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CHANGE IN EXHALED VOLATILE ORGANIC COMPOUNDS (VOC) PROFILE AND INTERLEUKIN-17 SERUM IN LUNG CANCER PATIENT Agil Dananjaya1, Ungky Agus Setyawan1, Susanthy Djajalaksana1, Arinto Yudi Ponco Wardoyo2 1 Departement of Pulmonology and Respiratory Medicine, Universitas Brawijaya – RSUD Saiful Anwar Malang 2 Departement of Physical Science, Universitas Brawijaya Abstract Background: In recent years, there has been study into biomarkers for early detection of lung cancer. The expansion of the tumor is accompanied by a distinct metabolic process product, which results in identifiable changes in the VOC emission profile. The content of such molecules differs between healthy and lung cancer patients. Furthermore, the expression of Interleukin-17 (IL-17) was linked to the clinical and pathological aspects of lung cancer patients. The aim of study to profile exhaled VOC of lung cancer and interleukin-17 serum of lung cancer patient. Methods: 40 patients with confirmed lung cancer and 42 subjects control participated. VOCs measurement by using Breath analyser and measured by using sensor aray. Then IL-17 measurement by ELISA. Statistical analysis using Kruscal Willis test and correlation test Spearman with significant p value <0.05. Results: We examined 15 VOCs and found that Ethanol (C2H5OH), Formaldehyde (CH2O), Toluene (C7H8) and Ammonia (NH3) in lung cancer patient were increase significantly compared with subject control (p < 0.05, p < 0.05, p < 0.05, p = 0.001, respectively). However, the concentration IL-17 subject control were higher (p = 0.299) than patient with lung cancer. Conclusion: Exhaled VOCs such as Ethanol, Formaldehyde, Toluene and Ammonia in lung cancer patient might be used as biomarker of lung cancer. Keywords: Interleukin-17, lung cancer, VOC. PERUBAHAN PROFIL VOLATILE ORGANIC COMPOUND (VOC) UDARA PERNAPASAN DAN SERUM INTERLEUKIN-17 PADA PASIEN KANKER PARU Abstrak Latar Belakang: Beberapa tahun terakhir, terdapat penelitian untuk deteksi dini kanker paru menggunakan biomarker. Pertumbuhan tumor akan disertai dengan produksi bahan metabolit yang akan keluar sebagai bahan yang dapat terdeteksi. Komposisi bahan tersebut berbeda antara orang sehat dan pasien kanker paru. Lebih lanjut lagi, ekspresi interleukin-17 berhubungan dengan pasein kanker paru secara penampakan klinis dan patologis. Penelitian ini bertujuan untuk menganalisis profile bahan VOCs pada udara pernapasan serta kadar serum IL-17 pada pasien kanker paru. Metode: 40 pasien kanker paru dan 42 orang subjek sehat terlibat dalam penelitian. Pengukuran VOC menggunakan Ubreath dengan metode sensor array. Kadar serum Interleukin-17 diukir menggunakan ELISA. Kami menganalisis secara statistik menggunakan tes Kruscal Willis dan tes Spearman dengan p value <0.05. Hasil: kami menganalisis 15 jenis VOC yang tertangkap dan menemukan bahwa Ethanol (C2H5OH), Formaldehyde (CH2O), Toluene (C7H8) dan Ammonia (NH3) pada pasien kanker paru meningkat secara signifikan dibanding dengan subjek kontrol (p < 0.05, p < 0.05, p < 0.05, p = 0.001, berurutan). Tetapi, konsentrasi serum interleukin-17 subjek kontrol lebih tinggi (p = 0.299) dibanding pasien kanker paru. Kesimpulan: VOC udara pernapasan meliputi Ethanol, Formaldehyde, Toluene dan Ammonia mungkin dapat digunakan sebagai biomarker kanker paru Keywords: Interleukin-17, kanker paru, VOC. Correspondence: Agil Dananjaya Email: akkun18@student.ub.ac.id Hp: 08121738139 INTRODUCTION In the global issue, lung cancer has become an important issue for cancer deaths. Data from GLOBOCAN 2018 database, lung cancer is estimated have 1.76 millions deaths and 2.09 new cases of lung cancer.1 Lung cancer is anticipated to the main cause of cancer death in men and women during the next 20 years.2 All lung malignancies (non- small cell lung cancer and small cell lung cancer combined) have a 5-year relative survival rate of 19%, and NSCLC has a higher 5-year survival rate (23%) than SCLC (6%).3 One of numerous variables that contribute to poor lung cancer patient outcomes is that the disease is frequently diagnosed at an advanced stage after the patient has developed symptoms. As a result, early lung cancer diagnosis should be addressed in order to enhance patient survival. 