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Results of Analysis of Volatile Organic Compound (VOC) Measurements Using Breath Analyzer on Coronavirus Disease 2019 (COVID-19) Confirmed Patients with Healthy People

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ABSTRACT

Background/aim: The analysis of VOCs through respiration has been used for biomarker analysis for the detection of novel coronaviruses and has found mainly six VOCs by breath analysis by GC-IMS are ethanol, octane, acetone, cluster mixture of acetone/butanone and methanol. Previous research found exhaled methanol concentrations were lower in COVID-19 patients. The aim of this study was to analyze differences in VOC concentration in Covid-19 patients with healthy people.
Methods: This Case Control study used 93 confirmed case samples of Covid-19 and 42 healthy people. Demographic and clinical data taken from anamnesis and/or medical records. VOC's data of respiratory track are taken through the exhalation air in a bag and analyzed with breath analyzer. Statistical analysis was conducted using Mann-Whitney test.
Results: VOC compound measured include CO2, C7H8, CH2O, NH4, TVOC, NO2, PM1.0, CO, NH3, and Acetone. Analysis between Covid-19 patients and healthy people showed significant differences in all VOC components CO2 (p=0,000), C7H8 (p=0,000), CH2O (p=0,000), NH4 (p=0,001), TVOC (p=0,000), NO2 (p=0,000), PM1.0 (p=0,000), CO (p=0,000), NH3 (P=0,000), Acetone (p=001). Logistic regression analysis was obtained no meaningful influence on each component of the VOC with covid/healthy people conditions of patients with components CO2 (p=1,000), C7H8 (p=1,000), CH2O (p=0,999), NH4 (p=1,000), TVOC (p=1,000), NO2 (p=1,000), PM1.0 (p=0,999), CO (p=0,999), NH3 (P=0,999), Acetone (p=1,000).
Conclusion: There is a significant difference between the VOC results of confirmed COVID 19 patients and healthy people

Keywords: breath analyzer, coronaviruses, COVID-19, healthy people, volatile organic component

INTRODUCTION

A coronavirus disease 2019 (COVID-19) outbreak was first reported in December 2019 in Wuhan City, Hubei Province, China. This virus became known as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The World Health Organization declared the COVID-19 pandemic on March 11, 2020 [1]. The spread of COVID-19 is fast and quite easy, especially through respiratory droplets with an average incubation period of five to six days with the longest incubation period of

14 days. COVID-19 has clinical symptoms that range from asymptomatic to severe symptoms such as septic shock, acute respiratory distress syndrome (ARDS), and multiple organ dysfunction syndrome (MODS) [2].

In Indonesia, there were 2.26 million cases of COVID-19, and there were 1.92 million recovered cases recorded as of last December 2021. As with severe acute respiratory syndrome (SARS) and Ebola, survivors of COVID-19 (COVID-19 survivors) are likely to face difficult challenges in everyday life. They may face challenges returning to work, socializing, and recovering. Several previous studies regarding the quality of life of SARS survivors concluded that they have many health burdens, including physical and mental health [3,4]

The SARS-CoV-2 infection might result in characteristic breath volatile organic compounds (VOCs) profiles that can be used to rapidly screen COVID-19. Rapid screening and diagnosis of COVID-19 plays a vital role in controlling the pandemic. Breath-borne VOCs have been investigated as biomarkers for lung cancer, oxidative stress, and many other diseases. VOC emission is described as being caused directly or indirectly by reactive oxygen species around the cells. When people are infected with SARS-CoV-2, characteristic protein and metabolite changes are observed; and more than 100 lipids have been reported to be down-regulated in their blood sera [5]. VOC's data of respiratory track are taken through the exhalation air in a bag and analyzed with breath analyzer [6]. In this study, profiling and analysis of Volatile Organic Compound (VOC) using a breathanalyzer will be carried out in patients diagnosed with Covid-19 and healthy people.

