR	NR
Westenbrink et al. (54)	2016	UK	case-control	urine	WOLF:13 electro-chemical sensors	26	23(IBS)	NR	LDA, KNN	sample box	84.1	82.4	NR	NR
Zonta et al. (55)	2020	Italy	cross-sectional	faeces	SCENT A1: 5 semiconductor gas sensors	398 (colonoscopy patients)	NR	NR	SVM	sample box	116	46	22	214

AA, advanced adenomas; ANN, artificial neural network; CDA, canonical discriminant analysis; CRC, colorectal cancer; DFA, discriminant function analysis; HNSCC, head and neck squamous cell carcinoma; IBS, Irritable bowel syndrome patients; KNN, K Nearest Neighbors; LDA, linear discriminant analysis; NR, Not reported; NN, Neural Network; PNN, Probabilistic Neural Network; RF, Random Forest; SVM, support vector machine.



test, only nine studies ensured adequate blinding (26, 29, 30, 35, 43–45, 48, 55), leaving 23 studies with an unspecified risk of bias concerning the ‘index test’. Concerning ‘reference standard’, none of the 13 studies (28, 32, 34, 39, 42, 46–50, 52–54) reported the reference standard test. Concerning ‘flow and timing’, five studies (39, 40, 42, 46, 52) faced a high risk of bias. The primary reason for this was that these studies do not account for the time interval between the index test and the reference test.

In evaluating clinical applicability, significant concerns in patient selection arose from the absence of matched patient groups, inadequate patient selection criteria, and applicability of the study design to the research question. Six studies exhibited a high applicability concern for patient selection criteria (26, 32, 42, 46, 49, 53). No high-risk concerns were identified regarding the applicability of the index and reference tests to the research questions.

3.4 Diagnostic accuracy

The pooled sensitivity and specificity of VOC analysis for detecting CRC were 0.88 (95% CI, 0.83–0.92) and 0.85 (95% CI, 0.78–0.90), respectively (Figure 3). Similarly, the pooled sensitivity of the e-nose was 0.87 (95% CI, 0.83–0.90), with a specificity of 0.78 (95% CI, 0.62–0.88) (Figure 4). Notably, in VOC studies, the I^2 index was 82.86% for sensitivity and 90.36% for specificity, while for e-nose studies, it was 23.31% for sensitivity and 89.46% for specificity. Pooled receiver operating characteristic analysis of VOC studies resulted in an area under the curve (AUC) of 0.93 (95% CI, 0.90–0.95) (Figure 5). For e-nose studies, the AUC was 0.90 (95% CI, 0.87–0.92) (Figure 6). The Positive Likelihood Ratio (PLR), Negative Likelihood Ratio (NLR), and Diagnostic Odds Ratio (DOR) of VOC studies were 5.8 (95% CI, 3.9–8.7), 0.14

(95% CI, 0.09–0.21), and 41 (95% CI, 19–87), respectively. For e-nose studies, the PLR, NLR, and DOR were 3.9 (95% CI, 2.2–6.7), 0.17 (95% CI, 0.13–0.21), and 23 (95% CI, 13–44), respectively.

The funnel plots for publication bias are displayed in Figures 7, 8. The Deeks’ regression test for funnel plot asymmetry demonstrated an absence of publication bias among the studies included, with slope coefficients P values of 0.28 and 0.62 for using VOC analysis and e-nose.

3.5 Subgroup analysis

We compared the accuracy of different samples of included studies. A separate pooled analysis of breath VOCs studies exhibited good efficacy, with a sensitivity of 0.819 (95% CI, 0.720–0.888) and a specificity of 0.907 (95% CI, 0.876–0.932) (Table 3). A separate pooled analysis of GC-MS, TD-GC-MS, and FAIMS methods, showed a sensitivity of 0.732 (95% CI, 0.519–0.874) and a specificity of 0.919 (95% CI, 0.867–0.952) for GC-MS, and a sensitivity of 0.898 (95% CI, 0.756–0.962) and a specificity of 0.889 (95% CI, 0.783–0.947) for TD-GC-MS, and a sensitivity of 0.635 (95% CI, 0.299–0.877) and a specificity of 0.775 (95% CI, 0.568–0.901) for FAIMS (Table 3).

