Meta-Analysis of Observational Studies in Epidemiology

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Volatile organic compounds analysis as a potential novel screening tool for colorectal cancer

A systematic review and meta-analysis

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Abstract

The purpose of this meta-analysis was to assess the usefulness of volatile organic compounds (VOC) as a potential novel biomarker for colorectal cancer (CRC).

We systematically searched PubMed, Embase, Web of Science, and Cochrane Library databases for observational studies (published before November 25th, 2019; no language restrictions) comparing the VOC analysis between patients with CRC and healthy controls. We evaluated the pooled sensitivity, specificity, diagnostic odds ratio, positive and negative likelihood ratio, as well as summary receiver operating characteristic curve and area under the curve.

We identified a total of 10 observational studies that included 381 patients with CRC and 436 healthy controls. Bivariate analysis yielded a pooled sensitivity of 0.82 (95% confidence interval [CI] = 0.77–0.86), specificity of 0.79 (95% CI = 0.71–0.85), positive likelihood ratio of 3.8 (95% CI = 2.8–5.3), and negative likelihood ratio of 0.23 (95% CI = 0.17–0.30). The area under the curve was 0.87 (95% CI = 0.84–0.90). The pooled diagnostic odds ratio was 17 (95% CI = 10–28). Sensitivity analysis indicated that the pooled results were stabilized. The Deeks' funnel plot asymmetry test ($P = .41$) suggested no potential publication bias.

Our pooled data confirmed the associations between VOC analysis and CRC, highlighting the usefulness of VOC analysis as a potential novel screening tool for CRC. However, standardization of VOC collection and analysis methods for CRC screening is required in future research.

Abbreviations: AUC = area under the curve, CI = confidence interval, CRC = colorectal cancer, DOR = diagnostic odds ratio, gFOBt = fecal occult blood testing, HC = healthy controls, NLR = negative likelihood ratio, PLR = positive likelihood ratio, QUADAS-2 = quality assessment of diagnostic accuracy studies 2, SROC = summary receiver operating characteristic, VOC = volatile organic compounds.

Keywords: colorectal cancer, meta-analysis, screening, volatile organic compounds

1. Introduction

Colorectal cancer (CRC) is one of the leading causes of cancer-related death in the Western world, with an estimated incidence of 43.5 per 100,000 in 2012 and mortality of 19.5 per 100,000 in Europe, which carries a significant financial burden for the National Health Service.[1] Therefore, feces-based screening tool has been applied to identify patients whether to perform colonoscopy.[2] Guaiac-based fecal occult blood testing (gFOBt) relies on the bleeding from neoplastic lesions, which could identify people with more than 10 mL rectal blood loss daily, whereas it is not specific for human hemoglobin and also fails to take into account blood that may originate from other sources such as hemorrhoids and peptic ulcers.[3] In general, sensitivity and specificity of gFOBt are low and variable, thus gFOBt is likely to be replaced by fecal immunochemical testing (FIT) that provides both qualitative and quantitative results and detects twice as many advanced cancers as guaiac testing.[4] Notably, previous observational studies from Italy have demonstrated that FIT contributes to a reduction in CRC-related mortality.[4,5] However, there is considerable heterogeneity in FIT devices for detection of CRC as well. Therefore, it is critical to develop a new non-invasive technology with enhanced sensitivity and specificity to screen CRC.[6]

Volatile organic compounds (VOC) reflect alterations in the pathophysiology and body metabolism processes, which have

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WZ and JT contributed equally to this work.

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been studied in various types of cancers.[7,8] Cancer-associated VOC are released from the affected tissue to feces or blood circulation by which the VOC are exhaled in breath or excreted in urine.[7] Several studies have reported VOC emitted from different substrates, including feces, urine, exhaled breath, and blood, could act as biomarkers for CRC.[9–13] In this sense, VOC analysis is expected to become an appealing population-based screening tool for CRC as a relatively novel and non-invasive testing.

In view of these compelling rationales, a series of clinical studies have assessed VOC analysis for screening CRC. Unfortunately, there was no diagnostic meta-analysis to integrate these results and derive conclusions. Recognizing that individual study might be unable to obtain sufficient data to affect practice on their own, we sought to objectively assess the potential role of VOC analysis as a new screening tool for CRC. We; therefore, did a systematic review and meta-analysis of observational studies to compare CRC patients with healthy controls (HC) on the VOC analysis.