METHOD

The research design was carried out using a Case Control Study. The study was conducted in vivo on patients diagnosed with Covid-19 who were treated at the Saiful Anwar General Hospital and Idjen Boelevard Field Hospital. The sample population is all patients who have confirmed Covid-19 and are being treated at the Idjen Boelevard Field Hospital and Saiful Anwar General Hospital who meet the inclusion and exclusion criteria, the participants and their families having signed the informed consent after being given an explanation.

Procedure for collecting case sample data:

1. The officer prepares a plastic bag that will be used as a reservoir for exhaled air
2. Officers make sure the bag is in good condition (no damage/leakage)
3. Subjects were asked to exhale in a plastic bag with the command exhale through the mouth.
4. The plastic bag is tightly closed
5. In the case of taking samples of infectious COVID-19 officers use standard PPE (hazzmat, particulate masks)
6. Samples analyzed by breath analyzer examination.

Procedures for collecting control sample data:

1. The officer prepares a plastic bag that will be used as a reservoir for exhaled air
2. The Officers make sure the bag is in good condition (no damage/leakage)
3. The subject performs an antigen swab examination with a negative antigen swab result
4. The subject is fasted for at least 6 hours before taking the sample
5. Subjects were asked to do exhalation in a plastic bag with the command to exhale through the mouth sir…soooo…continues….‖
6. The plastic bag is tightly closed
7. In the case of non-infectious sampling, the officer uses a 3 ply surgical mask with a faceshield or uses a particulate mask (N95, KN95 or equivalent)

8. Samples were analyzed with a breathanalyzer.

The data obtained were recorded on the research sheet to be processed and analyzed and interpreted. Statistical tests were used to analyze the data. Variable data with normal distribution was assessed by unpaired t test and Wilcoxon test if the distribution was not normal. The relationship of variables was tested by logistic regression test. Statistics done with SPSS version 26.

RESULT

Demography Characteristic of Subjects in table 1 obtained were 62 samples of men (66.67%) and women as many as 31 samples (33.33%), while the control obtained the same comparison between men and women. The age distribution in the age range of 31-59 years was 45 samples (48.39%), under 30 years, there were 28 samples (30.11%) and above 60 years were 20 samples (21.52%), while in the control there were 52.38% in the age below 30 years, the rest are in the range of 31-59 years and not found in the sample aged over 60 years. Based on the smoking history in the case sample, it was found that 50.54% (47 samples) did not smoke, with a small number of samples who were still smoking (active smokers) before being treated as many as 6.45% (6 samples), with passive smokers as much as 12.9% (12 samples) and 30.11% samples quit smoking (28 samples), while in the control group, most (90.42%) did not smoke, the rest were active, passive smokers and quit smoking.

Table 1. Demography Characteristic of Subjects

Demography Characteristic	Case Samples		Control Samples	
	Amount (N=93)	Percentages (%)	Amount (N=42)	Percentages (%)
Gender				
Man	62	66,67	21	50,0
Woman	31	33,33	21	50,0
Age				
≤30	28	30,11	22	52,38
31-59	45	48,39	20	47,62
≥60	20	21,51	0	0,0
History of Smoking				
Active Smoker	6	6,45	2	4,76
Quit Smoking	28	30,11	1	2,38
Passive Smoker	12	12,90	1	2,38
Do not Smoke	47	50,54	38	90,42

Clinical manifestation of the subjects in table 2 obtained 63 samples (67.74%) with symptoms of cough, fever as many as 39 samples (41.94%). Symptoms of shortness of breath and anosmia were obtained in 31 samples (33.33%), headache in 20 samples (21.51%), diarrhea in 10 patients (10.75%), ageusia and nausea/vomiting respectively. as many as 16 samples (17.20%). Meanwhile, at the asymptomatic level, 15 samples (16.13%) did not have clinical symptoms of Covid-19.