For e-nose studies, exhaled breath samples demonstrated a better specificity of 0.911 (95% CI, 0.859–0.945) but a lower sensitivity of 0.708 (95% CI, 0.543–0.833) (Table 4). A separate pooled analysis for different types of e-Nose demonstrated that Aeonose could detect colorectal with a sensitivity of 0.682 (95% CI, 0.506–0.817) and a specificity of 0.916 (95% CI, 0.832–0.960). Separate pooled analysis for PEN3 showed a sensitivity of 0.654 (95% CI, 0.401–0.843) and a specificity of 0.791 (95% CI, 0.605–

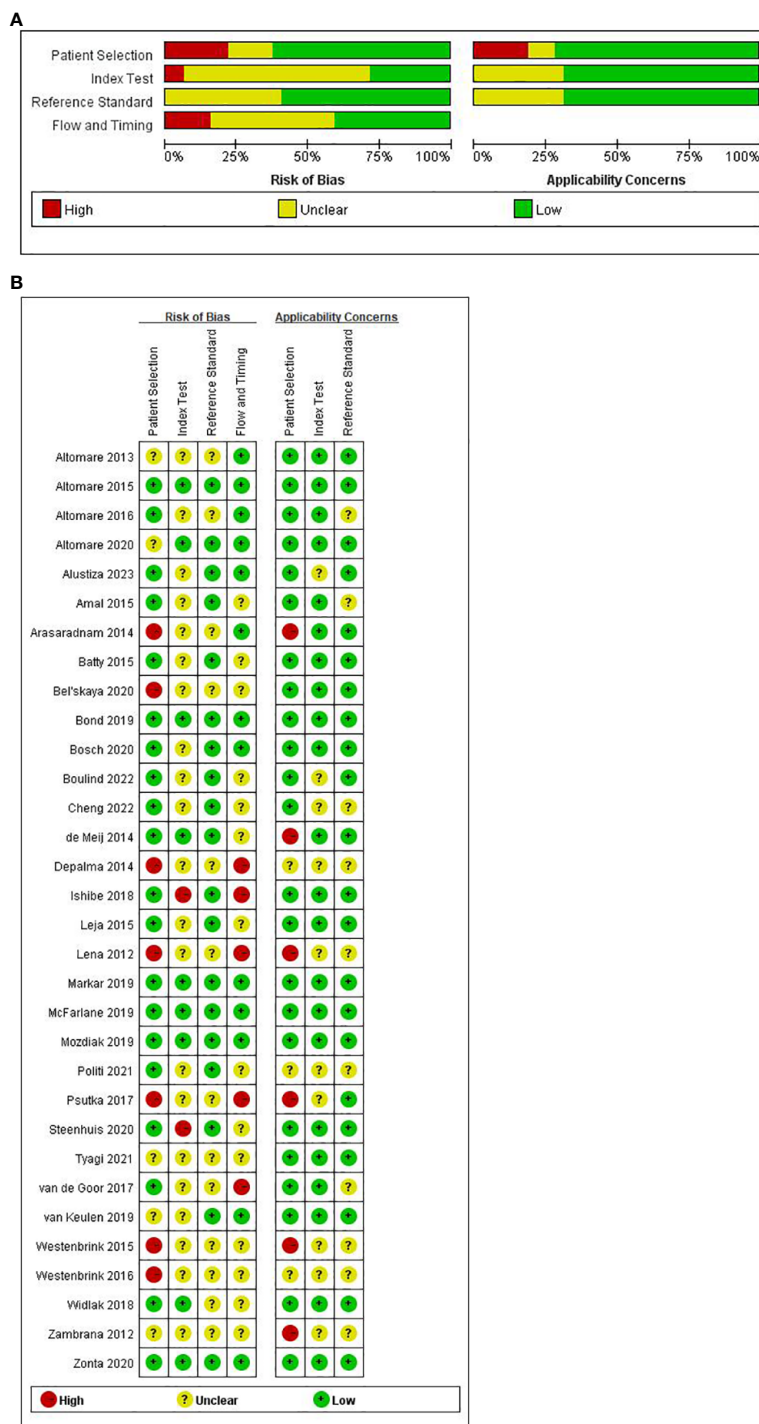


FIGURE 2 (A) Summary and separate outcome of risk of bias and concerns. (B) Summary and separate outcome of risk of bias and concerns regarding applicability for included studies using QUADAS-2 tool.

0.903). For WOLF the sensitivity was 0.906 (95%CI, 0.790-0.961) and the specificity was 0.790 (95%CI, 0.359-0.962) (Table 4).

Additional sensitivity analysis for advanced adenomas demonstrated good accuracy in VOC analysis, with a sensitivity of 0.824 (95% CI, 0.770-0.867) and specificity of 0.908 (95% CI, 0.658-0.981) (Table 3). For e-nose studies, the sensitivity and specificity for the detection of advanced adenomas were 0.755

