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REVIEW

Mass Spectrometry-Based Human Breath Analysis: Towards COVID-19 Diagnosis and Research

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Abstract
COVID-19 is a highly contagious respiratory disease that can be infected through human exhaled breath. Human breath analysis is an attractive strategy for rapid diagnosis of COVID-19 in a non-invasive way by monitoring breath biomarkers. Mass spectrometry (MS)-based approaches offer a promising analytical platform for human breath analysis due to their high speed, specificity, sensitivity, reproducibility, and broad coverage, as well as its versatile coupling methods with different chromatographic separation, and thus can lead to a better understanding of the clinical and biochemical processes of COVID-19. Herein, we try to review the developments and applications of MS-based approaches for multidimensional analysis of COVID-19 breath samples, including metabolites, proteins, microorganisms, and elements. New features of breath sampling and analysis are highlighted. Prospects and challenges on MS-based breath analysis related to COVID-19 diagnosis and study are discussed.

Keywords COVID-19 · SARS-CoV-2 · Breath analysis · Breath sampling · Multidimensional analysis · Mass spectrometry

1 Introduction

Coronavirus disease (COVID-19) is an infectious disease can be infected through person-to-person transmission by human exhaled breath when an infected person coughing, sneezing, or exhaling [1–3]. Human exhaled breath is a kind of bioaerosol (i.e., exhaled breath aerosol, EBA) containing water, volatile organic compounds (VOCs), droplets which can dissolve various non-volatile metabolites, salts, proteins, and microorganisms such as bacterial and viral particles. EBA is a significant source of coronavirus (SARS-CoV-2) emission because EBA can suspend in the contaminated air and cause infection by respiration action [4]. Diagnosing COVID-19 now mainly depends on polymerase chain reaction (PCR) technique [5], which is highly expected to be the most reliable test for diagnosing COVID-19 by the genomic identification of SARS-CoV-2. Theoretically, the limit of PCR is a single molecule, since PCR is a molecular technology that can exponentially amplify a fragment of nucleic acid, making PCR as a powerful tool for identifying special nucleic acid sequences. During PCR testing, coronavirus should be collected from specimen swab for RNA extraction and transcription to diagnose COVID-19 [6]. Although PCR technique is effective and sensitive for diagnosing COVID-19, many limitations such as sampling quality, sample pretreatment, and tedious result time were frequently reported in practice applications. False-negative results of PCR detection drive the new development of other supportive analytical methods for diagnosing COVID-19 [6–19]. To improve the accuracy of COVID-19 diagnosis, different clinical samples such as blood, urine, feces, saliva, and breath are considered for screening viruses or/and virus-specific metabolites [20–29], which are also expected to provide new insight into the health impact of COVID-19 [30].

Mass spectrometry (MS) is a powerful analytical tool for investigating genomics, proteomics, metabolomics, and microbiomics of human diseases, due to its unique advantages including sensitivity, specificity, and speed [31–33]. MS-based technologies are powerful analytical tools to investigate COVID-19 disease [34, 35]. Different MS approaches with various sampling, separation, and ionization techniques, such as gas chromatography (GC), liquid chromatography (LC), and inductively couple plasma (ICP),

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and matrix-assisted laser desorption/ionization (MALDI), can be used in omics research, biomarker discovers, qualitative and quantitative detection [36]. Particularly, ambient ionization (AI)-MS (e.g., paper spray [37]; desorption electrospray ionization, DESI) [38], and direct ionization (DI)-MS techniques (e.g., proton transfer reaction, PTR) [17], have been used for diagnosing COVID-19, and other direct ionization/sampling methods using direct sampling/ionization with medical swab [39, 40] also show potential for COVID-19 studies. Significant MS-based metabolomic and proteomic studies on COVID-19-related human body fluids have been achieved [30, 41–47].