Table 2. Clinical Manifestation of the Subjects

Clinical Manifestation	Amount (N=93)	Percentages (%)
Asymptomatic	15	16,13
Fever	39	41,94
Cough	63	67,74
Flu	23	24,73
Dyspnea	31	33,33
Anosmia	31	33,33
Ageusia	16	17,20
Nausea and Vomiting	16	17,20
Diarrhoea	10	10,75
Headache	20	21,51

The degree of severity based on the recapitulation results obtained the highest degree of severity in Figure 1, the form of mild degree in 33 patients (35%) followed by severe degree in 24 samples (26%), and asymptomatic in 15 samples (16%). While the moderate degree obtained 12 samples (13%) and 9 samples (10%) critically ill. The comorbidities of the research subjects obtained were Diabetes Mellitus as many as 13 subjects (13.98%), hypertension as many as 12 samples (12.9%), Obesity 10 samples (10.75%), Heart disease 6 samples (6.45%), Asthma 4 sample (4.3%), CVA history 2 samples (2.15%), renal failure and malignancy 1 sample each (1.08%) and 60 samples without comorbid patients (64.52%) (Table 3).

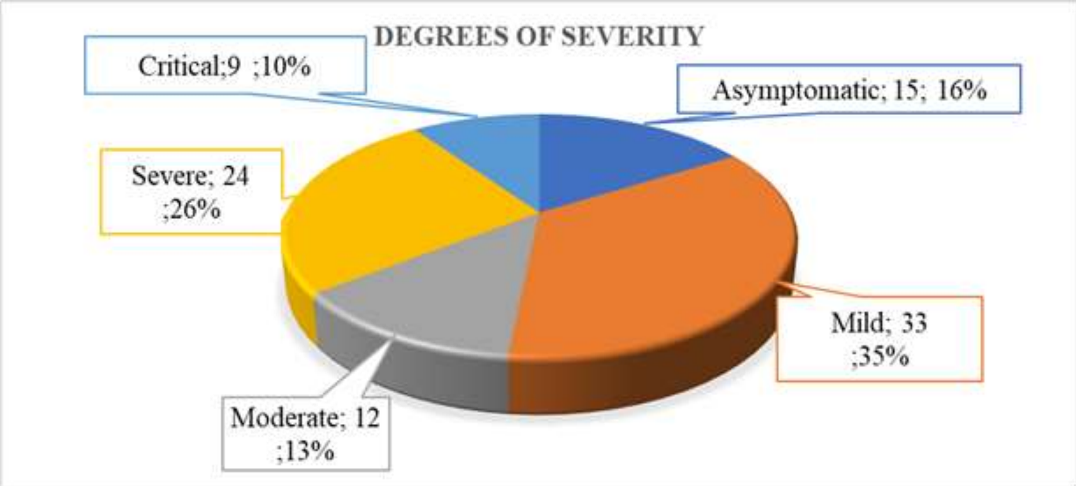

Figure 1. Severity Degree of Case Samples

Table 3. Comorbidity of the Patients

Comorbid	Amount (N=93)	Percentage (%)
Diabetes Melitus	13	13,98
Hypertension	12	12,9
Cardiac Disease	6	6, 45
Renal Failure	1	1,08
History of CVA	2	2,15
Lung TBC	0	0
COPD	0	0
Asthma	4	4,3
Cancer	1	1,08
Obesity	10	10,75
Without Comorbidities	60	64,52

The VOC examination through exhalation with a breathanalyzer has 14 sensors, but among the 14 sensors, only 10 sensors were found that could be detected in all patients including CO2, C7H8, CH2O, NH4, TVOC, NO2, PM 1.0, CO, NH3 and Acetone Table 4.

An increase in VOC gas components was found in the case group, namely C7H8, CH20, PM1.0, CO and NH3. While the components whose values were lower than the control group were CO2, NH4, TVOC, NO2 and Acetone. Data on the concentration of CO2, C7, H8, CH2O, NH4, TVOC, NO2, PM1.0, CO, NH3, acetone have an abnormal data distribution so that for further testing, non-parametric statistics can be used.

