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Volatile Organic Compounds Associated with Mild COVID-19

(Running title: Volatile Organic Compounds associated with COVID-19)

Donatini Bruno*, Le Blaye Isabelle

Medecine Information Formation (Research). 40 rue du Dr Roux, 51350 Cormontreuil, France

*Corresponding author: Dr Donatini Bruno, gastroenterology-hepatology, 40 rue du Dr Roux, 51350 Cormontreuil France. Tel : 06-08-58-46-29.

Abstract

Background: SARS-COV-2 may first infect the gut and pre-existing inflammatory dysbiosis may favour its spread to the lung.

Objective: Assess whether convalescents of mild COVID19 disease (m-COVID) have a specific type of small intestinal bacterial overgrowth (SIBO). Investigate whether such a specific SIBO could be associated with pre-existing medical conditions known to favour immunosuppression and viral infections.

Methods: Descriptive retrospective epidemiological study with data collected during routine consultations for Small Intestinal Bowel Overgrowth (SIBO). SIBO diagnosis was based on the presence of volatile organic compounds (VOCs) in exhaled air measured by X-PID 8500®.

Results: 650 patients were included. 26 patients presented with previous m-COVID. Risk factors were a medical history of herpetic flares, ulcerative colitis (UC), nickel intolerance (NI), cancer or precancerous lesions, arrhythmia or psoriasis. Four different clusters of volatile organic compounds (VOCs) were associated with the COVID group: the cluster with a retention time from 42 to 43.9s, the cluster from 58 to 74.9s, the cluster from 86 to 88.9s, and the cluster from 89 to 97s. Arrhythmia was dependent of the first three VOCs clusters. Cancer and precancerous lesions were mainly dependent of the cluster 58 to 74.9s.

The risk factors are related to TH1-immunosuppression. We hypothesized that the cluster 58 to 74.9s could be a marker of IFN deficit and could indicate a potential viral spread from the gut to the lung.

Conclusion: X-pid 8500® is able to detect VOCs associated with m-COVID in ambulatory practice. These VOCs could be markers of TH1-immunodepression associated with dysbiosis.

Keywords: Breath test-COVID-19-chromatography.

Introduction

SARS-COV-2 may infect and multiply in the lung and in the bowel [1]. Bowel involvement may precede the lung infection, especially when interferons and CD8+ responses are defective [2, 3]. COVID-19 infection has therefore been associated with dysbiosis [4-9].

Treatment of dysbiosis or at least improvement of intestinal flora could become a strategy to prevent severe COVID-19 infection [10]. In addition, early detection of dysbiosis may become the corner stone of the fight against the spread of SARS-CoV-2 infection.

A new ambulatory device - X-PID 8500® - may detect 50ppb of volatile organic compounds (VOCs) and can be used in clinical practice since it takes only 2 minutes to get reliable chromatographic curves of exhales VOCs. Such a device is already able to detect specific gas exhaled by a subgroup of depressed patients [11].

We wonder whether X-PID 8500® is able to detect VOCs associated with mild COVID19 (m-COVID).

Since many parameters may interfere with dysbiosis, we collected data on weight, liver steatosis, ulcerative colitis or Crohn disease, periodontitis, flares of oral or nasal herpes, IgG CMV+, auto-immune diseases, allergic reactions, arrhythmia, cancer and precancerous lesions, gastroparesis, depression, as well as severe acne treated with isotretinoin. Abdominal ultrasound was therefore performed to investigate gastric, jejunal and ileal movements [12,13].

In case specific VOCs could be associated with m-COVID, we investigated whether they are independent of the risk factors identified from the medical history.

Material and methods

This work is a descriptive retrospective epidemiological study. Data were collected during the normal course of routine gastroenterological consultations for Small Intestinal Bowel Overgrowth (SIBO), from 2020 March 1st to 2020 September 30th. There was no hypothesis testing before data collection, no data collection beyond that which is part of routine clinical practice, no scheduled data analysis before the work has already been done. This retrospective analysis of Case Series cannot therefore be qualified as "research" and does not requires approval from ethics boards designed to protect humans involved in clinical research, according to the International Committee of Medical Journal Editors (ICMJE).

