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The Role of Serum IL-23 and Volatile Organic Compound Levels to RECIST 1.1 in The Evaluation of Therapeutic Response in Lung Cancer

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Abstract

The Response Evaluation Criteria in Solid Tumors (RECIST 1.1) is the gold standard for the assessment of lung cancer progression. However, the assessment and diagnosis of early treatment failure is challenging due to the limitations of current tools, as well as the long intervals and unavoidable side effects.This study aims to correlate volatile organic compound (VOC) patterns, serum level of interleukin-23 (IL-23), and RECIST 1.1 to assess chemotherapy response in lung cancer patients at Saiful Anwar Hospital. A prospective observational study was performed to 47 lung cancer patients who received three cycles of platinum-based chemotherapy. Using the Breath Analyzer to measure certain volatile organic compounds (VOCs), the study observed that three of the seven VOCs examined, formaldehyde (CH_2O), toluene (C_7H_8), and hexane (C_6H_{14}), showed lower levels after three cycles of chemotherapy. Furthermore, there was a negative correlation between RECIST1.1 and acetone (C_3H_6O) (p=0.023), while RECIST1.1 and methane (CH_4) had a positive correlation (p=0.011). Moreover, a significant positive correlation was observed between IL-23 after-chemotherapy and RECIST 1.1 (p=0.000). According to this study, a correlation exists between methane, IL-23, and RECIST 1.1 after three cycles of chemotherapy. The increase in methane and IL-23 aligns with the disease progression determined by RECIST 1.1. Furthermore, The decrease in acetone after chemotherapy showed a negative correlation with RECIST1.1, consistent with disease progression.

Keywords: *Volatile Organic Compound, Interleukin-23, RECIST 1.1.*

INTRODUCTION

Lung cancer is a major public health concern, representing 12.4% of all cancers worldwide and being the primary cause of cancer-related mortality. In the United States, there are over 234,000 new cases and over 154,000 deaths from lung cancer each year (Siegel, *et al*., 2017; Sung, *et al*., 2021; WHO IARC, 2021). In Indonesia, lung cancer is the third most common cancer and the most prevalent type in men (Pangribowo, 2019). Currently, lung cancer treatment is based on the clinical

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stage at diagnosis, but the varied nature of cancer cells results in different outcomes for each patient (Marino, *et al*., 2019). Therefore, regular monitoring of cancer therapy response is crucial (Badan Pengawas Tenaga Nuklir, 2020; Nardi-Agmon, *et al*., 2016).

The gold standard for evaluating lung cancer treatment is Response Evaluation Criteria in Solid Tumors (RECIST 1.1), which has better measurement variability compared to RECIST 1.0 and WHO Criteria. In addition, RECIST 1.1 can also detect early changes in physiology and pathology before clinical detection in patients, and act as a surrogate endpoint to optimize the time and resources used in cancer clinical trials. However, the time between CT scans is often too long to detect treatment failure early, so a potential non-invasive approach to accelerate diagnosis and therapy is to use VOCs and IL-23 (Einoch Amor, *et al*., 2019; Ko, *et al*., 2021; Marzorati, *et al*., 2019). Interleukin-23 (IL-23), an important proinflammatory cytokine, could serve as an indicator of prognosis and therapeutic success in lung cancer (Baird, *et al*., 2013; Koh, *et al*., 2019; Liu, *et al*., 2020). Interleukin-23 (IL-23) is known to have the ability to induce lung cancer cell proliferation and metastase. IL-23 induces naive T cell CD-4 differentiation and maintains T helper cell 17 (Th-17). IL-23 also stimulates the downstream signaling pathway of interleukin 17 (IL-17) through Janus kinase 2/signal transducer and Activator of Transcription 3 (JAK2/STAT3) (Listiandoko, *et al*., 2023). The expression of IL-23R has been reported in adenocarcinoma and small cell carcinoma (Listiandoko, *et al*., 2022). Several previous studies have linked VOCs to cancer incidence, such as propane, isobutane, acetonitrile, acetone, and carbon disulfide have been reported as potential biomarker of cancer (Becker, 2020; Rocco, *et al*., 2018; Santonico, *et al*., 2012). However, no previous studies have combined volatile organic compound (VOC) gas patterns and IL-23 in evaluating lung cancer therapy response. Therefore, this study aims to correlate VOC patterns, serum level of IL-23, and RECIST 1.1 to assess chemotherapy response in lung cancer patients at Saiful Anwar Hospital.

