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Volatile Organic Compounds of Exhaled Air, Feces and Urine as Biomarkers in the Diagnosis of Inflammatory Bowel Diseases

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Aim: to analyze the results of studies that examined volatile organic compounds of various analytes (exhaled air, feces, urine) for the diagnosis of inflammatory bowel diseases.
Materials and methods. A systematic electronic literature search was conducted (without restrictions on the language or type of publication) using the Medline/PubMed, Embase, Scopus and Web of Science databases using keywords. In the process of analyzing the published articles, the quality of the created diagnostic models was evaluated.
Results. To study volatile organic compounds, metabolomic methods involving the quantification of compounds and so-called "electronic noses" are used — various types of sensors to create a "pattern" of metabolites. It has been shown that the determination of volatile organic compounds in exhaled air, feces, urine is inexpensive, affordable, acceptable to patients and doctors, has high diagnostic accuracy, allowing to distinguish patients with inflammatory bowel diseases from healthy individuals, differentiate nosological forms — ulcerative colitis and Crohn's disease, the activity of the disease, monitor the nature of its course. Sensitivity and specificity indicators for solving different diagnostic tasks vary depending on the method used (the combined sensitivity and specificity of volatile organic compounds as biomarkers for distinguishing patients with inflammatory bowel diseases from healthy individuals were 87 % (95 % confidence interval (CI): 0.79–0.92) and 83 % (95 % CI: 0.73–0.90), respectively, with an AUC of 0.92), the analyte under study, the number of volatile organic compounds analyzed, the number of patients examined, and consideration of influencing factors.
Conclusion. Volatile organic compounds demonstrate great potential as noninvasive biomarkers of inflammatory bowel diseases. In the future, more extensive multicenter prospective studies are needed to develop optimal approaches to sampling, standardizing the analysis and interpretation of volatile organic compounds data in solving various diagnostic tasks in patients with inflammatory bowel diseases.
Keywords: volatile organic compounds, biomarkers, inflammatory bowel diseases, ulcerative colitis, Crohn's disease, diagnosis, exhaled air, feces, urine, diagnosis
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Летучие органические соединения выдыхаемого воздуха, фекалий и мочи как биомаркеры в диагностике воспалительных заболеваний кишечника

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Цель: проанализировать результаты исследований, изучавших летучие органические соединения различных аналитов (выдыхаемый воздух, фекалии, моча) с целью диагностики воспалительных заболеваний кишечника.
Материалы и методы. Проведен систематический электронный поиск литературы (без ограничений по языку или типу публикации) с использованием баз данных Medline/PubMed, Embase, Scopus и Web of Science с применением ключевых слов. В процессе анализа опубликованных статей оценивалось качество созданных диагностических моделей.
Результаты. Для изучения летучих органических соединений используются метаболомные методы, предполагающие количественное определение соединений, и так называемые «электронные носы» — различные

типы сенсоров для создания «паттерна» метаболитов. Показано, что определение летучих органических соединений в выдыхаемом воздухе, фекалиях, моче является недорогим, доступным, приемлемым для пациентов и врачей, обладает высокой диагностической точностью, позволяя различать пациентов с воспалительными заболеваниями кишечника от здоровых лиц, дифференцировать нозологические формы — язвенный колит и болезнь Крона, активность заболевания, мониторировать характер его течения. Показатели чувствительности и специфичности при решении разных диагностических задач варьируют в зависимости от используемого метода (совокупная чувствительность и специфичность летучих органических соединений в качестве биомаркеров для различения пациентов с воспалительными заболеваниями кишечника от здоровых лиц составили 87 % (95%-ный доверительный интервал (95% ДИ): 0,79–0,92) и 83 % (95% ДИ: 0,73–0,90) соответственно с AUC 0,92), исследуемого аналита, количества анализируемых летучих органических соединений, числа обследованных пациентов, учета влияющих факторов.

Заключение. Исследование летучих органических соединений демонстрирует большой потенциал в качестве неинвазивного биомаркера воспалительных заболеваний кишечника. В дальнейшем необходимы более масштабные многоцентровые проспективные исследования для разработки оптимальных подходов к отбору проб, стандартизации анализа и интерпретации данных по летучим органическим соединениям при решении разных диагностических задач у пациентов с воспалительными заболеваниями кишечника.

Ключевые слова: летучие органические соединения, биомаркеры, воспалительные заболевания кишечника, язвенный колит, болезнь Крона, диагностика, выдыхаемый воздух, фекалии, моча, диагностика

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Introduction

The diagnosis of inflammatory bowel disease (IBD) and the differentiation of Crohn's disease (CD) from ulcerative colitis (UC) require a comprehensive approach that includes clinical, endoscopic, histological, serological, and radiological methods. Verification of the diagnosis in patients with IBD takes a long time; according to some studies, the median duration of symptoms before diagnosis is 2–12 months for Crohn's disease and 2–7 months for ulcerative colitis. The time to diagnosis is associated with clinical outcomes, the development of complications including intestinal strictures in Crohn's disease and the need for surgical intervention. Consequently, delays in diagnosis limit the ability to influence disease progression. During the verification of an IBD diagnosis, determining its nosological form as Crohn's disease or ulcerative colitis is crucial for developing an optimal treatment strategy. It remains unclear which patients with IBD will subsequently develop a more severe phenotype and which will develop a benign one. Therefore, it is important to identify risk groups among patients with IBD to whom an individualized therapeutic approach can be applied at the onset of the disease. The use of biologics and/or immunomodulators for therapy may be justified in the early stages of the disease in patients at risk of rapid progression of IBD.