2. Materials and methods

This meta-analysis was conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[14] The MOOSE checklist is included in Supplemental Digital Content (Table S1, http://links.lww.com/MD/E479). All analyses were based on previous published studies, and thus no ethical approval and patient consent are required.

2.1. Search strategy

We selected related studies published before November 25th, 2019, by searching Embase, PubMed, Web of Science, and Cochrane Library databases. All relevant articles were retrieved without language or geographic limitations. We used the following combined text and MeSH terms: "volatile organic compounds" and "colorectal cancer." The complete search used for PubMed was: ((Volatile organic compounds [MeSH Terms] OR Compounds, Volatile Organic [Text Word] OR Organic Compounds, Volatile [Text Word]) AND (Colorectal Neoplasms [MeSH Terms] OR Neoplasms, Colorectal [Text word] OR Colorectal Neoplasm [Text word] OR L Neoplasm, Colorectal [Text word] OR Colorectal Tumors [Text word] OR Colorectal Tumor [Text word] OR Tumor, Colorectal [Text word] OR Tumors, Colorectal [Text word] OR Colorectal Carcinoma [Text word] OR Carcinoma, Colorectal [Text word] OR Carcinomas, Colorectal [Text word] OR Colorectal Carcinomas [Text word] OR Colorectal Cancer [Text word] OR Cancer, Colorectal [Text word] OR Cancers, Colorectal [Text word] OR Colorectal Cancers [Text word])). Furthermore, the reference lists of relevant articles were manually examined to determine additional potentially related studies. The searches were carried out independently by 2 investigators (WCZ, JXT).

2.2. Eligibility criteria

Studies were included if they met the following criteria:

(1) observational studies: cross-sectional, case-control, or prospective designs;
(2) population: CRC patients diagnosed in according with colonoscopy and established diagnostic systems (eg, International Union Against Cancer tumor node metastasis staging system for CRC) and HC undergoing colonoscopy;
(3) studies that provided sufficient information to construct the 2×2 contingency table, including false-, true-positive or false-, true-negative;
(4) studies that analyzed endogenous VOC within feces, blood, exhaled breath, or urine to screen or assess CRC.

The exclusion criteria were

(1) duplicate publications;
(2) letters or review articles;
(3) cadaver subjects or animal studies;
(4) studies of low quality using quality assessment of diagnostic accuracy studies 2 (QUADAS-2) tool.

2.3. Data extraction and quality assessment

Two investigators (WCZ, JXT) independently reviewed the study titles and abstracts, and extracted data from the articles. Disagreements were resolved by consensus and discussion with the corresponding authors (JL, SYT). We extracted the following study characteristics from each eligible study, including name of first author, publication year, location, number of participants, mean age, cancer stages, VOC sources, and analytical platforms. Each investigator also recorded and calculated the number of false-, true-positives and false-, true-negatives. We have contacted the corresponding authors if further information was needed. If no response was received, the study was excluded from the meta-analysis. The QUADAS-2 tool is an evidence-based quality assessment tool for systematic reviews of diagnostic accuracy studies, which assess the risk of bias and concerns regarding applicability on 14 items (each of which is scored as yes, no, or unclear).[15] The QUADAS-2 sheet was performed by RevMan5.3 according to 4 domains including patient selection, index test, reference standard, as well as flow and timing.

2.4. Statistical Analysis

The numbers of false-, true-positives or false-, true-negatives in patients with CRC and HC were used to calculate sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR)[16] and 95% confidence interval (CI). Based on validated methods of Harbord et al,[17] bivariate meta-analyses were conducted to generate pooled point estimates of the summary receiver operating curve (SROC) of VOC analysis.[18] The software used for this analysis was the custom-designed statistical package MIDAS in Stata MP 16.0. An area under the summary receiver operating curve (AUC) was obtained directly from the MIDAS output.[19,20] The Spearman correlation coefficient calculated by MetaDiSc1.40 was used to explore the threshold effect between the pooled sensitivity and 1-specificity. A P-value less than .05 indicated the existence of a threshold effect. Statistical heterogeneity caused by nonthreshold effects was tested by the Q test and I^2 test. A P-value less than .1 for the Q test and an I^2 value greater than 50% were considered to indicate significant heterogeneity. If the significant heterogeneity could not be eliminated, a random-effects model was used.[21] The stability of the results was assessed using sensitivity analysis, which omits single study each time to evaluate the influence of each study on the pooled results. Publication bias was assessed using Deeks funnel plot asymmetry test.[22] A P-value less than .10 indicated obvious publication bias. Subgroup analysis and meta-regression analysis were performed to explore the sources of heterogeneity according to

the characteristics of the included articles. We used Stata MP 16.0, Revman 5.3, and MetaDiSc1.40 statistical software for all statistical analyses.