METHODS

This study is an observational study that aims to assess the differences in VOC patterns and serum IL-23 levels in lung cancer patients before and after their third cycle of chemotherapy. The study included lung cancer patients who met certain criteria such as being newly diagnosed with lung cancer, being above 18 years old, and being in a stable clinical condition. Patients with acute infections or other primary cancers were excluded from the study. A total of 47 samples were collected using purposive and consecutive sampling methods. Briefly, prior to VOC gas sampling, patients were not allowed to eat odoriferous foods and smoke for ½-1 before the examination. Subjects were asked to rinse their mouths and were asked to exhale 2-3 times (with a mask protected position) before exhaling into the bag. Breath gas samples were analyzed in real-time using a breath analyzer, while IL-23 serum samples were examined by ELISA in the Clinical Pathology laboratory. Baseline and evaluation after 3 cycles chemotherapy of thoracic CT scan examinations were performed. The unpaired t-test and wilcoxon test were used to assess differences in VOC patterns and serum IL-23 concentrations. spearman test was used to examine the correlation between VOCs and IL-23 with RECIST 1.1. ROC analysis and path analysis were used to determine the magnitude of the influence of VOCs and IL-23 on RECIST 1.1. The study obtained research ethics approval from the Health Research Ethics Commission of Dr. Saiful Anwar Hospital East Java number: 400/036/K.3/102.7/2023.

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RESULTS

Subject Characteristics

The study subjects used consisted of 47 lung cancer patients who had not received cancer treatment. The sociodemographic characteristics of the study subjects are shown in Table 1.

The average age of patients in the study is 57.94 years, with an age range of 25 to 74 years and most of them are male (59.6%). In terms of smoking status, nearly half of the patients were active smokers (48.9%), while 42.6% were non-smokers and 8.5% were former smokers. When it comes to cell type classification of lung cancer, adenocarcinoma was the most common (48.9%).

Table 1. Sociodemographic characteristics.

Characteristic of Sample	Frequency (N=47)	Persentage (%)
Age		
• Mean±SD	57.94+11.09	
Sex		
• Male	28	59.6%
• Female	19	40.4%
Smoking history		
• Non-smoker	20	42.6%
• Smoker	23	48.9%
• Ex-smoker	4	8.5%
Type of carcinoma		
• *Adenocarcinoma*	23	48.9%
• *Adenosquamous cell carcinoma*	3	6.4%
• *Squamous cell carcinoma*	16	34.0%
• *Small cell carcinoma*	5	10.6%
Stage (Before chemotherapy)		
• IIIa	2	4.3%
• IIIb	4	8.5%
• IIIc	1	2.1%
• Iva	24	51.1%
• Ivb	16	34.0%

Evaluation of Certain Volatile Organic Compounds (VOCs)

According to the t-test conducted to determine the difference in VOC levels before and after chemotherapy, it is known that there is a significant decrease in CH_2O, C_7H_8, C_6H_{14} and an increase in C_3H_6O after the third cycle of chemotherapy.

The comparison test results found that there was a significant difference in acetone levels before the test, with higher levels in the non-progressive group. After testing, there was no significant difference in acetone levels between the two groups. Furthermore, the methane levels were significantly higher in the progressive group compared to the non-progressive group. It could be important factors to consider in relation to the progression of the disease.

Interleukin-23 (IL-23) Serum Levels

As shown in Table 4, the average IL-23 levels increased after chemotherapy, suggesting no significant difference in IL-23 between before and after 3 cycles of chemotherapy.