New diagnostic approaches are needed to solve these clinical issues, and biomarkers derived from metabolites of various chemical classes appear to be promising.

Metabolomics involves the study of a group of intermediate or final metabolites of a physiological or pathophysiological process, which may potentially serve as a characteristic marker of specific pathological conditions. Metabolomic studies in IBD have been conducted in humans and animal models using samples of serum, urine, feces, and intestinal tissue. Recent technical advances now allow for the detection of certain metabolites in the form of volatile organic compounds.

Volatile organic compounds (VOC) are carbon-containing molecules that are gaseous at room temperature and can be excreted by the body as end products of metabolism via exhaled air, sweat, urine, and feces. However, this definition is not universally accepted, as some authors also include chemicals that are not gaseous at room temperature, or are not particularly volatile, such as amino acids. Depending on their origin, VOCs can be divided into exogenous and endogenous compounds. Exogenous VOCs are derived from the environment, including food and smoking. Endogenous VOCs are the end products of human or microbial metabolism.

Pathological processes in the body are often associated with changes in metabolic pathways and, consequently, with the formation of new VOCs or alterations in existing pathways for their formation. This is the basis for the potential use of VOCs as biomarkers of gastrointestinal diseases. It should be noted that certain VOC patterns are associated not only with digestive system

pathologies but also with diseases of other organs, such as the bronchopulmonary system (bronchial asthma, chronic obstructive pulmonary disease), chronic kidney disease, heart failure, and others. In the past, the volatility and very low concentrations of breath components, as well as difficulties with standardizing and normalizing the obtained concentrations of compounds, limited the possibilities for VOC analysis. However, these problems have been largely overcome with the help of advanced analytical methods, including selective ion flow-through mass spectrometry (SIFT-MS).

Most studies examining VOC as biomarkers of gastrointestinal diseases have focused on three methods of sample collection from participants: exhaled breath, urine, and stool. It is believed that VOCs can be directly detected in feces or enter the systemic circulation and are then excreted from the body either through the kidneys as urine or through the lungs in exhaled breath. All three of these approaches, with their respective samples, are considered "non-invasive" compared to blood tests, endoscopy, and liquid or tissue biopsies. However, even among these three methods, urine sampling is considered simpler and more accessible than fecal sampling, and exhaled breath testing is even more acceptable from the patient's perspective.

Therefore, the use of VOCs as non-invasive biomarkers for IBD has advantages over other potential biomarkers, such as methylated DNA or microRNA analysis. This is crucial when searching for a biomarker for potential use in disease screening and monitoring, it has to be relatively inexpensive, non-invasive, and acceptable to patients, as well as sensitive and specific. VOCs as biomarkers have the potential to meet all these criteria.

When it comes to detecting VOC, there are generally two main categories of detection technologies: metabolomic analytical methods and "electronic noses".

Metabolomic methods include various platforms for the chemical detection of compounds, such as gas chromatography–mass spectrometry (GC-MS, GC-MS), gas chromatography–ion mobility spectrometry (GC-IMS), ion-molecular reaction mass spectrometry (IMR-MS, IMR-MS), nuclear magnetic resonance spectroscopy (NMR), ion flow mass spectrometry (SIFT-MS), high-field asymmetric ion mobility spectrometry, time-of-flight ion mobility spectrometry (FAIMS), direct infusion liquid chromatography/tandem mass spectrometry, and gas chromatography–mass spectrometry (LC-MS/MS + GC-MS). All of them are used to detect specific VOC in clinical samples. These methods typically involve the use of complex equipment and software to quantify specific chemicals in the sample provided. One of the advantages of such approaches is their high specificity in detecting specific chemical substances, which allows researchers to focus on particular metabolic pathways indicative of specific pathological processes. They also provide more detailed chemical information about compounds, offer high reproducibility, and exhibit almost no "sensor drift" over time. The disadvantages of these approaches include high operating and equipment maintenance costs, the need for highly qualified personnel, labor-intensive processes, and, finally, the time required to obtain results.