Considering the respiratory properties of COVID-19, analyzing human EBA profiles is useful in clinical and pathologic studies on COVID-19 [48]. Breath sampling technologies combining with MS methods with great potentials have been emerged. Multifarious analytes in human breath samples can be easily introduced or collected by well-designed devices for online or offline analysis. Breath samples including exhaled breath condensate (EBC), VOCs, and EBA are commonly analyzed by MS-based approaches. A variety of MS-based methods on the advances of breath analysis have been developed, some of which have been successfully used for diagnosis and research of COVID-19. Undoubtedly, MS-based breath analysis could provide a better diagnosis and understanding of COVID-19. Thus, this paper will review and prospect the MS-based multidimensional analysis of human breath samples for diagnosis and research of COVID-19, including small organic molecules, inorganic constituents, biomacromolecules and microorganisms. The future opportunities and challenges of these MS-based methods will be discussed.

2 MS-Based Multidimensional Breath Analysis

Compared to other COVID-19 diagnostic techniques, MS-based multidimensional analysis of human breath samples has many advantages, including total noninvasiveness, in vivo, easy operation, good analytical performances and applicability, as summarized in Tables 1 and 2. Breath analysis has the potential of complementary of human body fluid analysis. EBC and EBA are commonly collected for MS diagnosis of various human diseases (Table 3). Particularly, metabolites, proteins, salts, and microorganisms could be exhaled from humans, and could provide abundant biological and clinical information for better understanding of COVID-19. Therefore, MS-based human breath analysis can be roughly divided into five categories according to the dimensions of analyte properties (Fig. 1): (1) DI-MS analysis of EBA using online sampling methods, (2) GC–MS analysis of volatile metabolites, (3) LC–MS analysis of non-volatile metabolites and proteins, (4) MALDI-MS analysis of proteins and microorganisms, (5) ICP-MS analysis of trace elements. These MS-based multidimensional technology

Table 1 Different methods for diagnosing COVID-19

Diagnostic methods	Samples	Analysis time	Cost	Performances	References
RT-PCR	Nasopharyngeal and throat swab, feces	3–4 h	High	Sensitivity: 97.2% (sputum); 62.3% (saliva); 73.3%	[8]
Loop-mediated isothermal amplification	Throat swabs	30–60 min	Medium	LOD: 118.6 copies of SARS-CoV-2 RNA per 25 μL	[9]
High-throughput automated sequencing	Oropharyngeal swab, blood, serum, plasma	1–2 days	High	/	[10]
Lateral flow immunoassay	Blood, serum, plasma	< 15 min	Low	Sensitivity: 88.66%; specificity: 90.63%	[6, 11]
Enzyme-linked immunosorbent assay	Blood, serum, plasma	1–5 h	Low	Sensitivity: 97.1%; specificity: 97.5%; Accuracy: 97.3%	[12]
Colloidal Gold-Immunochromatographic assay	Plasma	10 min	Low	Sensitivity: 82.4%; specificity: 100%	[13]
CRISPR-Cas12-based lateral flow assay	Nasopharyngeal or oropharyngeal swabs	~30 min	Low	LOD: 10 copies/μL, Sensitivity: 90%; specificity: 100%	[14]
Computed tomography scan	Human body (lung)	< 1 h	High	Sensitivity: ~95 to 100%	[8, 15]
Biosensor	Respiratory and blood samples	~2 h	Low	Sensitivity: 86.43–93.75%; specificity: 90.63–100%	[16]
Mass spectrometry	Breath, blood, serum, plasma, urine, nasopharyngeal and throat swab	~5 min	High	Accuracy: 93%, specificity: 85.7–100%	[17–19]

