# Diagnostic Ability of Volatile Organic Compounds in Digestive Cancer: A Systematic Review With Meta-Analysis

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**ABSTRACT**

**BACKGROUND:** Volatile organic compounds (VOCs) have been involved in cancer diagnosis via breath, urine, and feces. We aimed to assess the diagnostic ability of VOCs on digestive cancers.

**METHODS:** We systematically reviewed prospective clinical trials evaluating VOCs' diagnostic ability on esophageal, gastric, colorectal, hepatic, and pancreatic cancer (PC). Databases including PubMed and Ovid-Medline were searched.

**RESULTS:** A total of 35 trials with 5314 patient-times qualified for inclusion. The pooled sensitivity of VOCs diagnosing gastroesophageal cancer from healthy controls is 0.89 (95% confidence interval [CI]: 0.82-0.94), the pooled specificity is 0.890 (95% CI: 0.84-0.93), and area under the curve (AUC) of the summary receiver operating characteristic curve is 0.95 (95% CI: 0.93-0.95). The pooled sensitivity of VOCs diagnosing colorectal cancer from heathy controls is 0.92 (95% CI: 0.85-0.96), the pooled specificity is 0.88 (95% CI: 0.77-0.94), and the AUC is 0.96 (95% CI: 0.94-0.97). The pooled sensitivity of VOCs distinguishing gastrointestinal (GI) cancer from precancerous lesions is 0.84 (95% CI: 0.67-0.92), the pooled specificity is 0.74 (95% CI: 0.43-0.91), and the AUC is 0.87 (95% CI: 0.84-0.89). The pooled sensitivity of VOCs diagnosing hepatocellular carcinoma is 0.68 (95% CI: 0.52-0.81), the pooled specificity is 0.81 (95% CI: 0.47-0.96), and the AUC is 0.78 (95% CI: 0.74-0.81). The pooled sensitivity of VOCs diagnosing PC is 0.88 (95% CI: 0.80-0.93), the pooled specificity is 0.82 (95% CI: 0.62-0.93), and the AUC is 0.92 (95% CI: 0.89-0.94).

**CONCLUSIONS:** Volatile organic compounds have potential role in diagnosing GI cancer with comparatively high sensitivity, specificity, and AUC (PROSPERO registration number: CRD42021260039).

**KEYWORDS:** Volatile organic compounds, digestive cancer, gas biopsy, diagnosis, meta-analysis

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## Introduction

Volatile organic compounds (VOCs) are carbon-based stable metabolites and generate in physiological and pathophysiological conditions.[1,2] Exogenous volatiles can be inhaled from the external environment, produced following the oral ingestion of food and derived from smoking cigarettes. Endogenous VOCs are usually produced from the destruction of cells caused by direct or indirect oxidative stress and inflammation.[3,4] For example, exhaled small-chain hydrocarbons are produced by lipid peroxidation in oxidative stress.[3] Sampling and preconcentration by sorbent tubes/traps and solid-phase microextraction, in combination with gas chromatography (GC) or GC-mass spectrometry(MS), are usually used to analyze VOCs. Real-time analysis can be performed using proton transfer reaction-time-of-flight-MS, selected ion flow tube-MS, ion mobility spectroscopy, laser spectrometry, photoacoustic spectroscopy or sensors, and sensor arrays without pre-concentration or storage.[5] Raw data further need to be processed using machine learning or deep learning tools including principal component analysis, canonic discriminant analysis, independent component analysis, discriminant factorial analysis, partial least squares analysis, artificial neural networks, support vector machine, and hierarchical cluster analysis to establish a detecting model after validation.[6] The VOCs are involved in changed metabolic processes of body cells or colonizing microbiota and may be considered as an individual "odor fingerprint" to identify diseases including infectious diseases, metabolic diseases, genetic disorders, and other kinds of diseases such as cancer, pulmonary diseases, cardiovascular diseases, and digestive diseases.[7-10] In this article, we systematically reviewed related research on the aspect of cancer of upper and lower digestive tract and 2 main digestive organs (liver and pancreas), and hoped to provide more comprehensive information and status quo of VOCs in this field.

## Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol of this study is documented on PROSPERO (CRD42021260039). Two authors independently searched the term combination of

* The first two authors contributed equally to this article.

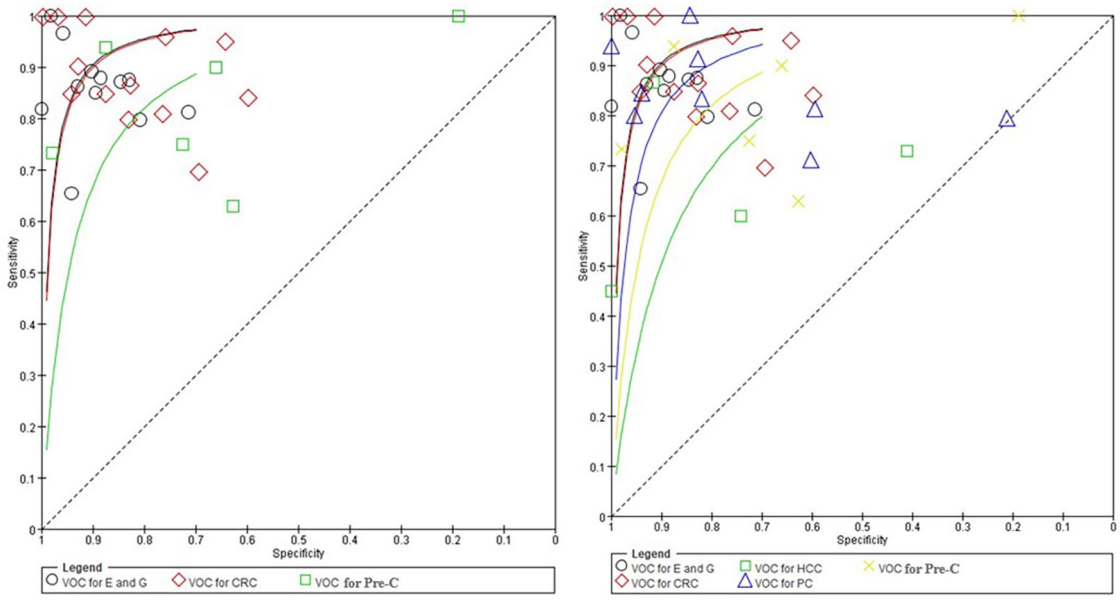


**Figure 1.** SROC curve of VOCs diagnosing digestive cancer. The similar diagnostic ability of VOCs on upper GI cancer (E and G cancer) and lower GI cancer (CRC), better than that on precancerous lesions of digestive tract. The AUC on diagnosing HCC is the weakest. AUC indicates area under the curve; CRC, colorectal cancer; E and G, esophageal and gastric cancer; GI, gastrointestinal; HCC, hepatocellular carcinoma; PC, pancreatic cancer; pre-C, precancerous lesion; SROC, summary receiver operating characteristic curve; VOCs, volatile organic compounds.

VOCs and targeted cancer in PubMed and Ovid-Medline (updated to May 25, 2020). The details of search strategy are described in Supplemental File S2.

### *Inclusion and exclusion criteria*

The inclusion criteria of related studies on VOCs diagnosing esophageal, gastric, colorectal, hepatic, and pancreatic cancer (PC) were as follows: (1) the establishment of the diagnosis of esophageal/gastric/colorectal/hepatocellular/PC; (2) clinical trials of VOCs diagnosing these cancers. The exclusion criteria were as follows: (1) no specific experimental details were provided, (2) commentary/review articles rather than research articles, (3) not clinical research articles, (4) non-English research, (5) other cancers or other samples.

### *Data extraction and quality assessment*

Two reviewers independently extracted data from the included trials using prespecified data collection forms. Discrepancies were resolved by discussion. For all trials included in the analysis, we collected and analyzed data relating to the characteristics of the trial, numbers of patients, characteristics of patients and their disease, and outcomes reported. The extracted information of included trials is demonstrated in Supplemental File S1. Cochrane's Review Manager (RevMan) 5.3 was used to generate the general sensitivity and specificity plots (Figure 1) and forest plots (Figure 2). We generated pooled sensitivity, specificity, positive/negative likelihood ratio, diagnostic score, diagnostic odds ratio, area under the curve (AUC) of summary receiver operating characteristic curve (SROC), $I^2$, and publication bias in Stata 12.1 shown in Figure 3 and Table 1.