3. Results

3.1. Overall characteristics of selected studies and quality assessment

Our databases retrieved 287 articles, of which 74 were excluded by EndnoteX9 because of duplication. We excluded 199 articles by screening through the titles and abstracts. After a full text review, we excluded a further 9, leaving 10 studies for inclusion.[10–12,23–29] As the study conducted by Altomare et al was designed in 2 phases,[10] we analyzed 11 datasets (with data for 817 participants). The 10 studies were all published between 2012 and 2019. The flow diagram of the search procedure was shown in Figure 1 and the characteristics of the included studies were described in Table 1. Among these studies, 8 were carried out in Europe,[10–12,24,25,27–29] and 2 in Asia.[23,26] Patients with CRC had mean age of 66.6 (60–72.7) years. These studies had a tendency to include patients with early and advanced cancer stages, ranging from 0 (carcinoma in situ) to IV, although cancer stage was not reported in 5 studies.[12,24,25,27,29] Concerning the VOC sources, 4 studies measured VOC patterns in fecal gas,[12,24–26] 3 in exhaled breath,[10,23] and 4 in urine.[11,27–29] Concerning the analytical platforms, 3 studies used the electronic nose,[23,25,29] 2 studies (3 datasets) used gas chromatography coupled with mass spectrometry,[10,24] and 5 studies used other analytical platforms, including field asymmetric ion mobility spectrometer, selected ion flow tube mass spectrometry, gas chromatography coupled with ion mobility spectrometry, gas chromatography using a sulfur chemiluminescence detector, and gas chromatography using a thermal conductivity detector.[11,12,26–28]

Assessment of biases and applicability on outcomes utilizing QUADAS-2 are detailed in Figure 2. The absence of selection criteria and a validation set for the index test might be the major sources of bias. There was no significant applicability concern for index test, reference standard, as well as flow and timing, which suggests that the overall quality of the included studies was moderately high.