Table 2 MS-based approaches for diagnosis and investigation of COVID-19

MS methods	Samples	Analytes	Sensitivity and specificity	References
DI-MS	Breath	VOCs	Sensitivity: 90%, accuracy: 93%, Specificity: 94% by PTR-MS	[17]
	Nasal swabs	SARS-CoV-2	Diagnostic accuracy: 86.7% and 84% for DESI-MS and LD-REIMS, respectively	[38]
	Lysed cell	Lipids	93.3% correlation to the PCR classification by PS-MS	[37]
GC–MS	Feces	Metabolites	COVID-19-altered fecal metabolites were correlated with clinical features, serum metabolites and gut microbes	[27]
	Breath	VOCs	Sensitivity: 68%; specificity: 85.7%, positive predictive value (PPV): 89.5%, negative predictive value (NPV): 60%	[19]
	Blood serum	VOCs	Sensitivity: 94%; specificity: 83%	[29]
LC–MS	Urine	Proteins	COVID-19 pathophysiology related molecular alterations could be detected	[20]
	Nasopharyngeal swabs	Proteins	LOD: 9×10^{-13} g, relationship was observed between summed MS peak intensities for SARS-CoV-2 proteins and Ct values reflecting the abundance of viral RNA	[21]
	Saliva	Proteins	Identifies unique peptides originating from SARS-CoV-2 nucleoprotein	[45]
MALDI-MS	Nasopharyngeal swabs	Proteins	Sensitivity: 61.76%; accuracy: 67.66%, specificity: 71.72%	[22]
	Plasma	Proteins	Sensitivity: 87.50%; accuracy: 93.10%; specificity: 100%	[18]
	Residual nasal swab	Proteins	Two models were identified, exhibiting accuracy of 98.3%, positive percent agreement (PPA) of 100%, negative percent agreement (NPA) of 96%, and accuracy of 96.6%, PPA of 98.5%, and NPA of 94%, respectively	[23]
	Nasal swabs	SARS-CoV-2	Accuracy: 93.9% with 7% false positives and 5% false negatives	[24]
	Serum	Serum peptidome	Sensitivity: 98%, accuracy: 99%, specificity: 100%	[25]
ICP-MS	Blood	Metals and metalloids	Whole blood iron, age, and sex were determined to be independent factors associated with the disease severity, while chromium, cadmium, and the comorbidity of cardiovascular disease were determined to be independent factors associated with the mortality	[26]
	Urine	Trace elements	Urinary creatinine-adjusted copper of ≥ 25.57 μg/g and ≥ 99.32 μg/g were associated with significantly increased risk of severe illness and fatal outcome in COVID-19, respectively	[28]

Table 3 Breath sampling methods for EBA and EBC

Breath samples	Sampling methods	References
EBA	Collecting into endotracheal tube	[17]
	Extracting or adsorbing onto SPME fiber	[55]
	Collecting into heated sampling tube	[67, 68]
	Collecting into a Mylar® bag	[69–71]
	Collecting into a Teflon®-bulb/Tedlar bags	[72–74]
	Collecting into a Bio-VOC® tube	[75]
	Direct introducing using heated PEEK capillary	[76]
EBC	Collecting into RTube kit (stored at − 80 °C)	[78–80]
	Collecting into TURBO-DECCS collection device (− 5.5 °C)	[81]
	Collecting into EcoScreen device (condensed at − 20 °C, stored at − 80 °C)	[82–84]
	Collecting into portable condenser at − 5 °C	[85, 86]

platforms (Table 2) could provide a feasible avenue and comprehensive bioinformation of EBA that towards to COVID-19 diagnosis and research.

2.1 DI-MS

The DI-MS and AI-MS analyses of EBA can be combined to one dimension here for its applicable to direct breath analysis

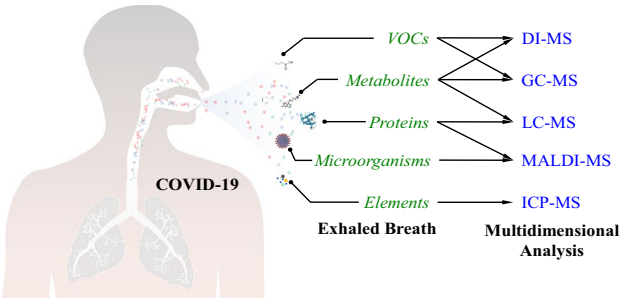

Fig. 1 MS-based multidimensional analysis of human breath with COVID-19

without pre-collection and preparation of breath samples. Under DI-MS analysis, EBA sample is directly introduced from human mouth into the ionization region for direct MS analysis. Several outstanding articles described the direct MS analysis of human breath samples, e.g., PTR-MS [49], selecting ion flow tube mass spectrometry (SIFT-MS) [50], extractive electrospray ionization mass spectrometry (EESI-MS) [51], secondary electrospray ionization mass spectrometry (SESI-MS) [52], and other MS techniques [53]. These DI-MS techniques are well-established methods for direct breath analysis. Due to the continuous and non-invasive introduction of gaseous breath sample, breath analysis has great clinical potential to allow direct, real-time, in vivo, and online analysis of small metabolites. These unique features of direct MS analysis make it an attractive analytical tool for rapid diagnosis of COVID-19.

