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Analysis of Urinary Midkine and Volatile Organic Compound (VOC) Levels Using a Breath Analyzer for Screening and Early Diagnosis of Lung Cancer

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ABSTRACT

Introduction: Lung cancer is the leading cause of cancer-related mortality worldwide. Midkine, a heparin-binding growth factor, promotes proliferation, angiogenesis, and metastasis. Volatile organic compounds (VOCs) reflect cellular and molecular changes, aiding in cancer diagnosis. This study explored urinary midkine and VOC profiles as biomarkers for lung cancer screening and early diagnosis.

Methods: A case-control, cross-sectional study was conducted on 20 controls (family members of lung cancer patients) and 20 lung cancer patients who had not received therapy. Volatile organic compounds breath analysis and urinary midkine measurements were performed. Volatile organic compounds, including total volatile organic compounds (TVOCs), ethanol (C₂H₅OH), formaldehyde (CH₂O), toluene (C₇H₈), acetone (C₃H₆O), hexane (C₆H₁₄), and methane (CH₄), were collected from exhaled breath using Tedlar bags and measured with a µBreath analyzer. Meanwhile, urinary midkine levels were determined using the Enzyme-Linked ImmunoSorbent Assay (ELISA) method. Statistical analyses included an independent t-test, Mann-Whitney U test, Spearman correlation, and diagnostic testing with receiver operating characteristic (ROC) analysis.

Results: Urinary midkine levels were higher in lung cancer patients than in controls (330.56±120.50 vs. 282.18±146.28 pg/mL), although not significant (p>0.05). The independent t-test revealed that ethanol levels were significantly elevated in lung cancer patients (p < 0.001), whereas methane levels were not (p > 0.50). Receiver operating characteristic analysis demonstrated sensitivity and specificity: urinary midkine (60%, 60%), ethanol (75%, 75%), and methane (45%, 45%).

Conclusion: Ethanol VOC appears to be a promising non-invasive biomarker for the early detection of lung cancer, whereas elevated urinary midkine levels did not demonstrate significant diagnostic value.

INTRODUCTION

Cancer remains one of the leading causes of mortality worldwide, with lung cancer being the primary contributor to cancer-related deaths.^{1,2} Early detection markedly improves prognosis, as the overall five-year survival rate increases from 10-20% to as high as 80% when lung cancer is diagnosed at stage I.^{2,3} Low-dose computed tomography (LDCT) is the standard screening tool. However, its high cost and radiation exposure limit

its widespread use.^{4,5} Consequently, alternative non-invasive diagnostic approaches, such as liquid biopsies, are under investigation.⁶ Biological fluids, including breath, blood, bronchoalveolar lavage fluid, and urine, have been explored.⁷

Urine is particularly advantageous due to its non-invasive, cost-effective, and stable collection properties.^{7,8} Among urinary biomarkers, midkine, a heparin-binding growth factor associated with tumor progression and angiogenesis in non-small cell lung

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cancer (NSCLC), has shown potential.⁹

Exhaled breath analysis, particularly the detection of volatile organic compounds (VOCs), is another promising approach, as VOCs can reflect metabolic and molecular changes associated with cancer.¹⁰⁻¹² Given these developments, further research on urinary midkine and exhaled VOCs in patients with lung cancer is warranted. Screening for lung cancer using breath and urine samples offers a non-invasive, affordable, and accessible approach suitable for routine clinical application. Such methods may contribute to the development of effective strategies for early detection and diagnosis of lung cancer, particularly by enhancing the availability of non-invasive screening tools.

METHODS

Study Design and Population

This case-control, cross-sectional study examined the presence of VOCs in exhaled breath and urinary midkine levels. The study population comprised two groups: lung cancer patients with histopathological confirmation (cases), and healthy individuals without comorbidities who were family members of the patients (controls). Each group consisted of 20 participants, all of whom provided informed consent. Patients were recruited from both inpatient and outpatient services at Dr. Saiful Anwar General Hospital (RSSA), Malang.

