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Breath biomarkers in Non-Carcinogenic diseases

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ABSTRACT

The analysis of volatile organic compounds (VOCs) from human matrices like breath, perspiration, and urine has received increasing attention from academic and medical researchers worldwide. These biological-borne VOCs molecules have characteristics that can be directly related to physiologic and pathophysiologic metabolic processes. In this work, gathers a total of 292 analytes that have been identified as potential biomarkers for the diagnosis of various non-carcinogenic diseases. Herein we review the advances in VOCs with a focus on breath biomarkers and their potential role as minimally invasive tools to improve diagnosis prognosis and therapeutic monitoring.

1. Introduction

Modern medicine is focused on developing and applying improved methodologies that help reduce the time required for the assessment of health state and diagnosis [1]. It is common knowledge that the success of most medical treatments is directly dependent on rapid analysis of biomatrices that include blood, urine and cerebrospinal fluid as well as tissue [2,3]. The latter, while highly diagnostic is invasive, painful, costly and not amendable for serial sampling. Imaging is also a consideration but has drawbacks due to cost and potential radiation exposure [4–6]. In contrast, breath-based testing represents a viable alternative to traditional methods of sample collection and analysis [1,7].

The detection and identification of organic-borne biomarkers have been deeply considered as a potential methodology to tackle the requirements of time-reducing diagnosis procedures [1,8]. A biomarker is commonly characterized as a biological-borne molecule whose characteristics can be indicative of the presence or development of specific health conditions and pathologies [9,10]. Nonetheless, they can be used for several purposes like risk assessment, health state screening, prognostic determination, evaluation of treatment response, and disease progression. In addition, the collection and analysis of these markers involve non-invasive, painless, and low-cost procedures; factors that also contribute to the interest in biomarkers for clinical purposes [11,12,13]. The techniques presently applied for the collection and analysis of these analytes in trace concentration have been discussed elsewhere [14].

A specific type of compounds has received substantial attention regarding their capacity to act as biomarkers. Volatile organic compounds (VOCs) are molecules usually present in the interior of the human body whose production can be directly related to both normal and abnormal biological processes [8,15]. Due to their organic nature, they can traverse biological tissues and, consequently, be exhaled [16]. Among all the body fluids which can carry the potential biomarkers to the exterior, the most common are blood, exhaled air, perspiration, urine, faeces, and even lacrimal fluid [17,18]. Once detected, these analytes can be accurately assessed and linked to pathological conditions and health conditions, representing a valuable source of information about the producer organism [19,20].

In order to explore all the potential of breath biomarkers, a proper sample collection for further composition analysis is a very relevant issue that must be briefly mentioned for informative purposes. The breath collection, transportation, and storage are often critical for the quality of VOCs analysis. Depending on the type of material used to manufacture the transfer lines and the storage containers, and due to the high affinity of VOCs to solid surfaces, the analytes can adsorb to the inner walls leading to a reduction of the concentration levels and even a complete loss of specific compounds. This adsorption process is dependent on the composition and length of the transfer line material, and the physicochemical properties of the compounds themselves. Furthermore, the sample can also be contaminated and, consequently, degraded due to the reactivity existent between the walls coating and the analytes, i.e., chemical reactions between the walls of the transfer line materials and of the storage containers can result in the formation of new compounds, leading to the alteration of the sample [21,22].

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Considering the aforementioned facts, four types of containers are often used for collecting, transporting, and storing the analytes collected from breath. These include Tedlar bags, sorbent tubes, needle trap devices, and syringes [23,24]. All have advantages and disadvantages. For example, Tedlar bags are often used for collecting larger volumes (in the range of litres). Their larger surface area maximizes the potential of side reactions between the material and the collected breath, potentially leading to the formation of exogenous compounds that degrade the original content and adulterate the results. Sorbent tubes and needle trap devices are often used in the research context; however, they are considerably more complex ways of collecting and storing exhaled air samples, not to mention the higher costs of both options. Due to these facts, sorbent tubes and needle trap devices are less adequate for clinical implementation and in-loco analyses. Finally, syringe-based containers are commonly interpreted as being the best option to collect and store breath samples. Their practicality, smaller inner surface area, complete isolation of the sample, and compatibility with a vast range of analytical techniques are important advantages of syringes regarding breath sampling [25,26,27].

Aiming to study the suitability of three different syringe-based containers for short- and long-term storage of breath samples, Santos et al. (2023) collected air samples and performed serial measurements using Gas Chromatography – Ion Mobility Spectrometry (GC-IMS) [28]. Three containers were used, ie, glass syringes, plastic syringes with plastic plunger, and plastic syringes with rubbered plunger. The authors concluded that glass syringes maintained the characteristics of the sample for short storage (less than one hour) but failed longer periods. Plastic syringes and, specifically, plastic syringes with rubbered plunger, preserved the sample for longer periods of storage. The results prove not only the suitability of syringes to easily collect breath samples but also, their capacity to preserve the sample.

Analytical methods most commonly used to analyse breath samples are array-based electronic noses and chromatographic/spectrometry-based techniques [29]. In the field of gas sensors, specific systems often based on quartz crystal microbalance sensors (QCMS), photoionization detector sensors (PIDS), surface acoustic wave sensors (SAWS), solid-state electrochemical sensors (SSES), or metal oxide sensors (MOS), are assembled and exposed to the volatile samples. These systems are highly responsive, have good selectivity, provide stable results, and are inexpensive [30,31,32]. On the other hand, techniques like gas chromatography (GC), mass spectrometry (MS), ion mobility spectrometry (IMS), and combinations thereof are the most commonly used for breath analysis [33,34]. All provide accurate and reproducible results with respect to identification and quantitation. In addition, their capability of detecting analytes even at trace levels of concentration, ie, ppb, makes them highly sensitive. Despite the advantages, their complexity and lack of portability are often limitations for in-loco studies in clinical scenarios [35,36,37].

The present paper stresses the importance of the VOCs emitted in the exhaled air for the identification and diagnosis in pathological states. As mentioned, breath is an important carrier of VOCs and, consequently, proper collection and analysis can lead to a very complete characterization of the health status [38,39]. Many VOCs have been identified as breath biomarkers for a vast range of non-carcinogenic pathologies and are reviewed herein. In addition, future perspectives regarding diseases with the potential to be diagnosed through biomarkers present in exhaled air are also discussed.

2. Non-Carcinogenic biomarkers from breath

A total of 292 biomarkers are reviewed for 10 pathologic conditions, ie, asthma [40], chronic obstructive pulmonary disease [41], tuberculosis [42], cystic fibrosis [43], covid-19 [44], chronic kidney disease [45], chronic liver disease [46], diabetes [47], malaria [48], and sleep apnoea [49]. Additionally, six other pathologies with the potential of breath biomarkers are explored. These include Alzheimer's disease [50], Crohn's disease [51], epilepsy [52], multiple sclerosis [53], obesity [54], and sepsis [55].

2.1. Asthma

Asthma is one of the most common pulmonary pathologies across the world. It leads to thousands of deaths every year and is responsible for most admissions of breathlessness patients in hospitals and health units [56]. Asthma is a chronic inflammatory disease usually categorized in the classes mild, moderate, and severe, according to the inflammation severity. Its diagnosis is possible through several methodologies but mainly through the evaluation of pathological changes in the walls of the bronchi and bronchioles, or the fractional exhaled nitric oxide (FeNO) test. Regardless of being the most common, they are invasive, expensive, and time-consuming methodologies [57,58,59]. For these reasons, the identification of VOCs as potential asthma biomarkers, in the exhaled breath, that enable a faster, non-invasive and patient-friendly (especially in children's cases) diagnostic, is gaining relevance and attention.

The potential to differentiate healthy individuals from asthmatic patients through the VOCs patterns of the exhaled breath was studied by Montuschi et al. (2010). In that study, pulmonary function tests were performed with an electronic nose and a mass spectrometer, on a cohort of 51 volunteers (24 healthy individuals and 27 intermittent and persistent mild asthma patients). Simultaneously, the FeNO was also evaluated for each subject. This cross-sectional study for asthma diagnostic enabled the authors to prove that the accuracy (87.5 %) of the methodology involving VOCs patterns supplanted the typical methods of FeNO (79.2 %) and lung function tests (70.8 %), proving the large potential of VOCs as asthma biomarkers [60]. Even without providing information on the detected VOCs, Rufo et al. (2019) developed a two-cluster exhaled VOCs-based hierarchical model capable of differentiating healthy individuals from persistent asthma patients with a diagnostic accuracy of 81 % [61].

Schleich et al. (2019) studied the potential of using patterns of VOCs to differentiate, in a non-invasive way, between different asthma inflammatory phenotypes like neutrophilic and eosinophilic asthma. The exhaled breath samples were analysed with a two-dimensional gas chromatography - high-resolution - time-of-flight - mass spectrometry (GC-GC-HR-ToF-MS) device. Authors were able to demonstrate that with the combination of only four VOCs, hexane, 2-hexanone, 1-propanol, and nonanal, in a single pattern, the categorization of asthma in neutrophilic or eosinophilic was done with considerably higher specificity and sensitivity values when compared with the typical FeNO and blood tests. In this way, the studied VOCs correspond to potential biomarkers for asthma diagnostic and phenotyping differentiation [62]. Caldeira et al. (2011) research group developed a methodology for profiling volatile metabolic patterns of allergic asthma. To do so, the authors assessed the metabolic volatile profiles of allergic asthma patients with a headspace - solid-phase microextraction - gas chromatography - quadrupole mass spectrometry (HS-SPME-GC-QMS) device. A total of 44 relevant volatiles were detected in the exhaled breath of both healthy individuals (15 subjects) and allergic asthma patients (35 subjects), and the differentiation of these two groups by HS-SPME-GC-QMS was achieved with an accuracy value of 88 % [63]. In a second study from the same research group, a pattern of six VOCs, nonane, decane, dodecane, tetradecane, 3,6-dimethyldecane and 2,2,4,6,6-pentamethylheptane, was identified as asthma-specific compounds. To do so, exhaled breath analysis of 59 children (32 patients with allergic asthma and 27 healthy subjects) by two-dimensional - gas chromatography - time-of-flight - mass spectrometry (GC-GC-ToF-MS) [64].

To detect predictive VOCs signatures of asthma in children, Smolinska et al. (2014) were able to identify 13 asthma-characteristic volatile organic compounds. A cohort of 252 children was used for exhaled breath studies with a gas chromatography - time-of-flight - mass spectrometer (GC-ToF-MS) device. An astonishing number of 3256 different compounds were detected from all the breath samples, however, the authors were able to select a set of 13 VOCs whose behaviour undoubtedly changes between the healthy and asthmatic groups. Specifically, VOCs like acetone or biphenyl decrease their concentration levels for early asthma scenarios and, on the other hand, VOCs like octane or 2-undecanal increase their concentrations [65]. Having a similar cohort, young-age children, Robroeks et al. (2013) detected six and identified five VOCs as being asthma indicators in the exhaled breath. The asthma diagnostic through these six VOCs was achieved with values of accuracy, sensitivity, and specificity of 96, 100 and 93 %, respectively [66]. A gas chromatography - mass spectrometry (GC–MS) device was selected by Gahleitner et al. (2013) to analyse the exhaled breath (2.5 L) of 23 children (11 asthmatic patients and 12 healthy subjects). Among all the detected compounds, the authors were able to identify eight VOCs as potential asthma biomarkers [67]. Again, the tremendous potential of VOCs as biomarkers for asthma diagnosis is clear and extremely patient-friendly even for children. Table 1 summarizes the main VOCs addressed in this chapter, their respective Chemical Abstract Service (CAS) and Human Metabolome Database (HMDB) codes, and bibliographic sources.

2.2. Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD), a pathology responsible for millions of deaths every year, is characterized by a chronic and progressive limitation of the respiration flow. Mostly caused by smoking habit, COPD's typical symptoms are cough and expectoration [68,69,70]. Due to the high prevalence and mortality of COPD, physicians are constantly looking for new techniques and methodologies that may enable a faster, non-invasive and accurate diagnosis. VOCs as biomarkers have been gaining relevance as an information source about the disease's existence in an individual [71,40].