Inclusion criteria. Patients consulting for SIBO and who underwent a breath test.
The consultation was planned before the start of the pandemic.
Patients should provide with a full medical history, especially regarding m-COVID, herpes simplex, herpes zoster, periodontitis, previous treatment of acne with isotretinoin, ulcerative colitis or Crohn disease, depression, thyroid pathologies, auto-immune diseases, allergic reactions, cancer and precancerous lesions, arrhythmia, depression, body weight and height, as well as *diabetes mellitus*.

CMV serology and transabdominal plus thyroid ultrasound examinations are routinely performed in patients consulting for SIBO.

Patients signed a written consent for the possible retrospective use of the epidemiological collected data.

Exclusion criteria

Ongoing tobacco abuse; lack of CMV serology analysis; lack of transabdominal ultrasound; lack of signed consent for possible retrospective epidemiological use of data; uncontrolled *diabetes mellitus*; lack of breath test or recent intake of antibiotic therapy or of essential oils leading to massive destruction of the digestive flora and less than 2 ppm of VOCs at the first measure, after 10 hours of fasting; uncontrolled endocrine disease (including thyroid insufficiency); incomplete data on drug or food complement intake.

m-COVID

The diagnosis of m-COVID was usually made by PCR and reported by the patient him or herself or written on his/her hospital record. It could also have been made by the general practitioner after suggestive symptoms and a serological control.

All patients of the COVID group should have discontinued antibiotic therapy for at least 3 weeks before coming to the consultation for SIBO in order to avoid altered digestive flora. The same criterion is applied to the control group.

They all have recovered (except one patient with asthenia) at least one month before the consultation.

Ultrasound

Gastroparesia was diagnosed when the surface of the stomach reached 10 cm². Ileal distension was diagnosed as soon as ileal diameter reached 2.2 cm at the ileo-coecal junction. Lack of gastro-duodenal voiding was diagnosed when no evacuation of bubbles between the superior mesenteric artery and the aorta was observed after 2 minutes of osteopathic abdominal manoeuvers. Jejunal hypotonia could also be implicated. In that case, the jejunum contains few bubbles and no peristalsis is visualized [12,13]. Abdominal ultrasound examination also enables to diagnose liver steatosis.

Gas measurement

The patient comes after at least 10 hours of fasting. He /she inhales room air and hold his/her breath for 20 seconds. He/she exhales the air of the lungs in a first neutral plastic bag (1.3 litre) and afterwards he/she exhales at least 100 ml (expected to belong to the expiratory reserve volume) in a small neutral plastic bag (Contralco®; Gignac; France; www.contralco.com).

VOCs from the second bag are then immediately measured by the X-pid 8500®, an ambulatory gas chromatograph associated with photoionization detection technology [Dräger; Lubeck; Germany; www.draeger.com › Products › Multi-Gas-Detectors]. X-pid 8500® detects VOC concentrations as low as 50 ppb. Isobutylene and methylacetate are detected within 5.6 to 6.4 seconds, isobutyric, butyric and acetic acids between 7.0 and 7.9 seconds, toluene between 42 and 44 seconds, m-xylene or p-xylene between 90 and 97 seconds and o-xylene around 115 seconds.

X-pid 8500® does not detect hydrogen and is therefore not suitable for the detection of SIBO related to sugar-malabsorption. X-pid 8500® was used after breath holding and only after fasting, not after sugar intake.

The air of the first bag is analysed by the Dräger X-am® 8000. We routinely use the Dräger X-am® 8000 [Dräger; Lubeck; Germany; www.draeger.com › Products › Multi-Gas-Detectors] to measure hydrogen before and two hours after the intake of lactulose in order to diagnose SIBO related to sugar-malabsorption. Results will be published separately.

Both devices are easily portable and equipped with powerful pumps. Patients could be placed in separate rooms when necessary. The setup is basic and similar for both devices. It requires only a short tube to connect the bag and the device.

The results are quantified and directly exported in Excel tables.

Control group

All consulting patients were pre-included in the study and no case was discarded except when at least one exclusion criteria were identified. As a consequence, no recruitment

or selection bias is expected. The control group is equal to the total number of included patients minus the COVID group. Classical demographic data will be compared. The control group appears appropriate.

Statistics

Comparisons of percentage used two-sample t-tests. Yates correction was used for small samples. The Poisson distribution was used for the analysis of very rare events.

m-COVID group and control group were compared for clinical parameters and VOCs. Since peaks of VOCs may be numerous, we looked for clusters. A cluster contains several VOCs with close retention times and which are separated from other clusters by at least 1 second of retention time.