### *Statistical analysis*

The statistical analysis was performed using RevMan software version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration 2014, Copenhagen) and Stata 12.1 (Stata Corporation, College Station, Texas). We estimated sensitivity, specificity, and AUC of SROC with 95% confidence intervals (CIs) for outcomes. Data were pooled using the random effects model to give a more conservative estimate, allowing for any heterogeneity between studies. Heterogeneity was expressed as the $I^2$ statistic, and $I^2 \geqslant 50\%$ indicated significant heterogeneity.

## Results

### *Description of the included studies*

There are 35 articles and 5314 patient-times which means VOCs of one patient can be compared with different controls at least one time. (1) In all, 12 papers are about esophageal (E) and gastric (G) cancer, 11 of which are differentiated with non-precancerous lesions, 1 with precancerous lesions. And 1 of the 11 papers contains 2 sets of complete data. (2) Of the 13 colorectal cancer (CRC) articles, CRC in 12 of 13 are differentiated from non-precancerous lesions, 1 of 12 contains 2 sets of complete data, and 4 of 12 contain data on the differentiation of adenomas. And 1 of 13 is on CRC differentiated from adenomas. Therefore, 12 sets of data from 11 E and G articles differentiated with non-precancerous lesions and 13 sets of data from 12 CRC articles differentiated with non-adenoma were included. And 1 G + 5 CRC differentiated from precancerous lesions were included. Among 3 hepatocellular carcinoma (HCC) articles, 1 contains 2 sets of data,