4 Low-dose computerized tomography is the current method for early lung cancer detection (LDCT). It can lower lung cancer mortality by 20% and is indicated for high-risk individuals. However, there is a risk of radiation exposure, a high expense, and a high likelihood of false positives when employing LDCT as a population screening approach.4,5 Therefore, several methods has been developed to become screening tools such as the analysis of volatile organic compounds (VOCs) or specific genomic approaches. VOCs referred to volatile organic compounds that can be found in the human body. VOCs can be metabolized and changed its profile by lung cancer. However, there are currently no consistent VOC biomarkers for lung cancer, and the VOC sets used in investigations varies. Therefore, breath analysis is still in an early stage of clinical application.6 Th17 cells are the principal producers of interleukin-17, a proinflammatory cytokine. IL-17 and IL-17-expressing cells have lately been investigated in a variety of cancers, including NSCLC. In NSCLC patients, high serum IL-17 levels were found to be associated with a late stage of the disease, overall survival (OS), and disease-free survival (DFS) (DFS). IL-17 expression was also significantly enhanced in human NSCLC tissues, and high IL-17 expression was associated with clinical and pathological characteristics of patients, such as TNM staging, OS, and DFS. Furthermore, in NSCLS patients, the frequencies of IL-17-producing T cells have been observed to be dysregulated..7 In this study, we aim to profile exhaled VOC biomarkers of lung cancer and interleukin-17 serum of lung cancer patient METHODS This study was conducted in RSUD dr. Saiful Anwar Malang East Java Province, Java, Indonesia. The time frame was between October 2021-January 2022. Patients with lung cancer were enrolled in the study, which took place in outpatient clinics and wards. The lung cancer patient was primary lung cancer, stabile condition and consent to take part of study. Subject with secondary lung cancer, acute condition or unstable condition and metastasis to the lung were not included in this study. Minimal samples from each variable is 31. Samples were obtained by consecutive sampling. Eighty-two subject who met inclusion and exclusion criteria were measured for their exhaled VOC profile and Interleukin-17 serum. Exhaled VOCs were measured by breath analyser examination. Breath analyser was developed by Universitas Brawijaya, Malang (Ubreath). Ubreath analyzed and measured by using sensor aray. Samples of VOC were collected by using breath apparatus and connected to Ubreath. Data was automatically collected in computer. Moreover, Interlukin-17 serum was conducted by phebothomy and the samples were collected to biomolekular laboratory. Interleukin-17 serum was measured by ELISA. Data were logarithm-transformed as necessary to meet normality and homoscedasticity criteria. Kruskal-Wallis one-way analysis of variance was used to see if there were any significant changes in VOC profile and interleukin-17 levels between lung cancer patients and controls. To examine the difference in VOC profiles in lung cancer patients depending on type lung cancer, stadium lung cancer, and therapy lung cancer, researchers used repeated measures analysis of variance. The Spearman correlation test was used to see if there was a link between VOC profile and interleukin-17 in two groups. At P 0.05, differences were judged significant using IBM SPSS software version 25.0 RESULTS Among the 82 subject, 40 were lung cancer patient and 42 subject control (Table 1). The median age of lung cancer patient was 56.6 year, this is older than subject control. Both groups were dominated by males 60% vs 40% in lung