Grassin-Delyle et al. [17] applied PTR-MS for detecting breath VOCs. Breath samples were directly introduced from COVID-19 patients to MS via a heated transfer line. MS data were analyzed by multivariate analysis strategy with principal component analysis (PCA) and machine-learning algorithms with different mathematical backgrounds, including orthogonal partial least-squares discriminant analysis (OPLS-DA), linear support vector machine, elastic net, and random forest (RF). PCA and OPLS-DA plots showed that breath fingerprints of COVID-19 were associated with a specific signature (Fig. 2). Some VOCs have been proposed as the biomarkers for discriminating COVID-19 and non-COVID-19 cases. This work showed that direct MS analysis of breath VOCs from patients with COVID-19 could obtain an accuracy of 93%, which might inspire to new development of online methods for large-scale COVID-19 screening.

The direct MS methods are mainly based on online breath introduction. However, the concentration of VOCs in EBA presents differences ranging from parts per million (ppm) to parts per trillion (ppt) even lower. Therefore, the concentration of VOCs in breath samples should be higher than the detection limit of MS methods. In spite of a highly efficient sample introduction, ionization, and detection in direct MS methods, many volatile biomarkers at extremely low concentrations could be undetectable. Therefore, collecting exhaled volatiles and EBC is still highly required to provide sufficient samples to extract biomarkers for offline MS analysis [54]. The collected breath samples also allow the couple with direct/ambient MS for enhanced detection of analytes from EBA. Solid-phase microextraction (SPME) technique is commonly used for VOCs sampling for MS analysis. For example, Yuan et al. [55] demonstrated the collection and enrichment of numerous breath metabolites from EBA using facemask-based microextraction technique (SPME-in-mask) followed by detection using MS with ambient ionization and GC–MS (Fig. 3). The unique feature of facemask-based SPME-MS of EBA is that the breath sampling process was separated from the MS detection in time and space. Wearable facemask sampling also is convenient for a long-time sampling even many hours in daily life, enabling enrichment of ultrarace VOCs. In addition, facemask could also protect humans from air pollutants in the ambient during the sampling process [55]. These new features have practical relevance for diagnosing COVID-19, because the breath sample is not easily handling due to their infectiousness.

2.2 GC–MS

GC–MS is a universal analytical platform, due to its excellent robustness, selectivity, sensitivity, reproducibility, separation capability, and comprehensive database [56, 57]. Exhaled breath volatiles are largely composed of inorganic volatiles such as NH_3, N_2, O_2, H_2O, CO_2, and trace VOCs. Breath volatiles can be originated from endogenous metabolites (generated by respiratory tract and internal organ systems and their microbiomes) and exogenous VOCs (generated by food, drugs, and environment and their metabolites). Thus, measurement of breath volatiles can gain an insight into the biochemical processes of human body. Pathogenic viruses such as COVID-19 may produce special volatiles serving as biomarkers.

Although inorganic volatiles is a main part of exhaled metabolites, however, a few studies have been conducted to assess the possible relationship between inorganic volatiles and metabolic characteristics of COVID-19. Aldhaleei et al. [58] reported a new case of hepatitis B virus reactivation caused by COVID-19, showing a higher level of ammonia (74 mmol/L) than the reference value (reference: 16–60 mmol/L). This finding could inspire measurements of exhaled inorganic volatiles using GC–MS system. VOCs are usually required to be collected into a gas bag or gas bottle for subsequentially GC–MS analysis (Table 3). GC–MS analysis of breath VOC and blood metabolites has been proposed for COVID-19 diagnosis and research [29, 59–61]. To improve biomarker discovery, SPME and needle trap device