The second group of devices consists of so-called "electronic noses". They use various types of sensors to mimic the mammalian olfactory system and generate a chemical reaction between a volatile organic compound and the sensor. There are various types of sensors: metal oxide-based sensors (detect changes in electrical resistance in response to exposure to certain volatile organic compounds) (Aeonose, PEN3); sensors based on conductive polymers (measure changes in resistance under the influence of certain vapors and volatile compounds) (Cyranose 320); quartz microbalances/piezoelectric sensors (exhibit different oscillation frequencies when exposed to certain gaseous chemicals, which can be measured), and electrochemical and optical sensors (WOLF).

These devices identify general "breath prints" and can distinguish between different scents by stimulating various gas sensors with different volatile compounds. They are generally not designed to quantify individual compounds, as in metabolomic analysis, and their results are negatively affected by "sensor drift". However, these devices are relatively compact, inexpensive, and easy to use, allowing for relatively rapid results.

The aim of this review is to analyze studies investigating volatile organic compounds from various analytes (exhaled air, feces, urine) for diagnosing inflammatory bowel diseases.

Materials and methods

A systematic electronic literature search (without restrictions on language or publication type) was conducted using the Medline/PubMed, Embase, Scopus, and Web of Science using the following keywords: volatile organic compounds, volatile organic metabolites, biomarkers, inflammatory bowel diseases, ulcerative colitis, Crohn's disease, diagnosis, exhaled breath, feces, urine, diagnosis. During the analysis of published articles, the development of diagnostic models, their sensitivity and specificity were evaluated for solving

various diagnostic tasks: distinguishing patients with IBD from healthy individuals, differentiating between nosological forms, differentiating IBD activity, and predicting the development of exacerbations.

Results

Prospective and retrospective comparative cohort studies, case-control studies, cross-sectional studies, and randomized controlled trials have been conducted to investigate the use of VOCs for various analytes, with the aim of establishing the diagnostic accuracy of VOCs in adults and children with a confirmed diagnosis of IBD.

Fecal samples proved to be the most studied medium for VOC testing in IBD; the articles by C. Walton et al. [31], T.G.J. De Meij et al. [32], I. Ahmed et al. [33], N. Van Gaal et al. [34], S. Bosch et al. 2018, 2020, 2022 [35–37], and S. El Manouni El Hassani et al. [38] are dedicated to them.

The analysis of exhaled breath VOCs was performed in the studies by N. Patel et al. [39], L.C. Hicks et al. [40], R.P. Arasaradnam et al. [41], L. Monasta et al. [42], K. Dryahina et al. [43], A. Tiele et al. [29].

In the studies by R.P. Arasaradnam et al. [44], S. El Manouni El Hassani et al. [38], A.H. Keshteli et al. [45], T. Dawiskiba et al. [46], and H.R.T. Williams et al. [47], VOCs in urine samples were analyzed.

As for analytical methods, a limited number of studies used "electronic noses" and NMR spectroscopy, while the majority of studies employed metabolomic methods such as GC-MS, SIFT-MS, FAIMS, ion mobility gas chromatography, and mass spectrometry with ion-molecule reactions.

While analyzing of studies examining the VOC profiles of various analytes (exhaled breath samples, feces, urine), distinct metabolite profiles that differentiate patients with IBD from healthy individuals, as well as specific IBD subtypes, disease stages, and levels of IBD activity that predict the onset of flare-ups have been identified.

In a study of differences in exhaled breath VOC patterns between patients with IBD and healthy individuals, K. Dryahina et al. [43] and M.A. Pelli et al. [48] identified elevated levels of pentane, which enabled differentiation with an AUC of 0.927. S. Sedghi et al. [49] and G.H. Koek et al. [50] identified additional VOCs associated with IBD: NO, ethane, and propane. In a cross-sectional study by N. Patel et al. [39], who analyzed 21 VOCs in the exhaled breath of 62 children with IBD using SIFT-MS, six VOCs were identified that allowed for differentiating between patients with IBD and healthy controls. In this study, levels of 1-octene, 3-methylhexane, and 1-decene were elevated, while levels of 1-nonene, 2-nonene, and hydrogen sulfide were reduced in individuals with IBD. The AUC of the model developed to differentiate IBD patients from the control group was 0.96. L.C. Hicks et al. [40] analyzed a diagnostic panel consisting of 26 exhaled air VOCs in 56 patients (38 patients with IBD and 18 healthy individuals). According to the authors, concentrations of dimethyl sulfide, hydrogen sulfide, butanal, and nonanal differed significantly between patients with Crohn's disease and healthy individuals (AUC 0.86). Ammonia levels proved to be key for differentiating patients with ulcerative colitis from healthy individuals (AUC 0.74), while concentrations of hydrogen cyanide, hydrogen sulfide, and butanal distinguished patients with CD from those with UC (AUC 0.82). This study found no correlations between the clinical activity of IBD and specific VOC patterns [40].

Several authors have proposed a mechanism for the formation of VOCs in VOC-exposed individuals that depends largely on oxidative stress, which causes lipid peroxidation. Several studies have established the potential role of VOCs released during a single exhalation, such as pentane and hexane, as markers of IBD [29, 35, 44]. Elevated concentrations of hydrogen sulfide, acetic, propanoic, and butyric acids in patients with IBD have allowed these compounds to be considered as potential biomarkers of the disease [44]. Unfortunately, the correlations between these VOCs and clinical indices (the Harvey — Bradshaw index for Crohn's disease and the simplified clinical colitis activity index for UC) were weak [44].