Table 1
Summary of all the reviewed VOCs breath biomarkers for the diagnosis of asthma.

Volatile Organic Compounds	CAS Number	HMDB Number	References
Acetone	67–64-1	HMDB0001659	[65]
Biphenyl	92–52-4	HMDB0034437	[65]
Decane	124–18-5	HMDB0031450	[64]
1,4-Dichlorobenzene	106–46-7	HMDB0041971	[67]
3,6-Dimethyldecane	17312–53-7	–	[64]
2,4-Dimethylheptane	2213–23-2	HMDB0031416	[65]
1,7-Dimethylnaphtalene	575–37-1	–	[67]
2,4-Dimethylpentane	108–08-7	–	[65]
Dodecane	112–40-3	HMDB0031444	[64]
2-Ethenylnaphtalene	939–27-5	–	[65]
Ethylbenzene	100–41-4	HMDB0059905	[67]
2-Ethyl-4-methylpentanol	106–67-2	HMDB0059859	[66]
Hexane	110–54-3	HMDB0029600	[62]
2-Hexanone	591–78-6	HMDB0005842	[62]
1-Isopropyl-3-methylbenzene	535–77-3	HMDB0037051	[67]
2-Methylhexane	591–76-4	HMDB0245230	[65]
1-Methyl-4-(1-methylethenyl) cyclohexene	5989–54-8	HMDB0037231	[65]
2-Methylpentane	107–83-5	HMDB0061884	[65]
3-Methylpentane	96–14-0	HMDB0061885	[66]
1-(Methylsulphonyl)propane	1977–37-3	–	[67]
4,6,9-Nonadecatriene	874302–34-8	–	[66]
Nonanal	124–19-6	HMDB0059835	[62]
Nonane	111–84-2	HMDB0029595	[64]
Octadecyne	629–89-0	–	[67]
Octane	111–65-9	HMDB0001485	[65]
2-Octenal	2363–89-5	HMDB0013809	[67]
2,2,4,6,6-Pentamethylheptane	13475–82-6	HMDB0094665	[64]
Phenylbutene	935–00-2	HMDB0059812	[66]
Propanol	71–23-8	HMDB0000820	[62]
Tetradecane	629–59-4	HMDB0059907	[64]
2,6,10-Trimethyldodecane	3891–98-3	HMDB0302691	[65]
2,2,4-Trimethylheptane	14720–74-2	HMDB0303093	[65]
2,3,6-Trimethyloctane	62016–33-5	–	[65]
2-Undecanal	53448–07-0	HMDB0030941	[65]
p-Xylene	106–42-3	HMDB0059924	[66]

To evaluate the suitability of VOCs as differentiation tools between healthy individuals and COPD patients, Cristescu et al. (2011) performed a breath test with a proton-transfer-reaction mass spectrometry (PTR-MS) device. The 204 volunteers were previously tested by computed tomography for COPD diagnosis. The exhaled breath profiles, once compared with the CT test results, enabled the diagnosis of COPD with an accuracy of around 95 %. These results prove the suitability and potentiality of VOCs as chronic obstructive pulmonary disease biomarkers [72]. In their turn, Dragonieri et al. (2016) used an electronic nose to differentiate three main groups through the pattern of VOCs in their respective exhaled breath. Patients suffering from chronic obstructive pulmonary disease (COPD – 15 subjects), obstructive sleep apnoea (OSA – 13 subjects) and overlap syndrome (OVS – 13 subjects) were included in the study. Even without information on the detected VOCs, the authors were able to use the pattern to successfully differentiate among the three groups. The distinction between OSA and OVS patients was achieved with a cross-validation accuracy (CVA) of 96.2 %. Between the OSA and COPD patients, the distinction was achieved with a CVA of 82.1 %. Finally, the groups of OVS and COPD patients were differentiated with a CVA of just 67.9 %, however, the suitability of the electronic nose and, specifically, of patterns of VOCs for disease diagnosis and differentiation is clear [73]. A cross-sectional study centralized in a gas chromatography time-of-flight mass spectrometry device (GC-ToF-MS) was developed by Basanta et al. (2012), to assess the VOCs signatures in exhaled breath suitability for distinguishing between COPD patients and healthy individuals. Breath tests of 71 subjects (32 healthy individuals and 39 COPD patients) were performed and the detected VOCs were statistically processed with principal component analysis (PCA). A total explained variance of 71 % was achieved as a PCA result, and the differentiation between COPD patients and healthy individuals attained specificity and sensitivity levels of 50 % and 85 %, respectively [74].

A total of 137 VOCs were detected in the exhaled breath tests performed on a group of COPD patients and on a group of healthy individuals, by Besa et al. (2015). From these, five VOCs were identified as COPD biomarkers, enabling differentiation between COPD patients and healthy subjects with an accuracy of 70 %. Unfortunately, the authors provide no information on the identification of these VOCs. In a parallel analysis, the authors were able to find 15 VOCs responsible for the distinction between non-smokers and smokers subjects. The exhaled breath analyses were performed by ion mobility spectrometry (IMS) [75]. A multicapillary column coupled to an ion mobility spectrometry device (MCC-IMS) was the analytical technique selected for an independent study developed by the same research group. Here, 46 individuals (33 healthy subjects and 13 COPD patients) participated in breath tests; the collection was performed through an inert Teflon tube directly connected to the spectrometer. Among the 98 detected signals, a single VOC was observed as a potential biomarker for COPD discrimination, with sensitivity and specificity values of 60 and 90 %, respectively. The authors were unable to identify this specific analyte; however, they propose four possibilities for its identity: 1,2,4-trimethylbenzol, phenol, 4-methyllanisol, and benzofuran [76]. To study the impact of COPD on the pattern of organism-produced and emitted VOCs, Scarlata et al. (2018) developed a scientific study around exhaled breath collection and analysis. An electronic nose device was selected for the analyses. The patterns of VOCs collected from 50 recently diagnosed COPD patients enabled the authors to distinguish three distinct clusters taking into consideration the existence/absence of remarkable comorbidities, the occurrence or not of air trapping, and the BODE (Body-mass index, airflow Obstruction, Dyspnoea, and Exercise) index. Patterns of VOCs proved to be extremely accurate (accuracy of around 95 %) in classifying and distinguishing COPD patients in different disease stages

[77].

Westhoff et al. (2010) developed a study in which the exhaled breath of 132 volunteers was analysed with an MCC-IMS apparatus. The cohort included 35 healthy subjects, 35 COPD patients and 62 COPD and lung cancer patients. Breath samples of 10 mL were analysed, and from all the spectra, 104 signals were detected. By statistically processing the analytes with principal component analysis (PCA). A single analyte, cyclohexanone, was characterized as a COPD biomarker with sensitivity and specificity levels of 60 % and 91 %, respectively [78]. In a study self-claimed as the first distinguishing COPD patients and healthy individuals solely by considering the VOCs of exhaled breath, Berkel et al. (2010) used a GC–MS device to analyse breath samples from 79 volunteers (29 healthy subjects and 50 COPD patients). From the 1179 analytes detected with the spectrometer, the authors reduced the group to 13 relevant VOCs. Considering six of these 13, authors could successfully distinguish between COPD patients and healthy volunteers in 92 % of the cases, corresponding to 88 % and 98 % of specificity and sensitivity, respectively [41]. A cohort of 181 individuals (63 healthy volunteers and 118 COPD patients) was used by Phillips et al. (2014) to assess eventual biomarkers of COPD in the exhaled breath. Among the detected VOCs with GC–MS, six of these were considered of special relevance for COPD diagnosis, namely, isoprene, toluene, benzene, hexanal, benzaldehyde and nonadecane. Based on the mentioned VOCs, COPD patients were successfully distinguished from healthy subjects with an accuracy of 73.4 %. [79].

The exhaled breath of a cohort of 157 volunteers (57 COPD patients and 100 healthy subjects (never, former, and active smokers)) was analysed by Jareño-Esteban et al. (2017), with thermal desorption and then by gas chromatography - mass spectrometry (GC–MS). Around 250 VOCs were detected in the breath samples and by a meticulous elimination process based on each VOC's origin, the authors were able to have a final group of five relevant analytes (hexanal, heptanal, nonanal, propanoic acid, and nonanoic acid). The developed study enabled the authors to prove that COPD patients are differentiable from healthy individuals through the hexanal concentration levels. In parallel, the authors were able to conclude that nonanal concentration levels are discriminators among smokers and non-smokers [80]. A GC–MS device was also the analytical technique selected by Cazzola et al. (2015) to analyse the exhaled breath in search of potential COPD biomarkers. From both healthy and COPD patient groups previously classified and separated with an electric nose device, a total of 37 VOCs were detected; nine of these were observed as COPD-characteristic. As defined by the authors, seven were negatively related (decreased their concentration levels) and two were positively related (increased their concentration levels) with COPD [81]. Rodríguez-Aguilar et al. (2019) used a device that couples gas chromatography (GC) to an electric nose, to perform breath analyses on 56 individuals (33 healthy subjects and 23 COPD patients). Among all the detected analytes, the authors were able to accurately identify 17 VOCs as potential COPD biomarkers. To differentiate between healthy subjects and COPD patients, a principal component analysis (PCA) was applied to the pattern of these VOCs, achieving levels of total explained variance of 55.282 % (PC1 – 25.804 %, PC2 – 16.972 % and PC3 – 12.506 %) [82]. Allers et al. (2016) selected two analytical technologies, gas chromatography - ion mobility spectrometry (GC-IMS) and gas chromatography - atmospheric pressure chemical ionization - mass spectrometry (GC-APCI-MS) to search for a relationship between exhaled VOCs and COPD. The detection of VOCs was performed in a concentration range of 0.1 ppt_v to 1 ppm_v. From all the breath samples of the 58 volunteers (9 non-smokers, 16 smokers, 21 smokers with COPD, and 12 non-smokers with COPD), a single analyte was identified as a COPD biomarker, 2-pentanone [83]. Finally, Pizzini et al. (2018) used a thermal desorption - gas chromatography - time of flight - mass spectrometry (TD-GC-ToF-MS) device to detect and identify the exhaled VOCs of 54 volunteers (24 healthy subjects, 16 stable COPD patients, and 14 acute exacerbations-COPD patients). Eight VOCs were detected and accurately identified as potential COPD biomarkers [84]. All the aforementioned studies and respective results prove the suitability of volatile organic compounds as a rapid, non-invasive and accurate diagnosis methodology. Table 2 summarizes the main VOCs addressed in this chapter, their respective Chemical Abstract Service (CAS) and Human Metabolome Database (HMDB) codes, and bibliographic sources.

2.3. Tuberculosis

Tuberculosis is an infectious disease usually caused by infectious agents like the mycobacterium tuberculosis, which affects not only but mainly the lungs and respiratory system but also leads to millions of deaths worldwide every year [85,86]. The interest in new metabolic, non-invasive and accurate approaches for the diagnosis of tuberculosis has been growing, in fact, the exhaled breath and urine of tuberculosis

Table 2
Summary of all the reviewed VOCs breath biomarkers for the diagnosis of chronic obstructive pulmonary disease.

