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Analysis of results of volatile organic compound (VOC) measurements using breathanalyzer on COVID-19 confirmed patients with pneumonia and without pneumonia

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***Abstract*---**WHO declared COVID-19 infection as a pandemic since 2020. A rapid noninvasive examination is needed for screening and diagnostic. Exhaled Volatile Organic Compound (VOC) is a sample directly connected to the affected organ, which is the lung, and can be measured as an endogenous volatile marker resulted from oxidative stress. This study aims to analyze differences in VOC concentration in COVID-19 patients with pneumonia and without pneumonia. This Case Control Study used 93 confirmed case samples of COVID-19 and 42 healthy subject. Demographic and clinical data taken from anamnesis

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and/or medical records. VOC's data of respiratory track are taken through the exhalation air in a bag and analyzed with breathanalyzer. Statistical analysis was conducted using Mann-Whitney test. In the analysis of confirmed samples of COVID-19 between pneumonia and without pneumonia, co components were found to affect the incidence of pneumonia in confirmed samples of COVID-19 (p=0.003). This conclusion is Components of CO in confirmed COVID-19 have a meaningful effect on an event of pneumonia.

***Keywords*---**VOC, COVID-19, Pneumonia.

Introduction

On December 31, 2019, China reported a mysterious case of pneumonia of unknown cause. Samples of isolates from patients were studied with the results showing the presence of a coronavirus infection, a new type of betacoronavirus, named 2019 novel Coronavirus (2019-nCoV). On February 11, 2020, the World Health Organization named the new virus Severa Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) and the name of the disease as Coronavirus disease 2019 (COVID-19) (World Health Organization (WHO)., 2020).

Swab PCR for the diagnosis of COVID-19 is a method with high accuracy but has a weakness in the identification speed of 4 to 6 days (Liu et al., 2020). On the other hand, antigen and antibody swab tests have a high speed with identification capability in the order of hours (1-4 hours) (Latiano et al., 2021). However, the antigen and antibody swab method has weaknesses in the area of accuracy. Another method offered is to use a breath content analysis (Ruszkiewicz et al., 2020).

E-Nose (electrical nose) technology is a new method for detecting chemical components present in the air. This technology combines various sensors that can detect odorless and odorless components in nature (Christensen et al., 2011). E-nose has often been used to identify food conditions, alcohol content, and VOC exposure. The results of this identification are then issued in the form of final data which is used as a reference in identifying a case (Sabilla et al., 2020).

In the case of influenza, it is known that the TVOC component changes both in type and concentration (Traxler et al., 2019). In the case of SARS-CoV2 infection, the presence of propanol-1, Acetonaldehyde, propyl Acetonate, butyraldehyde, isopropanol-1, Acetonone, and Acetonic acid was observed in varying amounts depending on the duration of viral infection (Chen et al., 2020; Schenck et al., 2020). In addition to TVOC, hydrogen and methane were also found in the breath due to anaerobic bacterial infection (De Lacy Costello, Ledochowski and Ratcliffe, 2013).

In this study, profiling and analysis of Volatile Organic Compound (VOC) using a breathanalyzer will be carried out in patients diagnosed with COVID-19 with or without pneumonia.

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 breathanalyzer 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.

Results and Discussion

The research subjects 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).

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 (years)				
≤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%), augesia 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
Augesia	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 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 (Table 3) 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. 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 case group showed that 52% (48 samples) did not have a diagnosis of pneumonia. The sample is a combination of asymptomatic and mild degrees. Meanwhile, 48% (45 samples) were patients with pneumonia conditions. The sample is a combination of patients with moderate severity, severe to critically ill.

In the VOC sample of patients with confirmed COVID-19, a comparison was made in patients with pneumonia and without pneumonia and then a regression test was performed to look for significantly different components.

Based on the results of the normality test, NO_2, PM1.0, CO, and NH_3 obtained significance values of 0.088, 0.120 0.263, and 0.603, which are greater than 0.05 ($p>0.05$), so it can be concluded that the components of NO_2, PM1.0, CO , and NH_3 has a normal distribution. Thus, the NO_2, PM1.0, CO, and NH_3 components can be tested using parametric statistics. Meanwhile, the CO_2, C_7H_8, CH_2O, NH_4, TVOC, and Aceton components have a significance value smaller than 0.05 ($p>0.05$), so it can be concluded that the CO_2, C_7H_8, CH_2O, NH_4, TVOC, and Acetone components have a similar distribution. abnormal. Thus, data for CO_2, C_7H_8, CH_2O, NH_4, TVOC, and Acetone can be tested using non-parametric statistics. The NO_2, PM1.0, CO, and NH_3 components have a normal distribution. Thus, data for NO_2, PM1.0, CO, and NH_3 can be tested using parametric statistics

It can be seen about the comparison of NO_2 between pneumonia patients and non-pneumonia patients which shows a significance value of $p> 0.05$, so it can be interpreted that NO_2, PM1.0, NH_3, between pneumonia patients and non-pneumonic patients have an average that is not much different, so the test results show no significant difference (Table 4).