Specific VOC profiles analyzed by GC-MS were used in a larger cohort of adult patients with Crohn's disease to distinguish healthy individuals from those with active CD (isoprene, acetone, 2,2,4-trimethylpentane, heptadecane, C12:0, 1-butoxy-2-propanol) and inactive forms of Crohn's disease (soprene, acetone, heptadecane) [51]. Two "panels" consisting of six discriminatory compounds were identified, showing sensitivity of 96 %, specificity of 99 %, and an AUC of 0.99, and sensitivity of 96 %, specificity of 97 %, and an AUC of 0.98, respectively. A model consisting of 10 VOCs (1-hydroxy-2-propanone, hexadecanal, 2,2,4-trimethylhexane, 2,2,4,4-tetramethyloctane, acetic acid methyl ester, and four unknown volatile organic compounds) proved to be effective in distinguishing between active and inactive forms of the disease (sensitivity 81 %, specificity 80 %, AUC 0.88) [51]. The reliability of the results was far from optimal, since disease activity was not assessed by endoscopy but was determined based

on fecal calprotectin, C-reactive protein, and the Harvey — Bradshaw index. Similar results were obtained by the same group of researchers in ulcerative colitis using a panel of 11 volatile organic compounds (including cumene, 2,4-dimethylpentane, methylcyclopentene, branched $C_{14}H_{30}$, $C_{15}H_{30}$ (pentadecene), 3-methyl-1-butanol, octane, acetic acid, -pinene; m-cymene) to differentiate clinically active disease from inactive disease, confirmed only by fecal calprotectin levels (sensitivity 92 % and specificity 77 %) [52].

There are individual studies that have examined the associations between VOC levels and various types of disease activity in IBD. According to J. Kokoszka et al., concentrations of pentane in exhaled air correlated with histological disease activity, as measured by leukocyte scintigraphy [53]. The results of a study by S. Sedghi et al. showed that levels of ethane, propane, and isoprene in exhaled breath samples were associated with clinical and/or endoscopic disease activity in ulcerative colitis [49].

F. Rieder et al. conducted a prospective study of VOCs levels in the exhaled air of patients with IBD (Crohn's disease, ulcerative colitis), other inflammatory bowel diseases, patients with ileoanal reservoir-anal anastomosis (IARA), and healthy individuals using selective ion-flow mass spectrometry [54]. The metabolome of exhaled air differed significantly in patients with IBD compared to patients with other inflammatory bowel diseases and healthy individuals (7 out of 22 volatile metabolites), but not between CD and UC. The authors found no association between VOC levels and IBD complications, the location of the disease in the intestine, clinical or endoscopic disease activity, or laboratory parameters or treatment regimen. VOC levels in exhaled air differed significantly in patients with IARA compared to any other group (17 out of 22 volatile metabolites), but the presence of inflammation in the reservoir did not affect VOC levels. According to the authors, the observed differences are caused either by microbial factors in the colon, changes in diet, altered metabolism of intestinal lumen components, or a combination of all these factors. The marked change in exhaled VOC levels in the absence of the colon in patients with IBD indicates its key role in the formation of volatile metabolites. The main metabolites whose concentrations distinguished patients with IBD from the group of healthy individuals were 2-propanol, acrylonitrile, carbon disulfide, dimethyl sulfide, ethanol, isoprene, and trimethylamine, whose elevated levels the authors attributed to bacterial fermentation, fatty acid and carbohydrate metabolism, as well as changes caused by an increase in reactive oxygen species [54]. F. Rieder et al. demonstrated that in a group of patients with IARA, antibiotic use during the preceding three months had a minimal effect on the VOC profile [54].

The gut microbiome is crucial for maintaining the homeostasis of the intestinal mucosa and is altered in IBD compared to healthy individuals, showing a reduction in diversity [55, 56]. According to C.S. Probert et al. [57], fecal VOCs differ in IBD compared to healthy individuals, confirming this association. C. Walton et al. [31] demonstrated that levels of certain fecal VOCs differ markedly in patients with CD compared to those with other conditions, including UC and irritable bowel syndrome. Using gas chromatography-mass spectrometry, the authors demonstrated that patients with CD exhibited a significant increase in the concentration of ether and alcohol derivatives of short-chain fatty acids and indole compared to patients in other groups. Following treatment, levels of many VOCs decreased significantly and were comparable to those in healthy individuals. The authors concluded that gut dysbiosis in IBD may contribute to the formation of various fecal metabolite profiles. They also concluded that the normalization of the fecal VOCs profile following treatment suggests the restoration of a relatively normal microbiota. The main limitation of this study was the absence of a diagnostic model for IBD with calculated diagnostic accuracy, which may reflect its status as one of the earliest studies on VOCs in IBD, published in 2013.