Volatile Organic Compounds	CAS Number	HMDB Number	References
Acetaldehyde	75–07-0	HMDB0000990	[82]
2-Acetylpyridine	1122–62-9	HMDB0035281	[82]
Benzaldehyde	100–52-7	HMDB0006115	[79]
Benzene	71–43-2	HMDB0001505	[79]
Benzonitrile	100–47-0	–	[41]
Butanal	123–72-8	HMDB0003543	[82]
Butane	106–97-8	–	[84]
Butylatedhydroxytoluene	128–37-0	HMDB0033826	[81]
2-Butyloctanol	3913–02-8	HMDB0041288	[82]
[E]-Cinnamaldehyde	14371–10-9	–	[82]
Cyclohexanone	108–94-1	HMDB0003315	[78 84]
Decane	124–18-5	HMDB0031450	[81]
Dimethyl disulphide	624–92-0	HMDB0005879	[84]
2,6-Dimethylheptane	1072–05-5	–	[41]
4,7-Dimethylundecane	17301–32-5	–	[41]
Δ-Dodecalactone	713–95-1	HMDB0037742	[82]
6,2-Ethylmethyldecane	62108–21-8	–	[81]
3,4-Ethylmethylhexane	3074–77-9	–	[81]
Heptanal	111–71-7	HMDB0031475	[80]
Heptane	142–82-5	HMDB0031447	[84]
4-Heptanone	123–19-3	HMDB0004814	[84]
Hexadecane	544–76-3	HMDB0033792	[41]
Hexanal	66–25-1	HMDB0005994	[41 79 80]
3-Hexanone	589–38-8	HMDB0000753	[82]
Hexylethylphosphonofluoridate	135445–19-1	–	[81]
Indole	120–72-9	HMDB0000738	[82]
Isoprene	78–79-5	HMDB0253673	[41 79]
Isopropanol	67–63-0	HMDB0000863	[81 82]
Limonene	138–86-3	HMDB0003375	[81]
2-Methylbutanoic acid	116–53-0	HMDB0002176	[82]
3-Methylcyclopentanone	1757–42-2	–	[82]
6-Methyl-5-hepten-2-one	110–93-0	HMDB0035915	[84]
Methylisobutyrate	547–63-7	–	[82]
4-Methyloctane	2216–34-4	–	[41]
Methylpropylsulphide	3877–15-4	–	[84]
Nonadecane	629–92-5	HMDB0034289	[79]
Nonanal	124–19-6	HMDB0059835	[80]
Nonanoic Acid	112–05-0	HMDB0000847	[80]
Octadecane	593–45-3	HMDB0033721	[41]
Octane	111–65-9	HMDB0001485	[82]
2-Pentanone	107–87-9	HMDB0034235	[83 84]
α-Pinene	80–56-8	HMDB0006525	[82]
Propanal	123–38-6	HMDB0003366	[82]
Propanoic Acid	79–09-4	HMDB0000237	[80]
Terpineol	8006–39-1	HMDB0004043	[41]
Tetradecane	629–59-4	HMDB0059907	[82]
Toluene	108–88-3	HMDB0034168	[79]
2,4,6-Trimethyldecane	62108–27-4	–	[41]
2,4,4-Trimethylpentene	107–39-1	HMDB0031197	[81]
1,3,5-Tri-*tert*-butylbenzene	1460–02-2	–	[81]
Undecane	1120–21-4	HMDB0031445	[41]
Vinylpyrazine	4177–16-6	HMDB0303343	[82]

patients have been deeply studied for the identification of VOCs as potential biomarkers. Phillips et al. (2010, 2012) research group has achieved outstanding results in this field by using a breath test internally developed for the detection and identification of exhaled breath VOCs. In a first study, the breath from 226 symptomatic patients was analysed with a gas chromatography - mass spectrometry (GC–MS) device. Authors were able to identify ten VOCs as potential biomarkers for tuberculosis with sensitivity and specificity of 84.0 % and 64.7 %, respectively, and overall accuracy of 85.0 % [42]. For a second study, the same research group used the mentioned breath test in a set of 279 volunteers (121 healthy subjects and 130 tuberculosis patients). Seven VOCs were used to differentiate between both groups 71.2 % and 72 % of sensitivity and specificity, and overall accuracy of 84 % [87]. The differentiation among healthy subjects and tuberculosis patients through VOCs was also the aim of Banday et al. (2011) however, the VOCs detection was performed in urine samples, not in the exhaled breath. Authors were able to remark on the increase in concentration levels of isopropyl acetate and o-xylene, and the decrease of 3-pentanol, 2,6-dimethylstyrene, and cymol concentrations, in this way, these five characteristic compounds were characterized as potential tuberculosis biomarkers [88]. Urinary VOCs were also studied by Lim et al. in the search for tuberculosis biomarkers. A colorimetric sensor array was developed for testing the urine of 63 volunteers (22 tuberculosis patients and 41 healthy subjects). Even without information about the analysed VOCs, the authors claim to have achieved sensitivity and specificity values of 85.5 % and 79.5 %, respectively, in the differentiation of both groups [85]. Table 3 summarizes the main VOCs addressed in this chapter, their respective Chemical Abstract Service (CAS) and Human Metabolome Database (HMDB) codes, and bibliographic sources.

2.4. Cystic fibrosis

Cystic fibrosis belongs to the same list of inflammatory diseases as asthma and COPD. The symptomatic profile is characterized by chronic inflammation of the airways, bronchiectasis, retention of viscous secretions, and even bacterial infection. The mentioned inflammatory processes are often assessed by biopsy, bronchoscopy lavage, chest radiography, or analytical tests like blood analysis, however, these invasive procedures lead to some unnecessary risks. The identification of VOCs in the exhaled breath as potential signatures for cystic fibrosis has gained relevance [89,90].

Table 3
Summary of all the reviewed VOCs breath biomarkers for the diagnosis of tuberculosis.

Volatile Organic Compounds	CAS Number	HMDB Number	References
Bis-(3,5,5-trimethylhexyl) phthalate	14103–61-8	–	[42]
2-Butyloctanol	3913–02-8	HMDB0041288	[87]
Camphene	79–92-5	HMDB0059839	[87]
Cymol	99–87-6	HMDB0005805	[88]
3,7-Dimethyldecane	17312–54-8	–	[42]
2,6-Dimethylstyrene	2039–90-9	HMDB0302922	[88]
5-Ethyl-2-methylheptane	13475–78-0	HMDB0061915	[42]
Hexylcyclohexane	4292–75-5	–	[42]
Isopropylacetate	108–21-4	HMDB0000718	[88]
Menthol	89–78-1	HMDB0003352	[87]
Methylbenzene	108–88-3	HMDB0034168	[87]
4-Methyldodecane	6117–97-1	–	[42]
3-(1-Methylethyl)oxetane	10317–17-6	–	[42]
4-Methylhexene-1,4-diol	40646–08-0	–	[42]
3-Pentanol	584–02-1	HMDB0303831	[88]
β-Pinene	127–91-3	HMDB0036559	[87]
Tridecane	629–50-5	HMDB0034284	[42 87]
1,3,5-Trimethylbenzene	108–67-8	HMDB0041924	[42 87]
4,6,8-Trimethylnonene	54410–98-9	–	[42]
o-Xylene	95–47-6	HMDB0059851	[88]

To develop a breath test for cystic fibrosis diagnosis, Kramer et al. (2015) analysed the headspace emitted by epithelial lung cells previously infected with human pathogens. In addition, 100 mL of exhaled breath from nine cystic fibrosis patients were collected using solid-phase microextraction (SPME) and analysed by GC–MS. Authors claimed that, through the detected analytes, it was possible to successfully identify 100 % of the cases proving the suitability of VOCs in the diagnosis of cystic fibrosis [43]. Paff et al. (2013) developed a study with a similar goal, to differentiate cystic fibrosis patients and primary ciliary dyskinesia. A cohort of 73 subjects (23 healthy individuals, 25 with primary ciliary dyskinesia and 25 with cystic fibrosis) was used for exhaled breath analyses with an electronic nose. Even without providing information on the used VOCs, authors claim that VOCs patterns enabled them to accurately differentiate cystic fibrosis from healthy subjects with sensitivity and specificity levels of 84 % and 65 %. The differentiation between cystic fibrosis and primary ciliary dyskinesia patients was achieved with selectivity and specificity levels of 84 % and 60 %, respectively [91]. An electronic nose was also used by Bannier et al. (2019) to analyse the exhaled breath of 55 children (22 healthy volunteers, 20 asthma patients, and 13 cystic fibrosis patients). Like in the previously addressed study, information on the detected analytes is not provided, however, authors were able to discriminate between cystic fibrosis patients and healthy subjects with sensitivity and specificity of 89 % and 77 % respectively, through the breath patterns [92]. Horck et al. (2021) used a GC-ToF-MS device to analyse exhaled breath samples of 49 cystic fibrosis patients, every two months for one year. The study aimed to detect and identify volatile analytes directly related to pulmonary exacerbations caused by the disease. A set of nine VOCs was selected as being the most discriminatory, enabling the identification of cystic fibrosis patients with specificity and sensitivity levels of 78 % and 79 %, respectively [93]. A real-time secondary electrospray ionisation - high-resolution mass spectrometry (SESI-HRMS) device was used by Weber et al. (2020) to analyse a cohort of 101 children (49 healthy individuals and 52 cystic fibrosis patients). From the 3468 found analytes, authors were able to detect 171 as significantly different between the two groups and, in this way, potential cystic fibrosis biomarkers. By developing these characteristics VOCs as a pattern, it was possible to differentiate the group of healthy individuals from the group of cystic fibrosis patients with accuracy, sensitivity and specificity levels of 72.1 %, 77.2 % and 67.7 % [94]. As proved, the detection and identification of VOCs and patterns of VOCs enable outstanding results in the field of cystic fibrosis diagnosis through exhaled breath biomarkers.

Regarding the identification of the VOCs assessed as potential biomarkers for cystic fibrosis, several scientific studies have been developed. Robroeks et al. (2010) analysed the volatile organic compounds produced and emitted during the inflammatory processes of cystic fibrosis. The study included 57 healthy volunteers and 48 cystic fibrosis patients. Exhaled breath samples were collected into inert tubes of active carbon for stabilization of the analytes. The measurements were performed with a GC-ToF-MS device. Among the 1099 detected compounds, the authors found 10 with special significance in the breath of cystic fibrosis patients. Seven were successfully identified [95]. Twelve VOCs with high potentiality for being cystic fibrosis biomarkers were identified by Mastrigt et al. (2016). Breath samples of 15 cystic fibrosis patients and 35 healthy individuals were collected into inert Tedlar bags and posteriorly analysed with a laser-based spectroscopy device. Besides being able to identify 12 potential biomarkers with the mentioned technique, the authors claim that additional studies are required to ensure the necessary repeatability and methodology validation [96].

Bacterial infection is one of the main morbidity and mortality causes in cystic fibrosis patients. Most of these bacteria release volatile organic compounds during their biochemical mechanisms. In this way, Bos et al. (2016) developed a study to evaluate VOCs released by bacterial DNA fragments in samples of sputum from cystic fibrosis patients. DNA fragments of five genera of bacteria were considered (*Streptococcus*, *Rothia*, *Lactococcus*, *Escherichia* and *Pseudomonas*). In parallel, exhaled breath samples from seven cystic fibrosis patients were analysed with a GC–MS device. Overall, the authors were able to conclude that the studied bacteria are responsible for the production and emission of four main VOCs (methanol, ethanol, acetaldehyde and 2,3-butanedione), potential biomarkers for infection processes in cystic fibrosis patients [97]. Similar results were achieved by Phan et al. (2017) in the measurements of headspace formed from three bacterial strains, *Rothia mucilaginosa*, *Streptococcus salivarius* and *Pseudomonas aeruginosa*. Ethanol, acetaldehyde, dimethyl sulphide and 2,3-butanedione were identified as biomarkers for the infection processes of the mentioned bacteria [98].

Dryahina et al. (2016) analysed the analytes produced and emitted by bacterial cultures prepared in-vitro. Four bacteria were considered, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Burkholderia cepacian* and *Stenotrophomonas maltophilia*. By analysing the headspace of the cultures with a SIFT-MS apparatus, the authors identified several specific VOCs for each bacterial strain. The characteristic analytes of *S. maltophilia* are butanol, pentanol, propanal and hexanal. Isoprene, methane and methanethiol are the VOCs emitted by *B. cepacia*. *S. aureus* presented one single analyte, butyric acid. Finally, the characteristic compounds of *P. aeruginosa* are phenol, nonanone, hydrogen cyanide and methyl thiocyanate [99]. Shestivska et al. (2011), addressing the relevance of *Pseudomonas aeruginosa* infection in cystic fibrosis patients, developed a methodology to detect, identify, and quantify methyl thiocyanate accurately, in real-time. For this, 36 strains with different genotypes of the bacteria were cultivated *in vitro*. The emitted analytes were measured with two distinct techniques, solid-phase microextraction - gas chromatography - mass spectrometry (SPME-GC–MS) and selected ion flow tube - mass spectrometry (SIFT-MS), for comparison. The authors were able to successfully detect and quantify methyl thiocyanate in 28 of the 36 prepared samples. To assess if this VOC can represent, in fact, a cystic fibrosis biomarker, the authors analysed the exhaled breath of 28 patients. In this complementary study, all the volunteers presented methyl thiocyanate in their exhaled breath (concentration range: 2 – 21 ppb_v; median: 7 ppb_v), proving the potentiality of this VOC as a biomarker for the disease [100]. The infection by Staphylococcus aureus in the airways of cystic fibrosis patients was also studied by Neerincx et al. (2016). To discriminate between bacterium-infected and non-infected cystic fibrosis patients, the authors used a GC–MS device to analyse exhaled breath samples previously collected into 3 L Tedlar bags. Nine VOCs were used as a discriminatory pattern, enabling discrimination between *S. aureus* infected and non-infected cystic fibrosis patients with specificity and sensitivity levels of 80 % and 100 %, respectively [101]. As seen, the field of cystic fibrosis biomarkers is in constant growth and has enabled the diagnosing of inflammatory and infection processes in rapid, non-invasive, and accurate ways. Table 4 summarizes the main VOCs addressed in this chapter, their respective Chemical Abstract Service (CAS) and Human Metabolome Database (HMDB) codes, and bibliographic sources.