The correlation analysis between IL-23 and RECIST 1.1 OR showed a significant correlation between the increase in after-chemotherapy IL-23 levels and an increase in RECIST 1.1 towards progressive.

Table 2. Difference between VOC gas before and after 3 cycles chemotherapy.

VOC		Median (ppm)	Min-Max (ppm)	*p value*
Ethanol (C_2H_5OH)	Before (mean±SD)	1.161±0.448	0.34-2.28	0.142
	After (mean±SD)	1.02±0.455	0.10-1.98	
Formaldehyde (CH_2O)	Before (mean±SD)	0.16±0.38	0-1.93	0.000
	After (mean±SD)	0.02±0.10	0-0.68	
Toluene (C_7H_8)	Before (mean±SD)	0.18±0.56	0-3.19	0.001
	After (mean±SD)	0.01±0.10	0-0.66	
Acetone (C_3H_6O)	Before	0.21	0-0.69	0.000
	After	0.40	0-0.85	
Hexane (C_6H_{14})	Before	0.39	0.11-0.49	0.040
	After	0.36	0.01-0.46	
Metane (CH_4)	Before	0.47	0.38-0.55	0.341
	After	0.47	0.18-0.57	

Based on Table 6, it is known that there is a significant increase in serum IL-23 levels in the progressive group before and after 3 cycles of chemotherapy with p value <0.05.

Based on the results of the Mann-Whitney comparison test as shown in Table 7, the before-chemotherapy IL-23 levels in the progressive lung cancer group has no significant difference. Meanwhile, the after- chemotherapy IL-23 showed that after-chemotherapy IL-23 levels in the progressive lung cancer group were significantly higher than in the non-progressive group.

Correlation Between Volatile Organic Compound (VOC) and Interleukin-23 (IL-23) Serum Levels

Based on the results of the correlation test between VOCs and IL-23, there was no significant correlation between various VOC compounds such as ethanol, formaldehyde, toluene, acetone, hexane, methane, and IL-23 either before chemotherapy or after 3 cycles of chemotherapy.

The correlation test results demonstrate that CH_2O (Before) and C_3H_6O (Before) have a significant relationship with RECIST 1.1 Overall Response. Higher levels of

Table 3 Comparative test results of VOCs in the RECIST group.

		RECIST Overall Response		*p* value
		Non Progressive	Progressive	
Ethanol (C_2H_5OH)	Before (mean±SD)	1.12±0.46	1.22±0.43	0.438
	After (mean±SD)	1.03±0.51	1.01±0.38	0.928
Formaldehyde (CH_2O)	Before (median, min-max)	0.0-1.93	0.0-1.16	0.051
	After (median, min-max)	0.0-0.16	0.0-0.68	0.722
Toluene (C_7H_8)	Before (median, min-max)	0.0-3.19	0.0-1.50	0.057
	After (median, min-max)	0.0-0.02	0.0-0.66	0.806
Acetone (C_3H_6O)	Before (median, min-max)	0.28, 0-0.69	0.10, 0-0.49	0.011
	After (mean±SD)	0.43±0.22	0.39±0.17	0.541
Hexane (C_6H_{14})	Before (median, min-max)	0.39, 0.11-0.49	0.40, 0.14-0.45	0.846
	After (median, min-max)	0.35, 0.01-0.43	0.37, 0.04-0.46	0.175
Metane (CH_4)	Before (mean±SD)	0.47, ±0.05	0.47±0.04	0.639
	After (median, min-max)	0.44, 0.18-0.51	0.48, 0.41-0.57	0.003

Table 4. Differences in IL-23 levels before and after chemotherapy.

