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ORIGINAL ARTICLE

Significant differences in volatile organic compounds and interleukin-12 (IL-12) serum levels between lung cancer patients and healthy controls: a cross-sectional study

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ABSTRACT

Aim To explore differences in exhaled volatile organic compounds (VOCs) and serum interleukin-12 (IL-12) levels between lung cancer patients and healthy controls, and their potential relationship with tumour-related metabolic and systemic immune alterations.

Methods A cross-sectional study was conducted involving lung cancer patients and healthy controls. Exhaled breath samples were analysed using the μβreath sensor to quantify VOCs, including total volatile organic compounds (TVOC)(1), TVOC(2), acetone, formaldehyde, toluene, hexane, and methane. Serum IL-12 levels were measured via ELISA. Significant limitations such as age mismatch, unvalidated sensor data, and potential confounders (smoking, chemotherapy, diet, environmental VOCs) were acknowledged.

Results Lung cancer patients exhibited significantly higher TVOC(1) and TVOC(2) levels, and higher acetone levels, while formaldehyde, toluene, hexane, and methane levels were lower than in controls. Serum IL-12 levels were markedly lower in patients, reflecting systemic immune modulation rather than direct diagnostic specificity. ROC analysis indicated high sensitivity for certain VOCs, but specificity remained limited, suggesting that these markers were exploratory rather than definitive diagnostic tools. No significant correlation was observed between VOCs and IL-12 levels.

Conclusion Differences in exhaled VOC profiles and serum IL-12 levels provide preliminary insight into tumour-related metabolic and immune alterations in lung cancer. However, due to major methodological limitations, particularly age mismatch and incomplete sensor validation, these findings should be interpreted with caution. Exhaled VOCs and IL-12 should be considered hypothesis-generating exploratory biomarkers that require validation in larger, age-matched cohorts using gold-standard analytical techniques and multivariate modelling.

Keywords: biomarkers, breathe tests, interleukin-12, lung neoplasms, volatile organic compounds

INTRODUCTION

Lung cancer remains one of the leading causes of cancer-related mortality worldwide, accounting for approximately 1.8 million deaths in 2020. Epidemiologically, it ranks second in global incidence and first in mortality, with a similar pattern observed in Indonesia, where an estimated 35,000 new cases and 30,000 deaths were reported in 2020 (1,2). Most patients are diagnosed at advanced stages, when symptoms have already appeared, resulting in a 5-year survival rate of around 19% (3). Although CT scans and bronchoscopic biopsies are standard diagnostic tools, they are limited by high cost, radiation exposure, the risk of false-positive results, and their invasive nature. Therefore, there is a growing need for accessible, non-invasive diagnostic approaches that can detect disease at earlier stages.

Breath analysis has emerged as a promising approach because it can generate profiles of volatile organic compounds (VOCs) that reflect underlying biochemical processes. VOCs may arise from oxidative stress and lipid peroxidation occurring within tumour cells. These processes produce volatile molecules such as aldehydes and alkanes, which have been reported to be altered or elevated in patients with lung cancer and are considered potential non-invasive biomarkers (4,5). In addition, tumour micro environmental factors, such as hypoxia, can modify cellular metabolism and increase the production of specific VOCs by

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enhancing enzymatic activity, including alcohol dehydrogenase, as demonstrated in A549 lung cancer cell models (6). Thus, alterations in exhaled VOCs may reflect biologically relevant pathways, including tumour metabolism, oxidative stress, and other cellular dynamics associated with lung cancer (4).

The immune response also plays a crucial role in lung cancer progression, particularly through interleukin-12 (IL-12), a cytokine with immunostimulatory and anti-angiogenic properties. IL-12 regulates T-cell differentiation, natural killer cell activation, and IFN-γ production, thereby contributing to antitumor immunity. Deficiency of IL-12 components has been associated with increased susceptibility to tumour growth in animal models, whereas enhanced IL-12 activity has been shown to inhibit lung cancer development (7). However, the relationship between systemic biomarkers such as IL-12 and exhaled VOC profiles remains unclear. Biologically, the inflammatory status and oxidative stress, involving cytokines such as IL-12, may interact with metabolic pathways that also generate VOCs, but this interplay has not yet been well characterized.