Table 4
Summary of all the reviewed VOCs breath biomarkers for the diagnosis of cystic fibrosis.

Volatile Organic Compounds	CAS Number	HMDB Number	References
Acetaldehyde	75–07-0	HMDB0000990	[97 98]
Acetone	67–64-1	HMDB0001659	[101]
Benzothiazole	95–16-9	HMDB0032930	[95]
2,3-Butanedione	431–03-8	HMDB0003407	[97 98]
Butanol	71–36-3	HMDB0004327	[99]
2-Butanone	78–93-3	HMDB0000474	[101]
2-Butenol	504–61-0	HMDB0033858	[95]
Butyl Acetate	123–86-4	HMDB0031325	[96]
Butyric Acid	107–92-6	HMDB0000039	[99]
Dichloronitromethane	7119–89-3	–	[96]
Dimethyl Carbonate	616–38-6	HMDB0029580	[96]
3,3-Dimethylhexane	563–16-6	HMDB0031418	[95]
Dimethyl sulphide	75–18-3	HMDB0002303	[98]
1,4-Dioxane	123–91-1	HMDB0244216	[96]
Ethanol	64–17-5	HMDB0000108	[97 98 101]
2-Ethoxyethyl acetate	111–15-9	HMDB0032158	[96]
Ethyl acetate	141–78-6	HMDB0031217	[96]
Ethyl acrylate	140–88-5	HMDB0033978	[96]
Ethyl butyrate	105–54-4	HMDB0033889	[96]
Hexanal	66–25-1	HMDB0005994	[99 101]
Hydrogen cyanide	74–90-8	HMDB0060292	[97]
3-Hydroxy-2-butanone	513–86-0	HMDB0003243	[101]
Isobutyl acetate	110–19-0	HMDB0031246	[96]
Isoprene	78–79-5	HMDB0253673	[99]
Isopropylacetate	108–21-4	HMDB0000718	[96]
Isopropyl myristate	110–27-0	HMDB0040392	[101]
Methane	74–82-8	HMDB0002714	[99]
Methanethiol	74–93-1	HMDB0003227	[99]
Methanol	67–56-1	HMDB0001875	[97]
1-(3-Methoxypropoxy) propanol	1589–49-7	HMDB0031716	[96]
Methyl Acetate	79–20-9	HMDB0031523	[96]
N-Methyl-2-methylpropylamine	39190–66-4	–	[95]
2-Methylnaphthalene	91–57-6	HMDB0032860	[101]
Methylthiocyanate	556–64-9	HMDB0259025	[99 100]
2-Nonanone	821–55-6	HMDB0031266	[99]
2-Octene	13389–42-9	HMDB0061903	[95]
3-Octene	14919–01-8	HMDB0061906	[95]
1,4-Pentadiene	591–93-5	–	[101]
Pentanol	71–41-0	HMDB0013036	[99]
Phenol	108–95-2	HMDB0000228	[99]
Propanal	123–38-6	HMDB0003366	[99]
Tolualdehyde	1334–78-7	HMDB0006236	[95]
Undecane	1120–21-4	HMDB0031445	[101]

2.5. Covid-19

The most spoken pathology nowadays is, undoubtedly, Covid-19. The SARS-CoV-2 infection has been responsible for one of the biggest and most relevant pandemics the world has ever witnessed. In contrast to bacteria and other organisms, viruses have no metabolism, in this way, they do not produce and release VOCs but the virus-infected tissues or organic structures do as a reaction to the infection [17,102]. In this way, the identification of potential biomarkers for Covid-19, even if they are not produced by the virus, is achievable [103]. A study carried out by Jendrny et al. (2020) proved that the VOCs emitted by biological tissues infected with the virus are detectable and differentiable from healthy tissue. Trained dogs were able to accurately distinguish the elements of both groups with sensitivity and specificity values of 82.63 % and 96.35 %. As no analytical technique was used, there is no information on the potential biomarkers [102]. Having a similar goal, Wintjens et al. (2021) used an electronic nose device for pre-operative SARS-CoV-2 screening. The exhaled breath of a cohort of 219 participants (57 infected with Covid-19 and 162 healthy individuals) was analysed and both groups were accurately discriminated (86 % of sensitivity) [104]. Ruszkiewicz et al. (2020), in their turn, used a gas chromatography - ion mobility spectrometry (GC-IMS) device to analyse the exhaled breath of 98 volunteers (31 individuals infected with SARS-CoV-2 virus and 67 healthy volunteers), searching by VOCs with the potentiality for being Covid-19 biomarkers. GC-IMS enabled the differentiation of the two groups with sensitivity and specificity values of 80 % and 81.5 %, respectively. Authors were able to state that ethanal (increased concentration), octanal (increased concentration), acetone (increased concentration), butanone (increased concentration), and methanol (decreased concentration) are Covid-19-discriminant VOCs [105]. A GC-IMS apparatus was also used by Chen et al. (2021) to analyse exhaled breath samples of covid-infected and non-covid-infected individuals. A total of 12 VOCs with potentiality for being Covid-19 biomarkers were detected and four of them were successfully identified (acetone, acetic acid, acetaldehyde, and propanol), for instance, the concentration level of breath-borne acetone is considerably lower in infected individuals than it is in healthy volunteers and the propanol concentration, in its turn, was seen to be higher in infection cases [106]. To study eventual alterations in the exhaled VOCs profiles of children infected by SARS-CoV-2, Berna et al. (2021) used a gas chromatography - gas chromatography - time of flight - mass spectrometry (GC-GC-ToF-MS) device. Among the 84 VOCs of interest detected from the exhaled breath analyses of the 24 children (12 infected with SARS-CoV-2 and 12 healthy individuals), 6 proved to be characteristic of Covid-19 infection, due to their increased concentration in infection cases, and 3 were successfully identified (octanal, nonanal, and heptanal) [107]. Table 5 summarizes the main VOCs addressed in this chapter, their respective Chemical Abstract Service (CAS) and Human Metabolome Database (HMDB) codes, and bibliographic sources.

2.6. Chronic kidney disease

Chronic kidney disease (CKD) leads thousands of people to the rooms for dialysis treatment every year. CKD is responsible, in end-stage scenarios, for acute renal failure and, consequently, death. Besides that, several other pathologies, like cardiovascular diseases, can be even more harmful in CKD patients [108,109,110]. For these reasons, a fast and accurate diagnosis is mandatory to avoid further pathologies. Some studies have addressed the VOCs emitted in the breath as biomarkers for CKD diagnosis that fulfil the necessary requisites of accuracy and rapidness [111,112].

An innovative approach, specifically an external cavity diodelaser–based technique, was developed and applied by Bayrakli et al. (2016) to detect ammonia in the exhaled breath of 42 volunteers (15 healthy individuals and 27 CKD patients). The quantification of this specific VOC enabled the authors to prove that ammonia levels in the breath of healthy individuals range between 120 and 530 ppb_v, but in the breath of CKD patients, it ranges from 710 to 10,400 ppb_v [113]. Ammonia was also the target analyte of Umapathy et al. (2019). A portable prototype was developed by the authors to detect ammonia in the exhaled breath of CKD patients and, in addition, collect breath patterns for posterior processing. Considering the respective breath patterns, the authors were able to distinguish between healthy individuals and CKD patients with an accuracy level of 76.3 % [114]. Naderi et al. (2020), in their turn, developed a methodology that enabled the recognition of ammonia with a detection limit of 212 ppb_v, in the exhaled breath of CKD patients [115].

Exhaled breath signatures were used to distinguish and characterize two distinct groups, CKD patients (15 subjects) and healthy individuals (10 subjects), by Zaim et al. (2019). The samples were collected into an inert Tedlar bag and prosperously analysed with an electronic nose. The processing of data with principal component analysis (PCA) enabled authors to successfully (accuracy level of 96.7 %) differentiate both groups considering their respective exhaled breath analytes [116]. With the main goal of detecting potential CKD biomarkers in the breath, Grabowska-Polanowska et al. (2013) analysed breath samples from 23 volunteers (9 healthy individuals and 14 CKD patients) with a GC–MS device. Three volatile organic compounds were identified as potential biomarkers, namely acetone, isoprene, and trimethylamine. The analyte trimethylamine, in particular, was only detected in the breath of CKD patients, in this way, it presents a huge potential to be categorized as a CKD biomarker [117]. The same research group analysed exhaled breath from a cohort of 30 individuals to distinguish between healthy individuals, CKD patients and CKD patients with type 2 diabetes. A gas chromatography - mass spectrometry (GC–MS) device was the analytical technique used to analyse the samples. The authors were able to successfully differentiate the three groups by considering a pattern of five VOCs, trimethylamine, isoprene, acetone, dimethyl sulphide, and methanethiol [118].

Exhaled breath samples from a cohort of 62 volunteers were used by Marom et al. (2012) to detect VOCs with gold nanoparticle sensors. A pattern of 13 VOCs enabled the differentiation of healthy individuals from CKD patients with accuracy levels of around 80 % [119]. Meinardi et al. (2013) analysed the volatile organic compounds emitted by both exhaled breath and faecal samples of rats with CKD and control rats. From the dozens of detected analytes, the concentration levels of four VOCs (isoprene, pentanal, hexanal and heptanal) seemed to mimic the existence of the disease. For instance, concentration levels of isoprene are considerably higher in CKD patients than in healthy individuals. The three aldehydes, on the other hand, present a significantly lower concentration in the exhaled breath of CKD patients [45].

Eight analytes were considered of interest by Obermeier et al. (2017) for the study of CKD biomarkers. With the results achieved from the exhaled breath measurements of 176 children (116 CKD patients and 60 healthy subjects), the authors were able to prove that five (heptanal, pentanal, isoprene, ethanol, and ammonia) analytes increased their concentration in CKD patients. Methylamine, on the other hand, decreases its concentration in these cases [120]. A total of 22 volatile organic compounds were studied by Saidi et al. (2018), regarding their suitability for diagnostic biomarkers of CKD. Exhaled breath samples of 44 individuals were collected into a 1 L inert Tedlar bag and posteriorly analysed with a gas chromatography - quadrupole time of flight - mass spectrometry (GC-QToF-MS) device. The mentioned analytes exhibit changes in their concentration levels from one group to the other [121]. A few volatile organic compounds are common to most of the reviewed works, namely, ammonia, isoprene, and acetone. In this way, these three analytes are of special interest in the field of breath biomarkers for the diagnosis of CKD. Table 6 summarizes the main VOCs addressed in this chapter, their respective Chemical Abstract Service (CAS) and Human Metabolome Database (HMDB) codes, and bibliographic sources.

2.7. Chronic liver disease

Chronic liver diseases (CLD) are generally classified as pathologies that lead to the loss of liver functions and liver impairment, for medium to long periods. CLD can be of several types, with some of them being largely known worldwide. Hepatic encephalopathy, liver cirrhosis and non-alcoholic fatty liver disease, for example, are three of the main CLD. They cause thousands of direct (loss of liver functionalities) and indirect (secondary pathologies caused by CLD) deaths every year across the planet and yet their incidence is considerably increasing [122,123,124].