The studies conducted have demonstrated varying diagnostic accuracy of VOCs in distinguishing patients with IBD from healthy individuals.

N. Patel et al. [39] used the SIFT-MS analytical platform to distinguish breath samples from patients with IBD and a control group, obtaining a diagnostic model with an AUC of 0.96 (95% confidence interval (95% CI): 0.93–0.99), but the authors were unable to demonstrate differences in VOCs profiles between UC and CD or to detect any significant correlation with disease activity. These results were confirmed by a study by L. Monasta et al. [42], which reported good sensitivity but low specificity in distinguishing IBD from the control group and UC from CD using a list of metabolites (methane, ammonia, propene, acetonitrile, nitrous oxide, nitrous acid, acetic acid, methyl ethyl ketone, methanimine, cyclopentane, carbon disulfide, methyl nitrate, pyridine, methylpyrrole, ethyl cyanoformate, dimethylpyridine, trimethylpentane, ethylene, acetaldehyde, acetone, isoprene, toluene, n-heptane). The authors did not identify any significant differences in VOC patterns depending on disease activity.

L.C. Hicks et al. [40] developed a statistical model to distinguish exhaled breath samples from children with IBD from those of healthy children, as well as to differentiate ulcerative colitis from Crohn's disease. Patients with CD were successfully distinguished from the control group with a sensitivity of 94 % and a specificity of 94 %, and those with UC from healthy individuals with a sensitivity of 91 % and a specificity of 94 %. The developed diagnostic model distinguished patients with Crohn's disease from those with ulcerative colitis with a sensitivity of 89 % and a specificity of 90 %. In addition, this study identified statistically significant differences in the concentrations of dimethyl sulfide, hydrogen sulfide, and nonanal in patients with Crohn's disease compared to healthy individuals. The authors were unable to find significant differences in the levels of individual VOCs in ulcerative colitis compared to healthy individuals.

K. Dryahina et al. [43] analyzed exhaled breath samples using SIFT-MS in patients with IBD and healthy individuals. The authors noted higher levels of pentane, hydrogen sulfide, acetic acid, propionic acid, and butyric acid in patients with IBD compared to the control group. They suggested that hydrogen sulfide and carboxylic acids could potentially serve as biomarkers of excessive bacterial overgrowth in the gut. The relative concentrations of pentane and other VOCs showed a weak correlation with clinical indices of IBD activity. A limitation of the study was the lack of a calculation of diagnostic accuracy.

I. Ahmed et al. [33] analyzed fecal VOC samples using GC-MS and found it possible to distinguish patients with active Crohn's disease from those with inactive disease and healthy individuals, but were unable to differentiate between stages of UC or between UC patients and healthy individuals. Levels of several VOCs (heptanal, 1-octen-3-ol, 2-piperidone, and 6-methyl-2-heptanone) were elevated in the group of patients with active CD (the variable significant for prediction (VIP) was 2.8, 2.7, 2.6, and 2.4, respectively), while the levels of methanethiol, 3-methylphenol, short-chain fatty acids, and ester derivatives were reduced (VIP scores of 3.5, 2.6, 1.5, and 1.2, respectively). The PLS-DA model distinguished patients with small bowel CD from healthy individuals ($p < 0.001$) and patients with large bowel CD from individuals with UC ($p < 0.001$).

Data on volatile organic compounds in urine in patients with IBD are scarce. Differences in VOC levels between urine samples from patients with IBD and a control group were first described by R.P. Arasaradnam et al. in 2009 using an "electronic nose" [58]. Samples from a small cohort of 48 patients with IBD were subsequently analyzed using an "electronic nose" and FAIMS by the same authors. Both technologies allowed for differentiating patients with IBD from the control group with an accuracy of 88 and 75 %, respectively ($p < 0.001$), as well as the active form of the disease from the inactive form [41].

GC-IMS revealed significantly different VOC profiles in 10 patients with IBD compared to 10 individuals in the control group (AUC 0.78; $p = 0.028$) [38]. In this small study, S. El Manouni El Hassani et al. reported better performance of urinary VOCs compared to fecal VOCs in terms of sensitivity (80 % vs. 70 %), but not specificity (70 % vs. 90 %).

A.H. Keshteli et al. [45] studied urinary metabolomic profiles using a combination of direct injection liquid chromatography/tandem mass spectrometry and GC-MS. Patients with ulcerative colitis in remission were distinguished from patients with IBS with high diagnostic accuracy (AUC 0.99), specificity of 99.9 %, and sensitivity of 99.8 % ($p < 0.001$).

Studies by T. Dawiskiba et al. [46] and H.R.T. Williams et al. [47] have shown that urine NMR spectroscopy may be useful for detecting metabolomic changes.