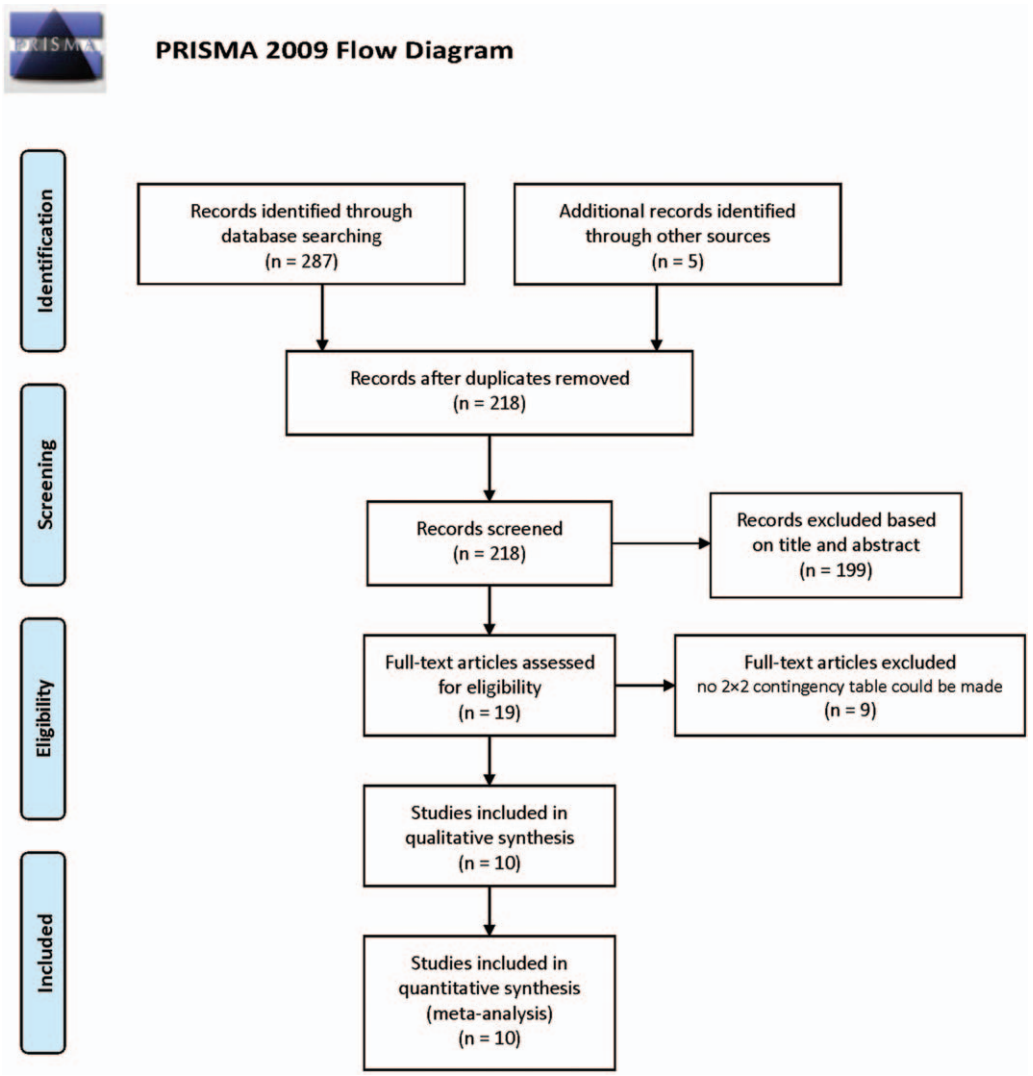

Figure 1. Flow diagram for identifying eligible studies.

Table 1

Baseline characteristics of included studies.

First author	Year	Location	Number of participants		Mean age (yr)		Cancer stage	VOC sources	Analytical platform	Sensitivity (%)	Specificity (%)
			CRC	HC	CRC	HC					
Altomare, D. F.(1)[10]	2012	Italy	37	41	63	47	I-IV	Exhaled breath	GC-MS	86	83
Altomare, D. F.(2)[10]	2012	Italy	15	10	67	56	I-IV	Exhaled breath	GC-MS	80	70
Amal, H.[23]	2015	Israel	20	36	66	60	0-IV	Exhaled breath	E-nose	85	94
Arasaradnam, R. P.[11]	2014	UK.	83	50	60	47	I-IV	Urine	FAIMS	88	60
Batty, C. A.[12]	2015	UK.	31	31	60–69	NR	feces	SIFT-MS	72	78	
Bond, A.[24]	2019	UK.	21	60	72.7	61.9	NR	Feces	GC-MS	87.9	84.6
de Meij, T. G.[25]	2013	Netherlands	40	57	69	38	NR	feces	E-nose	85	87
Ishibe, A.[26]	2018	Japan	30	26	68	NR	I-IV	Feces	GC/SCD;GC/TCD	90	57.7
Mozdiak, E.[28]	2019	UK.	10	24	67	NR	I-IV	Urine	GC–IMS	80	83
McFarlane, M.[27]	2019	UK.	56	82	65.4	55.4	NR	Urine	FAIMS	69	69
Westenbrink, E.[29]	2014	UK.	39	18	70	41	NR	Urine	E-nose	78	79

CI = confidence intervals, CRC = colorectal cancer, E-nose = electronic nose, FAIMS = field asymmetric ion mobility spectrometer, FN = false negatives, FP = false positives, GC/SCD = gas chromatography using a sulfur chemiluminescence detector, GC/TCD = gas chromatography using a thermal conductivity detector, GC-IMS = gas chromatography coupled with ion mobility spectrometry, GC-MS = gas chromatography coupled with mass spectrometry, HC = healthy controls, NR = not reported, SIFT-MS = selected ion flow tube mass spectrometry, TN = true negatives, TP = true positives.