(95% CI, 0.609-0.859) and 0.704 (95% CI, 0.628-0.770), respectively (Table 4).

4 Discussion

We conducted a systematic review and meta-analysis to evaluate VOC analysis and electronic nose in detecting colorectal

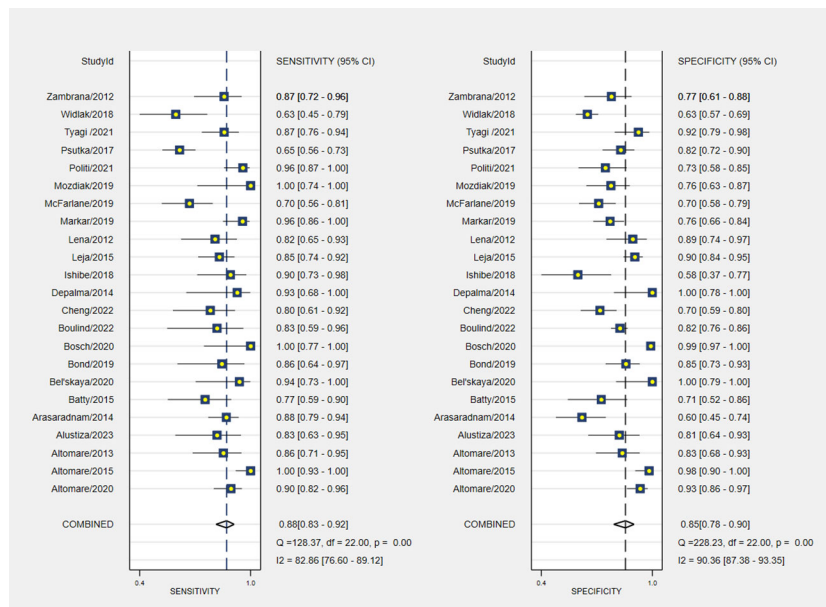


FIGURE 3 Pooled sensitivity and specificity analyses of VOC studies.

cancer, aiming to compare the diagnostic accuracy and clinical application value of these two methods. Pooled analysis of VOC and electronic-nose studies demonstrated high diagnostic accuracy for CRC detection, with a pooled sensitivity of 0.88 and specificity of 0.85 for VOC analysis and a sensitivity of 0.87 and specificity of 0.78 for e-nose studies. The visually assessed SROC curves indicated clinical accuracy, with VOC analysis and e-nose having SROC curves of approximately 0.93 and 0.90, respectively, both close to 1, signifying superior accuracy and diagnostic efficacy in CRC

diagnosis. These findings align with prior reviews (22, 59, 60), but the notable heterogeneity between studies and the identified high risk of bias warrant cautious interpretation. The heterogeneity was largely due to the sample media and the analytical methods used.