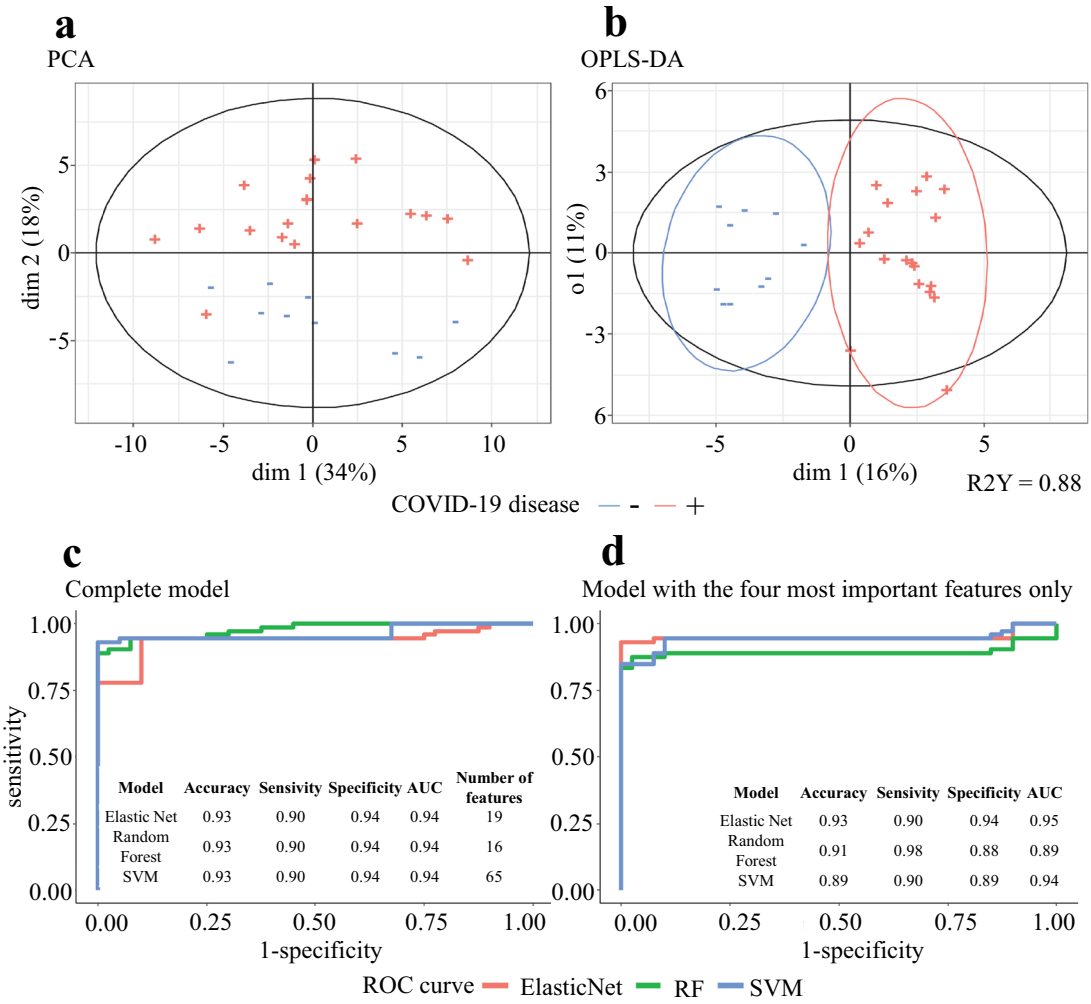

Fig. 2 Representative MS data process methods for COVID-19 diagnosis: **a** PCA, **b** OPLS-DA, **c** complete mode with three machine-learning algorithms, **d** model with the most important features only. Adapted from [17] with permission

techniques were also proposed to couple with GC–MS for enhanced breath analysis in COVID-19 research [55, 61–63].