Since VOCs and clinical diseases could be associated, we performed an additional comparison of percentages for all subgroup of patients with each clinical condition and without each cluster of VOCs. Unmodified p values identify independent variables (diseases and VOCs). On the contrary, reversion or modification of p values suggests that the detected VOCs might be a marker of the clinical condition. Because of the large number of tests necessary for this specific analysis the threshold of statistical significance was set to $p < 0.01$.

Results

This descriptive epidemiological study included 650 patients. 26 patients (COVID group) presented with m-COVID. None was hospitalized in an emergency ward and all fully recovered except one patient who still experiences severe asthenia. The descriptive demographic data are summarized in (table 1).

	COVID group	Control Group
Males	10	203
Females	16	421
Age (years)	49.7 +/- 9.4	50.8 +/- 15.3
Body weight (kg)	66.2 +/- 14.0	65.8 +/- 15.2
Height (cm)	170.2 +/- 8.0	168.0 +/- 11.6
Body Mass Index	22.7 +/- 4.1	24.2 +/- 16.4

Table 1: Descriptive demographic data of the 650 included patients, according to m-COVID (mean +/-standard deviation).

Patients with oral or nasal herpes, nickel intolerance, UC, cancer or precancerous lesions, arrhythmia or psoriasis developed more frequently m-COVID; respectively: 73.1% versus 41% ($p < 0.001$), 11.5% versus 4.5% (<0.001), 15.4% versus 6.7% (<0.001), 42.3% versus 23.4% ($p < 0.001$), 11.5% versus 7.7% (<0.01) and 26.9% versus 16.8% ($p < 0.01$). Urticaria, rheumatoid arthritis or multiple sclerosis was only mentioned by patients from the control group (respectively 0% versus 10.6%; 0% versus1.6%; 0% versus 2.1%; $p < 0.001$). See (table 2).

The COVID group and the control group did not differ regarding other clinical parameters. See (table 3).

	Group COVID 26 patients	Control Group 624 patients	P value
Oral or nasal herpes	19 (73.1%)	90 (14.4%)	<0.001
Nickel intolerance	3 (11.5%)	27 (4.5%)	<0.001
Ulcerative colitis	4 (15.4%)	38 (6.7%)	<0.001
Cancer or pre-cancerous lesions*	11 (42.3%)	146 (23.4%)	<0.001
Arrhythmia	3 (11.5%)	78 (7.7%)	<0.01
Psoriasis	7 (26.9%)	105 (16.8%)	<0.001
Urticaria	0	66 (10.6%)	<0.001
Rheumatoid arthritis	0	10 (1.6%)	<0.001
Multiple sclerosis	0	13 (2.1%)	<0.001
*precancerous lesions = dysplastic polyps of the colon or dysplastic lesion of the cervix. 63.3% of cancers or precancerous lesions have a digestive origin. In the COVID group, 90.9% have a digestive origin.			

Table 2: Relevant clinical differences between the COVID group and the control group.

	COVID group 26 patients	Control Group 624 patients	P value
IgG CMV+	3 (7.7%)	90 (14.4%)	NS
Crohn disease	1 (3.8%)	29 (4.65%)	NS
Severe acne treated with isotretinoin	4 (15.4%)	76 (12.2%)	NS
Medical history of allergy except urticaria	7 (26.9%)	166 (26.6%)	NS
Liver steatosis at ultrasound	2 (7.7%)	35 (5.6%)	NS
Non-Alcoholic steato-hepatitis	0	6 (1%)	NS
Gastroparesia at ultrasound	5 (19.2%)	104 (16.7%)	NS
Thyroid nodules	7 (26.9%)	186 (29.8%)	NS
Depression	3 (11.5%)	65 (10.4%)	NS
*precancerous lesions = dysplastic polyps of the colon or dysplastic lesion of the cervix			

Table 3: Clinical parameters which did not differ between the COVID group and the control group.

Glycaemia was similar in both groups (5.2 +/- 0.3 versus 5.3 +/- 0.8 µmol/l; p>0.05). Neutrophil/lymphocyte ratio or eosinophil counts were normal in both groups: respectively 1.23 +/- 0.35 versus 1.85 +/- 1.02 and 195 +/- 105 cells/mm3 versus 184 +/-158.