Subgroup analyses revealed that breath samples in VOC analysis and urine and breath samples in e-nose studies exhibited higher sensitivity or specificity. Breath sampling is easily performed and well-received by patients, and urine samples, boasting high sensitivity and specificity, emerge as valuable alternatives. Recent

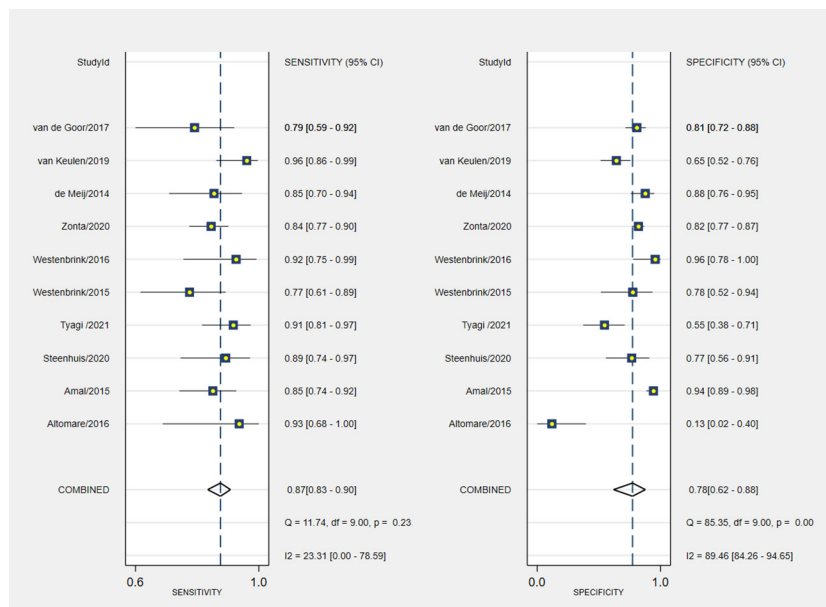


FIGURE 4 Pooled sensitivity and specificity analyses of e-noses studies.

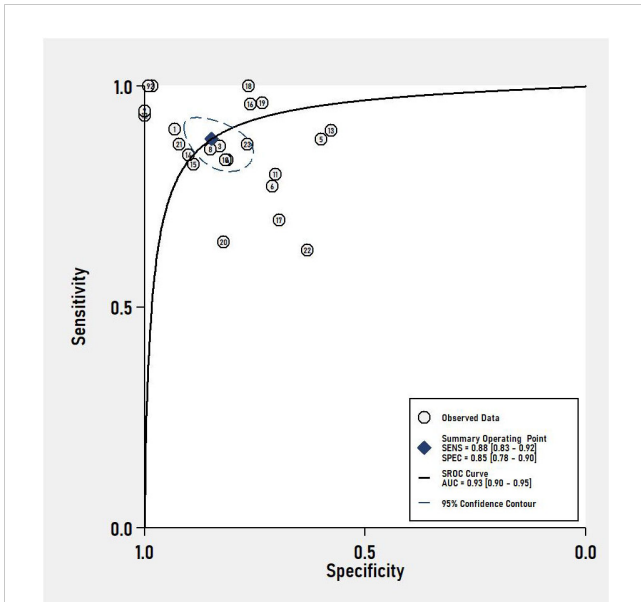


FIGURE 5 Summary receiver operating characteristic (SROC) curve Analysis of VOC studies.