	Median (pg/mL)	Mean±SD (pg/mL))	Min-Max (pg/mL)	*P* value
IL-23 (before)	304.32	588.38±865.77 2	7.63-4978.50	
IL-23 (after)	345.56	750.16±723.35 2	5.51-2853.64	0.212

CH_2O (Before) are associated with a progressive increase in response, while a decrease in C_3H_6O (Before) is linked to an increase in response. CH_4 (After) and IL-23 (After) also show a significant positive correlation with RECIST 1.1 Overall Response. This suggests that the levels of these compounds are related to the overall response according to RECIST criteria.

DISCUSSION

This study examines the use of μβreath, a breath analysis tool developed by Universitas Brawijaya to investigate VOC compounds in the exhaled breath of lung cancer patients. Unlike other breath analyzers, μβreath not only identifies VOC compounds but also measures their levels.

Table 5. Correlation between IL-23 levels and RECIST 1.1 overall response.

	Correlation coefficient (n=47)	*P Value*
IL-23 (before) and RECIST 1.1 OR	0.159	0.287
IL-23 (after) and RECIST 1.1 OR	0.606	0.000

Identification of VOCs is important as it requires an understanding of the inflammatory process (Ratiu, *et al*., 2020). Endogenous volatiles can help diagnose chronic inflammatory conditions and oxidative stress. A before study has shown a link between peroxidative activity caused by reactive oxygen species (ROS) reactions and membrane lipids. Increased oxidative stress and the induction of cytochrome *p*-450 enzymes are important risk factors for cancer development. Oxidative stress occurs when there is an imbalance between the generation and deactivation of ROS and free radicals (Haick, *et al*., 2014; Tong, *et al*., 2017). Cells produce ROS during cellular processes in the mitochondria, and other sources of ROS can be exogenous, such as cigarette smoke and pollution. Accumulated ROS can damage molecules in the body, and during oxidative stress, volatile alkanes are exhaled through breath. ROS can also upregulate cytochrome *p*-450 enzymes in human tissues, which catalyze the oxidation of organic chemicals (Haick, *et al*., 2014; Tong, *et al*., 2017).

In the early stages of cancer, cells become hypoxic and switch to glycolysis, leading to an acidic microenvironment and immunity evasion (Jia, *et al*., 2018). VOCs produced by gene and protein changes can be detected in body fluids. Exogenous VOCs from carcinogen exposure can also cause damage (Haick, *et al*., 2014; Jia, *et*

Table 6. Difference of IL-23 in progressive and non-progressive groups.

	Observation Result				
	Before-chemotherapy (pg/mL)		After-chemotherapy (pg/mL)		*P* value
IL-23 Non-progressive (median, min-max)	267.61	27.63-4978.50	199.53	25.51-1604.84	0.113
IL-23 Progressive (median, min-max)	319.74	72.48-2708.84	1197.71	91.30-2853.64	0.005

Table 7. Comparison of IL-23 levels based on RECIST 1.1.

	RECIST Overall Response		*P* value
	Non Progressive	Progressive	
IL-23 (before) (median, min-max)	267.61 (27.63-4978.50)	319.74 (72.48-2708.84)	0.282
IL-23 (after) (median, min-max)	199.53 (25.51-1604.84)	1197.71 (91.30-2853.64)	0.000

al., 2018). Alkanes and formaldehyde in breath are associated with lipid peroxidation and lung cancer (Listiandoko, *et al*., 2023; Stefanuto, *et al*., 2020). Endogenous formaldehyde is produced through enzymatic reactions and can be detected in urine in breast and prostate cancer (Burgos-Barragan, *et al*., 2017; Hartwig, *et al*., 2020). Tsou, *et al* (2021), who investigated the differences in VOCs in lung cancer patients and healthy controls, reported that of the two groups, ethanol, formic acid, ethanediol, methanol, acetone, butane, and hexane had higher levels in cancer cases compared with healthy controls. Other groups of VOCs, such as benzoic acid and beta-caryophyllene, showed very low concentrations in most healthy controls. All of these dominant VOCs, except hexane, were significantly different between lung cancer cases and healthy controls (Tsou, *et al*., 2021).