The aim of this study was to evaluate differences in exhaled VOC profiles and serum IL-12 levels between patients with lung cancer and healthy individuals. This exploratory investigation aims to provide initial insights into the potential of VOCs and IL-12 as non-invasive biomarkers for early lung cancer detection. The findings are expected to contribute to the development of more affordable and clinically feasible diagnostic strategies, and to serve as a foundation for validation studies in larger, more controlled cohorts.

PATIENTS AND METHODS

Patients and study design

This analytical observational study included two groups: patients diagnosed with lung cancer and a healthy control group. Lung cancer patients were recruited consecutively from the Pulmonology Department of Dr. Saiful Anwar General Hospital between January 2024 and July 2024 after meeting the inclusion criteria and providing written informed consent. Participants in the lung cancer group were treatment-naïve outpatients or hospitalized patients in stable clinical condition who were diagnosed with non-small-cell lung cancer (NSCLC) based on histopathological confirmation. Eligible patients had no evidence of primary malignancy in other organs and had not received any prior oncologic treatment at the time of breath sampling. All participants provided written informed consent before enrolment in the study. The control group consisted of healthy adults aged 20–30 years. The individuals who volunteered to serve as controls happened to fall within this age range. All controls had no history of chronic respiratory disease, malignancy, or acute infection at the time of sampling.

Demographic and clinical data collected from participants included smoking history, asbestos exposure, radon exposure, metastatic status, and metastatic organ involvement.

The concentrations of exhaled volatile organic compounds (VOCs), including total volatile organic compounds (TVOC), acetone, formaldehyde, toluene, hexane, and methane, were analysed in both the lung cancer and healthy control groups. Serum interleukin-12 (IL-12) levels were also measured in all participants. Comparative analyses were performed between the lung cancer and control groups to evaluate differences in VOC profiles and IL-12 levels. Additionally, correlations between VOC concentrations and IL-12 levels were assessed within the lung cancer group.

All participants provided written informed consent prior to enrolment.

The study was approved by the Health Research Ethics Commission of Dr. Saiful Anwar General Hospital (Approval No. 400/082/K.3/102.7/2024).

Methods

Breath samples were collected using standardized procedures in accordance with established methodological recommendations for breath analysis (8). Participants were instructed to rinse their mouths with clean water before sampling to reduce oral contaminants. Sampling was performed in a controlled environment using the same protocol for both groups.

Volatile organic compounds (VOCs) were analysed using an electronic nose (e-nose) system developed in collaboration with the Physics Laboratory of Universitas Brawijaya. Due to logistical constraints, breath sample collection was conducted at the hospital, while VOC analysis was performed at a separate laboratory, resulting in an unavoidable time interval between sampling and analysis.

Data acquisition was conducted over several months. After sample collection was completed, the dataset was transferred to the collaborating physics laboratory for signal processing and pattern recognition analysis. Some zero-value readings occurred due to intermittent sensor instability, which was identified during post-collection data validation. Sensors exhibiting instability were documented and excluded from final modelling to minimize analytical bias.

Statistical analysis

Statistical analysis, including data preprocessing and pattern classification, was conducted by the Physics Laboratory using established multivariate and machine-learning approaches. Clinical variables, including smoking status, environmental exposure, and metastatic status, were analysed descriptively and incorporated into the interpretation of VOC patterns.

RESULTS

A total of 40 lung cancer patients and 40 healthy controls were included in the analysis. The study flow and subject selection were completed in accordance with predetermined criteria (Table 1).

Sex distribution was identical between the groups (52.5% male and 47.5% female). Smoking status differed significantly, with lung cancer patients demonstrating higher proportions of smokers and former smokers ($p = 0.006$). The mean age of lung cancer patients (60.00 ± 10.42 years) was considerably higher than that of controls (31.73 ± 3.37 years) ($p = 0.000$).