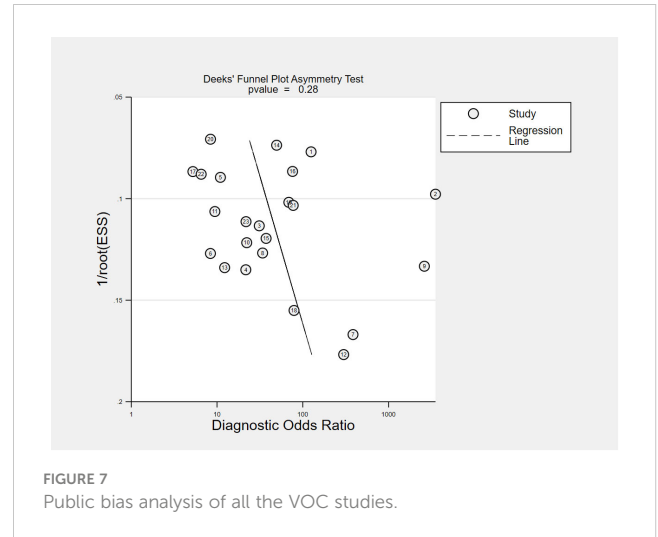


FIGURE 7 Public bias analysis of all the VOC studies.

meta-analysis evaluated the performance of the combined FIT and urinary. The findings revealed that the combined FIT-VOC approach could detect 33% more cases of colorectal cancers (60). Chandrapalan S et al. (61) showed that the combination of FIT and VOC can be a better triage tool, for CRC in patients with lower gastrointestinal symptoms than FIT alone.

Due to the lack of standardization in sample collection, handling, and storage, technical barriers exist in measuring and analyzing various VOC characteristics during sampling, whether it involves alveolar air, urine, or feces. In several studies, exhaled

breath was collected into a bag and subsequently analyzed (28, 29, 33, 38–40, 42, 50). The use of bag collection aligns more closely with real-world medical applications. However, this approach may be influenced by several factors, including interference from ambient VOCs, the material used for collection, and the impact of temperature, humidity, and storage time on specimens (62). For breath samples, it is essential to examine them within 6 hours of the collection's conclusion to ensure test accuracy (63). Therefore, developing methods for the collection, transmission, and handling of breath samples is crucial for the success of this approach. Some studies have indicated that the diagnostic accuracy of fecal and urine VOCs is not significantly affected by storage time (20 months for fecal and 12 months for urine VOCs) (64, 65).

Urine samples are ideal detection medium because they have limited confounding factors compared to breath samples which is influenced by smoking or fecal samples influenced by diet. Further research should standardize the method of collection of such samples and investigate the effects of potential confounding factors.

Among all studies, only six reported on CRC stages, indicating limited generalizability and clinical applicability. Multi-center

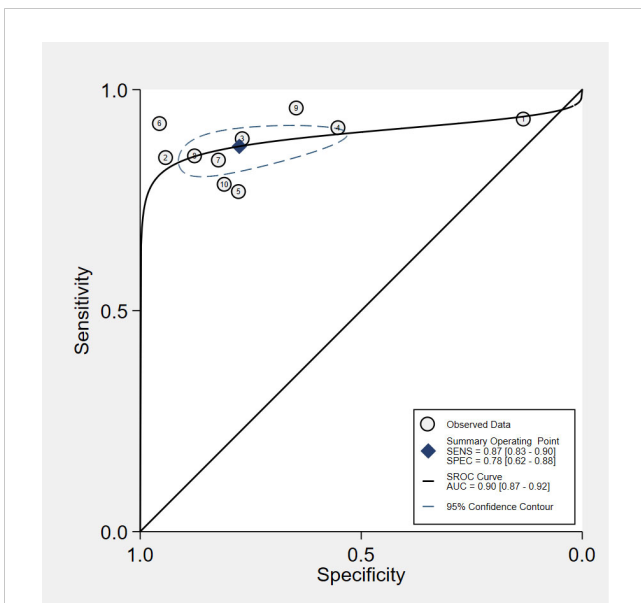


FIGURE 6 Summary receiver operating characteristic (SROC) curve Analysis of e-noses studies.