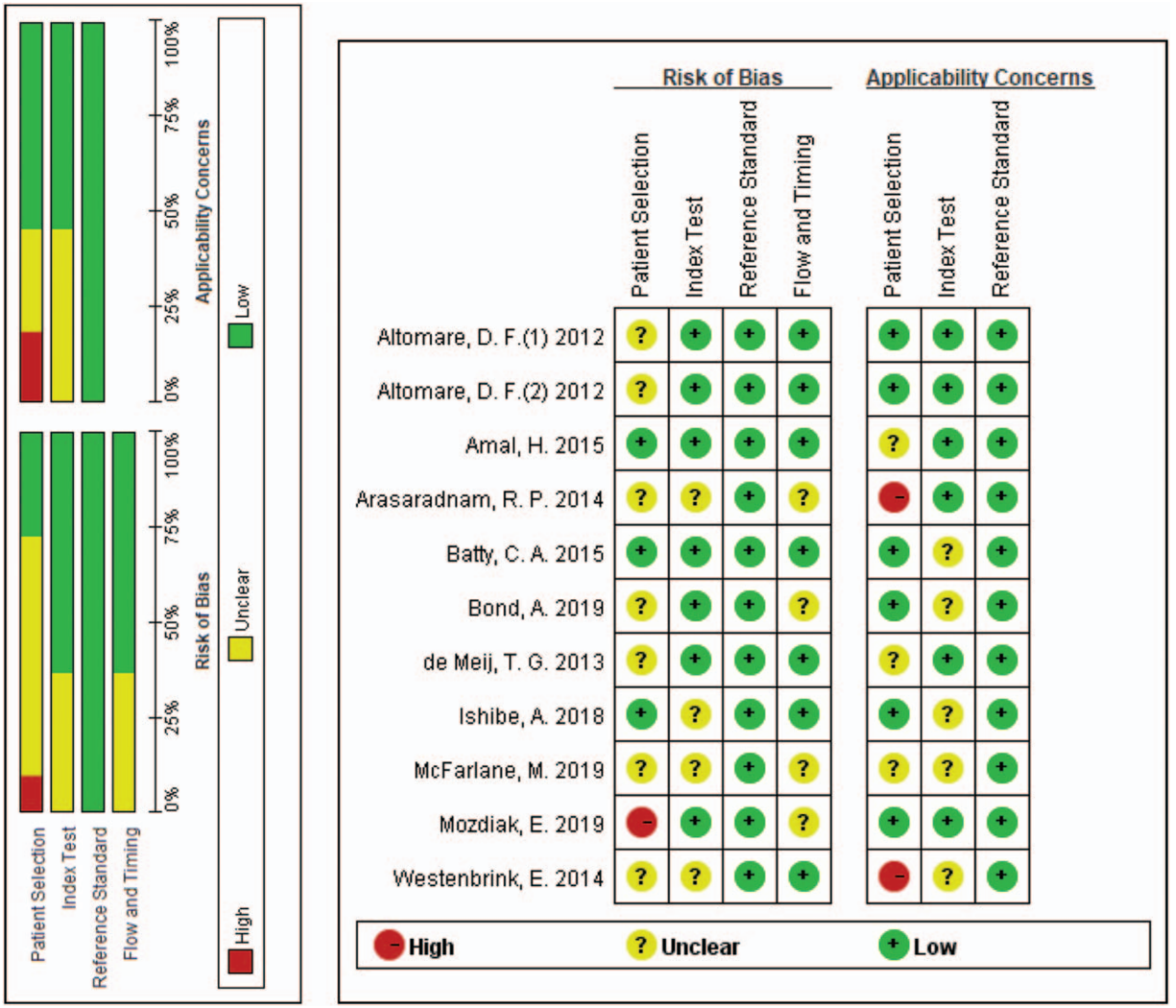

Figure 2. Quality assessment of included studies by using the QUADAS-2 tool: (A) Risk of bias graph: review authors' judgments about each item presented as percentages across all included studies; (B) Risk of bias summary: review authors' judgments about each risk of bias item for each included study. QUADAS-2 = quality assessment of diagnostic accuracy studies 2.