cancer patient and 57.14% vs 42.86% in subject control. We found that most of lung cancer patient were smoker 55.00% vs 45.00%, wherein subject control were non-smoker 97.7% vs 2.3%. In lung cancer patient (n=40), the most common type of lung cancer was adenocarcinoma (67.50%), followed by squamous cell carcinoma (12.50%), adeno-squamous cell carcinoma (10.00%), small cell carcinoma (10.00%). All of the patient were at late stadium; IV b (57.50%), IV a (37.50%) and III b (5.00%). According to therapy, all of the lung cancer patient have already treated by chemotherapy (85.00%) and targeted therapy (tyrosine kinase inhibitor) (15.00%). Profile of Exhaled Volatile Organic Compound (VOC) We evaluated the concentrations of 15 distinct VOCs in exhaled air between lung cancer patients and healthy controls, using a p value < 0.05 to account for multiple comparisons (Table 2). Ethanol, Toluene, Formaldehyde, and Ammonia concentrations in the exhaled air of lung cancer patients were considerably higher (p 0.05, p 0.05, p 0.05, p = 0.001, respectively) than in the subject control group. Table 1. Demography of Study Subject Characteristic Lung Cancer (n=40) Subject Control (n=42) Age Mean Sex 40-72 56.6 Male 24 (60.00%) Female 16 (40.00%) 25-38 30.8 Male 24 (57.14%) Female 18 (42.86 %) Smoking Smoker 22 (55.00%) Non-smoker 18 (45.00%) Smoker 1 (2.3 %) Non-smoker 41 (97.7%) Histological type Adenocarcinoma 27 (67.50%) Adeno-squamous cell carcinoma 4 (10.00%) Squamous cell carcinoma 5 (12.50%) Small cell lung cancer 4 (10.00%) V/A Stadium III B 2 (5.00%) IVA 15 (37.50%) IVB 23 (57.50%) V/A Chemotherapy Chemotherapy 34 (85.00%) Targeted Therapy 6 (15.00%) V/A Furthermore, by these VOCs, we investigated the differences between histological kinds of lung cancer, stage of lung cancer, and therapy (Table 3). The quantities of Ethanol, Toluene, Formaldehyde, and Ammonia in the exhaled air of lung cancer patients did not differ substantially (p = 0.404, p = 0.978, p= 0.967, and p = 0.535, respectively) depending on the histological type of lung cancer.. We found that the concentrations of Ethanol, Toluene, Formaldehyde and Ammonia, in the exhaled air of patients with lung cancer were no significantly difference (p = 0.298, p = 0.086, p= 0.086, p = 0.107, respectively) on patient with stadium III and IV. Then, the concentrations of Ethanol, Toluene, Formaldehyde and Ammonia, in the exhaled air of patients with lung cancer were no significantly difference (p = 0.570, p = 0.081, p= 0.081, p = 0.130, respectively) between chemotherapy and targeted therapy. Interleukin-17 (IL-17) of the Study Subject In comparing the concentrations of IL-17 patient with lung cancer and subject control, we found the concentration IL-17 subject control were higher (p = 0.299) than patient with lung cancer (Graphic 1). Graphic 1. Interleukin-17 comparasion between lung cancer patient and subject control Table 2. Profile of Volatile Organic Compound Subject There were no significantly difference between two groups. We also examined concentration IL-17 on patient with lung cancer, according histological type of lung cancer, stadium lung cancer and therapy. We found that there were no significantly differences with (p = 0.751, 0.342, p = 0.363, respectively) (Table 3). Relationship exhaled VOCs and Interleukin-17 We examined of the concentrations of Ethanol, Toluene, Formaldehyde and Ammonia with Interleukin-17 statistically, using p < 0.05. We found that there no relationship with (p = 0.277, p = 0.477, p= 0.412, p = 0.269, respectively). (Table 4). VOCs Lung Cancer (Mean) ppm Subject Control p value (Mean) ppm Oxygen (O2) Ozone (O3) Carbon Dioxide (CO2) (1) Carbon Dioxide (CO2) (2) Ethanol (C2H5OH) Formaldehyde (CH2O) Toluene (C7H8) Acetone (C3H6O) Ammonium (NH4) Hexane (C6H14) Nitrogen (NO2) Carbon Monoxide (CO) Ammonia (NH3) Methane (CH4) Sulphur Dioxide (SO2) 21.22254 58.14644 1470.21055 1496.00533 1.24580 0.51899 0.61858 0.08536 0.44946 0.41880 0.98333 0.00009 0.90681 0.47846 2.59492 20.7988 