Eight clusters of VOCs were identified: VOCs with retention time <41s; VOCs with RT between 42 and 43.9 seconds (cluster 42 to 43.9; including toluene); VOCs with RT between 45 and 56.9s; VOCs with RT between 58 and 74.9s (cluster 58 to 74.9; including butyl acetate), VOCs with RT between 76 and 84.9s, VOCs with RT between 86 and 88.9s (cluster 86 to 88.9; including ethylbenzene), VOCs with RT between 90 and 97s (cluster 90 to 97; including xylene) and VOCs with RT above 98s.

Cluster 42 to 43.9s, cluster 58 to 74.9s, cluster 86 to 88.9s and cluster 90 to 97s were more frequently detected in patients who experienced m-COVID. Respectively: 11.5% versus 4.5%, 53.4% versus 28.5%; 19.2% versus5.4% and 30.8% versus 18.2% (p<0.001). See table 4.

	COVID group 26 patients	Control group 624 patients	P value
RT <41s	12 (46.1%)	335 (53.6%)	NS
RT between 42 and 43.9s	3 (11.5%)	28 (4.5%)	<0.001
RT between 45 and 56.9s	9 (34.0%)	188 (30.1%)	NS
RT between 58 and 74.9s	14 (53.4%)	178 (28.5%)	<0.001
RT between 76 and 84.9s	7 (26.9%)	122 (19.5%)	NS
RT between 86 and 88.9s	5 (19.2%)	34 (5.4%)	<0.001
RT between 90 and 97s	8 (30.8%)	114 (18.3%)	<0.001
RT>98s	8 (30.8%)	233 (37.3%)	NS

Table 4: Comparison of occurrence of exhaled VOCs in the COVID group versus the control group.

We investigated whether the four identified clusters were independent markers or whether they correlate with one of the 6 identified clinical conditions associated with an increased risk of m-COVID. We therefore compared COVID group and control group for all subgroup of patients with each clinical condition and without each relevant cluster of VOCs. See table 5.

Clinical conditions	Cluster of VOCs excluded for the comparison	COVID group Number of cases (percentage)	Control group Number of cases (percentage)	P value
Herpetic flares	42 to 43.9s	17 (70.8%)	249 (41.6%)	<0.001
	58 to 74.9s	9 (75%)	179 (39.3%)	<0.001
	86 to 88.9s	19 (73.1%)	256 (41.0%)	<0.001
	90 to 97s	12 (66.7%)	214 (41.9%)	<0.001
Nickel intolerance	42 to 43.9s	2 (8.3%)	24 (4.0)	<0.001
	58 to 74.9s	1 (8.3%)	15 (3.3%)	<0.001
	86 to 88.9s	3 (11.5%)	27 (4.3%)	<0.001
	90 to 97s	1 (5.6%	18 (3.5%)	NS
Ulcerative colitis	42 to 43.9s	4 (16.7%)	35 (5.9%)	<0.001
	58 to 74.9s	1 (8.3%)	23 (5.1%)	<0.001
	86 to 88.9s	4 (15.4%)	38 (6.1)	<0.001
	90 to 97s	1 (5.6%)	28 (5.5%)	NS
Cancers or precancerous lesions	42 to 43.9s	9 (38.0%)	39 (23.2%)	NS
	58 to 74.9s	0 (0%)	36 (8.0%)	Reversed (<0.001)
	86 to 88.9s	13. (50%)	480 (23.1%)	<0.001
	90 to 97s	6 (33.3%)	510 (21.6%)	NS
Arrhythmia	42 to 43.9s	0 (0%)	3 (0.7%)	NS
	58 to 74.9s	2 (8.3%)	47 (7.9%)	NS
	86 to 88.9s	0 (0%)	35 (0.69%)	NS
	90 to 97s	8 (30.8%)	43 (6.0)	<0.001
Psoriasis	42 to 43.9s	7 (29.2%)	100 (16.7%)	<0.001
	58 to 74.9s	4 (33.3%)	73 (16.0%)	<0.001
	86 to 88.9s	7 (26.9%)	105 (16.8%)	<0.001
	90 to 97s	5 (27.8%)	88 (17.2%)	<0.001

Table 5: Comparison of COVID group and control group for all subgroup of patients with each clinical condition identified in table 2 and without each relevant cluster of VOCs (comparison of percentages; relevant statistical threshold reached when p<0.01).

Clinical conditions and clusters of VOCs were independent variables except for nickel intolerance and cluster 89 to 97s, for UC and the same peak, for cancers and precancerous lesions especially for the cluster 58 to 74.9s, as well as for arrhythmia and the three first clusters.