Due to the invasive nature of the current diagnostic procedures, VOCs have gained relevance as a potential tool for a non-invasive but accurate way of diagnosing chronic liver pathologies [125]. In fact, the suitability of breath analysis for the identification of CLD biomarkers was studied by Vincentis et al. (2016). A cohort of 160 subjects (56 healthy individuals, 65 liver cirrhosis patients and 65 non-cirrhotic CLD patients) was gathered by the authors. An electronic nose (E-nose) was used to analyse the exhaled breath of all the volunteers. Considering the specific breath patterns, the authors were able to differentiate between CLD patients and healthy individuals with sensitivity and specificity levels of 86.2 and 98.2 %, respectively. The distinction between cirrhosis patients and non-cirrhotic CLD patients was achieved with sensitivity and specificity levels of 87.5 and 69.2 %, respectively [126]. Seven

Table 5
Summary of all the reviewed VOCs breath biomarkers for the diagnosis of covid-19.

Volatile Organic Compounds	CAS Number	HMDB Number	References
Acetaldehyde	75–07-0	HMDB0000990	[106]
Acetic Acid	64–19-7	HMDB0000042	[106]
Acetone	67–64-1	HMDB0001659	[105 106]
2-Butanone	78–93-3	HMDB0000474	[105]
Ethanal	75–07-0	HMDB0000990	[105]
Heptanal	111–71-7	HMDB0031475	[105 107]
Isoprene	78–79-5	HMDB0253673	[105]
Methanol	67–56-1	HMDB0001875	[105]
Nonanal	124–19-6	HMDB0059835	[107]
Octanal	124–13-0	HMDB0001140	[105 107]
Propanal	123–38-6	HMDB0003366	[105]
Propanol	71–23-8	HMDB0000820	[105 106]

Table 6
Summary of all the reviewed VOCs breath biomarkers for the diagnosis of chronic kidney disease.

Volatile Organic Compounds	CAS Number	HMDB Number	References
Acetone	67–64-1	HMDB0001659	[117 118 119 120]
Ammonia	7664–41-7	HMDB0000051	[113 115 120]
Aniline	62–53-3	HMDB0003012	[121]
Bicyclo[4.1.0]hepta-1,3,5-triene	4646–69-9	–	[121]
2-Butanone	78–93-3	HMDB0000474	[119]
2-Chloroethylester-carbonochloridic acid	627–11-2	–	[121]
3-Chloropropanoylchloride	625–36-5	–	[121]
o-Cymene	527–84-4	–	[119]
Dichloronitromethane	7119–89-3	–	[121]
2,4-Dimethylheptane	2213–23-2	HMDB0031416	[119]
Dimethyl sulphide	75–18-3	HMDB0002303	[118 120]
Ethanol	64–17-5	HMDB0000108	[120]
Ethenesulfonyl chloride	6608–47-5	–	[121]
M−Ethylmethylbenzene	620–14-4	HMDB0059848	[119]
2-Ethylpentane	589–34-4	HMDB0061884	[119]
3-Ethylpentane	617–78-7	HMDB0061885	[121]
Heptanal	111–71-7	HMDB0031475	[45 120]
Hexanal	66–25-1	HMDB0005994	[45]
Iodide cycloheptatrienylium	142182–71-6	–	[121]
Isoprene	78–79-5	HMDB0253673	[117 118 119 45 120]
Limonene	138–86-3	HMDB0003375	[121]
Methane sulfonyl chloride	124–63-0	–	[121]
Methanethiol	74–93-1	HMDB0003227	[120]
Methylamine	74–89-5	HMDB0000164	[120]
Methylene Chloride	75–09-2	HMDB0031548	[121]
2-Methylhexane	591–76-4	HMDB0245230	[119]
3-Methylpentane	96–14-0	HMDB0061885	[121]
6-Nitro-2-picoline	18368–61-1	–	[121]
Nonanal	124–19-6	HMDB0059835	[119]
Pentanal	110–62-3	HMDB0031206	[45 120]
4-(1-Phenyl-2-propenyloxy)-benzaldehyde	447428–96-8	HMDB0031206	[121]
1H-Pyrazole-4-carbonitrile	31108–57-3	–	[121]
2-Pyridinecarbonitrile	100–70-9	–	[121]
1H-Pyrrole-3-carbonitrile	7126–38-7	–	[121]
Silicon tetrafluoride	7783–61-1	–	[121]
Styrene	100–42-5	HMDB0034240	[119 121]
Toluene	108–88-3	HMDB0034168	[119 121]
4H-1,2,4-Triazol-4-amine	584–13-4	HMDB0246991	[121]
Trichloromethane	67–66-3	HMDB0029596	[121]
Trimethylamine	75–50-3	HMDB0000906	[117 118]
2,2,3-Trimethylhexane	16747–25-4	–	[119]
2,2,6-Trimethyloctane	62016–28-8	–	[119]

VOCs were identified as potential biomarkers for CLD diagnosis by Eng et al. (2015), due to their concentration level changes in CLD patients. In specific, the analytes 3-methylhexane, 1-heptene, 1-decene, and 1-octane were seen to be significantly more concentrated in the breath of CLD patients. Dimethyl sulphide, (E)-2-nonane and 1-nonene, on the other hand, present lower concentration levels in the breath samples of CLD patients [127]. Alkhouri et al. (2015) proved the relevance of a specific VOC, isoprene, for the CLD diagnostic (advanced fibrosis, specifically) through exhaled breath biomarkers. A cohort of 61 CLD patients was used by the authors to achieve such results [128].

2.7.1. Hepatic encephalopathy

Not being exactly a CLD, hepatic encephalopathy (HE) is a medium to long-term consequence of chronic hepatic pathologies. Due to the bad functioning of the liver, several hazardous substances that should be eliminated in the urine, stay in the organism. The accumulation of these toxic compounds leads to the deterioration of neurological functions. Some of the symptoms are disorientation, dizziness, humour and behaviour changes, sleeping pattern changes, and even coma [129,130].

To prevent deeper comorbidities, some efforts have been made to find faster and more accurate ways of diagnosing hepatic encephalopathy in CLD patients. Breath biomarkers have played a crucial role in this research field. Khalid et al. (2013), for instance, developed a study to assess the suitability of breath patterns for the differentiation among alcoholic cirrhosis patients with hepatic encephalopathy (11 volunteers), alcoholic cirrhosis patients without hepatic encephalopathy (23 volunteers), non-alcoholic cirrhosis patients without hepatic encephalopathy (13 volunteers), harmful drinkers without cirrhosis (7 volunteers) and 15 healthy volunteers. Breath samples (1 L) were analysed with a GC–MS device and the breath patterns of each group were assessed. By considering these patterns, the authors were able to successfully identify hepatic encephalopathy in 90.9 % of the cases. Furthermore, the breath signatures enabled the identification of liver cirrhosis with 100 % accuracy [131].

Arasaradnam et al. (2016) also focused their work on the diagnosis of hepatic encephalopathy through exhaled VOCs. An ultraviolet-field asymmetric ion mobility spectrometry (UV-FAIMS) device was the analytical technique selected to analyse the breath samples collected from 42 volunteers (20 healthy individuals and 22 hepatic encephalopathy patients). Considering the respective VOCs patterns, the authors were able to distinguish both groups with specificity and sensitivity levels of 68 % and 88 %, respectively [132]. Limonene was seen, by O'Hara et al. (2016), as being of extreme interest in the study of hepatic encephalopathy biomarkers. The achieve such results, breath samples of 61 volunteers (31 hepatic encephalopathy patients and 30 healthy subjects) were collected and analysed with a proton transfer reaction - quadrupole - mass spectrometry (PTR-Quad-MS) device. Among all the detected compounds, authors identified limonene as a clear biomarker due to its lower levels of concentration in hepatic encephalopathy patients when compared with healthy individuals [133].

2.7.2. Liver cirrhosis

Also known as alcoholic hepatitis, liver cirrhosis (LC) is typically caused by risk behaviours, namely, alcoholic drinking in excess. The pathology is characterized by the loss of hepatic functions and, in dangerous scenarios, can lead to hepatic carcinoma. The current methodology to diagnose liver cirrhosis, liver biopsy, is an extremely invasive procedure that can even lead to several consequences [134,135,136]. The identification of VOCs in the breath as biomarkers for LC has gained relevance as a diagnosing methodology. Pijls et al. (2016), for example, assessed the potentialities of VOCs as biomarkers for differentiating CLD patients with cirrhosis (34 individuals) from CLD patients without cirrhosis (87 individuals). A GC–MS device was used to analyse the exhaled breath samples from all the subjects. Unfortunately, no information is provided on the identified compounds, however, a set of 11 VOCs enabled the authors to distinguish both groups (with and without cirrhosis) with sensitivity and specificity levels of 71 and 84 %, respectively [137].

A total of 23 volatile organic compounds were assessed by Dadamio et al. (2012) as potential biomarkers for LC diagnosis. Exhaled breath samples of LC patients and healthy individuals were analysed with a GC–MS device. By using the identified VOCs as a specific pattern, authors were able to differentiate between both groups with sensitivity and selectivity levels ranging from 82 to 88 % and from 96 to 100 %, respectively [138]. Morisco et al. (2013) were also able to identify a group of VOCs with a high potential for serving as biomarkers for LC diagnosis. The results achieved by the PTR-ToF-MS device measurements correspond, accordingly with the authors, to the first-ever breathprint of liver cirrhosis [139]. Exhaled breath samples from a cohort of 123 volunteers (43 healthy individuals, 40 alcoholic cirrhosis patients and 40 non-alcoholic cirrhosis patients) were analysed by Hanouneh et al. (2014). From the measurements performed with a mass spectrometer, the authors identified six VOCs, trimethylamine, pentane, ethanol, acetone, acetaldehyde and isopropanol, whose concentration levels were increased in LC patients when compared with healthy volunteers [140]. Exhaled breath samples were collected from 61 subjects (30 healthy individuals and 31 LC patients) and analysed with a proton transfer reaction–mass spectrometry (PTR-MS) device. Among all the detected analytes, three VOCs (limonene, 2-pentanone and methanol) were considered of special interest for the study of LC diagnostic through exhaled breath biomarkers [141].

2.7.3. Non-Alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of CLD worldwide and, additionally, is the main responsible for the necessity of liver transplantation. Typically, NAFLD is related not to the extreme consumption of alcohol but to other risk behaviours like overweight and obesity scenarios [142,143,144]. As for other chronic liver diseases, the methodologies for assessment and diagnosis are highly invasive and involve serious risks. VOCs have been addressed as potential for a rapid, non-invasive, and accurate methodology for NAFLD diagnosis. Some studies have aimed at faecal and urinary volatile organic compounds; however, breath analytes must also be considered [54,145]. Han et al. (2019), for example, designed, fabricated, and successfully tested a micro gas chromatography (GC) column for a specific application, the study of NAFLD biomarkers in the exhaled breath of CLD patients [146].

Verdam et al. (2013) studied the suitability of breath analysis as an accurate and non-invasive procedure for NAFLD diagnosis. The exhaled analytes of 65 individuals (26 healthy individuals and 39 NAFLD patients) were detected with a gas chromatography - mass spectrometry (GC–MS) device. Among all the detected compounds, authors were able to identify four specific VOCs (3-methylbutanonitrile, propanol, α-terpinene and tridecane) that enabled them to distinguish both groups with accuracy, negative predictive value and positive predictive value of 77, 82 and 81 %, respectively [147]. A total of seven volatile organic compounds were remarked as of special interest for the study of NAFLD biomarkers, specifically, dimethyl sulphide, limonene, acetophenone, α-terpinene, isoprene, acetone, and styrene. Such results were achieved by analysing the exhaled breath of 43 volunteers (14 healthy subjects, 15 cirrhotic NAFLD patients and 14 non-cirrhotic NAFLD patients). Considering these seven VOCs, the authors were able to differentiate healthy volunteers from NAFLD patients with an accuracy level of 95 %. The differentiation between cirrhotic and non-cirrhotic NAFLD patients was accomplished with an accuracy level of 95 % [148].