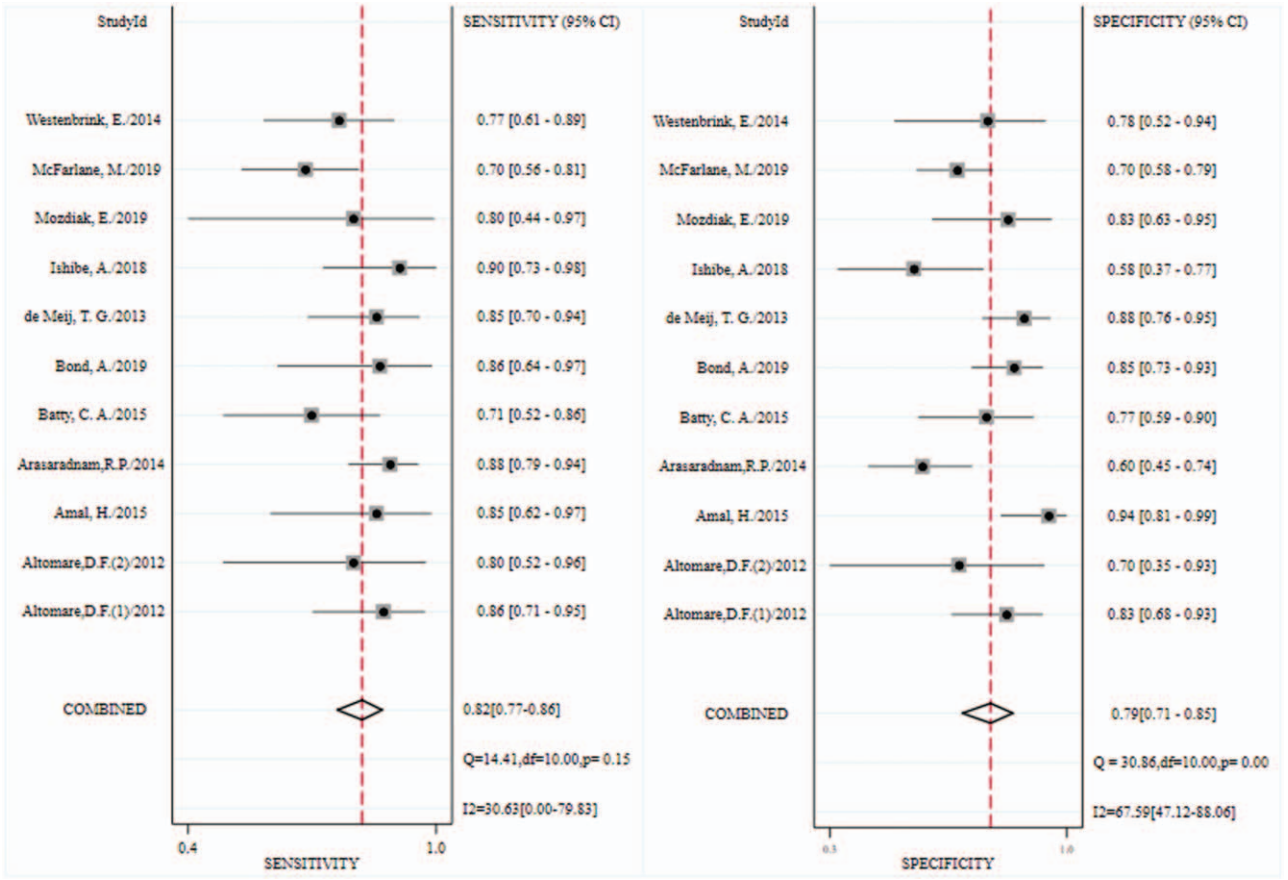

Figure 3. Forest plots of the sensitivity and specificity for VOC analysis in the diagnosis of colorectal cancer. Different heterogeneity was shown for pooled sensitivity and specificity (I^2 = 30.63% and I^2 = 67.59%, respectively). VOC = volatile organic compounds.

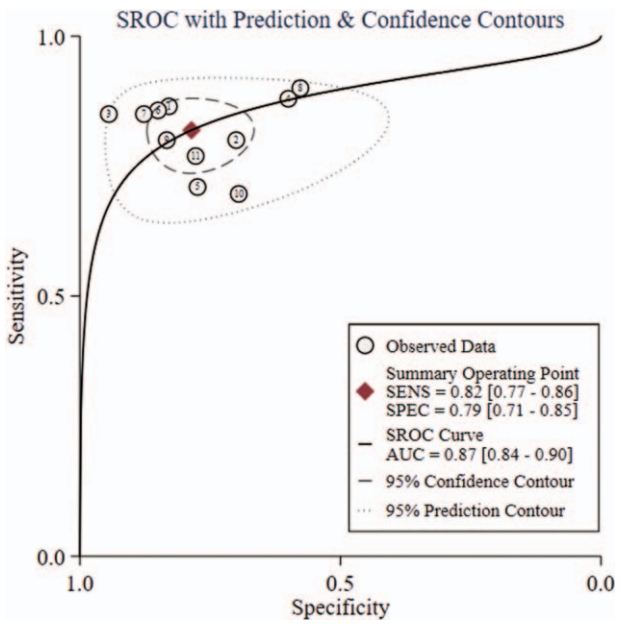

Figure 4. Summary receiver operating characteristic graph of included studies.

3.2. Diagnostic accuracy

The indicators applied to estimate diagnostic accuracy consist of sensitivity, specificity, PLR, NLR, and DOR. As shown in Figure 3, pooled sensitivity was 0.82 (95% CI = 0.77–0.86) and specificity was 0.79 (95% CI = 0.71–0.85). Heterogeneity obviously existed in the pooled specificity (I^2 = 67.59%, P = .00), while the pooled results of sensitivity were stable (I^2 = 30.63%, P = .15). PLR, NLR, and DOR were 3.8 (95% CI = 2.8–5.3), 0.23 (95% CI = 0.17–0.30), and 17 (95% CI = 10–28), respectively.