Several studies have attempted to answer the question of whether the analysis of volatile organic compounds can differentiate UC from CD, since it is known that the pathophysiology (and, consequently, the underlying metabolic processes) differ in these nosological forms of inflammatory bowel disease. In clinical practice, the differential diagnosis of ulcerative colitis can be a complex task and involves distinguishing between a range of endoscopic and histological features. Several studies have reported different VOC patterns in UC and CD; however, the results obtained were inconclusive.

Three studies involving a limited number of patients reported that analyzing VOCs levels demonstrated positive discriminatory ability between UC and CD. L.C. Hicks et al. [40] used their model to differentiate 18 cases of CD from 20 cases of UC with a sensitivity and specificity of 89 % and 90 %, respectively. R.P. Arasaradnam et al. [41] applied FAIMS to study exhaled breath samples from adults to differentiate 29 cases of UC from 25 cases of CD with a sensitivity of 67 % (0.54–0.79) and a specificity of 67 % (0.54–0.79), AUC 0.70 (0.60–0.80) ($p = 0.0009$). Finally, A. Tiele et al. [29] reported that they were able to distinguish 16 cases of UC from 14 cases of CD with a sensitivity and specificity of 71 and 88 %, respectively ($p < 0.0001$).

At the same time, N. Van Gaal et al. [34], when analyzing differences in exhaled air VOCs profiles

of 13 patients with UC and 23 patients with CD, created a diagnostic model with sensitivity and specificity of 65 and 62 %, respectively, for differentiating between the two groups, but found this to be statistically insignificant ($p = 0.1$). The authors concluded that VOC analysis does not allow for reliable differentiation between patients with UC and CD.

This view was confirmed by a study by S. Bosch et al. [35], conducted in 2018, in which the authors were unable to differentiate 15 cases of ulcerative colitis from 15 cases of Crohn's disease based on fecal VOCs profiles. Continuing the study with a larger number of patients, S. Bosch et al. [36] reported in 2020 that VOC profiles in feces differed between UC and CD, but diagnostic accuracy was very low: sensitivity was 17 %, and negative predictive value was 36 % (AUC 0.55; 95% CI: 0.50–0.6), there were no differences between active disease and remission in IBD (for individuals with active UC versus inactive UC — AUC 0.63 (95% CI: 0.44–0.82); for active UC versus inactive UC — AUC 0.52 (95% CI: 0.39–0.65)).

Thus, at present, it is not possible to draw a definitive conclusion regarding the diagnostic accuracy of models incorporating volatile organic compound levels for differentiating between nosological forms of IBD.

One of the key functions of a biomarker is to monitor disease progression, enabling the prediction of relapses in patients in remission, which is particularly relevant in IBD.

Five studies [31–33, 35, 41] demonstrated a clear difference in VOC profiles after patients achieved remission compared to the active phase of the disease, although only C. Walton et al. [31] specified the medications used (steroids and 5-aminosalicylic acid preparations for patients with UC; only diet for patients with CD). These studies did not involve long-term follow-up of patients and did not track IBD relapses. Only S. Bosch et al. [37] studied the effectiveness of using fecal VOCs levels to monitor relapses of inflammatory bowel disease over a specific period of time. The authors observed changes in VOCs profiles in the feces of patients with IBD preceding changes in fecal calprotectin levels, which they attributed to fluctuations in the composition of the microbiota. S. Bosch et al. concluded that VOC profiles may serve as useful markers for predicting disease progression, allowing for earlier initiation of therapy and a reduction in the frequency of complications and hospitalizations. In this study, changes in fecal VOC profiles did not predict IBD clinical activity. The authors identified a difference in fecal volatile organic compound profiles between patients who experienced relapses and those who remained in remission, with an AUC of 0.75 ($p < 0.01$).

In the published reviews by K. van Malderen et al. in 2020 [59] and F. Vernia et al. in 2021 [60] also examined the use of VOCs as diagnostic biomarkers for IBD; both concluded that volatile organic compounds hold significant promise in this regard.

According to a systematic review by A. Krishnamoorthy et al. [61], the overall sensitivity and specificity of volatile organic compounds as biomarkers for distinguishing between IBD patients ($n = 696$) and control subjects ($n = 605$) were 87 % (95% CI: 0.79–0.92) and 83 % (95% CI: 0.73–0.90), respectively, with an AUC of 0.92, confirming that VOCs demonstrate great potential as non-invasive biomarkers for IBD. No blood samples are required for their collection; increasingly, VOCs are collected and transported using various devices, such as thermal desorption tubes, and their concentrations are analyzed using instruments such as "electronic noses", the number of which is expected to grow.

At present, there is no consensus on which sample matrix is optimal for analyzing volatile organic compounds — urine, stool, or exhaled breath. From the patient's perspective, exhaled breath and urine samples are more acceptable than stool collection.