A similar mechanism was also reported the effects of toluene and IL-23 on lung cancer proliferation and development (Gashimova, *et al*., 2020; Hartwig, *et al*., 2020). Toluene is shown to increase phosphorylation of *p*-53 and cause mutations in tumour suppression genes,

Table 8. Correlation between VOC and IL-23 levels before and after chemotherapy.

		Correlation Coefficient (n=47)	*P* value
Ethanol (C_2H_5OH) - IL-23	Before	0.027	0.856
	After	0.050	0.740
Formaldehyde (CH_2O) - IL-23	Before	0.249	0.091
	After	0.213	0.150
Toluene (C_7H_8) - IL-23	Before	0.171	0.252
	After	0.227	0.125
Acetone (C_3H_6O) - IL-23	Before	-0.250	0.090
	After	-0.204	0.168
Hexane (C_6H_{14}) - IL-23	Before	0.002	0.987
	After	0.203	0.172
Metane (CH_4) - IL-23	Before	0.005	0.976
	After	0.185	0.214

leading to uncontrollable cell proliferation in cancer cells (Rudnicka, *et al*., 2019). Toluene levels in breath samples can be affected by environmental contamination (Ratiu, *et al*., 2020). Additionally, methanol, acetone, propanol, and pentane levels are increased in patients with a history of smoking, with higher concentrations in stage IV lung cancer patients, especially those with diabetes (Horváth, *et al*., 2017). IL-23 is a proinflammatory cytokine that promotes lung cancer proliferation and has a role in cancer persistence, survival, and growth. A study showed a significant increase in IL-23 levels in progressive lung cancer patients after chemotherapy (Yan. *et al*., 2018). IL-23 supports the propagation of Th17 cells, and IL-17 and IL-23 work together in biological processes (Baird, *et al*., 2013). Elevated IL-23 levels are associated with poor diagnosis and an increase in small cell

Table 9. Correlation between VOCs and IL-23 toward RECIST 1.1 overall response.

		Correlation Coefficient	*P* value
Ethanol (C_2H_5OH) and RECIST 1.1	Before	0.133	0.372
	After	0.013	0.933
Formaldehyde (CH_2O) and RECIST 1.1	Before	0.289	0.049
	After	0.052	0.726
Toluene (C_7H_8) and RECIST 1.1	Before	0.280	0.056
	After	0.036	0.809
Acetone (C_3H_6O) and RECIST 1.1	Before	-0.374	0.010
	After	-0.103	0.490
Hexane (C_6H_{14}) and RECIST 1.1	Before	0.029	0.849
	After	0.200	0.178
Metane (CH_4) and RECIST 1.1	Before	0.040	0.791
	After	0.442	0.002
IL-23 and RECIST 1.1	Before	0.159	0.287
	After	0.606	0.000

lung cancer compared to non-small cell lung cancer (Cam, *et al*., 2016). IL-23 levels are also elevated in colorectal cancer patients and associated with the expression of Vascular Endothelial Growth Factor (VEGF) (Baird, *et al*., 2013; Pastor-Fernández, *et al*., 2020).

Cancer cells and external cytokine signaling play a role in immune evasion and tumor progression. Cytokines such as IL-7 or IL-11 activate the PI3K-AKT-mTOR signaling pathway, which regulates glycolysis and induces metabolic reprogramming of various factors involved in tumor growth. These pathways lead to epithelial-mesenchymal transition (EMT), increased proliferation, reduced apoptosis, increased migration, and the production of cytokines linked to angiogenesis. Other cytokines, like IL-1β, IL-13, IL-17, IL-22, IL-23, and IL-35, also induce EMT and promote tumor progression. Specifically, IL-23 has been found to stimulate glycolysis, lactic acid production, and angiogenic activity in tumor cells (Briukhovetska, *et al*., 2021).