Among lung cancer patients, adenocarcinoma was the most common histopathological type, 27 (67.5%), and most patients were diagnosed at stage IVA, 27 (67.5%). All patients received chemotherapy, and the most frequent regimen was Carboplatin-Paclitaxel, 18 patients (45%).

Several VOC components showed statistically significant differences between the groups, including total volatile organic compounds (TVOC)(1), TVOC(2), acetone (C_3H_6O), hexane (C_6H_{14}), and methane (CH_4) ($p < 0.05$). Ethanol levels (C_3H_5OH) did not differ significantly ($p = 0.387$).

Formaldehyde (CH_2O) and toluene (C_7H_8) values in lung cancer patients were consistently recorded as zero, reflecting measurements below the sensor's detection threshold, resulting in apparent group differences driven by control values (Table 2).

Table 1. Demographic and clinical characteristics of the two groups of study participants

Variable	Number (%) of patients in the group	
	Lung cancer	Control
Sex		
Male	21 (52.5)	21 (52.5)
Female	19 (47.5)	19 (47.5)
Smoking status		
Smoker	8 (20.0)	3 (7.5)
Former smoker	6 (15.0)	0
Non-smoker	26 (65.0)	37 (92.5)
Mean age ± SD (min.–max.) (years)	60.00 ± 10.42 (33.0–80.0)	31.73 ± 3.37 (26.0–38.0)
Histopathology		
Adenocarcinoma	27 (67.5)	NA
Adenosquamous cell	2 (5.0)	NA
Squamous cell	11 (27.5)	NA
Stadium		
IIIb	2 (5.0)	NA
IIIc	1 (2.5)	NA
IVa	27 (67.5)	NA
IVb	10 (25.0)	NA
Chemotherapy drugs		
Carboplatin, Paclitaxel	18 (45.0)	NA
Carboplatin, Gemcitabine	1 (2.5)	NA
Cisplatin, Paclitaxel	3 (7.5)	NA
Carboplatin, Etoposide	1 (2.5)	NA
Cisplatin, Pemetrexed	14 (35.0)	NA
Carboplatin, Pemetrexed	3 (7.5)	NA

SD, standard deviation; Min.–Max., minimum to maximum; NA, not applicable.

Table 2. Analysis of volatile organic compounds (VOCs) in two groups of study participants

Variable	Control		Lung cancer		p
	Mean ± SD	Min.–Max.	Mean ± SD	Min.–Max.	
TVOC(1)	422.51 ± 612.40	10.76–2411.49	1736.05 ±3376.72	16.47–19137.92	0.002*
TVOC(2)	455.06 ± 640.79	11.49–2379.41	1751.60 ±3427.78	16.34–19457.52	0.003*
Ethanol	0.83 ± 0.39	0.08–1.65	0.92 ±0.49	(−0.14)–2.13	0.387
Formaldehyde	0.05 ± 0.10	0.00–0.55	0.00 ± 0.00	0.00–0.00	< 0.001*
Toluene	0.02 ± 0.07	0.00–0.43	0.00 ± 0.00	0.00–0.00	0.002*
Acetone	0.22 ± 0.15	0.00–0.49	0.38 ± 0.23	0.00–0.78	0.002*
Hexane	0.46 ± 0.04	0.39–0.53	0.16 ± 0.13	0.00–0.43	< 0.001*
Methane	0.52 ± 0.04	0.44–0.58	0.39 ± 0.07	0.26–0.49	< 0.001*

* Statistically significant difference between control and lung cancer groups ($p < 0.05$).
SD, standard deviation; Min.–Max., minimum to maximum; TVOC, total volatile organic compounds.

IL-12 levels were substantially higher in the control group (563.14 ± 488.85 pg/mL) compared with lung cancer patients (81.91 ± 21.61 pg/mL) (p = 0.000).

No significant correlations were identified between IL-12 and most VOC parameters. A weak but statistically significant correlation was observed for hexane (C_6H_{14}) (p = 0.030). Formaldehyde and toluene were excluded from the correlation analysis because all measured values in lung cancer patients were below the sensor's detection threshold, resulting in zero recorded readings (Table 3).