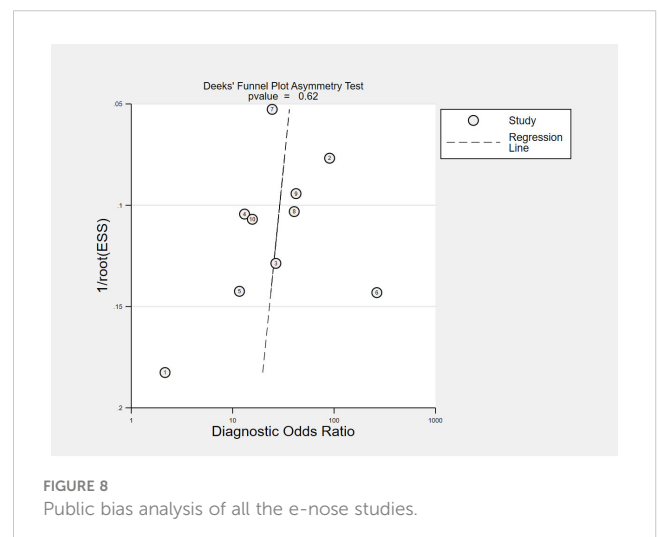


FIGURE 8 Public bias analysis of all the e-nose studies.

TABLE 3 Subgroup analysis in VOC studies.

Subgroup	Sensitivity (95% CI)	I ²	Specificity (95% CI)	I ²
Detects medium				
Breath Samples (n=10)	0.819 (0.720, 0.888)	80.64%	0.907 (0.876, 0.932)	15.58%
Urine Samples (n=7)	0.627(0.365, 0.831)	95.68%	0.862 (0.710, 0.941)	92.09%
Fecal Samples (n=5)	0.730 (0.649, 0.797)	0%	0.905 (0.769, 0.965)	72.52%
The sample analysis method used				
GC-MS (n=7)	0.732 (0.519, 0.874)	0%	0.919 (0.867, 0.952)	60.11%
TD-GC-MS (n=4)	0.898 (0.756, 0.962)	34.83%	0.889 (0.783, 0.947)	30.68%
FAIM (n=4)	0.635 (0.299, 0.877)	3.8%	0.775 (0.568, 0.901)	92.47%
CRC stage				
Advanced adenomas VS. non-cancer control (n=3)	0.824 (0.770, 0.867)	0%	0.908 (0.658, 0.981)	94.03%

validation studies of the diagnostic performance of VOCs on early stages of CRC and its precursor lesions (adenomas or not) is warranted, which could reduce the incidence of CRC.

It has been demonstrated that various factors, such as age, gender, smoking, alcohol consumption, coffee intake, and the consumption of stimulating foods like leeks and garlic, as well as comorbidities and medication, may influence the composition of VOCs in exhaled breath (66). However, only a few studies considered confounding or modifying effects, limiting the validity and reliability of the results. Therefore, future studies should account for the impact of such factors on breath prints during the design phase.

Gas chromatography-mass spectrometry (GC-MS), a traditional method for VOC analysis, is a highly standardized technique providing qualitative and quantitative information on exhaled VOCs (67, 68). In this study, TD-GC-MS demonstrated high sensitivity and specificity in detecting colorectal cancer, while GC-MS exhibited improved specificity but suboptimal sensitivity. The use of GC-MS and newer mass spectrometry technology devices remains

the gold standard for identifying specific VOCs for analysis. However, GC-MS technology is costly and complex, with long analysis times, and it demands a high level of expertise from operators.

Based on sensors, electronic nose technology serves as a novel analytical method for disease diagnosis, offering the advantages of being cost-effective, user-friendly, portable, sensitive, and responsive. Nevertheless, there are existing shortcomings that require refinement in the application of e-nose in clinical practice. Unlike GC-MS and other techniques, e-nose lacks the precision to measure specific types and composition ratios of components in VOCs (24). It also cannot identify specific pathophysiological pathways or therapeutic targets. Furthermore, as the e-nose relies on arrays of gas sensors to distinguish and identify response spectra of mixtures composed of multiple VOCs, the diverse sensor types with distinct signal responses prevent the integration of results from one e-nose with different devices or sensor types (69). Van der Sar IG (70) recommends the establishment of a comprehensive worldwide shared database encompassing patient characteristics and other pretest probabilities.

TABLE 4 Subgroup analysis in e-nose studies.