There is also no consensus on the best analytical method, whether to use more complex metabolomic methods or "electronic noses". However, compounds detectable only in pathological conditions, as opposed to healthy individuals, have yet to be identified. The overall picture, the "pattern" of the changing composition of volatile organic compounds, is more relevant and meaningful; therefore, technology based on metal oxides in "electronic noses" may be more suitable in the future for a range of inflammatory and oncological diseases. The advantage of this approach lies in its minimal preparation requirements. The fact that VOCs from all environments are associated with disease stages implies that there are more potential diagnostic applications for using VOC patterns without being limited to a specific sample type.

The analysis showed that while studies using volatile organic compounds clearly distinguished UC from the control group, distinguishing UC from CD was more difficult. Nevertheless, the VOC profile in patients with CD appears more distinct than in UC patients compared to healthy individuals, as reported by L.C. Hicks et al. [40] and I. Ahmed et al. [33]. This is likely due to the fact that in CD, there is transmural damage to the

intestinal wall, with more pronounced disruption of metabolic pathways compared to UC.

The influence of other factors, such as age, sex, body mass index, dietary habits, medication use, smoking, and comorbid metabolic diseases, on the concentration of volatile organic compounds is another aspect of this research field requiring further clarification and potential adjustment when using VOCs as biomarkers for IBD [62]. For example, smoking is associated with the introduction of certain exogenous VOCs into exhaled breath samples analyzed for disease detection. When analyzing VOC patterns, these factors must be accounted for by correcting the probabilistic neural networks which were generated based on "electronic nose" data.

The Table summarizes data on diagnostic accuracy in using VOCs to solve various diagnostic challenges in patients with IBD.

Currently, fecal calprotectin (FCP) and C-reactive protein (CRP) are the most widely used noninvasive biomarkers for inflammatory bowel disease and are frequently used for initial diagnosis and disease monitoring. Calprotectin is a protein secreted by neutrophils during intestinal inflammation; it is stable in feces and can be measured by laboratory methods [63]. CRP is an acute-phase protein secreted by the liver in response to stimulation by macrophages and T cells during the immune response to systemic inflammation [63]. Thus, these two indicators serve as surrogate markers for both local and systemic intestinal inflammation. Elevated CRP levels are nonspecific for gastrointestinal inflammation, and elevated calprotectin levels are nonspecific for inflammatory bowel disease.

It is possible that the measurement of volatile organic compounds may be more appealing than the analysis of existing biomarkers. First, the ability to use exhaled breath and urine samples to adjust ongoing therapy may improve patient adherence and lay the groundwork for future point-of-care testing. These samples are easier to collect from patients than blood or stool samples, especially when it comes to children with IBD, whose numbers are likely to increase. When testing is conducted on a large scale, the cost of VOC testing is comparable to that of fecal calprotectin testing.

Since VOC are not merely surrogate markers of an inflammatory process, they can provide additional information and help distinguish between pathologies of different etiologies, including infectious gastroenteritis, ulcerative colitis, Crohn's disease, and colorectal cancer, as these conditions are associated with distinct VOC patterns [64–66]. This creates new opportunities for non-invasive screening and monitoring of a range of socially significant pathologies.

When using VOCs as a biomarker for IBD, one must consider not only patient-related factors but also a range of technical conditions, including the specifics of sample collection, transport, storage, and analysis. This can lead to additional steps in the workflow, potential variations, or errors, and therefore requires standardization of measurement methods [67].

Individual metabolic and environmental factors, such as renal, hepatic, or cardiac insufficiency, or medications being taken, can lead to variations in VOC patterns compared to reference biomarkers, and this must be considered [68]. Currently, data are emerging showing differences in VOC composition, for example, between patients with irritable bowel syndrome with diarrhea and those with halogen-induced diarrhea [69], and between types of cancer of different cellular origins [70]. The studies conducted have not identified variations in VOC among different phenotypes of IBD, such as acute severe UC or CD with fibrotic strictures and prestenotic dilation; however, fecal calprotectin is also unable to distinguish between these subgroups.

These issues can likely be solved through further investigation in double-blind controlled, multicenter studies involving a larger number of patients to minimize any potential confounding factors. Greater attention should also be paid to differentiating ulcerative colitis from Crohn's disease and to the use of VOCs as markers of IBD activity or remission. The long-term chronic course of IBD increases the risk of developing colorectal cancer [71]. The ability to detect high-grade dysplasia using non-invasive methods by identifying specific patterns of VOCs would be of primary clinical importance for the early diagnosis of cancer in patients with IBD.