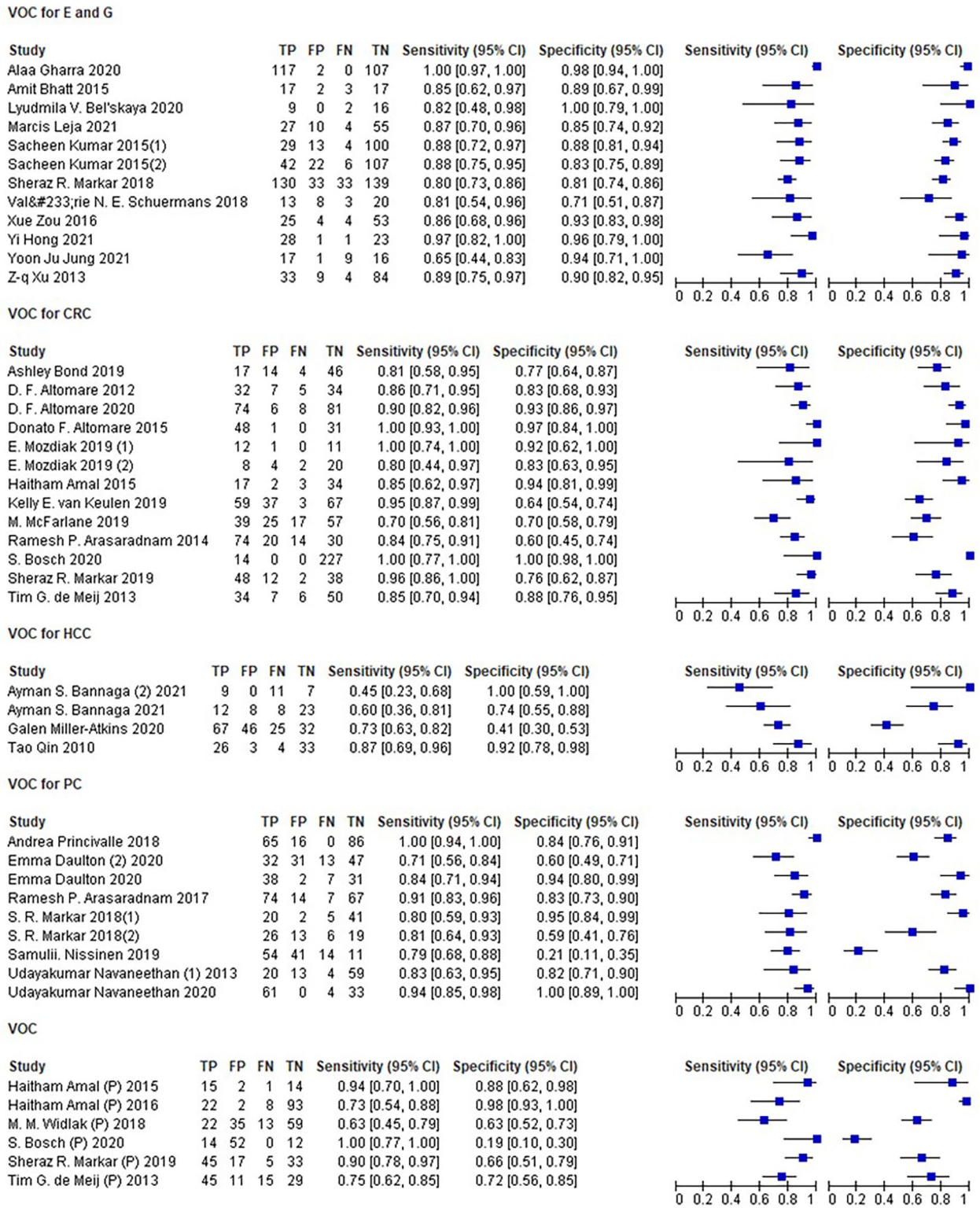


**Figure 2.** Forest plot of VOCs' diagnostic ability. CRC indicates colorectal cancer; E and G, esophageal and gastric cancer; HCC, hepatocellular carcinoma; PC, pancreatic cancer; VOCs, volatile organic compounds.

so there are 4 sets of data in total. There are 7 PC articles, 2 of which have 2 sets of data, so there are 9 sets of PC in total. A total of 44 sets of complete data from 35 articles were included in the final meta-analysis. The detailed information is shown in Supplemental File S1.

### *VOCs diagnosing gastrointestinal tract cancer: esophagogastric cancer and CRC*

The VOCs were detected from samples of both cancer and non-cancer tissue,[11,12] urine,[13] plasma,[14] saliva,[15] bacteria culture,[16] and breath[17-22] and achieved more than 0.9 AUC of SROC to