Interestingly 3 patients in the COVID-19 group reported acute alcohol abuse within the fortnight before the occurrence of infection (11.5%). These do not present with other clinical disease recorded in table 2. They do not exhaled VOCs associated with m-COVID infection and identified in table 4. No patient in the control group reported acute alcohol abuse.

Discussion

Clinical parameters and immunity

Age, sex ratio, body mass index or glycaemia were similar in both groups. No patient with uncontrolled hypertension or diabetes was enrolled into this cohort. There was no difference between the COVID-19 group and the control group regarding liver steatosis ou NASH. However, the limited number of cases precludes any conclusion. As a matter of fact, this finding does not match with the conclusion of a recent meta-analysis [14]. A recent review of the literature suggests that NAFLD can play a role in the outcome of COVID-19 illness due to frequent association with comorbidities rather than NASH itself [15].

In this cohort, the most relevant clinical parameters associated with m-COVID are those which suggest an underlying immunosuppressive condition or a specific cluster of exhaled VOCs. This latter point may suggest dysbiosis, malabsorption and deficiencies, or digestive inflammation. These specific VOCs could be the consequence or a favouring cause of m-COVID. It this latter instance, they could be a marker of pre-existing anti-viral immunosuppression.

Neutrophil/lymphocyte ratio or eosinophil counts are considered to be reliable marker of immunity, especially in patients with colonic cancer [16-19]. They were normal in both groups. Immunosuppression can therefore not be explained by a decreased number of immune cells. SARS-CoV-2 appears to be particularly sensible to type I interferon response [20, 21]. Inhibition of type 1 Interferon, for example by auto-antibodies, predispose to life-threatening COVID-19 [22, 23]. Such auto-antibodies also predispose to herpes simplex type 1 infection [24-26].

IFNs play also a key role in anticancer immunity [27-29]. Cancerous patients are at increased risk to develop a COVID-19 infection [30]. Most of the cancer or precancerous lesions have a digestive origin. The association between interferon, natural killer cell activity and the risk of colorectal neoplasia is well established [31-33].

The exclusion of patients who exhaled the cluster 58 to 74.5 reversed the association between cancer of precancerous lesions and m-COVID. This latter point suggests a strong association between m-COVID and cluster 58 to 74.5. Interestingly, exhaled VOCs may contain fatty acids produced by bacteria. Fatty acids are known to interfere with Natural killers functions [34, 35].

Alpha interferon could block the cutaneous delayed hypersensitivity induced by nickel [36]. UC flares are mainly dependant on TH17 cells [37]. Many patients received anti-TNF alpha therapy which may down-regulate TH1 and TH17 status. However, current reviews do not confirm any increased risk of COVID-19 infection [39, 39], which does not match with our findings. An increased incidence of m-COVID is not observed in patients with Crohn's disease. To differentiate UC and Crohn's disease is sometimes very difficult. Misclassification may lead to misinterpretation [40]. It is noteworthy that a higher prevalence of nickel intolerance is observed in patients with UC [41].

Serum concentrations of IL17 are increased in patients with psoriasis [42] except when they are treated with anti-TNF-alpha which down-regulate TH1 and TH17 pathways [43].

We may conclude that patients with herpetic flares, cancer or precancerous lesions, nickel intolerance, treated UC or treated psoriasis could present with a decreased IFN level and therefore may be at increased risk of m-COVID.

Pre-existing arrhythmia

An increased level of IL17 may be detected in arrhythmia [44, 45]. However, no increased frequency of decreased level of IFNs has been published.

In this cohort, an association has been found on the one hand between pre-existing arrhythmia and m-COVID and on the second hand between cluster 42 to 43.9s, cluster 58 to 74.9s and cluster 75 to 88.9s. However, this association disappears when the analysis is performed on subgroup with the exclusion of these specific clusters of VOCs. The relevant variables are therefore the exhaled VOCs.

This finding speaks in favour of an immunosuppression associated with at least one of the three exhaled clusters of VOCs. Since arrhythmia pre-existed the occurrence of m-COVID, SARS-COV-2 cannot therefore be the cause of the synthesis of these VOCs.

MS [46, 47] and RA [48, 49] are at least partly associated with an increased TH1immunity and did not favour the occurrence of m-COVID.