The correlation between VOC gas and IL-23 levels before and after chemotherapy did not show a significant correlation, suggesting that more research is needed to understand the connection between VOCs and IL-23 levels. Additionally, chronic exposure to inflammatory cigarette smoke has been found to increase certain VOCs in breath samples (Koh, *et al*., 2019). Overall, further investigation is required to fully combeforehend the relationship between IL-23 levels and VOCs in breath analysis (Ratiu, *et al*., 2020). Clinical application of breath analysis in lung cancer remains a challenging task. There are significant differences in breath sampling procedures, study designs, and data analysis methods involved in the studies, leading to inconsistent results. Dietary habits, metabolic processes, inflammation, or redox status, or the condition of the gut microbiota affect breath VOCs (Tsou, *et al*., 2021). The mechanism of most VOCs exhaled by the human body remains unclear. The following molecular factors may influence the concentration and composition of lung cancer VOCs in the human body: oxidative stress, cytochrome P450, liver enzymes, carbohydrate metabolism (glycolysis/gluconeogenesis pathway), and lipid metabolism (Hakim, *et al*., 2012). These possible biochemical pathways vary from one person to another, resulting in increased or decreased VOC concentrations (Tsou, *et al*., 2021).

Nardi-Agmon (2016) found that VOC concentrations change in anticancer treatment response, with some VOCs increasing as the disease progression (Nardi-Agmon, *et al*., 2016). IL-23 levels were also found to be related to

cancer progression and cell proliferation (Baird, *et al*., 2013). IL-23 regulates the growth of lung cancer cells by affecting the expression and phosphorylation of STAT3. The Ki-67 gene is involved in this process (Li, *et al*., 2013). Adenocarcinoma and small cell carcinoma tissues showed positive expression of IL-23r and IL-12Rβ1 with lower yield. No expression of IL-23r and IL-12Rβ1 was detected in squamous cell carcinoma tissue. IL-23r was detected in 90.0% of adenocarcinoma samples (36/40) and in 86.5% of SCLC tissues, whereas IL-12Rβ1 was found to be exbeforessed in 82.5% of adenocarcinoma samples (33/40) and in 81.1% of SCLC tissues (30/37). Strong positive expression of IL-23r and IL-12β1 was observed in A549 and SPCA-1 cells (adenocarcinoma) but was not detected in SK-MES-1 cells (SCC cells). The present of IL-23 receptors on lung cancer cells indicates that IL-23 may have a direct effect on lung cancer cells (Liu, *et al*., 2020).

CONCLUSION

According to this study, a correlation exists between methane, IL-23, and RECIST 1.1 after three cycles of chemotherapy. The increase in methane and IL-23 aligns with the disease progression determined by RECIST 1.1. Furthermore, The decrease in acetone after chemotherapy showed a negative correlation with RECIST1.1, consistent with disease progression.

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REFERENCES

Badan Pengawas Tenaga Nuklir, 2020, *Diagnostic Reference Level (DRL) dan Status Terkini di Indonesia*, Sist. Inf. Data Dosis Pasien.

Baird, A.-M., Dockry, É., Daly, A., Stack, E., Doherty, D.G., O'Byrne, K.J., and Gray, S.G., 2013, IL-23R is Epigenetically Regulated and Modulated by Chemotherapy in Non-Small Cell Lung Cancer, *Front Oncol*, **3**, 162.

Becker, R., 2020, Non-invasive cancer detection using volatile biomarkers: Is urine superior to breath?, *Med Hypotheses*, **143**, 110060.

Briukhovetska, D., Dörr, J., Endres, S., Libby, P., Dinarello, C.A., and Kobold, S., 2021, Interleukins in cancer: from biology to therapy, *Nat Rev Cancer*, **21**, 481–499.

Burgos-Barragan, G., Wit, N., Meiser, J., Dingler, F.A., Pietzke, M., Mulderrig, L., *et. al*., 2017, Mammals divert endogenous genotoxic formaldehyde into one-carbon metabolism, *Nature*, **548**, 549–554.