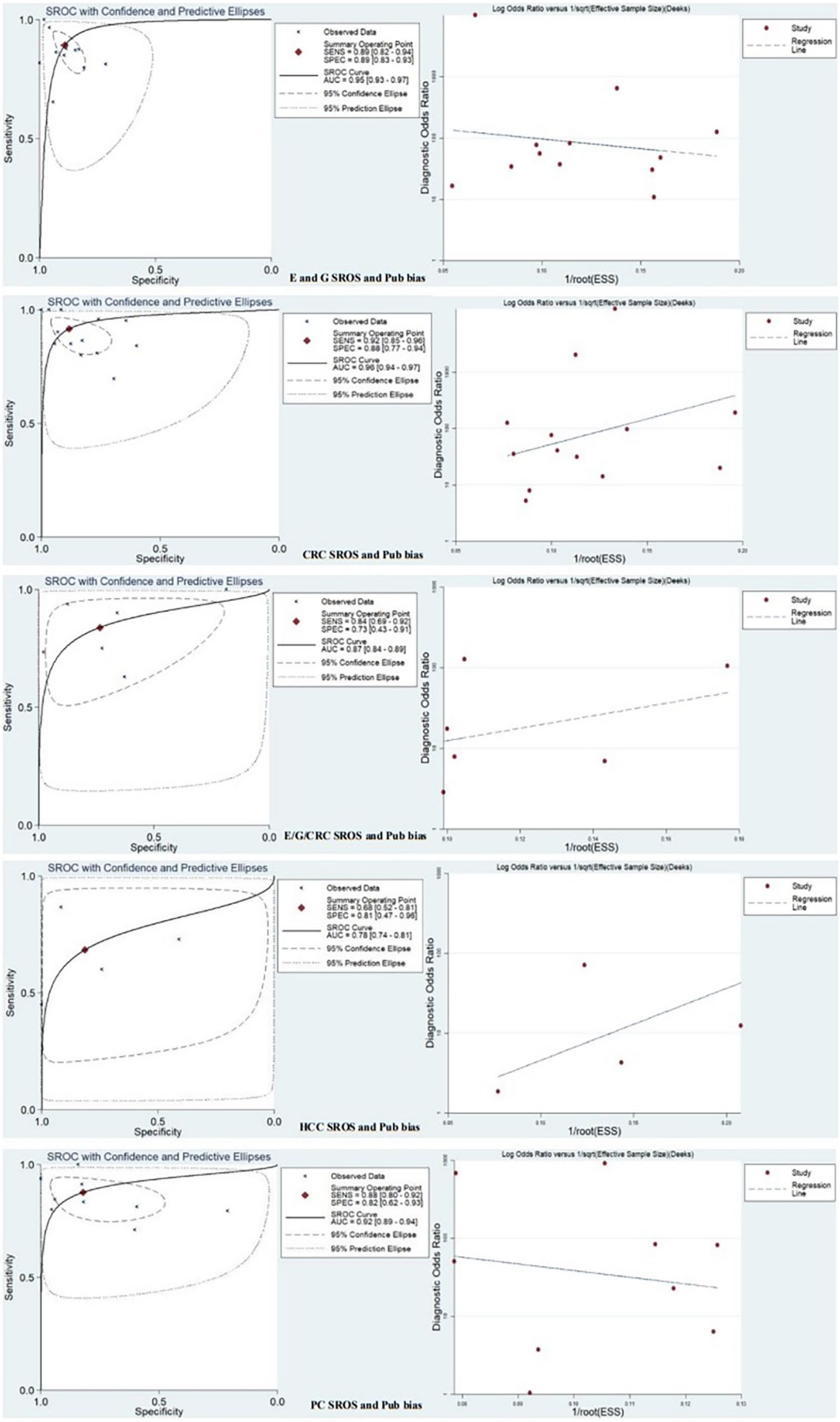


**Figure 3.** SROC curve and publication bias. There is no publication bias. AUC indicates area under the curve; CRC, colorectal cancer; E and G, esophageal and gastric cancer; HCC, hepatocellular carcinoma; SROC, summary receiver operating characteristic curve.

**Table 1.** Diagnostic ability of VOCs.

| PARAMETER (ESTIMATE/95% CI) | E AND G C | CRC | E/G/CRC FROM PRE-C | HCC | PC |
|---|---|---|---|---|---|
| Sensitivity | 0.892 (0.82-0.94) | 0.92 (0.85-0.96) | 0.84 (0.67-0.92) | 0.683 (0.52-0.81) | 0.88 (0.80-0.93) |
| Specificity | 0.89 (0.84-0.93) | 0.88 (0.77-0.94) | 0.735 (0.43-0.91) | 0.81 (0.47-0.96) | 0.82 (0.62-0.93) |
| Positive likelihood ratio | 8.10 (5.08-12.94) | 7.82 (3.73-16.36) | 3.16 (1.29-7.76) | 3.68 (1.02-13.32) | 4.91 (2.03-11.89) |
| Negative likelihood ratio | 0.121 (0.07-0.22) | 0.10 (0.05-0.19) | 0.22 (0.11-0.43) | 0.39 (0.24-0.64) | 0.15 (0.08-0.27) |
| Diagnostic score | 4.20 (3.21-5.19) | 4.40 (3.10-5.70) | 2.66 (1.44-3.89) | 2.25 (0.63-3.86) | 3.48 (2.12-4.84) |
| Diagnostic odds ratio | 66.79 (24.77-180.08) | 81.45 (22.281-297.74) | 14.33 (4.21-48.79) | 9.45 (1.87-47.67) | 32.51 (8.34-126.73) |
| AUC of ROC | 0.95 (0.93-0.95) | 0.96 (0.94-0.97) | 0.87 (0.84-0.89) | 0.78 (0.74-0.81) | 0.92 (0.89-0.94) |
| *Q* (chi-square) | 0.64 (*P* = .364) | 11.38 (*P* = .002) | 41.39 (*P* = .000) | 14.54 (*P* = .000) | 24.72 (*P* = .000) |
| $I^2$ | 0.00 | 82.42 | 95.17 | 86.25 | 91.91 |
| Pub bias (p>\|t\|) | 0.73 | 0.33 | 0.58 | 0.44 | 0.67 |