As evident, the research on the potentiality of breath VOCs as biomarkers for chronic liver disease and, in specific, for hepatic encephalopathy, liver cirrhosis and non-alcoholic fatty liver disease diagnosis already produced very interesting results, notwithstanding, a long path is yet to be walked. Table 7 summarizes the main VOCs addressed in this chapter, their respective Chemical Abstract Service (CAS) and Human Metabolome Database (HMDB) codes, and bibliographic sources.

Table 7
Summary of all the reviewed VOCs breath biomarkers for the diagnosis of chronic liver disease.

Volatile Organic Compounds	CAS Number	HMDB Number	References
Acetaldehyde	75–07-0	HMDB0000990	[140]
Acetone	67–64-1	HMDB0001659	[138 140 148]
Acetophenone	98–86-2	HMDB0033910	[148]
Ammonia	7664–41-7	HMDB0000051	[132]
2-Butanone	78–93-3	HMDB0000474	[138 139]
Caryophyllene	87–44-5	HMDB0036792	[138]
Decene	872–05-9	–	[127]
Dimethyl Selenide	593–79-3	HMDB0033212	[138]
Dimethyl sulphide	75–18-3	HMDB0002303	[127 138 148]
Ethanol	64–17-5	HMDB0000108	[140]
Heptene	592–76-7	HMDB0061892	[127]
Indole	120–72-9	HMDB0000738	[138]
Isoprene	78–79-5	HMDB0253673	[128 138 148]
Isopropanol	67–63-0	HMDB0000863	[140]
Limonene	138–86-3	HMDB0003375	[133 138 141 148]
Methanol	67–56-1	HMDB0001875	[139 141]
3-Methylbutanonitrile	625–28-5	HMDB0302369	[147]
2-Methylhexane	591–76-4	HMDB0245230	[138]
3-Methylhexane	589–34-4	HMDB0245932	[127]
2-Methylpropene	115–11-7	HMDB0253606	[138]
1-(Methylthio)propane	3877–15-4	HMDB0061871	[138]
Nonane	111–84-2	HMDB0029595	[127 138]
(E)-2-Nonene	6434–78-2	–	[127]
Octane	111–65-9	HMDB0001485	[138]
Octene	111–66-0	HMDB0032449	[127]
Pentane	109–66-0	HMDB0029603	[140]
2-Pentanone	107–87-9	HMDB0034235	[138 139 141]
3-Pentanone	96–22-0	–	[139]
2-Pentylfuran	3777–69-3	HMDB0013824	[138]
Phenol	108–95-2	HMDB0000228	[138]
α-Pinene	80–56-8	HMDB0006525	[138]
β-Pinene	127–91-3	HMDB0036559	[138]
Propanol	71–23-8	HMDB0000820	[147]
Styrene	100–42-5	HMDB0034240	[138 148]
α-Terpinene	99–86-5	HMDB0036995	[147]
γ-Terpinene	99–85-4	HMDB0005806	[138]
Tetradecane	629–59-4	HMDB0059907	[138]
Tridecane	629–50-5	HMDB0034284	[138 147]
Trimethylamine	75–50-3	HMDB0000906	[140]

2.8. Diabetes

It is predicted that the number of diabetes cases will be as high as 350 million by 2030, making it one of the most common health conditions across the planet. A significant portion of these cases correspond to unidentified situations, however, the comorbidities caused by the pathology are relevant and can even be life-threatening [149,150]. The diagnostic procedures of diabetes are quite defined but recent work has been developed on the suitability of several volatile organic compounds emitted in the breath, to have the role of biomarker [151,152].

Acetone is a well-established and validated biomarker of diabetes. Wang et al. (2010), for example, addressed the correlation between the concentration levels of acetone in the exhaled breath and the blood glucose levels. A cohort of 59 volunteers (15 healthy individuals, 34 type-1 diabetes and 10 type-2 diabetes) was gathered for breath analyses. The authors were able to successfully observe a linear relationship between both breath acetone and blood glucose levels ($R = 0.98$) [153]. Some methodologies and procedures have been developed aiming at rapid detection of acetone in breath for diabetes diagnosis. Righettoni et al. (2010), as an example, assessed the suitability of Si-doped WO_3 nanoparticles, with a diameter ranging from 10 to 13 nm, directly deposited onto interdigitated electrodes as a selective system for acetone detection in the breath. Authors could see that, typically, healthy individuals present acetone levels under 900 ppb_v and diabetes patients, on the other hand, presented concentration levels above 1800 ppb_v [154]. Ethanol, dimethyl sulphide, and acetone were seen to be of special interest for gestational diabetes mellitus identification. To achieve such results, the exhaled breath of diabetes patients (20 individuals) and healthy volunteers (32 individuals) was analysed, and the volatile organic compounds were identified [155].

Righettoni et al. (2013) addressed the issue of diabetes biomarkers by analysing breath samples of diabetes patients (8 individuals). The samples were collected into 3 L inert Tedlar bags and analysed with a proton-transfer-reaction – mass spectrometry (PTR-MS) device. Four analytes were identified as potential biomarkers, namely, isoprene, ethanol, methanol, and acetone [156]. Isoprene was also defined as relevant for the biomarkers field of study by Neupane et al. (2016) [157]. Finally, one work proposes isopropanol as a diabetes biomarker in the breath. Exhaled breath samples of 141 volunteers (85 diabetes patients and 56 healthy individuals) were collected and analysed with a GC–MS apparatus. The authors conclude that the concentration level of isopropanol in the breath of diabetes patients is significantly higher (mean value of 85.44 ppb_v) than in the breath of healthy subjects (mean value of 17.99 ppb_v). In addition, the authors used isopropanol as a discriminant factor and could successfully differentiate both groups with sensitivity and specificity levels of 75.3 % and 85.7 %, respectively [158].

As reviewed, the field of breath biomarkers for the diagnosis of diabetes already presents very solid results. In fact, acetone is scientifically validated as a biomarker. On the other hand, other analytes, mostly alcohols, have arisen as potential biomarkers so, further studies must be developed to assess their real suitability. Table 8 summarizes the main VOCs addressed in this chapter, their respective Chemical Abstract Service (CAS) and Human Metabolome Database (HMDB) codes, and bibliographic sources.

2.9. Malaria

Transmitted by the bite of an infected mosquito, the parasites of the genus Plasmodium are responsible for malaria in humans. Malaria is a serious pathology that leads to millions of deaths every year around the globe but especially in developing countries of Africa, Asia and America, and even with the already existing and efficient treatments, the number of cases has grown [159,160,161]. An early diagnosis and rapid treatment are crucial to avoid the consequences of the disease and diminish the mortality rate [162]. The assessment of volatile organic compounds in the exhaled breath as potential biomarkers for malaria diagnosis has gained relevance [163,164,165].

The evaluate the direct impact of malaria infection on the exhaled VOCs, Berna et al. analysed the metabolomic content of breath during a day, in both infected and non-infected patients. For this, volunteers underwent controlled infection with *Plasmodium falciparum* and *Plasmodium vivax*, two of the main parasites responsible for malaria. Exhaled breath samples were performed with a quadrupole time-of-flight gas chromatography - mass spectrometry (Q-ToF-GC–MS) device. This protocol enabled the authors to accurately verify the evolution of VOCs concentration levels relative to the evolution of the parasite infection, through time. The potentiality of VOC and patterns of VOCs for the role of biomarkers for malaria infections was, in this way, confirmed [166].

As mentioned, malaria is caused by the infection of a parasite. Regarding this statement, Wong et al. (2012) studied the headspace formed above *in vitro* cultures of infected and non-infected blood cells. A GC–MS device was selected to measure the emitted analytes; however, the authors couldn't identify specific VOCs for each type of culture [167]. With a similar goal, Capuano et al. (2019) prepared blood cell cultures (infected and non-infected) and analysed the analytes emitted by both types of samples. For comparison purposes, two analytical techniques were used, specifically, an electronic nose and a proton transfer - time-of-flight - mass spectrometry (PT-ToF-MS) device. Considering the signature of the VOCs emitted from each sample, and in opposition to the lack of results of Wong et al. (2012), principal component analysis enabled samples differentiation with a total explained variance of 81 %. [168].

The identification of possible biomarkers for malaria infection is being done in several human-borne analytes. Skin-emitted VOCs, for example, were evaluated regarding a possible detection of malaria infection, by Pulido et al. (2021). Authors claim that, considering the emitted pattern of VOCs, it was possible to identify malaria-infected patients with an accuracy level of 100 % [169]. In a previous study, the same research group also reported an accuracy of 100 % in the diagnosis of malaria-infected situations [170]. Nevertheless, most studies have considered breath-emitted analytes in the search for biomarkers of malaria infection. For instance, Jisha et al. (2021) proposed and developed a chemiresistive breath sensor for the detection of two specific VOCs, α-pinene and 3-carene. This sensor is based on the properties of nanostructured trioxide-doped polyaniline (WO_3-PAni) nanocomposite to diagnose volatile organic compounds related to malaria infection. The sensor showed sensitivity levels of 31.99 % and 62.49 % for the respective detection of 3-carene and α-pinene. The main purpose of the sensor development is its posterior utilization in a portable device for exhaled breath analysis and eventual biomarkers detection [171]. Both 3-carene and α-pinene were also detected in the study developed by Schaber et al. (2018). From the exhaled breath samples collected from healthy (18 subjects) and malaria-infected (17 subjects) children and analysed with a thermal desorption - gas chromatography - mass spectrometry (TD-GC–MS) device, the authors were able to identify six possible malaria biomarkers. The differentiation between infected and non-infected children considering the pattern of six VOCs (nonanal, isoprene, tridecane, methyl undecane, dimethyl decane and trimethyl hexane) was achieved with an accuracy level of 85 % [172]. Breath samples of individuals infected and non-infected with malaria were collected into a 3 L impermeable aluminium gas bag and posteriorly analysed by GC–MS, in the study developed by Berna et al. (2015). The authors were able to identify nine volatile organic compounds with evident potentiality for being malaria biomarkers [48]. All the addressed scientific studies prove, not only, the suitability of VOCs as biomarkers for the diagnosis of malaria infection, but also, make clear the extensive path that this field still needs to traverse. Table 9 summarizes the main VOCs addressed in this chapter, their respective Chemical Abstract Service (CAS) and Human Metabolome Database (HMDB) codes, and bibliographic sources.

2.10. Sleep apnoea

Obstructive sleep apnoea (OSA), simply known as sleep apnoea, is

Table 8
Summary of all the reviewed VOCs breath biomarkers for the diagnosis of diabetes.

Volatile Organic Compounds	CAS Number	HMDB Number	References
Acetone	67–64-1	HMDB0001659	[153 154 155 156 158]
Dimethyl sulphide	75–18-3	HMDB0002303	[155]
Ethanol	64–17-5	HMDB0000108	[156]
Isoprene	78–79-5	HMDB0253673	[156 157]
Isopropanol	67–63-0	HMDB0000863	[158]
Methanol	67–56-1	HMDB0001875	[155 156]

Table 9
Summary of all the reviewed VOCs breath biomarkers for the diagnosis of malaria.