The recent emergence of portable GC–MS equipment could further improve the capability of COVID-19 diagnosis as it can be easily moved for onsite testing as needed. A Hexin portable GC–MS 2000 (weighing 19 kg with battery) can analyze breath samples within 15 min of starting up, provide a fast analysis less than 4 min (Fig. 3) and have a long continuous monitoring time over 2 h and battery standby time over 4 h. Furthermore, the availability of breath sampling, the SPME-in-mask (wearable facemask microextraction) [55], has been developed for direct coupling with GC–MS for breath sampling and analysis. The portable GC–MS can be programmed to monitor biomarkers for non-specialist users and allow onsite sampling and analysis. This breath analysis based on potable SPME-MS would be a huge step forward in molecular medicine. Thus, rather than shipping samples (e.g., medical swab), the portable GC–MS can be used for not only onsite sampling and analyzing of COVID-19 but also other human diseases in the community, school, hospital, etc.

2.3 LC–MS

EBC contains a variety of non-volatile organic compounds and biological matrices that are potential clinical sources for providing valuable biochemical information about respiratory diseases [48, 64]. Compared to EBA sampling, there are many methods for EBC sampling (Table 3). LC–MS is commonly used for analyzing organic and biological compounds and protein digestion from EBC [65, 66]. Various key factors may significantly affect the results of EBC sampling, as listed in Table 3. Unlike collecting VOCs and nonvolatiles in EBA sampling under normal-temperature [17, 55, 67–76], the main factor of EBC sampling is that water vapor, metabolites, and bioparticles from exhaled samples

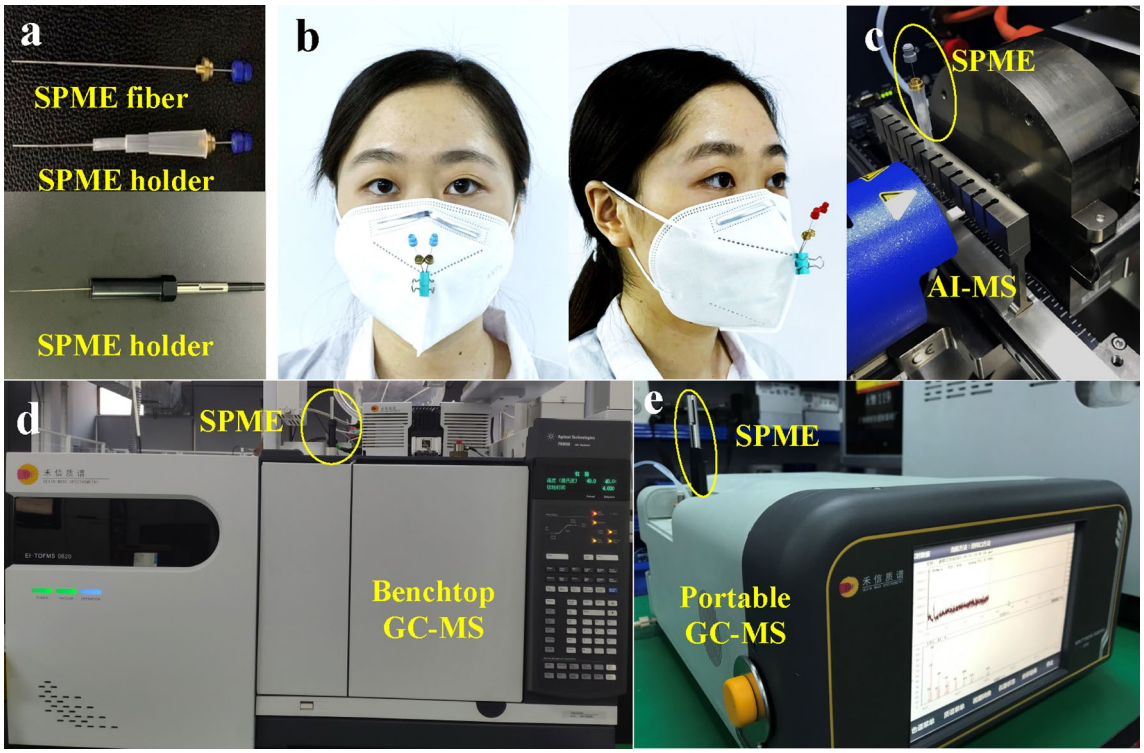

Fig. 3 Representative MS-related approaches towards to COVID-19 study: **a** SPME fiber and SPME holders, **b** facemask-SPME breath sampling, **c** ambient SPME-MS analysis, **d** benchtop SPME–GC–MS analysis, **e** potable SPME–GC–MS analysis. **a-c** are adapted from [55] with permission