Subgroup	Sensitivity (95% CI)	I ²	Specificity (95% CI)	I ²
Detects medium				
Breath Samples (n=5)	0.708 (0.543, 0.833)	80.64%	0.911 (0.859, 0.945)	15.58%
Urine Samples (n=3)	0.857 (0.689, 0.942)	95.68%	0.786 (0.563, 0.913)	92.09%
Fecal Samples (n=2)	0.758 (0.631, 0.852)	0%	0.904 (0.864, 0.933)	72.52%
E-Nose type				
Aeonose (n=3)	0.682 (0.506, 0.817)	74.62%	0.916 (0.832, 0.960)	37.95%
PEN3 (n=2)	0.654 (0.401, 0.843)	79.99%	0.791 (0.605, 0.903)	0%
WOLF (n=2)	0.906 (0.790, 0.961)	2.06%	0.790 (0.359, 0.962)	80.97%
CRC stage				
Advanced adenomas VS. non-cancer control (n=3)	0.755 (0.609, 0.859)	55.43%	0.704 (0.628, 0.770)	0%

Various algorithms and methods were employed to analyze VOCs in this study, with PLA-DA and logistic regression analysis emerging as the most commonly used approaches. However, the majority of studies fail to elucidate the rationale behind selecting a specific machine learning model for analysis, only reporting the highest accuracy value, thereby impacting the reliability of the results. Additionally, studies with small sample sizes may compromise the reported accuracy. Few studies have conducted external validation to affirm the validity and reliability of these findings. Consequently, large, multi-center external validation studies should be conducted in the future to explore the applicability and reproducibility of the results in different study settings and among diverse target populations.

4.1 Limitation

This study has certain limitations. Heterogeneity was observed among studies, potentially attributed to variations in sample media and analytical methods. Some studies exhibited a high risk of bias, with seven showing concern regarding patient selection and ten having applicability concerns in one or two domains. Furthermore, the study included fewer investigations employing both VOC analysis and e-nose technology, thus impeding an accurate evaluation of the complementary effects of the two methods. In addition, VOC combined with FIT approach could increase the detection of colorectal cancer. However, there are no prospective studies evaluating the positive effect on VOC-FIT for screening prior to the onset of CRC.

5 Conclusion

Based on our meta-analysis, VOC analysis and e-nose technology show promise in the detection of CRC. However, several milestones must be achieved in colorectal cancer detection with these two non-invasive methods before clinical implementation. Firstly, for patients presenting with common non-specific symptoms, which may be an early indication of CRC, an exhaled breath test or a urine test or FIT +VOC could serve as screening tool. Secondly, electronic nose could be utilized in primary care units and community healthcare centers for mass screening of various intestinal diseases due to their portability, ease of use, cost-effectiveness, speed, and independence from specialized technicians. Thirdly, the identification of colorectal cancer-specific VOC biomarkers and combinations of biomarkers for colorectal cancer diagnosis is still necessary. This requires comprehensive metabolomics studies to elucidate the production of endogenous VOCs and the metabolic transformation of exogenous VOCs in colorectal cancer, aiding in the identification of VOC markers for cancer. Finally, large, multi-center external validation trials should be conducted to verify the generalizability and reproducibility of the results in different research settings and at different stages of CRC.

Data availability statement

The original contributions presented in the study are included in the article/[Supplementary Material](#), further inquiries can be directed to the corresponding authors.

Author contributions

QW: Formal analysis, Funding acquisition, Supervision, Writing – original draft. YF: Investigation, Project administration, Writing – original draft. ST: Methodology, Writing – review & editing. ZL: Data curation, Project administration, Writing – review & editing. RZ: Data curation, Investigation, Writing – review & editing. YR: Methodology, Project administration, Writing – original draft. YJ: Project administration, Software, Writing – original draft. XH: Supervision, Validation, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This study was supported by the Natural Science Foundation of Sichuan Province [No. 2022NSFSC0670] and [No. 24NSFSC5858]. The fund sponsor had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fonc.2024.1397259/full#supplementary-material>

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