Volatile Organic Compounds	CAS Number	HMDB Number	References
Acetone	67–64-1	HMDB0001659	[48]
Allylmethylsulphide	10152–76-8	HMDB0031653	[48]
Benzene	71–43-2	HMDB0001505	[48]
3-Carene	13466–78-9	HMDB0035619	[171 172]
Cyclohexanone	108–94-1	HMDB0003315	[48]
2,2-Dimethyldecane	17302–37-3	HMDB0302690	[172]
3,6-Dimethyldecane	17312–53-7	–	[172]
3,7-Dimethyldecane	17312–54-8	–	[172]
Ethylbenzene	100–41-4	HMDB0059905	[170]
Ethylcyclohexane	1678–91-7	–	[170]
2-Ethylhexanol	104–76-7	HMDB0031231	[170]
Hexanal	66–25-1	HMDB0005994	[170]
4-Hydroxy-4-methylpentan-2-one	123–42-2	HMDB0031511	[170]
Isoprene	78–79-5	HMDB0253673	[172 48]
1-(Methylthio)propane	3877–15-4	HMDB0061871	[48]
Methylthiopropene	10152–77-9	–	[48]
Methylundecane	1632–70-8	HMDB0059888	[172]
Nonanal	124–19-6	HMDB0059835	[170 172]
α-Pinene	80–56-8	HMDB0006525	[171 172]
Propylcyclohexane	1678–92-8	HMDB0038191	[170]
Toluene	108–88-3	HMDB0034168	[170]
Tridecane	629–50-5	HMDB0034284	[172]
2,2,3-Trimethylhexane	16747–25-4	–	[172]
2,3,5-Trimethylhexane	1069–53-0	–	[172]

characterized by the alternation between breathing and non-breathing state during sleep caused by the collapse of the upper airways and subsequent oxygenation interruption [49,173]. As with other respiratory system pathologies, obstructive sleep apnoea has been studied regarding eventual biomarkers, specifically VOCs, that can lead to a rapid, accurate and non-invasive diagnosis. Benedek et al. (2013), for example, were able to successfully differentiate between two groups of healthy individuals (ten subjects) and OSA patients (18 subjects) through the exhaled pattern of VOCs. For this purpose, an electronic nose (E-nose) device was used, and sensitivity and specificity values of 78 % and 70 %, respectively, were achieved. Unfortunately, information regarding the addressed VOCs is not provided [174]. A similar methodology was followed by Greulich et al. (2013); an E-nose was also the selected device for the measurement and analysis of VOCs patterns from OSA patients (40 subjects) and healthy individuals (20 subjects). Even without information regarding the analysed VOCs, authors achieved sensitivity and specificity values of 93 % and 70 %, respectively [175]. A GC–MS device was the elected analytical technique, by Dragonieri et al. (2015), to analyse exhaled breath samples of three distinct groups, obese patients with OSA (19 subjects), obese patients without OSA (14 subjects), and non-obese healthy volunteers (20 subjects). The characterization and differentiation of the three groups were performed considering eight VOCs (tetrachloroethene, 2,3,5-trimethyl-hexane, β-pinene, 1,3,5-trimethyl-benzene, 9-methyl-acridine, tetradecane and 6,10-dimethyl-5,9-undecadien-2-one) that can be considered as potential OSA biomarkers, however, some of these compounds may be related to the obesity of the volunteers rather than the OSA [176]. Aoki et al. (2017) developed one of the most complete studies in the identification of potential VOCs as OSA biomarkers. The exhaled breath of a cohort of 65 volunteers (32 OSA patients and 33 healthy individuals) was analysed with a GC–MS apparatus. Authors remark that most of the VOCs exhibit elevated concentration levels in OSA patients when compared with healthy individuals and, additionally, the concentration levels of some specific VOCs (nonane, phenylacetic acid, p-xylene, and ethylbenzene) even increased linearly with the severity of the disease [177]. Table 10 summarizes the main VOCs addressed in this chapter, their respective Chemical Abstract Service (CAS) and Human Metabolome Database (HMDB) codes, and bibliographic sources.

As seen, there is a vast range of compounds often detected in the human exhaled air that has been linked to several non-carcinogenic diseases. A total of 292 biomarkers for the 10 most relevant non-carcinogenic pathologies were addressed during this study. It is important to reinforce that these 10 pathologies and the respective bibliographic sources were selected based on their relevance in the current state-of-the-art. From the identified analytes, one can draw relevant conclusions.

Most of the studied biomarkers are often linked to a single pathology or health condition. Nonetheless, from the 292 biomarkers, 21 were already linked to two pathologies and other 12 have been studied regarding their suitability to diagnose three pathologies. Interestingly, the VOCs acetaldehyde, 2-butanone, dimethyl sulphide, ethanol, hexanal, methanol, octane, and tetradecane have been connected to a total of four distinct pathologies among the 10 reviewed in this work. Fig. 1 summarizes the four conditions potentially diagnosed by the detection of these eight breath biomarkers.

Finally, three specific analytes proved to be not only the most studied among all of the compounds but also, the ones whose presence in breath can be linked to the highest number of pathologies; an impressive value of five and eight conditions. Nonanal has been reported as a potential biomarker in breath to diagnose asthma, chronic kidney diseases, chronic obstructive pulmonary disease, malaria, and covid-19. Acetone has been studied regarding its suitability to diagnose asthma, chronic kidney diseases, chronic liver diseases, covid-19, cystic fibrosis, diabetes, malaria, and sleep apnoea. Isoprene, in turn, can be explored to diagnose conditions like chronic kidney diseases, chronic liver diseases, chronic obstructive pulmonary disease, covid-19, cystic fibrosis, diabetes, malaria, and sleep apnoea. Fig. 2 a) summarizes all the conditions potentially diagnosed through the detection of nonanal, acetone, and isoprene in exhaled air. Fig. 2 summarizes all the conditions potentially diagnosed by the detection of these three breath biomarkers.

Table 10
Summary of all the reviewed VOCs breath biomarkers for the diagnosis of sleep apnoea.

Volatile Organic Compounds	CAS Number	HMDB Number	References
Acetone	67–64-1	HMDB0001659	[177]
Decane	124–18-5	HMDB0031450	[177]
6,10-Dimethyl-5,9-undecadien-2-one	689–67-8	HMDB0031846	[176]
Ethylbenzene	100–41-4	HMDB0059905	[177]
Heptane	142–82-5	HMDB0031447	[177]
Hexane	110–54-3	HMDB0029600	[177]
β-Ionone	14901–07-6	HMDB0036565	[176]
Isoprene	78–79-5	HMDB0253673	[177]
9-Methylacridine	611–64-3	–	[176]
Nonane	111–84-2	HMDB0029595	[177]
Octane	111–65-9	HMDB0001485	[177]
Phenylacetic acid	103–82-2	HMDB0000209	[177]
β-Pinene	127–91-3	HMDB0036559	[176]
Tetrachloroethene	127–18-4	HMDB0041980	[176]
Tetradecane	629–59-4	HMDB0059907	[176]
Toluene	108–88-3	HMDB0034168	[177]
1,3,5-Trimethylbenzene	108–67-8	HMDB0041924	[176]
2,3,5-Trimethylhexane	1069–53-0	–	[176]
p-Xylene	106–42-3	HMDB0059924	[177]

2.11. Pathologies with research potential

Several pathologies deserved to be addressed in this review, however, in a distinct section. Most of these pathologies still require deeper scientific knowledge in the area of breath biomarkers and, in this way, their identification through the emitted VOCs is still a field to be explored. Other diseases are known to have biological-borne biomarkers emitted by the human body; however, this emission does not occur throughout the breath. Broadly speaking, the health conditions here included deserving special mentions due to their currently unexplored potential.

2.11.1. Alzheimer's disease

Alzheimer's disease is the most common progressive degenerative neurological disorder and the main responsible for most contemporary dementia cases (60 % to 80 %). The initial symptoms are, normally, loss of memory and disorientation but they usually progress to confusion, changes in behaviour and, ultimately, difficulties in talking, walking, and doing other everyday tasks [178,179]. The diagnosis of Alzheimer's should happen at the earliest possible, preferably before the manifestation of the first symptoms, however, the diagnosis of the disease is hard and challenging [180]. Several studies were already developed around the suitability of VOCs for Alzheimer's disease identification, notwithstanding, much more is waiting to be explored [50].

Tisch et al. (2013) studied the exhaled breath of Alzheimer's disease (15 individuals) and healthy subjects (12 individuals) with a GC–MS device. Considering the breath signatures of both groups, the authors were able to distinguish them with an accuracy of 85 % [181]. Ion mobility spectrometry (IMS) and electronic nose (e-Nose) were the analytical techniques selected by Bach et al. (2015) to analyse breath samples of Alzheimer's disease patients and healthy individuals. Even without providing information on the identified VOCs, authors were able to differentiate Alzheimer's disease patients from patients with other pathologies, with accuracy, sensitivity and specificity levels of 94 %, 100 % and 100 %, respectively [182]. A gas chromatography - ion mobility spectrometry (GC-IMS) device was used by Tiele et al. (2020) to analyse breath samples of healthy individuals (50 subjects) and

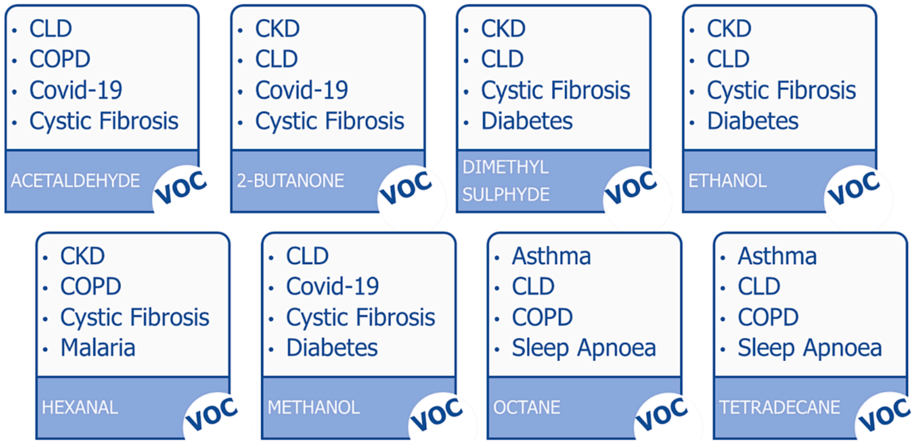

Fig. 1. Summary of the four diseases potentially diagnosed by eight of the most frequently detected biomarkers in breath, namely, acetaldehyde, 2-butanone, dimethyl sulphide, ethanol, hexanal, methanol, octane, and tetradecane.

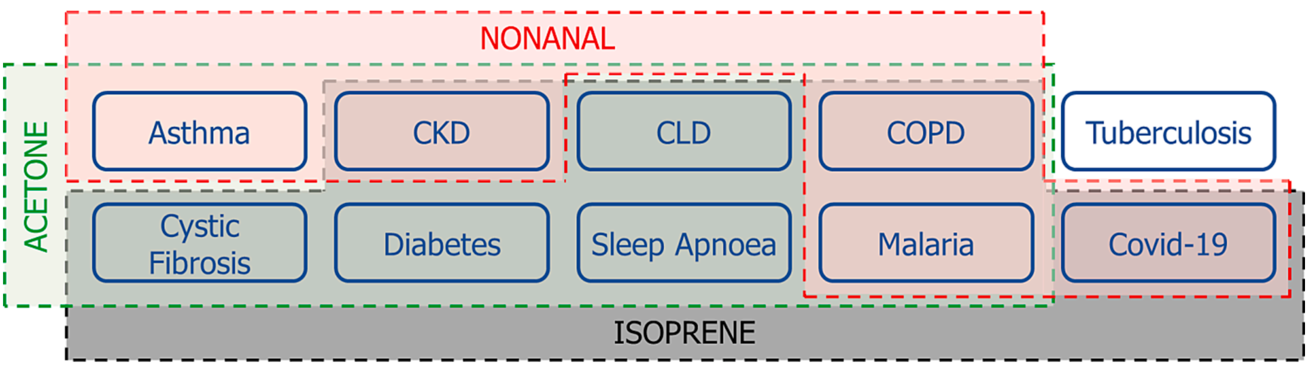

Fig. 2. Summary of all the diseases potentially diagnosed by the three most frequently detected biomarkers in breath, namely, nonanal (asthma, chronic kidney diseases, chronic obstructive pulmonary disease, malaria and covid-19), acetone (asthma, chronic kidney diseases, chronic liver diseases, covid-19, cystic fibrosis, diabetes, malaria and sleep apnoea), and isoprene (chronic kidney diseases, chronic liver diseases, chronic obstructive pulmonary disease, covid-19, cystic fibrosis, diabetes, malaria and sleep apnoea).

Alzheimer's disease patients (50 subjects). Six specific VOCs, 2-butanone, 2-propanol, acetone, hexanal, 1-butanol and heptanal, were identified as potential biomarkers for the Alzheimer's disease diagnostic [183]. Considering the reviewed works and the achieved results, the field of breath biomarkers for an early diagnosis of Alzheimer's disease seems to be promising and of great relevance.