Variables and Setting

The independent variable was lung cancer status, while the dependent variables were VOC levels in exhaled breath and midkine levels in urine. Obesity and smoking status were considered potential confounders. This study was conducted between January 2024 and April 2025 at the pulmonary clinics of RSSA, Malang. Urine and breath samples were collected at the hospital, while further analyses were performed at the Clinical Pathology and Parasitology Laboratories of Universitas Brawijaya, Malang.

Materials, Data Collection, and Analysis

Instruments used included informed consent forms, case report forms, a breath analyzer, and an Enzyme-Linked ImmunoSorbent Assay (ELISA) kit (E1633Hu-48T Human Midkine, Bioassay Technology Laboratory). Urine samples were obtained after a 12-hour fast and analyzed using the ELISA method. Breath VOCs were collected after a one-hour fast and mouth rinsing, using a breath analyzer. Background environmental VOC levels were not measured as controls.

Data analysis was conducted using the International Business Machines Corporation (IBM) Statistical Package for the Social Sciences (SPSS) version 26.0. Normality was assessed using the Shapiro-Wilk test. Group comparisons were performed using the independent t-test or the Mann-Whitney U test, while Spearman correlation was used to evaluate the correlations between VOCs and midkine levels. Diagnostic values were assessed using 2x2 tables, and receiver operating characteristic (ROC) curve analysis was used to determine cut-off points for VOCs and midkine in predicting lung cancer. A p-value of less than 0.05 was deemed statistically significant.

Ethical Approval

Ethical approval was obtained by the Health Research Ethics Committee of RSSA, Malang, under the registration number 400/017/K.3/102.7/2025.

RESULTS

Characteristics of Study Subjects

This study included 20 patients with lung cancer who had not received cancer therapy and 20 healthy control subjects. The demographic and clinical characteristics of both groups are presented in [Table 1](#).

Table 1. Demographic characteristics

Characteristic	Group				p-value
	Control		Case		
	n	%	n	%	
Gender					
Male	9	45%	16	80%	0.000
Female	11	55%	4	20%	
Age					
<45 years old	17	85%	0	0%	0.022
45-65 years old	3	15%	12	60%	
>65 years old	0	0%	8	40%	
Smoking Status					
Non-smoker	12	60%	5	25%	0.019
Passive smoker	1	5%	3	15%	
Former smoker	0	0%	6	30%	
Active smoker	7	35%	6	30%	

Based on age distribution, the majority of lung cancer patients (n=20) were between 45 and 65 years old compared to those over 65 years old (60% vs. 40%). In contrast, among the control subjects, 85% were under 45 years old, and 15% were between 45 and 65 years old.

Regarding sex distribution, 45% of the control group were males and 55% were females. Among the lung cancer patients, 80% were males and 20% were females.

In terms of smoking status, among the control group (n=20), 35% were active smokers, 0% were former smokers, 5% were passive smokers, and 60%

were non-smokers. In the lung cancer group, 30% were active smokers, 30% were former smokers, 15% were passive smokers, and 25% were non-smokers.

Chi-squared test results showed statistically significant differences ($p < 0.05$) in age, sex, and smoking status between the healthy control group and the lung cancer patient group. These findings indicated significant demographic variations between the two groups.

Characteristics of Cell Types, Stages, and Epidermal Growth Factor Receptor Mutations

Table 2. Characteristics of cell types, stages, and epidermal growth factor receptor (EGFR) mutations in the case group (lung cancer patients)

Characteristic	Frequency (N=20)	Percentage (%)
Cell Type		
Adenocarcinoma	16	80.0%
Squamous-cell carcinoma	4	20.0%
Stadium		
IIIA	1	5.0%
IVA	11	55.0%
IVB	8	15.0%
EGFR Mutation		
Not tested	11	55.0%
Wild-type	6	30.0%
Exon 19 deletion mutation	2	10.0%
Exon 21 mutation	1	5.0%

Based on the histopathological classification, adenocarcinoma was the predominant cell type, accounting for 80% of cases, while squamous-cell carcinoma was observed in 20% of cases. Regarding clinical staging at the time of diagnosis, 5% of patients were in stage III A, 55% in stage IV A, and 15% in stage IVB.