110.8965 701.1388 714.5339 0.8148 0.0453 0.0167 0.2279 0.9996 0.4589 1.5615 0.0000 0.6637 0.5175 2.5316 .282 .000 .188 .204 .000 .000 .000 .000 .000 .000 .001 .306 .001 .000 .133 Table 3. The differences between the histological types stadium of lung cancer and therapy with VOCs and IL-17 VOCs Ethanol Formaldehyde Toluene Ammonia IL-17 (p value) (p value) (p value) (p value) (p value) Histological type ? Adenocarcinoma ? Adeno-squamous cell ca ? Squamous cell ca ? Small cell ca Stadium lung cancer ? III b ? IV a ? IV b Therapy ? ? Chemotherapy Targeted Therapy 0.404 0.967 0.298 0.084 0.570 0.081 0.978 0.535 0.086 0.081 0.751 0.107 0.342 0.130 0.363 Table 4. Relationship between VOC and IL-17 VOCs IL-17 (p value) Ethanol 0.277 Formaldehyde 0.477 Toluene 0.412 Ammonia 0.269 DISCUSSION The goal of this study was to profile a VOC that may be assessed to diagnose lung cancer by analyzing at exhaled volatile organic compounds (VOCs) and IL-17. Lung cancer is a disease that silent in the early stages but becomes fatal at an advanced stage. Modalities are currently used for lung cancer screening based on radiological imaging and a definitive diagnosis with histopathology types examination. VOCs from respiratory air may reflect metabolic changes caused by disease and may play a role in biomarkers of lung cancer.8 We identified Ethanol, Toluene, Formaldehyde and Ammonia as possible biomarkers of lung cancer, especially in advanced stages. Several studies have been conducted to identify components of VOC compounds. The study, which was conducted by Oguma et al., concluded that ethanol and toluene had identified an increase in lung cancer compared to the control group.9 Differences in VOC values that can be caught on sensor devices, one of which is influenced by metabolic activity in cancer cells. Cancer cells directly undergo changes in their metabolic products, this is because cancer cells must need large amounts of energy to support its uncontrolled proliferation. The Warburg effect is a cancer metabolism process in which the activation of aerobic glycolysis occurs as the main pathway for obtaining energy. Changes in cellular metabolism result in metabolic changes that can accelerate the growth of cancer cells and also change the profile of respiratory VOCs.10 The increased ethanol concentrations in the study were most likely due to the Warburg effect on the cancer patient group. In addition, the concentration of formaldehyde compounds also increases. Endogenous formaldehyde may increase in malignancy conditions. In studies involving breast cancer and prostate cancer patients, it has been reported that there was an increase in the amount of endogenous formaldehyde concentrations in the urine. In vivo studies, cancer cell tissue from certain cancer patients was analyzed and found abnormally elevated concentrations. Endogenous formaldehyde is produced through a number of biochemical pathways in cells through the enzymatic reaction process of oxidative demethylation. Other factors could also be the determinants of the increase in the amount of formaldehyde, such as cigarette smoke, electronic cigarettes and aspartame sweeteners.11 This study found that there was an increase in the amount of ammonia compound concentrations. Ammonia is formed as a result of the breakdown of glutamine into glutamate. Glutamine is a non- essential amino acid that can be synthesized by cells through glutamine synthetase. Glutamine is present in the blood in the form of free amino acids. Cancer cells absorb and process high amounts of glutamine, this is because glutamine serves as a supplement for nucleotide biosynthesis.12 This is similar to Spinelli's research (2018) which stated that ammonia as a cellular metabolism product that is mainly excreted by proliferating cells. An example in this case is cancer cells. Ammonia can accumulate in the microenvironment tumor 10 times when compared to healthy tissue. 