AUC, area under the curve; CI, confidence interval; CRC, colorectal cancer; E and G C, esophageal and gastric cancer; HCC, hepatocellular carcinoma; PC, pancreatic cancer; pre-C, precancerous lesion; Pub bias, publication bias; ROC, receiver operating characteristic curve; VOCs, volatile organic compounds.

diagnosing E and G cancer and differentiating them from healthy controls or benign upper gastrointestinal (GI) diseases via different models constructed by different VOC combinations. These combinations achieve the pooled sensitivity 0.89 (95% CI: 0.82-0.94), the pooled specificity 0.890 (95% CI: 0.84-0.93), and the AUC of SROC 0.95 (95% CI: 0.93-0.95).[14,15,17,18,20-27] On the aspect of CRC, VOCs diagnosing CRC are mainly based on 3 kinds of sample (feces, urine, and breath and achieve the pooled sensitivity of 0.92 (95% CI: 0.85-0.96), the pooled specificity of 0.88 (95% CI: 0.77-0.94), and the AUC of SROC 0.96 (95% CI: 0.94-0.97).[28-40]

The pooled sensitivity of VOCs differentiating GI cancer from precancerous lesions is 0.84 (95% CI: 0.67-0.92), the pooled specificity is 0.74 (95% CI: 0.43-0.91), and the AUC of SROC is 0.87 (95% CI: 0.84-0.89).[20,28,29,31,33,37] It was found that VOC combinations detected from different samples were different. We took VOCs for esophagogastric cancer as an example. Six VOCs (acetaldehyde, acetone, acetic acid, hexanoic acid, hydrogen sulfide, and methanol) in urine were detected by SIFT-MS to diagnose gastroesophageal cancer, 9 VOCs (acetonitrile, acrylonitrile, carbon disulfide, isoprene, 1-heptene, 3-methylhexane, (E)-2-nonene, hydrogen sulfide, and triethylamine) were detected in plasma, and 12 VOCs (pentanoic acid, hexanoic acid, phenol, methyl phenol, ethyl phenol, butanal, pentanal, hexanal, heptanal, octanal, nonanal, and decanal) were detected in breath sample, as well as 4 VOCs (hexanoic acid, phenol, methyl phenol, and ethyl phenol) and 5 VOCs (butyric acid, pentanoic acid, hexanoic acid, butanal, and decanal) in breath. It can be different in different samples which may reflect the metabolism process of VOCs, as the primary metabolites are absorbed in blood and further excreted as final stable VOCs after the metabolism of liver, kidney, or lung. However, these metabolic processes are unclear, and further research is needed.

### *VOCs diagnosing cancer of main alimentary organs: HCC and PC*

Included studies on HCC have demonstrated that VOCs detected from breath and urine samples diagnosed HCC and differentiated it from healthy controls, liver cirrhosis, and other cancers with the pooled sensitivity of 0.68 (95% CI: 0.52-0.81), the pooled specificity of 0.81 (95% CI: 0.47-0.96), and the AUC of SROC 0.78 (95% CI: 0.74-0.81). Acetaldehyde, acetone, 3-hydroxy-2-butanone, styrene, and decane were detected in breath samples.[41,42] And 4-methyl-2,4-bis(p-hydroxyphenyl)pent-1-ene(2TMS derivative), 2-butanone, 2-hexanone, benzene, 1-ethyl-2-methyl-, 3-butene-1,2-diol, 1-(2-furanyl)-, bicyclo(4.1.0) heptane, and 3,7,7-trimethyl- [1S-(1a,3β,6a)]-sulpiride were detected in urinary samples.[43]