Table 4. Comparison VC of Covid and Non-Covid

VOC Components	Covid		Non Covid		P Value
	Standard deviation	Median	Standard deviation	Median	
CO2	610,95	1175,14	344,49	598,64	0,000
C7H8	0,07	0,00	0,68	0,96	0,000
CH2O	0,10	0,01	2,03	0,81	0,000
NH4	0,62	1,05	1,98	0,00	0,001
TVOC	599,51	146,61	0,20	0,05	0,000
NO2	0,76	1,54	0,02	0,04	0,000
PM1.0	0,00	0,00	3,59	4,07	0,000
CO	0,00	0,00	0,07	0,24	0,000
NH3	0,32	0,66	1,42	1,97	0,000
ACETON	0,15	0,23	2,10	0,00	0,001

The concentrations of CO2, NH4, TVOC, NO2, Acetone between non-covid patients and covid patients showed a significance value of ($p<0.05$), which was lower in covid patients than in non-covid patients. Concentrations of C7H8, CH2O, PM1.0, CO, NH3 between non-covid patients and covid patients showed a significance value of ($p<0.05$), where the concentration was higher in covid patients than in non-covid patients.

Based on the results of the regression test, it was found that $p>0.5$ in all components examined (CO2, C7H8, CH2O, NH4, TVOC, NO2, PM1.0, CO, NH3, Acetone), so it was concluded that the concentration of each component had no significant effect. on the status of patients with covid/non-covid. In other words, high or low concentrations of each component (CO2, C7H8, CH2O, NH4, TVOC, NO2, PM1.0, CO, NH3, Acetone) have no effect on sample status (covid/non-covid) (Table 5)

Table 5. Logistic Regression Test

Variable	B	S.E.	Wald	df	Sig	Exp(B)	95% CI	
							Lower	Upper
Step 1								
CO2	-0,004	11,754	0,000	1	1,000	0,996	0,000	1E+010
C7H8	-7,189	6563,629	0,000	1	1,000	0,001	0,000	
CH2O	8,079	4453,859	0,000	1	0,999	3225,737	0,000	
NH4	-3,287	6663,464	0,000	1	1,000	0,037	0,000	
TVOC	0,002	17,711	0,000	1	1,000	1,002	0,000	1E+015
NO2	-3,134	6675,243	0,000	1	1,000	0,044	0,000	
PM1.0	1,460	1078,990	0,000	1	0,999	4,305	0,000	
CO	158,011	4066,812	0,000	1	0,999	201E+068	0,000	
NH3	-5,281	7318,123	0,000	1	0,999	0,005	0,000	
ACETON	1,580	6481,572	0,000	1	1,000	4,854	0,000	
Constanta	-7,616	8858,006	0,000	1	1,000	0,000		

DISCUSSION

The results of this study indicate that patients with confirmed Covid-19 are found to be more male than female, this is in accordance with research conducted by Wang, 2020, the percentage of male patients was higher (54.3%) than women. This study is also in accordance with research conducted by Ruong, it was found that a higher percentage of men (54.3%) than women [7]. The age prevalence in this study is in accordance with epidemiological data published by Chen, 2020 which stated that most of the confirmed cases were aged 30-79 years (86.6%). Individuals with old age (>65 years) and having comorbidities have a risk of being infected with Covid-19 compared to younger age groups [8].

Based on smoking history data in this study, smokers were 1.4 times more likely to have severe COVID-19 symptoms and about 2.4 times more likely to be admitted to the ICU, require mechanical ventilation or die compared to non-smokers [9].

Based on the comorbidities suffered by the study samples, hyperglycemia and insulin resistance increase the synthesis of glycosylation end products and pro-inflammatory cytokines, oxidative stress, in addition to stimulating the production of adhesion molecules that mediate tissue inflammation. This process may structure the underlying mechanism leading to a higher predisposition to infection, with poorer outcomes in patients with diabetes [10]. Patient confirmed COVID-19 with pneumonia and without pneumonia differences in VOC results. There was an increase in the CO, NH4 and Acetone components in confirmed samples of COVID-19 with pneumonia, and a decrease in the components in CO2 and TVOC in samples confirmed for COVID-19 accompanied by pneumonia [6].