were condensed into a cold collector under a low temperature (below zero degrees centigrade) [77–86]. Numerous special metabolites have been studied based on LC–MS approaches. Proteins could also be biomarkers of respiratory diseases [78, 87–89]. Optimistically, LC–MS, therefore, have been proposed to COVID-19 diagnosis and research that could bring new insight into biological impact of COVID-19 [48, 60]. Various breath sampling systems (Table 3) have been successfully developed for collecting EBC [90]. Because of the low concentration of organic metabolites in EBC, further sample preparation preconcentration of breath components is usually required before LC–MS analysis. Lyophilization has been proposed as the best preconcentration option for a metabolic analysis of EBC [48].

Although breath proteins are easily collected by EBC sampling, breath proteomics analysis is difficult to investigate because of the extremely low concentration and complex biometrics. Previous studies on breath proteomics were usually conducted by protein collection, lyophilization, matrix removal, and in-solution/gel digestion before LC–MS/MS analysis [78, 87, 88]. Most experiments were performed using pooled EBC samples to improve protein detection and proteome coverage. For example, Bredberg et al. [89] applied LC–MS system to characterize protein composition of endogenous EBA from pooled samples from six (3000 L exhaled air) and ten (4400 L exhaled air) healthy donors, respectively. It was found that various proteins could be shared by blood and bronchoalveolar lavage proteins, such as albumin, serotransferrin, surfactant protein A, α1-antitrypsin, and immunoglobulins. Lacombe et al. [87] further performed LC–MS-based proteomics characterization of pooled samples of EBC. Detailed bioinformatics analysis of 153 proteins showed that most of the proteins identified corresponded to proteins secreted in the respiratory tract (e.g., lung and bronchi). A comparison study indicated that protein composition can be influenced by EBC sampling method [87]. These results revealed that EBC sampling method (Table 3) is one of the key factors for LC–MS-based proteomics and metabolomics study. A long-time and comfortable breath sampling would be beneficial to EBC collection. A facemask-based wearable microextraction device can performed breath sampling for several hours [55]. Although further studies and improvements are needed, EBC sampling coupled with LC–MS strategy may constitute a powerful tool for investigating breath proteomics and breath metabolomics of COVID-19, and thus support biomarker discovery and provide new biomedical knowledge.

2.4 MALDI-MS

Given the fact that SARS-CoV-2 can be spread through breath droplets, direct identifying SARS-CoV-2 from breath samples is highly needed [91, 92]. MALDI-MS is an effective analytical tool for identifying microorganisms, including bacteria, fungi, and viruses, for its high accuracy, mass range, and tolerance of mixtures [93–97]. Under MALDI-MS, identifying microbes is performed by matching peptide mass fingerprinting of unknown organisms or by biomarkers of unknown organisms with the protein, peptide, and nucleic acid sequence database. Human coronavirus screening using MALDI-MS can trace back to a previous work by Xiu and co-workers in 2017 [98], the time before the COVID-19 outbreak. This work established a screening platform for screening pharyngeal and/or anal swab samples collected from human patients, bats, and rodents. The results obtained by MALDI-MS showed good concordance with those results by metagenomic analysis. Recently, many outstanding studies on versatile applications of MALDI-MS for clinical diagnosis or molecular medicine research of COVID-19 have been achieved [18, 22–25]. MALDI-MS system could be used for accurately screening known coronaviruses to provide pathophysiological evidence for emerging unknown human coronaviruses. Like LC–MS analysis, a minimum amount of microbial concentration is also required for MALDI-MS identification. Due to the low concentration of virus in breath samples, collection and preconcentration (i.e., lyophilization) of EBA and EBC are also required [83, 84]. Virus-specific proteins/nucleic acids in nasopharyngeal swab samples, plasma, or serum could be analyzed by MALDI-MS. A challenging task is that MALDI-MS analysis is based on the known coronavirus sequence, which is difficult to identify a new virus. MS data analysis and process for identifying microorganisms is another challenging task. Database development, multivariate analysis, artificial intelligence, and machine learning are promising data tools for diagnosing and predicting human diseases like COVID-19.