The VOCs diagnosing PC based on breath, urine, and bile samples achieved the pooled sensitivity of 0.88 (95% CI: 0.80-0.93), the pooled specificity of 0.82 (95% CI: 0.62-0.93), and the AUC of SROC 0.92 (95% CI: 0.89-0.94). Formaldehyde, pentane, acetone, isopropyl alcohol, n-hexane, 1-(methylthio)-propane, acetoin, benzaldehyde, undecane, tetradecane, amylene hydrate, and 1-butanol were detected in breath samples.[44,45] Acetone, ammonia, trimethylamine, isoprene, dimethyl sulfide, and acetaldehyde were detected in biliary samples.[46,47] 2,6-dimethyl-octane, nonanal, 4-ethyl-1, 2-dimethyl-benzene, and 2-pentanone were detected in urinary samples.[48-50]

## Discussion

Screening and diagnosis of digestive cancers currently rely on endoscopy and histopathology. The determination of VOCs, as a need for noninvasive, easy-to-use, and low-cost methods, is under research, although a single VOC as a specific noninvasive biomarker for digestive cancers has not been identified. It has been reported that acetone, ammonia, benzaldehyde, butanal, butyric acid, decane, dimethyl/hydrogen sulfide, dimethyl/undecane, ethylbenzene, 1,2,3-tri-methylbenzene, 1,2-dimethylbenzene, furfural, hexanoic acid, hexane/hexanal, isoprene, phenol, pentanoic acid, p-xylene, and tetradecane are associated with digestive cancers.[51] Metabolites can be absorbed in the blood and exhaled directly. They may also be absorbed and further metabolized in liver, kidney, and other internal organ systems and their microbiomes and exhaled as final stable states. A total of 2746 VOCs has been identified from healthy humans. The numbers of VOCs found in breath and the other bodily fluids are as follows: blood 379, breath 1488, feces 443, milk 290, saliva 549, semen 196, skin 623, and urine 444.[52] These indicate the rich diversity and uncertainty of VOCs in composition and proportion. However, exact metabolic processes are unclear, and there is little related research. Based on machine learning, several combinations of different VOCs have achieved satisfactory accuracy.

In this article, the diagnostic efficiency of all the current studies is acceptable, while the liver is slightly inadequate. From the perspective of VOC generation, it is currently believed that it is related to inflammation and oxidative stress, and VOC generation is greatly affected by metabolic factors. The liver is the main location of VOC metabolism and may affect the diagnosis of HCC, especially with cirrhosis. From the source of VOCs, it can be endogenous and exogenous, which requires very high requirements for the collection process of specimens and is easily affected by the VOCs in the surrounding environment and produced by diseases other than the target disease. The current research is mainly based on small sample size, and specimen collection and processing are also the main influence factors. The VOCs reflect metabolic factors, so the interference factors should be accurately controlled, such as subjects' health status, diet and medication, exercise, environment for specimen collection, container for specimen collection, the cleaning and pollution of real-time monitoring equipment, inter-instrument agreement, and intra-experimenter agreement, which will all become factors affecting the development of the experiment. Therefore, more relevant tests are required to establish the conditions and standards required for different specimens. In addition, for the detection of targeted disease, other background diseases need to be strictly controlled, and large sample tests are an important condition for finding markers and establishing diagnostic models.

There are also limitations. $I^2$ was more than 50% in CRC, HCC, and PC subgroups, maybe due to different specimens and detection methods, etc. Although it cannot be made a further subgroup analysis, since the small number of recruited research, results from E and G subgroup and other recruited research can still reflect the potential diagnostic role. As the determination of VOCs is noninvasive and easily accessible method with high discernibility, if there is a reliable diagnosis model, it will contribute a lot to the present screening and diagnosing of GI cancer.

## Conclusions

The VOCs have potential role in diagnosing GI cancer with comparatively high sensitivity, specificity, and AUC. More research is needed for the clinical application of VOCs in GI cancer diagnosis in the future.

## Author Contributions

HY and BH conceived the study. HY and YM collected and analyzed the data. HY drafted the article. All authors approved the final version of this article.

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## Supplemental Material

Supplemental material for this article is available online.

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