Hypertension is one of the most common comorbidities in COVID-19 patients. Uncontrolled hypertension is a risk factor for contracting COVID-19, but controlling blood pressure is still considered important to reduce the burden of disease. Several systematic reviews and meta-analyses reported that administration of ACE inhibitors and ARBs did not increase the progression of Covid-19 disease, so that ACE inhibitors and ARBs could still be used as antihypertensive therapy in the COVID-19 patient population. The European Society of Cardiology (ESC) also still recommends giving ACE inhibitors and ARBs as an effort to control hypertension in COVID-19 patients because the negative effects of these two drugs do not have a scientific basis. The use of ACE inhibitors or ARBs was not associated with an increased risk of COVID-19 and there was a reduction in the severity of COVID-19 with ACE inhibitors or ARBs in the general population and groups of patients with hypertension [11].

Based on data obtained during the COVID-19 epidemic in the US, Johns Hopkins Hospital reported, younger, obese patients were admitted to the ICU. Obesity as a risk factor for COVID-19 is under-appreciated. This risk is particularly relevant in the US because the prevalence of obesity is approximately 40%, compared with a prevalence of 6-2% in China, 20% in Italy, and 24% in Spain. Obesity can restrict ventilation by inhibiting diaphragmatic passage, impairing the immune response to viral infections, is proinflammatory, and induces diabetes and oxidant stress that adversely affects cardiovascular function [12].

This study is also in line with research conducted by Wang, 2020 and Ruong, 2020 where fever and cough are symptoms that often appear in patients with confirmed Covid-19, gastrointestinal symptoms such as diarrhea and vomiting are found in a small proportion of patients with confirmed Covid-19. COVID-19 infection can cause mild, moderate or severe symptoms. The main clinical symptoms that appear are fever (temperature >380C), cough and difficulty breathing. In addition, it can be accompanied by severe shortness of breath, fatigue, myalgia, gastrointestinal symptoms such as diarrhea and other respiratory symptoms. Half of patients develop shortness of breath within one week. In severe cases rapidly and progressively worsens, such as ARDS, septic shock, uncorrected metabolic acidosis and bleeding or coagulation system dysfunction within a few days. In some patients, symptoms appear mild, not even accompanied by fever. Most patients have a good prognosis, with a small proportion in critical condition or even death [13].

The analysis of VOCs through respiration has been used for biomarker analysis for the detection of novel coronaviruses and has found mainly six VOCs by breath analysis by GC-IMS are ethanol, octane, acetone, cluster mixture of acetone/butanone and methanol. Previous research found exhaled methanol concentrations were lower in COVID-19 patients while the other five compounds were elevated in COVID-19 patients. More research is needed analyzing VOCs from exhalations to detect COVID-19 disease, and this is a promising approach in the future[18]. VOCs in human breath were identified as noninvasive health indicators in individuals. Emissions from humans include hydrocarbons, alcohols, ketones, and aldehydes at levels of ppb to ppm. High concentrations of CO2 and water in human breath have made VOCs difficult to measure [14,15]

Based on the results of the study, it was found that the concentration of Acetone gas in confirmed COVID-19 patients was lower than the Acetone gas concentration of non-covid patients with a significance value of ($p<0.05$). Respiratory acetone concentrations are elevated in patients with (uncontrolled) diabetes mellitus [5,16]

The concentration of CO gas in confirmed Covid-19 patients is higher than the concentration of CO gas in non-covid patients. Under physiological conditions, the rate of endogenous CO production is estimated to be 18 mol CO per hour. Switching of other hemoprotein species contributes to endogenous systemic CO production as a function of relative abundance and turnover rate, myoglobin, cytochrome p-450, catalase, and others. Hemoglobin binds more strongly to CO, about 425 times more strongly than to oxygen. On exhaled VOC analysis, COPD patients had a higher measured eCO value than non-COPD patients. ECO values were also measured in -1 anti-trypsin (α1-AT) deficiency, which is a genetic cause of emphysema and is associated with increased neutrophil elastase activity and lung tissue damage that occurs independently of smoking. In addition, eCO levels in asthmatic patients taking -agonists decreased in response to a four-week regimen of inhaled corticosteroid therapy and correlated with decreased sputum eosinophil counts. In people with allergic asthma, eCO increases in response to allergen challenge that precedes the decline in peak lung function assessed by FEV1. The eCO values in these patients were insensitive to stimuli that reduce FEV1, including histamine, or to subsequent recovery by -agonists, suggesting that eCO values are correlated with airway function [17,18]