In terms of epidermal growth factor receptor (EGFR) mutation status, 55% of patients did not undergo EGFR testing, 30% were identified as wild-type, 10% exhibited an exon 19 deletion mutation, and 5% had an exon 21 mutation.

Urinary Midkine Analysis

Table 3. Comparison of urinary midkine levels between healthy individuals and lung cancer patients

	Control		Case		p- value
	Mean±Standard Deviation (SD)	Minimum (Min)-Maximum (Max)	Mean±SD	Min-Max	
Urinary midkine	282.18±146.28	85.94-566.57	330.56±120.50	118.44-573.87	0.261

Based on Table 3, the mean urinary midkine level in the control group was 282.18 pg/mL, while the mean level in the case group was 330.56 pg/mL. Although urinary midkine levels were higher in the lung cancer

patients than in the controls, the Mann-Whitney U test yielded a p-value of 0.261 ($p > 0.05$). Therefore, the difference in urinary midkine levels between the case and control groups was not statistically significant.

Volatile Organic Compounds Analysis

Table 4. Comparison of volatile organic compounds levels between healthy individuals and lung cancer patients

	Control		Case		p-value
	Mean±SD	Min-Max	Mean±SD	Min-Max	
TVOCs	11.6±5613.29	72.9-23115.5	29.4±5613.29	72.9-23115.5	0.00
Ethanol (C ₂ H ₅ OH)	12.0±0.57	0.00-2.354	29.0±0.57	0.00-2.354	0.00
Formaldehyde (CH ₂ O)	0.0±0.0	0.0-0.0	0.0±0.0	0.0-0.0	1.00
Toluene (C ₇ H ₈)	0.0±0.0	0.0-0.0	0.0±0.0	0.0-0.0	1.00
Acetone (C ₃ H ₆ O)	23.5±0.26	0.01-0.93	17.5±0.26	0.01-0.93	0.105
Hexane (C ₆ H ₁₄)	23.85±0.90	0.00-0.29	17.15±0.90	0.00-0.29	0.07
Methane (CH ₄)	19.35±0.68	0.21-0.51	21.65±0	0.21-0.51	0.53

TVOC: total volatile organic compounds; SD: standard deviation; Min: minimum; Max: maximum

Based on Table 4, the levels of certain VOC components, specifically total volatile organic compounds (TVOCs), ethanol, and methane, were elevated in the case group compared to the control group. In contrast, the levels of acetone and hexane were lower in the case group. Additionally, both formaldehyde and toluene showed values of 0 in both the case and control groups.

Normality testing revealed that TVOC and ethanol were normally distributed ($p < 0.05$), whereas the remaining VOC parameters exhibited non-normal distributions ($p > 0.05$). Accordingly, statistical analysis was performed using the independent t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. The results showed that both TVOC and ethanol had p-values of less than 0.05, indicating a statistically significant difference

between the case and control groups for these parameters. Meanwhile, methane levels were higher in lung cancer patients, although the difference was not statistically significant ($p > 0.05$).

Relationship between Volatile Organic Compounds, Gas Patterns, and Urinary Midkine Levels

Based on Table 5, the correlation analysis between urinary midkine levels and VOC components (TVOC, ethanol, formaldehyde, toluene, acetone, hexane, and methane) in the case group yielded correlation coefficients categorized as weak to very weak, with p-values greater than 0.05. Therefore, no statistically significant correlations were observed between urinary midkine levels and VOC components in patients with lung cancer.