Urticaria is explained by a strong innate immunity involving eosinophils and mastocytes [50]. Children mount a less robust T cell response, antibody titres and cellular phagocytosis to the COVID-19 spike protein compared to adult patients. Since, they experience less severe COVID-infections, the difference is attributed to a stronger innate immunity [51].

Exhaled VOCs

Cluster 42 to 43.9s and cluster 90 to 97s.

Cluster 90 to 97s could include m-xylene which is known to induce central nervous system toxicity in human workers, especially in case of concomitant ethanol ingestion [52]. In animals, the m-xylene-induced central nervous system toxicity, especially when associated with toluene (cluster 42 to 43.9s) is established [53-55]. These two clusters are associated with depression [11].

Alcohol abuse has not been implicated in the occurrence of UC [56]. However, it probably favours *per se* the occurrence and the severity of COVID-19 infection [57].

SARS-COV-2 is known to be neuro-invasive and to induce neurological complications [58]. Concomitant neurotoxic agents such as alcohol or dysbiosis-induced VOCs may trigger the occurrence of symptoms. In addition, the immunosuppressive effect of alcohol – especially on NK and on IFN synthesis – is established [59].

These two clusters are independent of other relevant clinical parameters. They are unlikely related to the COVID infection itself since they are not infrequent in the control group.

Cluster 58 to 74.9s

This cluster may contain butyl acetate which belongs to exhaled human volatilome and which is used for human presence detection of hidden or entrapped people [60].

To our knowledge, such a gas has never been reported on association with COVID-19 infection, cancer or immunosuppression.

This cluster is associated with m-COVID and is linked to cancer or precancerous lesions. Cluster 58 to 74.9s may be a marker of gut-TH1-immunosuppression which could favour the spread of SARS-COV-2 from the gut to the lung.

This cluster is unlikely related to the m-COVID itself since it is not rare in the control group.

Cluster 86 to 88.9s

Gases with RT between 86 and 88.9s may include ethylbenzene. Ethylbenzene has been reported in patients with and without non-small-cell lung cancer, with a poor discriminating index [61]. It might be a marker of pulmonary inflammation.

To our knowledge, such a gas has never been reported on association with COVID-19 infection, cancer or immunosuppression.

This peak is independent of any of the identified general parameters associated with m-COVID infection, including cancer.

Since it might be a marker of pulmonary inflammation, a role of COVID-19 infection itself cannot be excluded.

Global interpretation of VOCs associated with m-COVID

VOCs clusters may relate to pre-existing gut-TH1 immunosuppression favouring spread of SARS-COV-2 to the lung or they may be attributed to m-COVID.

Since patients consulted at least one month after recovery, it was very unlikely that SARS-COV-2 was still present in faeces [62]. This point was however not checked by PCR in faeces because this retrospective epidemiological study was performed in a gastroenterological ambulatory ward and routine PCR of faeces was not available.

25 out of 26 patients fully recovered of m-COVID. They all come only for a detection of SIBO. The consultation was planned before the start of the pandemic.

The cluster 58 to 74.9s is clearly associated with m-COVID and cancer or precancerous lesions. This cluster is unlikely specific to post m-COVID since it is not rare in the control group.

All these indirect arguments speak in favour of the hypothesis that cluster 58 to 74.9s could be a marker of gut-TH1-immunosuppression enabling the spread of SARS-COV-2 to the lung.

Conclusion

All relevant clinical variables associated with m-COVID are associated with TH1-immunosuppression. Increased innate immunity is protective. Specific clusters of exhaled VOCs are associated with m-COVID infection and are frequently independent from relevant clinical variables. The most relevant exception is the peak 58-74.9s which is associated with cancer ou precancerous lesions, especially for digestive origin. This cluster might be a good marker of gut-TH1-immunosuppression.

The breath test performed by X-PID 8500® was able to detect peaks of exhaled VOCS associated with m- COVID. SARS-COV-2 infection is probably not per se changing the exhaled VOCs, except perhaps for the peak 86 to 88.9.

X-PID 8500® may become an ambulatory tool for detection of gut-TH1-immunosuppression and therefore for detection of increased risks of viral infection or cancer.

Further analysis is necessary to determine the sensibility and the specificity of these clusters to plea for the use of this ambulatory new device in medical gastroenterology devoted to microbiota analysis and detection of hindered gut-TH1-immunity.

Acknowledgment(S) And Conflicts of Interest

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