CO inhibits the production of proinflammatory cytokines, such as TNF-, MIF and interleukin-1, from macrophages and interleukin-2 secretion from activated T cells [19,20]. CO stimulates the synthesis of the anti-inflammatory cytokine interleukin-10 [19]. The anti-inflammatory effect of CO is mediated by p38 kinase, but is independent of the cGMP pathway. Interleukin-10, in turn, induces HO-1 expression and the latter produces more CO. In this way, it will strengthen the anti-inflammatory effect of CO [7,19,20]

The concentration of NH_3 gas in confirmed Covid-19 patients is higher than the NH_3 gas concentration in non-covid patients. Ammonia has a close relationship with CKD where CKD is associated with ammonia breath odor, which is commonly called uremic fetor. Increased concentrations of ammonia in exhaled breath from patients treated on peritoneal dialysis (PD) and before and during hemodialysis (HD) treatment were demonstrated by the SIFT-MS study of a sample of breath bag exhaled through the mouth. Further confirmed by other studies, ammonia has been the focus of many studies in breath analysis which stimulated the development of absorption and photoacoustic spectroscopy, and solid state sensors dedicated to ammonia analysis [21].

Limitation this study:

1. In the sampling process there was no uniformity regarding the patient's eating history. Some types of food and the duration of the patient's meal will affect the results of the VOC measurement in the patient.
2. In the sampling procedure, a conscious exhalation maneuver was carried out, so that sampling of patients with severe/critical degrees who were using an oxygen mask, Jackson Reese and in an intubated state could not be performed.
3. There are no VOC sensors that are theoretically related to the inflammatory process and there are additional sensors on the device during the research, so that not all VOC results are analyzed, especially on newly added sensors

CONCLUSION

1. Obtained VOC values in confirmed samples of Covid-19 with a breathanalyzer with a CO_2 value of 598.64; C_7H_8 0.96; CH_2O 0.81; NH_4 0.00; TVOC 0.05; NO_2 0.04; CO 0.24; NH_3 1.97; Acetone 0.00
2. The concentration of VOC in the control sample was obtained with a median value of CO_2 1175.14; C_7H_8 0.00; CH_2O 0.01; NH_4 1.05; TVOC 146.61; NO_2 1.54; CO 0.0; NH_3 0.66; Acetone 0.23
3. There is a significant difference in the concentration of VOC components using a breathanalyzer in confirmed samples of Covid-19 and control samples with higher VOC components such as C_7H_8, CH_2O, PM1.0, CO, NH_3 and the lower one in the form of CO_2, NH_4, TVOC, NO_2, Acetone

Suggestions that can be given in connection with further development of this research are:

1. Uniformity was carried out in the preparation of sampling, so as to reduce the bias of the VOC measurement results in future studies.
2. It is necessary to develop further tools that can be connected to oxygen therapy devices so that samples can be taken in patients receiving special oxygen therapy.
3. Added sensors that have been theoretically proven related to inflammatory processes such as NO, Isoprene, Acetaldehyde, ethanol, etc.
4. Further research is needed regarding the role of VOCs in Covid-19 with a larger sample and better sample preparation to test and complete the VOC profile on Covid-19 with the role of artificial intelligence, so that the role of VOCs in Covid-19 can be obtained as a diagnostic, predictive or prognostic alternative.

Declaration by Authors

Ethical Approval: Approved

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Conflict of Interest: There are no conflicts of interest to declare by any of the authors of this study.

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