Table 5. Correlation test results between volatile organic compound (VOC) levels and urinary midkine

Relationship between VOC Levels and Urinary Midkine	Correlation Coefficient	p-value
Total volatile organic compounds (lung cancer patients)	0.284	0.23
Ethanol (lung cancer patients)	0.323	0.16
Formaldehyde (lung cancer patients)	-	-
Toluene (lung cancer patients)	-	-
Acetone (lung cancer patients)	0.164	0.49
Hexane (lung cancer patients)	0.301	0.19
Methane (lung cancer patients)	0.17	0.45

Receiver Operating Characteristic Analysis

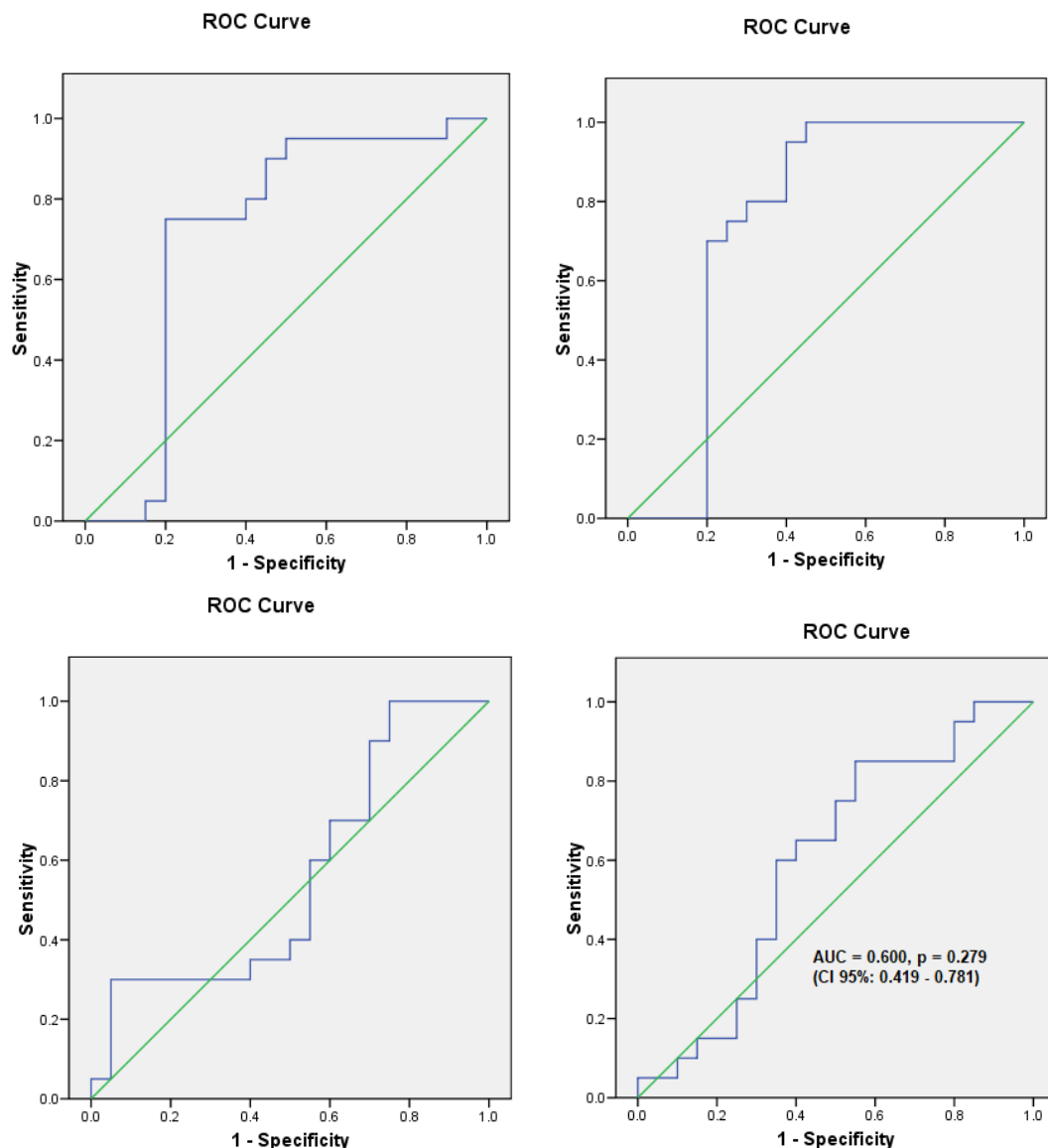


Figure 1. Receiver operating characteristic for total volatile organic compounds, ethanol, methane, and urinary midkine levels