Cam, C., Karagoz, B., Muftuoglu, T., Bigi, O., Emirzeoglu, L., Celik, S., *et al*., 2016, The inflammatory cytokine interleukin-23 is elevated in lung cancer, particularly small cell type, *Współczesna Onkologia*, **20**(3), 215–219.

Einoch Amor, R., Nakhleh, M.K., Barash, O., and Haick, H., 2019, Breath analysis of cancer in the present and the future, *European Respiratory Review*, **28**, 190002.

Gashimova, E., Temerdashev, A., Porkhanov, V., Polyakov, I., Perunov, D., Azaryan, A., and Dmitrieva, E., 2020, Investigation of different approaches for exhaled breath and tumor tissue analyses to identify lung cancer biomarkers, *Heliyon*, **6**(6), e04224.

Haick, H., Broza, Y.Y., Mochalski, P., Ruzsanyi, V., and Amann, A., 2014, Assessment, origin, and implementation of breath volatile cancer markers, *Chem. Soc. Rev.*, **43**(5), 1423–1449.

Hakim, M., Broza, Y.Y., Barash, O., Peled, N., Phillips, M., Amann, A., and Haick, H., 2012,

Volatile Organic Compounds of Lung Cancer and Possible Biochemical Pathways, *Chem. Rev.*, **112**(11), 5949–5966.

Hartwig, A., Arand, M., Epe, B., Guth, S., Jahnke, G., Lampen, A., *et al.*, 2020, Mode of action-based risk assessment of genotoxic carcinogens, *Arch Toxicol.*, **94**, 1787–1877.

Horváth, I., Barnes, P.J., Loukides, S., Sterk, P.J., Högman, M., Olin, A.-C., *et al.*, 2017, A European Respiratory Society technical standard: exhaled biomarkers in lung disease, *European Respiratory Journal*, **49**(4), 1600965.

Jia, Z., Zhang, H., Ong, C.N., Patra, A., Lu, Y., Lim, C.T., and Venkatesan, T., 2018, Detection of Lung Cancer: Concomitant Volatile Organic Compounds and Metabolomic Profiling of Six Cancer Cell Lines of Different Histological Origins, *ACS Omega*, **3**, 5131–5140.

Ko, C.-C., Yeh, L.-R., Kuo, Y.-T., and Chen, J.-H., 2021, Imaging biomarkers for evaluating tumor response: RECIST and beyond, *Biomark. Res.*, **9**, 52.

Koh, J., Kim, H.Y., Lee, Y., Park, I.K., Kang, C.H., Kim, Y.T., *et al.*, 2019, IL23-Producing Human Lung Cancer Cells Promote Tumor Growth via Conversion of Innate Lymphoid Cell 1 (ILC1) into ILC3, *Clinical Cancer Research*, **25**(13), 4026–4037.

Li, J., Zhang, L., Zhang, J., Wei, Y., Li, K., Huang, L., *et al.*, 2013, Interleukin 23 regulates proliferation of lung cancer cells in a concentration-dependent way in association with the interleukin-23 receptor, *Carcinogenesis*, **34**(3), 658–666.

Listiandoko, R.D.W., Setyawan, U.A., and Astuti, T., 2022, EP01.01-004 The Correlation Between Exhaled Volatile Organic Compounds Using Breath Analyzer and Interleukin-23 (IL-23) in Lung Cancer, *Journal of Thoracic Oncology*, **17**(9), S161.

Listiandoko, R.D.W., Setyawan, U.A., Tri Wahju Astuti, Djajalaksana, S., Listyoko, A.S., and Ponco, A.Y., 2023, Volatile Organic Compounds (VOCs) and Interleukin-23 Levels in Lung Cancer: A Future Biomarker, *Jurnal Respirasi*, **9**(2), 80–86.

Liu, D., Xing, S., Wang, W., Huang, X., Lin, H., Chen, Y., *et al.*, 2020, Prognostic value of serum soluble interleukin-23 receptor and related T-helper 17 cell cytokines in non-small cell lung carcinoma, *Cancer Sci.*, **111**(4), 1093–1102.