2.11.2. Crohn's disease

Described as an inflammatory disease that affects the gastrointestinal tract, Crohn's disease can be triggered by several factors like environmental conditions, altered gut microbiota and even genetic susceptibility. The commonest effects of the disease are abdominal pain and chronic diarrhoea, but fatigue and weight loss are also quite typical comorbidities. The current diagnostic methodologies are based on endoscopic procedures, in this way, there is a completely unknown field to be explored around biomarkers [184,185]. Some works that address the potentiality of VOCs as diagnostic biomarkers have been developed around urinary and faecal samples [186,187]. In the same way, a few studies were already developed around the possibility of using VOCs emitted in the breath as Crohn's disease biomarkers.

Bodelier et al. (2015) were one of the first groups which achieved results in this field. They gathered a cohort of 385 (110 healthy individuals, 140 active Crohn's disease patients and 135 inactive Crohn's disease patients) and analysed the exhaled breath samples previously collected into 5 L Tedlar bags, with a GC-ToF-MS device. From all the detected analytes, the authors were able to identify a set of ten VOCs which enabled a correct and accurate diagnosis of the active and inactive state of the disease in 81.5 % and 86.4 % of the cases [188]. Dryahina et al. (2017), in a vast study, analysed and compared breath samples collected from three groups, healthy volunteers (14 individuals), Crohn's disease patients (136 individuals) and ulcerative colitis (51 individuals). A SIFT-MS device was the analytical technique selected for the separation of the analytes. The authors conclude that the concentration of pentane was elevated in Crohn's disease patients when compared with healthy individuals. In addition, the VOCs of butanoic acid, propanoic acid, acetic acid and hydrogen sulphide were seen as potential biomarkers for both Crohn's disease and ulcerative colitis, due to the changes in their concentration levels [51]. As evident, the results already accomplished are very promising and a stronger and more dedicated focus should be given to the field of breath biomarkers for Crohn's disease diagnostic.

2.11.3. Epilepsy

Characterized by its bimodal distribution, epilepsy affects mainly children and older individuals. This neurological condition affects the quality of life of the patients and also their families, and it is responsible for hundreds of indirect deaths every year [189,190]. An accurate and successful diagnosis is a very challenging task due to the lack of knowledge of neurological structures, however, interesting studies have been developed around urinary VOCs, cutaneous VOCs, and also around the canine olfactory capacity of detecting and differentiating different analytes [52,191,192]. One single study addressing exhaled breath VOCs as epilepsy disease diagnostic was found. Dartel et al (2020) gathered a cohort composed of 110 healthy individuals and 74 epilepsy patients and analysed their exhaled breath with an electronic nose (E-nose) device. Authors were able to use the breath signatures to discriminate both groups with accuracy, sensitivity and specificity levels of 71 %, 76 %, and 67 %, respectively. Unfortunately, the authors do not provide information on the identified volatile organic compounds [193]. The field of breath biomarkers for epilepsy diagnosis is a rather undeveloped area but with a promising future.

2.11.4. Multiple sclerosis

Multiple Sclerosis is the most common non-traumatic chronic neurological disabling disease in the contemporary world. It destroys the myelin in the myelinated axons and affects mainly young adults. The mechanisms behind the pathology aren't completely understood and the disease evolution is unpredictable. The field of VOCs as possible biomarkers for multiple sclerosis diagnosis is barely established however the potentiality is limitless [194,195,196].

The work developed by Broza et al. (2017) is one of the few, or perhaps the only study addressing the potentiality of VOCs in the exhaled breath as biomarkers for multiple sclerosis diagnosis. A cohort of 204 volunteers (58 healthy individuals and 146 multiple sclerosis patients) was analysed with a GC–MS apparatus. A total of 160 volatile organic compounds were detected in the exhaled breath samples and five (sulphur dioxide, decanal, nonanal, heptadecane and acetophenone) of those were identified as potential biomarkers due to their significant differences in multiple sclerosis patients. Additionally, the differentiation of both analysed groups through their breath signatures was achieved with accuracy and sensitivity levels up to 90 % [53]. As evident, there is enough room for new studies regarding this outstanding possibility.

2.11.5. Obesity

Obesity is one of the pathologies with the fastest growth in incidence, especially in developed countries. In the specific case of children, it has grown at an alarming rate. Obesity leads to a wide range of other pathologies and health conditions with different severity levels and distinct comorbidities. Some of these conditions may be diagnosed or evaluated through the breath signature and eventual changes in it, in this way, the assessment of the breath signature in healthy and obese individuals is mandatory [197,198,199].

Some work has been done on the identification of volatile organic compounds in the field of overweight patients. Cozzolino et al. (2017), for example, compared the urinary profile of volatile organic compounds between two groups, normal-weight (28 individuals) and overweight (21 individuals) children. The headspace emitted by the urine samples was analysed with a solid-phase microextraction - gas chromatography - mass spectrometry (SPME-GC–MS) device. Among all the detected analytes, authors identified 12 whose concentration levels increased in overweight children, and two with the opposite behaviour [200]. Raman et al. (2013), in their turn, analysed the headspace of faecal samples collected from obese volunteers. The study aimed to distinguish between obese people with non-alcoholic fatty liver disease (30 individuals) and those without the pathology (30 individuals). The samples were analysed with a GC–MS device. The authors were able to successfully discriminate between both groups through their respective VOCs signatures and, additionally, proved that the concentration levels of most VOCs increase in obese individuals with non-alcoholic fatty liver disease [54].

Regarding the volatile organic compounds in the exhaled breath of obese individuals, deeper studies are required. Nevertheless, Alkhouri et al. (2014) analysed exhaled breath of overweight children (60 individuals) and healthy volunteers (55 individuals) to identify possible changes between the two groups. The breath samples previously collected into an inert Tedlar bag were analysed with a selective ion flow tube - mass spectrometry (SIFT-MS) device. From all the exhaled analytes, the authors were able to identify four (hydrogen sulphide, ammonia, 1-decene and 1-octene) VOCs that fully distinguish obese and healthy individuals [201]. The promising results achieved with both urinary and faecal, and even with breath volatile organic compounds prove that deeper studies must be developed in the area of VOCs as biomarkers for obesity and obesity-related pathologies.

2.11.6. Sepsis

The syndrome known as sepsis is caused by the organism's systematic response to microbial infectious processes that can be caused by bacteria, viruses or even fungi. The response corresponds to an inflammatory reaction in several organs of the patient, and, in more drastic scenarios, it can lead to a septic shock and consequent multiple organ failure. In this way, sepsis has a high rate of morbidity and mortality and is particularly dangerous in new-born children and elderly individuals [202,203,204]. Rapid and accurate detection of the responsible for the infectious processes is crucial to avoid more severe scenarios. In this way, the identification of volatile organic compounds as potential biomarkers for sepsis diagnosis has gained relevance [205,206,207].

The assessment of potential VOCs as sepsis biomarkers has been achieved more often in faecal samples. Berkhout et al. (2017), for example, collected and analysed the VOCs emitted by faecal samples of 36 preterm infants (gestational age of fewer than 30 weeks) with sepsis and 40 healthy infants. The distinction between both groups was successfully achieved only by considering the pattern of VOCs of the classes [208]. In a complementary study, the same research group analysed a cohort of 254 individuals (127 healthy subjects and 127 sepsis patients) with a high-field asymmetric waveform ion mobility spectrometry (FAIMS). Besides not providing information on the identified VOCs, the authors were able to accurately distinguish both classes of the cohort [209]. These and other scientific studies prove the suitability of faecal VOCs in sepsis diagnosis.

Considering the scope of this review work, few studies were developed addressing the exhaled breath in the field of human sepsis; however, some work has been done on rats' breath. Guamán et al. (2012) used an ion mobility spectrometry (IMS) device and a solid-phase microextraction - gas chromatography - mass spectrometry (SPME-GC–MS) device to analyse breath samples of 20 rats in sepsis condition and 10 healthy rats. The authors achieved discrimination between both groups with accuracy, specificity and sensitivity levels of 92 %, 85 % and 98 %, respectively [210]. The exhaled breath of rats was also analysed with an IMS device by Fink et al. (2015). Twenty rats (10 healthy and 10 in sepsis situations) were used for exhaled breath measurements and VOCs detection. The identified VOCs with potential for sepsis biomarkers were acetone, 3-pentanone, acetophenone, butanal, 1-propanal, 2-hexanone and 1,2-butanediol [55].

One of the few scientific studies in which the human exhaled breath is addressed as a potential source of information regarding sepsis diagnosis was developed by Peters et al. (2017). Eighteen volunteers were infected with a bacterium, to achieve a controlled sepsis condition. Exhaled breath and blood analyses were performed to assess the patients' health condition during the following hours after the infection. A GC–MS device was selected as the analytical technique for exhaled breath measurements. From all the detected analytes, the authors were able to assess five volatile organic compounds whose concentration levels changed significantly after the infection, namely, decane, 2,4-dimethyl-heptane, 1-hexanol, 4-methyl-pentanol and 3-methyl-pentane [211].

As seen, there is a long path to cross in the field of sepsis breath biomarkers, however, the results achieved in experiments with rats and even in the scarce studies already developed in humans prove the high potential of this field. The identification of several volatile organic compounds in the exhaled breath that represent potential sepsis biomarkers is an imminent and inevitable scenario.

3. Conclusions

Contemporary medicine is relying on newer clinical methodologies to improve the accuracy and shorten the diagnosis time of a vast range of pathologies and health conditions. The field of organic-borne biomarkers has received deep attention regarding their suitability for detecting several health states, evaluating the evolution of a disease, and even assessing the response to treatment. Among these biomarkers, the volatile organic compounds exhaled in the breath represent a valuable source of information for the interior of the human organism and for most of its normal and abnormal biological processes. In addition, the collection, analysis, and identification of VOCs in breath are rapid, low-cost, accurate, simple, and repeatable processes, unlike many other medical procedures.

In order to assess the state of the art on the VOCs breath biomarkers, the most relevant scientific publications were reviewed and a total of 10 non-carcinogenic pathologies were addressed. Among all the identified analytes, 292 biomarkers were gathered in this review paper. In addition, future perspectives on the suitability of breath biomarkers for the diagnosis of six other health conditions were discussed.

Considering all the addressed facts, the number of identified biomarkers, and all the scientific work being developed in this field, it is safe to state that VOCs as breath biomarkers have a promising future as a procedure to identify and diagnose a vast range of health conditions and, consequently, be implemented and adopted for clinical purposes.

Besides all the potentialities and advantages of the detection and consequent identification and quantification of the volatile organic compounds emitted in breath, it is important to summarily address all the limitations still existing in this field and all the challenges that must be overcome before the use of biomarkers for clinical purposes become a reality.

As previously mentioned, the overall goal of this field is to achieve the certification of breath biomarkers for medical use and clinical applications. In order to achieve that, some limitations must be overcome. One of the main current challenges is the lack of standardized procedures to collect and analyse the samples of exhaled air. It is visible, throughout the document, that there is not yet a specific equipment, technique or procedure globally employed and accepted as correct. In this way, the standardization of the procedures must be achieved in order to attain the certification. Then, most of the analytical techniques used to explore the samples and detect the analytes often fail to process the information and produce reproducible and trustable results due to the lack of proper detection limits. The majority of the current techniques fail to achieve detection limits in the range of breath concentrations (ppb_v and even ppt_v) and, consequently, are unable to detect potential biomarkers in breath. The lack of specificity of some analytes, on the other hand, is also a challenge to overcome. As aforementioned, a considerably high number of analytes can be linked to more than one pathology or health condition. This fact increases the difficulty in identifying and certifying all the breath biomarkers for medical purposes.

In summary, the field of breath biomarkers has proven results that leave no doubts regarding its suitability for the medical field and clinical applications, nonetheless, major challenges must be overcome before such a thing becomes a reality.

CRediT authorship contribution statement

Pedro Catalão Moura: Writing – original draft, Software, Methodology, Investigation, Data curation, Formal analysis. **Maria Raposo:** Writing – review & editing, Visualization, Supervision, Resources, Project administration, Methodology, Funding acquisition. **Valentina Vassilenko:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Data availability

No data was used for the research described in the article.

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