The evaluated VOCs and serum IL-12 showed heterogeneous discriminatory performance, with sensitivity ranging from 50.0% to 100.0% and specificity from 17.5% to 82.5%. Several parameters, including formaldehyde, methane, hexane, and IL-12, demonstrated high sensitivity; however, their specificity remained limited. Accuracy, positive predictive value, and negative predictive value varied substantially across biomarkers, reflecting variability in discriminatory performance rather than definitive diagnostic utility (Table 4).

DISCUSSION

This study demonstrated that TVOC(1), TVOC(2), and acetone (C_3H_6O) levels were elevated in lung cancer patients, whereas formaldehyde (CH_2O), toluene (C_7H_8), hexane (C_6H_{14}), and methane (CH_4) were reduced. These alterations are biologically plausible and may reflect oxidative stress and lipid peroxidation processes in tumour cells. Cancer cells generate excessive reactive oxygen species (ROS), which promote peroxidation of unsaturated fatty acids and produce volatile aldehydes and alkanes detectable in exhaled breath (4). Lipid peroxidation products, including volatile aldehydes, have previously been proposed as lung cancer breath biomarkers (4). Additionally, tumour metabolic reprogramming, including enhanced lipid

Table 3. Correlation test between volatile organic compounds (VOC) levels and interleukin (IL)-12 in lung cancer patients

VOC variable	Correlation coefficient	p
TVOC (1)	−0.063	0.701
TVOC (2)	−0.073	0.655
Ethanol (C_2H_5OH)	−0.296	0.064
Formaldehyde (CH_2O)	—	—
Toluene (C_7H_8)	—	—
Acetone (C_3H_6O)	0.288	0.072
Hexane (C_6H_{14})	0.344	0.030
Methane (CH_4)	0.221	0.171

SD, standard deviation; TVOC, total volatile organic compounds.

Table 4. Receiver operating characteristic (ROC)-based diagnostic performance of volatile organic compounds (VOCs) and interleukin (IL)-12

Biomarker	Cut-off point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+	Accuracy (%)
Formaldehyde	0.00895	100.0	57.5	70.2	100.0	2.35	78.8
Toluene	0.00015	100.0	17.5	54.8	100.0	1.21	58.8
Hexane	0.4569	100.0	50.0	66.7	100.0	2	75.0
TVOC(1)	738.2067	50.0	80.0	71.4	61.5	2.5	65.0
TVOC(2)	746.3654	50.0	80.0	71.4	61.5	2.5	65.0
Acetone	0.399038	52.5	82.5	75.0	63.5	3	67.5
Methane	0.5198	100.0	55.0	69.0	100.0	2.22	77.5
IL-12	276.456	100.0	50.0	66.7	100.0	2	75.0

PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; TVOC, volatile organic compounds.

biosynthesis, may increase substrate availability for peroxidation, thereby altering VOC release. Aging and oxidative stress have also been associated with variations in alkanes and related VOCs (9).

The reduced levels of formaldehyde and toluene may result from differential tumour metabolism, tissue reabsorption, or local degradation. In contrast, acetone elevation may reflect hypoxia-related metabolic shifts and enzymatic activity within the tumour microenvironment (10).

Overall, the observed VOC pattern likely reflects tumour-related metabolic alterations rather than isolated compound-specific effects.

Serum IL-12 levels were significantly lower in lung cancer patients, consistent with systemic immune suppression. Although IL-12 plays a central role in antitumor immunity by activating T cells and NK cells, its circulating levels are influenced by circadian rhythm and physiological factors. Monocyte-derived IL-12 exhibits rhythmic variation, peaking during sleep and declining with prolonged wakefulness (11). The absence of correlation between IL-12 and VOCs is biologically plausible, as VOCs primarily represent local tumour metabolic activity, whereas IL-12 reflects systemic immune status. These parameters, therefore, operate at different biological levels.