In addition to the calculated data, the satisfactory diagnostic performance of VOC analysis for distinguishing CRC patients from HC was manifested in the SROC curve. The AUC was 0.87 (95% CI = 0.84–0.90) (Fig. 4). Statistically significant heterogeneity exists among the studies (likelihood ratio test (LRT)-I^2 = 63%, 95% CI = 16–100). Distribution of accurate estimator points in the plots did not show a "shoulder arm" pattern, indicating no evidence of a threshold effect, which was consistent with the result of Spearman correlation coefficient (P = .821, Supplemental Digital Content [Table S2, http://links.lww.com/MD/E480]).

3.3. Subgroup analysis and meta-regression

Subgroup analysis was performed based on the VOC sources, and the pooled results showed that statistically significant between-study heterogeneity still existed in specificity (Table 2).

Table 2

Subgroup analysis based on volatile organic compound sources.

VOC sources	Datasets, n	Sample Size		Sensitivity (95%CI)	*P* of χ^2	I^2	Specificity (95%CI)	*P* of χ^2	I^2
		CRC	HC						
Exhaled breath	3	71	88	0.85 [0.74–0.92]	.85	0.0%	0.86 [0.78–0.93]	.10	**57.1%**
Feces	4	122	174	0.83 [0.75–0.89]	.25	27.9%	0.81[0.74–0.86]	.02	**70.5%**
Urine	4	188	174	0.80 [0.73–0.85]	.06	**58.8%**	0.70 [0.62–0.76]	.17	40.8%

Boldface values indicate statistical significance of the 95% confidence limit.

CI = confidence intervals, CRC = colorectal cancer, HC = healthy controls, VOC = volatile organic compound.

Next, meta-regression analysis to assess covariates, including "location (Europe)," "mean age," "VOC sources (Feces)," and "analytical platform (E-nose)," was conducted to find the source of heterogeneity. Pooled results demonstrated that analytical platforms and VOC sources might be the major sources of heterogeneity (Supplemental Digital Content [Table S3, http://links.lww.com/MD/E481]).

3.4. Sensitivity analysis and publication bias

A sensitivity analysis was performed to determine if there was undue influence exerted by a single study on the results of the combined studies, suggesting the influence of each study on the pooled results was acceptable and the pooled results were robust to some extent (Supplemental Digital Content [Fig. S1, http://links.lww.com/MD/E482]). The Deeks' regression test of asymmetry was carried out to assess the potential publication bias ($P = .41$), which indicated the absence of publication bias in our meta-analysis (Supplemental Digital Content [Fig. S2, http://links.lww.com/MD/E483]).

4. Discussion

Diagnosis of CRC depends on the invasive and expensive colonoscopy which is usually performed after a positive screening test. Unfortunately, existing screening tests, including gFOBt and FIT, lack stable specificity and sensitivity; thus many unnecessary colonoscopies are carried out.[30–33] Increasing evidence has demonstrated the associations between specific VOC profiles and various cancers, including mesothelioma, melanoma, hepatocellular carcinoma, lung and breast cancer.[34–37] Cancer-associated VOCs are directly excreted from the affected organ and tissue to feces, urine, saliva, semen, tear, as well as vaginal, nasal and nipple discharges, which can also enter the blood circulation and then are excreted in urine, exhaled in breath, or emitted from the skin.[7] Metabolite profiling of VOC in human colon cell lines provides biochemical phenotyping of normal and neoplastic colon tissue, as well as differences in the volatile metabolome at different disease stages.[38,39] Therefore, numerous studies have focused on whether the VOC testing is expected to be a potential new screening tool for CRC.

Pooled results including sensitivity, specificity, DOR, PLR, and NLR have estimated the diagnostic accuracy in our meta-analysis. The pooled sensitivity and specificity were 0.82 and 0.79, respectively. In addition, the SROC curve was used to assess the overall diagnostic performance, and the AUC calculated for the SROC curves was 0.87, which indicates a moderate (AUC: 0.7–0.9) diagnostic value of VOC analysis. DOR is a single indicator of test accuracy and it was 17 (DOR >10) in our included studies, which suggests good discriminatory test performance. Furthermore, likelihood ratios and post-test probabilities indicate information about the likelihood that a patient with a positive or negative test result actually has CRC or not. The PLR in our pooled data was 4, which implies that a person with CRC is 4-times more likely to have a positive test result than a healthy person. Given a pre-test probability of 20%, the post-test probability for a positive test result is 49%. Likewise, a NLR of 0.23 reduces the post-test probability to 5% for a negative test result (likelihood ratio positive (LRP) <10, likelihood ratio negative (LRN) >0.1, Supplemental Digital Content [Fig. S3, http://links.lww.com/MD/E484 and Fig. S4, http://links.lww.com/MD/E485]). These results suggest that the VOC analysis provides a promising and stable approach to the screening of CRC, but not a tool to make a CRC diagnosis alone.