2.5 ICP-MS

Constitution, distribution, and dynamics of trace elements in human body have increasingly become key clinical information in medicine. Trace elements could serve as biomarkers for diagnosing human disease [99]. ICP-MS is a powerful analytical technique to measure elements at trace levels in human tissues, body fluids, and exhaled breath samples for better understanding of medical conditions [99]. It is reported that severe cases of COVID-19 patients experienced an imbalance of mineral status [100, 101]. Thus, the balance of mineral status in body fluids and exhaled breath of COVID-19 patients might be significantly influenced through a yet-to-be-discovered bioinorganic mechanism. Zeng et al. [26, 28] applied ICP-MS to determinate various elements, including Mn, Ca, Cr, Mn, Fe, Cu, Zn, As, Cd, Hg, Tl, Pb, and others from COVID-19 and non-severe COVID-19 patients' body fluids. These studies revealed that significant variations of elements associated with the disease development of COVID-19 can be performed using ICP-MS.

The variation of trace elements in breath samples of COVID-19 patients is still unclear. ICP-MS characterization of trace elements in breath samples associated with COVID-19 as novel biomarkers is highly expected to better understand the underlying bioinorganic processes of COVID-19. Various previous investigations have shown that trace elements in breath samples are detectable to explore the patients' variations using ICP-MS [85, 86]. These studies demonstrated the feasibility of ICP-MS for detecting trace elements in breath samples of COVID-19. Like other offline MS analysis, collection, and preparation of trace elements in breath samples (e.g., EBC, EBA) are usually required before ICP-MS analysis. Compared with other MS-based methods, the unique feature of ICP-MS is that COVID-19 could gain new insight at atomic dimension. Therefore, point-of-care treatment (e.g., micronutrient supplement) of COVID-19 would be a new strategy based on the elemental changes associated with the bioinorganic process in the future.

3 Conclusions and Prospects

Currently, PCR testing is still the golden standard for diagnosing COVID-19. There is still a demand to develop new methods for COVID-19 diagnosis and research. MS-based multidimensional analytical platform offers a new strategy for detecting metabolites, proteins, microorganisms, and trace elements in breath samples, which contributes important factors to develop new methods for diagnosing COVID-19 and better understanding of the underlying physiological, biochemical, and bioinorganic processes and the health impact of COVID-19. Technically, MS-based breath analysis is a practical and powerful method for investigating COVID-19 with many advantages. However, there is a lack of organized clinical resources and sufficient related literature for investigating breath samples from different dimensions.

Prospects of MS-based breath analysis are bright: (1) breath EBA sampling (e.g., facemask microextraction sampling) coupled with portable MS approaches, potable GC–MS or potable ambient MS (e.g., miniature MS [102, 103]) could provide attractive onsite diagnosis; (2) detectability of MS-based breath analysis could be further improved by a long-time breath sampling and sample preparation methods by collecting VOCs, organic metabolites, proteins, microorganisms, and elements; e.g., extracting trace compounds in daily life using facemask-related methods;

(3) combining different MS approaches (e.g., ultrasensitive and ultrahigh-resolution MS) to establish a higher dimensional MS-based platform is highly needed to extend insight to biologically and clinically relevant breath responses of COVID-19; (4) to promote deep understanding of the health impact of COVID-19, new data-dependent acquisition and data analysis methods can be expected with the new development of big data, artificial intelligence, machine learning and other mathematical methods. Together with different types of biomarkers in breath samples, the MS-based multidimensional platform of human breath analysis may be clinically useful in COVID-19 and other human diseases. Indeed, this research requires constant collaboration from different disciplines, including but not limited to analytical, instrumental, biochemical, clinical, medical, and mathematical researchers. Therefore, it can be expected that new improvements and developments of multidimensional MS-based breath analysis will bear fruits for a better diagnosis and understanding of human diseases in the future.

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Declarations

Conflict of Interest The authors declare no competing financial interest.

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