A major limitation of this study is the substantial age mismatch between the groups. Age is known to influence the composition of breath VOCs. Electronic-nose studies have demonstrated age-related changes in VOC patterns (12), and GC–MS analyses have shown increased alveolar alkane gradients with aging, likely due to accumulated oxidative stress (13). Consequently, age may act as a strong confounder in interpreting VOC differences. Because age-adjusted analyses were not performed, this limitation must be carefully considered.

The presence of "0.00" values for formaldehyde and toluene in the cancer group likely reflects technical limitations of the μβreath sensor. Array-based sensors typically have higher limits of detection than GC–MS and are prone to baseline drift and signal interference (14). Very low concentrations may therefore fall below the detection threshold rather than represent true absence. Furthermore, without available calibration and repeatability data, the reliability of these measurements remains uncertain (8,15). Validation using gold-standard methods such as GC–MS and environmental background VOC monitoring should be incorporated into future studies (15).

Although several biomarkers demonstrated relatively high AUC values in ROC analysis, their clinical applicability is limited by low specificity and the univariate nature of the analysis. Meta-analyses indicate that while VOC-based breath testing often achieves high sensitivity, specificity varies widely across studies and methodologies (16). Single-compound markers with limited specificity are unlikely to function as standalone diagnostic tools.

Multivariate approaches may substantially improve predictive performance. Previous work using machine learning in breath analysis has demonstrated improved classification compared to univariate models. For example, Li et al. reported an AUC of approximately 0.77 using a machine-learning model (17). Qin et al. applied multivariate regression and neural networks to classify lung cancer, achieving 93.5% diagnostic accuracy after feature selection (18). Other studies using PLS-DA and related models have reported sensitivities of around 82% and precisions of up to 90% (19). In a prospective perioperative study, multivariable logistic regression incorporating 16 VOCs achieved an AUC of 0.952 after adjustment for age, sex, smoking, and comorbidities (20). These findings support the development of VOC panels rather than reliance on individual compounds.

Several potential confounders should also be acknowledged. Smoking substantially alters breath VOC composition (21). Chemotherapy may influence metabolic pathways and VOC pro-

duction. Dietary patterns, including ketogenic or fasting states, can modify volatile metabolite profiles (22). Environmental VOC exposure in clinical settings may additionally contribute to measured concentrations. These factors were not fully controlled and may influence interpretation.

Despite these limitations, this study provides preliminary evidence that alterations in breath VOCs and reduced IL-12 levels are associated with lung cancer. The findings should be interpreted as exploratory and hypothesis-generating rather than definitive diagnostic validation. Future studies should incorporate age-matched cohorts, gold-standard analytical validation (e.g., GC–MS) (23), environmental control, and multivariate modelling strategies to enhance robustness and clinical applicability.

In conclusion, alterations in specific exhaled VOCs (TVOC(1), TVOC(2), acetone) and decreased serum IL-12 levels reflect metabolic and immune changes associated with lung cancer. Breath analysis may represent a promising non-invasive approach for metabolic characterization, but further methodological refinement and multivariate validation are required before clinical implementation.

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CONFLICTS OF INTEREST

None to declare.

ETHICS STATEMENT

This study was approved by the Health Research Ethics Commission of Dr. Saiful Anwar General Hospital (Approval No. 400/082/K.3/102.7/2024). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding author upon reasonable request and with permission of the institution.

AUTHOR CONTRIBUTIONS (CRediT)

Conceptualization: M.N., U.A.S.; **Data curation:** M.N., A.S.L.; **Formal analysis:** M.N., A.Y.P.W.; **Investigation:** M.N., U.A.S., A.S.L.; **Methodology:** M.N., U.A.S., A.Y.P.W.; **Project administration:** U.A.S.; **Resources:** U.A.S., S.D.; **Software:** A.Y.P.W.; **Supervision:** S.D.; **Validation:** U.A.S., S.D.; **Visualization:** A.Y.P.W.; **Writing – original draft:** M.N.; **Writing – review & editing:** U.A.S., S.D., A.Y.P.W. All authors have read and agreed to the published version of the manuscript.

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