Marino, F.Z., Bianco, R., Accardo, M., Ronchi, A., Cozzolino, I., Morgillo, F., *et al.*, 2019, Molecular heterogeneity in lung cancer: from mechanisms of origin to clinical implications, *Int J Med Sci.*, **16**(7), 981–989.

Marzorati, D., Mainardi, L., Sedda, G., Gasparri, R., Spaggiari, L., and Cerveri, P., 2019, A review of exhaled breath: a key role in lung cancer diagnosis, *J Breath Res.*, **13**, 034001.

Nardi-Agmon, I., Abud-Hawa, M., Liran, O., Gai-Mor, N., Ilouze, M., Onn, A., *et al.*, 2016, Exhaled Breath Analysis for Monitoring Response to Treatment in Advanced Lung Cancer, *Journal of Thoracic Oncology*, **11**(6), 827–837.

Pangribowo, S., 2019, *Beban Kanker di Indonesia, Pusat Data Dan Informasi Kesehatan Kementerian Kesehatan RI*, 1–16.

Pastor-Fernández, G., Mariblanca, I.R., and Navarro, M.N., 2020, Decoding IL-23 Signaling Cascade for New Therapeutic Opportunities, *Cells*, **9**(9), 2044.

Ratiu, I.A., Ligor, T., Bocos-Bintintan, V., Mayhew, C.A., and uszewski, B., 2020, Volatile Organic Compounds in Exhaled Breath as Fingerprints of Lung Cancer, Asthma and COPD, *J. Clin. Med.*, **10**(1), 32.

Rocco, G., Pennazza, G., Santonico, M., Longo, F., Rocco, R., Crucitti, P., and Incalzi, R.A., 2018, Breathprinting and Early Diagnosis of Lung Cancer, *Journal of Thoracic Oncology*, **13**(7), 883–894.

Rudnicka, J., Kowalkowski, T., and Buszewski, B., 2019, Searching for selected VOCs in human breath samples as potential markers of lung cancer, *Lung Cancer*, **135**, 123–129.

Santonico, M., Lucantoni, G., Pennazza, G., Capuano, R., Galluccio, G., Roscioni, C., *et al.*, 2012, In situ detection of lung cancer volatile fingerprints using bronchoscopic air-sampling, *Lung Cancer*, **77**(1), 46–50.

Siegel, R.L., Miller, K.D., and Jemal, A., 2017, Cancer statistics, 2017, *CA Cancer J Clin.*, **67**(1), 7–30.

Stefanuto, P.-H., Zanella, D., Vercammen, J., Henket, M., Schleich, F., Louis, R., and Focant, J.-F., 2020, Multimodal combination of GC×GC-HRTOFMS and SIFT-MS for asthma phenotyping using exhaled breath, *Sci Rep.*, **10**, 16159.

Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., Soerjomataram, I., Jemal, A., and Bray, F., 2021, Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries, *CA Cancer J Clin.*, **71**(3), 209–249.

Tong, H., Wang, Y., Li, Y., Liu, S., Chi, C., Liu, D., *et al.*, 2017, Volatile organic metabolites identify patients with gastric carcinoma, gastric ulcer, or gastritis and control patients, *Cancer Cell Int.*, **17**, 108.

Tsou, P.-H., Lin, Z.-L., Pan, Y.-C., Yang, H.-C., Chang, C.-J., Liang, S.-K., *et al.*, 2021, Exploring Volatile Organic Compounds in Breath for High-Accuracy Prediction of Lung Cancer, *Cancers (Basel)*, **13**(6), 1431.

WHO IARC, 2021, *Cancer today: Lung cancer*, WHO IARC Cancer Today.

Yan, J., Smyth, M.J., and Teng, M.W.L., 2018, Interleukin (IL)-12 and IL-23 and Their Conflicting Roles in Cancer, *Cold Spring Harb Perspect Biol.*, **10**, a028530.