13 The global incidence of lung cancer shows that NSCLC lung cancer accounts for 80-85 percent of all occurrences. The cytokine IL-17 is vital in the process of micro-angiogenesis in the tumor microenvironment, stimulates cell proliferation, and has a role in the metastatic process, according to Chen et al. Wu et al., IL-17 promotes tumor angiogenesis and cell proliferation while also inhibiting apoptosis via inflammatory activation pathways.14,15 Several studies have been conducted to investigate the expression of IL-17 cytokines in the peripheral blood of NSCLC patients. In our study, the average levels of IL-17 in lung cancer were smaller than those of healthy subjects (87.77 and 101.03 (pg/mL) with a p > 0.05. We assumed the patient has been already treated by chemotherapy that could be affect the concentration of IL-17. The results of this examination are not in line with research conducted by Chen et al., which found that iL-17 expression in lung cancer was higher compared to the control group. Likewise with the expression of IL-17 serum patient lung cancer, the expression of IL-17 lung cancer was higher than with the control group. Wang et al.'s study explored prognosis by looking at iL-17 values in lung cancer, the increase in IL-17 expression was closely related to poor clinical output in lung cancer patients. The study also linked IL-17 levels to lung cancer stadium and lung cancer types concluded there were significant differences.15,16 Dutkowska et al., revealed that IL-17 is a proinflammatory cytokine that plays a role in chronic inflammation, autoimmunity, and malignancies 6 associated with inflammation. They further claim that IL-17 plays a direct or indirect function in lung cancer spread and progression, boosting tumor angiogenesis and cell proliferation while blocking apoptosis. Higher levels of il-17 expression were linked to earlier stages of cancer, according to the findings. Chen et al. lung cancer patients have higher IL-17 expression than healthy people. 15,17 On the other hand, there was a study that examines the effects of chemotherapy on serum IL- 17 levels in cancer patients. Research conducted by Xiang et al, revealed that there was a decrease in serum IL-17 levels in breast cancer patients who received chemotherapy and radiotherapy compared to the control group.18 But the underlying mechanism remains unclear. Our research has a number of limitations. First, our study included patients who were receiving lung cancer chemotherapy at the time of enrolment, which may have influenced the concentration of inhaled VOCs and IL-17. Second, due to the small number of early-stage patients, the current investigation was underpowered to discover exhaled VOCs relevant for early diagnosis of lung cancer. To continue and complete the profile VOC and IL-17 that is useful in evaluating patients with suspected lung cancer, a prospective study is required. CONCLUSIONS To summarize, we found that some exhaled VOCs such as Ethanol (C2H5OH), Formaldehyde (CH2O), Toluene (C7H8) and Ammonia (NH3) in lung cancer patient were increase compared with subject control. They might be used as biomarker of lung cancer. However, the concentration of IL-17 was higher in subject control at Saiful Anwar Hospital, Malang. REFERENCES 1. Ferlay, J., Colombet, M., Soerjomataram, I., Mathers, C., Parkin, D. M., Piñeros, M., et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. International journal of cancer, 2019; 144(8), 1941-1953. 2. Rahib, L., Wehner, M. R., Matrisian, L. M., & Nead, K. T. Estimated projection of US cancer incidence and death to 2040. JAMA network open, 2021.4(4), e214708-e214708. 3. Schabath, M. B., & Cote, M. L. Cancer progress and priorities: lung cancer. Cancer Epidemiology and Prevention Biomarkers, 2019; 28(10), 1563-1579. 4. Li, C., Lv, Y., Shao, C., Chen, C., Zhang, T., Wei, Y., et al. (2019). Tumor-derived exosomal lncRNA GAS5 as a biomarker for early-stage non-small-cell lung cancer diagnosis. Journal of cellular physiology, 2019; 234(11), 20721- 20727. 5. 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