Table 4 T – test

Variable	t	df	p-value	Mean difference	Std. Error Difference	95% CI	
						lower	Upper
NO2	-0,743	91	0,460	-0,00357	0,00481	-0,1312	0,00598
PM1.0	-1,712	91	0,090	-1,25883	0,73530	-2,71941	0,20175
CO	7,514	91	<0,001	0,09232	0,01229	0,06791	0,11673
NH3	1,012	91	0,314	0,29915	0,29556	0,28795	0,88625

Meanwhile, the comparison of CO between pneumonia patients and non-pneumonia patients showed a significance value of 0.000 ($p<0.05$), so it could be interpreted that CO between pneumonia patients and non-pneumonia patients had medians that differed greatly, so the test results showed a significant difference. The median CO in the pneumonia patients (mean = 0.274 ppm) was higher than the median CO in the non-pneumonic patients (mean = 0.181 ppm). The components of CO2, C7H8, CH2O, NH4, TVOC, and Acetone have an abnormal distribution. Thus, data for CO2, C7H8, CH2O, NH4, TVOC, and Acetone can be tested using non-parametric statistics using the Mann Withney test (Table 5).

Table 5. Mann-withney Test

Variable	Mann-Whitney U	Z	p-value
CO2	534.000	-4.202	<0,001
C7H8	1068.000	-0.092	0.926
CH20	897.500	-1.432	0.152
NH4	513.500	-4.689	<0.001
TVOC	365.500	-5.505	<0.001
ACET	665.500	-3.761	<0.001

It is known about the comparison of CO2, NH4, TVOC, Aceton between pneumonia patients and non-pneumonia patients which shows a significance value of $p<0.05$, so it can be interpreted that CO2, NH4, TVOC, Aceton between pneumonia patients and non-pneumonia patients has a median that is much different, so the test results show that there are significant differences.

The comparison of C7H8 and CH2O between pneumonia patients and non-pneumonia patients showed a significance value of $p>0.05$, so it can be interpreted that C7H8 and CH2O between pneumonia patients and non-pneumonia patients had a median that was not much different, so the test results showed no significant difference.

The effect of the concentration of CO2, CH2O, NH4, TVOC, PM1.0, and Aceton on the incidence of pneumonia showed a value of $p>0.05$, meaning that the concentration of CO2 gas had no significant effect on the incidence of pneumonia. In other words, high or low concentrations of CO2, CH2O, NH4, TVOC, PM1.0, and Acetone had no effect on the incidence of pneumonia.

The effect of CO concentration on the incidence of pneumonia as shown in table 6 shows a p value of 0.003 (p <0.05), meaning that CO concentration has a significant effect on the incidence of pneumonia. In other words, the higher CO concentration affects the incidence of pneumonia, while non-pneumonia tends to have lower CO.

Table 6 Logistic regression

Variable	B	S.E	Wald	df	Sig.	Exp(B)	95% CI for ext (B)	
							Lower	Upper
CO2	-0,004	0,004	1,186	1	0,276	0,996	0,989	1,003
CH20	-0,541	0,364	2,211	1	0,137	0,582	0,285	1,188
NH4	0,290	0,590	0,243	1	0,622	1,337	0,421	4,247
TVOC	21,289	12,183	3,053	1	0,081	1,8E+009	0,075	4E+019
PM1.0	0,108	0,123	0,767	1	0,381	1,114	0,075	1,4E+019
CO	28,492	9,525	8,949	1	0,003	0,000	0,875	1,418
ACET	-0,472	0,511	0,853	1	0,356	0,624	0,000	0,000
Pneumonia	8,126	3,194	6,474	1	0,011	3382,074	0,299	1,699

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 (Wu and Wang, 2005). 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 (Chen, 2020).

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 (Yakoh et al., 2021).

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 (Huang et al., 2020).

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 (Burhan, 2022).

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 (Kilic, Shim and Pourdeyhimi, 2015).

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 (Perhimpunan Dokter Paru Indonesia (PADI), 2020).

The results of the study on the incidence of pneumonia in case samples with pneumonia were 48% and case samples without pneumonia were 52%. asymptomatic patients by 16%, for patients with moderate degrees of 13% and critical degrees only by 10%. This happened because the sample in this study was taken through confirmed COVID-19 patients who were fully conscious and able to blow air bags, so that in patients with decreased consciousness and in patients with oxygen masks, NIV and patients on mechanical ventilation were excluded from this study. Patients without symptoms are the mildest condition, in patients there are no symptoms. Patients with mild symptoms are patients with respiratory symptoms but have no evidence of pneumonia and no signs of hypoxia. In moderate degree clinical signs of pneumonia were found but no signs of severe pneumonia were found (saturation > 93% with room air). In severe degrees, clinical symptoms of pneumonia are obtained plus one of the signs, namely respiratory rate > 30 x/minute, severe respiratory distress, or SpO2 < 93% in room air. While in critical condition found in patients with ARDS, sepsis and septic shock (Burhan, 2022)

Comparison of VOC result in case sample with pneumonia and without pneumonia, CO concentration in pneumonia patient shows $p = 0,003$ ($p<0,05$), indicate that CO was significantly affect the incidence of pneumonia. 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 (Pearson et al., 2005; Ryter and Choi, 2013).

CO inhibits the production of proinflammatory cytokines, such as TNF-, MIF and interleukin-1, from macrophages[23] and interleukin-2 secretion from activated T cells[24]. CO stimulates the synthesis of the anti-inflammatory cytokine interleukin-10[23]. 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 (Otterbein et al., 2000; Davies, Španěl and Smith, 2014; Labarca et al., 2021).

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. 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. 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.

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on the device during the research, so that not all VOC results are analyzed, especially on newly added sensors.

Conclusion

1. There are differences in VOC results in confirmed COVID-19 patients with pneumonia and without pneumonia. 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.
2. CO has a statistical effect on the condition of the occurrence of a pneumonia in samples confirmed for COVID-19.

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