Conclusion

Research into volatile organic compounds as biomarkers for inflammatory bowel diseases is at a relatively early but promising stage, with great potential for further development and benefits for patients. It should be noted that the samples of analytes (exhaled breath, urine, feces) for VOC analysis are non-invasive, acceptable to patients and physicians, and VOC pattern analysis is inexpensive and highly accurate, allowing for the distinction of patients with IBD from healthy individuals, the differentiation of nosological form, if it is ulcerative colitis or Crohn's disease and the assessment of disease activity, as well as the monitoring of its course. Sensitivity and specificity

Table. Possibilities of using volatile organic compounds for solving various diagnostic problems

Aim	Substrates	Methods of determination	Maximum values of area under the curve, sensitivity and specificity	Authors of publications
Diagnostics of IBD	Exhaled breath	SIFT-MS	- AUC 0.96 [39]; - AUC 0.86, sens. 94 %, spec. 94 % [40]; - AUC 0.927 [43]; - AUC 0.810 [54]	Patel N. et al. [39], Hicks L.C. et al. [40], Dryahina K. et al. [43], Rieder F. et al. [54]
		GC-MS	AUC 0.99, sens. 96 %, spec. 99 %	Bodelier A.G. et al. [51]
		IMR-MS	AUC 0.925, sens. 95 %, spec. 69 %	Monasta L. et al. [42]
		GC	were not determined	Pelli M.A. et al. [48], Sedghi S. et al. [49]
		Chemiluminescent analyzer	were not determined	Koek G.H. et al. [50]
		EN	sens. 67 %, spec. 89 %	Tiele A. et al. [29]
		GC-IMS	sens. 87 %, spec. 89 %	Tiele A. et al. [29]
	Feces	GC-MS	- were not determined [31, 33]; - sens. 90 %, spec. 80 % [57]	Walton C. et al. [31] Ahmed I. et al., [33] Probert C.S. et al. [57]
		GC-IMS	- AUC 0.96 [36]; - sens. 80 %, spec. 70 % [38]	Bosch S. et al. [36], El Manouni El Hassani S. et al. [38]
		FAIMS	UC 0.9, sens. 83 %, spec. 83 %	Van Gaal N. et al. [34]
	Urine	EN	were not determined	Arasaradnam R.P. et al. [58]
		EN + FAIMS	Diagnostic accuracy for EN — 88 %, for FAIMS — 75 %	R.P. Arasaradnam et al. [41]
		GC-IMS	sens. 70 %, spec. 80 %	El Manouni El Hassani S. et al. [38]
		LC-MS/MS + GC-MS	AUC 0.99, sens. 99.8 %, spec. 99.9 %	Keshteli A.H. et al. [45]
		Proton NMR spectroscopy	- AUC 0.9 [46], - were not determined [47]	Dawiskiba T. et al. [46], Williams H.R.T. et al. [47]
	Exhaled breath + Feces + Urine	GC-MS, GC-IMS, EN, FAIMS	AUC 0.92, sens. 87 %, spec. 83 %	Krishnamoorthy A. et al. [61]
Differential diagnostics of UC and CD	Exhaled breath	EN/GC-IMS	sens. 71 %, spec. 88 %	Tiele A. et al. [29]
		SIFT-MS	AUC 0.82, sens. 89 %, spec. 90 %	Hicks L.C. et al. [40]
		FAIMS	AUC 0.7, sens. 67 %, spec. 67 %	Arasaradnam R.P. et al. [41]
		IMR-MS	AUC 0.934, sens. 94 %, spec. 76 %	Monasta L. et al. [42]
	Feces	GC-MS	were not determined	Walton C. et al. [31] Ahmed I. et al. [33]
		GC-IMS	AUC 0.55	Bosch S. et al. [36]
		FAIMS	AUC 0.67, sens. 67 %, spec. 62 %	Van Gaal N. et al. [34]

End of the Table. Possibilities of using volatile organic compounds for solving various diagnostic problems

Aim	Substrates	Methods of determination	Maximum values of area under the curve, sensitivity and specificity	Authors of publications
Diagnostics of IBD activity	Exhaled breath	GC-MS	- AUC 0.88, sens. 81 %, spec. 80 % [51]; - sens. 92 %, spec. 77 % [52]	Bodelier A.G. et al. [51] Smolinska A. et al. [52]
		GC	were not determined	Sedghi S. et al. [49] Kokoszka J. et al. [53]
	Feces	GC-MS	were not determined	Ahmed I. et al. [33]
		FAIMS	AUC 0.63	Bosch S. et al. [36]
	Моча	Proton NMR spectroscopy	AUC 0.909	Dawiskiba T. et al. [46]

Note: *sens. — sensitivity; spec. — specificity; FAIMS — high-field asymmetric waveform ion mobility spectrometry; GC-IMS — gas chromatography — ion mobility spectrometry; GC-MS — gas chromatography — mass spectrometry; LC-MS/MS + GC-MS — liquid chromatography — tandem mass spectrometry and gas chromatography — mass spectrometry; IMR-MS — ion molecule reaction mass spectrometry; SIFT-MS — selected ion flow tube mass spectrometry; EN — "electronic nose"; NMR — nuclear magnetic resonance spectroscopy.*

values for various diagnostic tasks vary depending on the method used (metabolomic analysis or "electronic noses"), the analyte being studied, the number of volatile organic compounds analyzed, the number of patients examined, and the consideration of confounding factors. Further large-scale, multicenter, prospective studies are needed to develop optimal approaches to sample collection, standardization of analysis, and interpretation of VOC data as biomarkers of IBD.

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