The sources of heterogeneity include threshold and non-threshold effects. In our meta-analysis, distribution of accurate estimator points in the plots did not show a "shoulder arm" pattern, indicating no evidence of a threshold effect. We performed subgroup analysis and meta-regression to explore the sources of heterogeneity caused by nonthreshold effects and found that analytical platforms and VOC sources might cause the heterogeneity. Although significant heterogeneity was observed in the pooled specificity, the results were shown to be stabilized by sensitivity analysis.

There are several strengths in our meta-analysis. First of all, this is the first meta-analysis to quantitatively analyze the VOC as a potential new biomarker for CRC. Existing systematic reviews have revealed the relations between exhaled breath VOC and cancers,[40] however, little available information about CRC and other VOC sources was reported. Second, there was no evidence of a threshold effect in our meta-analysis, and no statistically significant between-study heterogeneity was found in pooled sensitivity. Therefore, findings yielded in our study are credible to some extent. Third, we conducted subgroup analysis and meta-regression and found that analytical platforms and VOC sources might cause the overall heterogeneity. Finally, 2 reviewers conducted comprehensive literature searches and quality assessments independently, which minimizes the risk of bias and makes the results more reliable.

A limitation of this analysis is that most available studies to date are case-control and cross-sectional studies. Cancer-specific biomarkers (eg, VOC) need to be used in prospective longitudinal studies that recruit patients with CRC to understand what extent the VOC are associated with disease severity. Second, limited available studies and participants are included in our meta-analysis, which may reduce the statistical power. More clinical studies with larger sample sizes need to be carried out in the future. Third, different VOC sources and analytical platforms are included in our meta-analysis, which might be the major sources of heterogeneity. Finally, this systematic review is not registered, and thus there may be minor biases, but it was still strictly performed in accordance with the MOOSE guidelines.

Previous meta-analysis highlighted the non-invasive nature of breath testing which enhances patient acceptability.[40] However, the composition of exhaled breath is affected by many factors, such as smoking, diet, and lung disease. Indeed, in addition to breath, lots of VOC in various bodily fluids and metabolic wastes are generated from a pure exogenous origin, which are neither human nor bacterial metabolites. These compounds might be related to medicines ingested, occupational exposure, household chemicals, environmental pollutants, and fuel combustion.[41] Therefore, it is critical to confirm which source of VOC is able to provide more accurate diagnosis results. Our study is the first one to explore the problem and perform a subgroup analysis based on the different sources. Unfortunately, the number of available studies to date was relatively limited and we failed to get the pooled area under the SROC curve of exhaled breath VOC.

Furthermore, current studies lack the standardization of VOC collection and analysis, which might be related to the potential heterogeneity of our study. The results of VOC testing depend on the method of sample collection and test environment. Although no evidence of a threshold effect was observed in our analysis, it is necessary to establish test thresholds for separating patients with CRC at different stage before embarking on masked validation studies in future research. In addition, although it is essential to explore potential novel technologies in VOC analysis, the reproducibility of results and reliability of instruments are also the future directions.

5. Conclusions

In conclusion, pooled results in our meta-analysis confirmed the differences in VOC analysis between CRC patients and HC, which suggest the usefulness of VOC analysis as a potential new screening tool for CRC. However, standardization of VOC collection and analysis methods for colorectal cancer screening is needed in the future research.

Author contributions

Conceptualization: Wen-Chuan Zhou, Jin-Xin Tao, Jin Li.
Formal analysis: Wen-Chuan Zhou, Jin-Xin Tao.
Funding acquisition: Jin Li, Shao-Yu Tao.
Methodology: Jin Li.
Supervision: Shao-Yu Tao.
Writing – original draft: Wen-Chuan Zhou, Jin-Xin Tao, Jin Li.
Writing – review & editing: Wen-Chuan Zhou, Jin-Xin Tao, Jin Li, Shao-Yu Tao.

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