Table 6. Area under the curve (AUC) values of urinary midkine and volatile organic compounds

	AUC	p	95% Confidence Interval (Lower-Upper)	
Ethanol (C ₂ H ₅ OH)	0.750	0.007	0.576	0.924
Methane (CH ₄)	0.558	0.558	0.372	0.743
Total volatile organic compounds	0.718	0.019	0.540	0.895
Urinary midkine	0.600	0.279	0.419	0.781

Based on [Figure 1](#) and [Table 6](#), TVOC, ethanol, methane, and urinary midkine demonstrated moderate diagnostic performance, as indicated by ROC curves deviating from the 50% reference line. The area under the curve (AUC) values were as follows: ethanol 0.75 ($p=0.007$), methane 0.558 ($p=0.558$), TVOC 0.718 ($p=0.019$), and urinary midkine 0.60 ($p=0.279$).

The AUC for methane was 0.558, corresponding to a correct classification rate of approximately 56 of 100 patients. Total volatile organic compounds showed an AUC of 0.718, corresponding to a correct

classification rate of approximately 72 of 100 patients, while ethanol demonstrated the highest performance with an AUC of 0.750 (75 of 100 patients correctly classified). Urinary midkine yielded an AUC of 0.600, with correct classification in approximately 60 of 100 patients. Statistically, urinary midkine showed weak performance (AUC >60–70%), while TVOC and ethanol demonstrated moderate performance (AUC >70–80%).

Although methane and urinary midkine exhibited AUC values above 50%, the associated p -values exceeded 0.05, indicating that their ability to

discriminate between healthy controls and lung cancer patients was not statistically significant. In contrast, TVOC and ethanol demonstrated statistically significant AUC values ($p < 0.05$), suggesting that these markers

may serve as meaningful diagnostic tools in differentiating between lung cancer patients and healthy individuals.

Table 7. Results of lung cancer diagnostic tests and sensitivity and specificity analysis

Biomarker	Threshold Value	Sensitivity	Specificity	PPV	NPV	LR	Accuracy
TVOC	1083.5	75.0%	80.0%	78.9%	76.2%	3.75	77.5%
Ethanol	0.41714	75.0%	75.0%	75.0%	75.0%	3	75.0%
Methane	0.4079	45.0%	45.0%	45.0%	45.0%	0.82	45.0%
Urinary midkine	310.495	60.0%	60.0%	60.0%	60.0%	1.5	60.0%

TVOC: total volatile organic compound; LR: likelihood ratio; PPV: positive predictive value; NPV: negative predictive value

Based on Table 7, ethanol demonstrated higher sensitivity and specificity compared to urinary midkine and methane (75.0% vs. 60% vs. 45%). The positive predictive value (PPV) and negative predictive value (NPV) of ethanol for distinguishing between control and case groups were also superior to those of methane and urinary midkine (75.0% vs. 60% vs. 45%).

The likelihood ratio (LR), which indicates the probability that a subject with the disease will test positive using the respective biomarker, was highest for ethanol, with an LR value of 3.0, compared to lower LR values for methane and urinary midkine.

In terms of predictive accuracy, ethanol also demonstrated the highest overall diagnostic accuracy (75.0%), outperforming methane (45%) and urinary midkine (60%) in differentiating between lung cancer patients and healthy individuals.

DISCUSSION

In this study, most lung cancer patients were aged 45-65 years or older, which aligns with the National Comprehensive Cancer Network (NCCN) data indicating that individuals 50 years old and above are at higher risk of developing lung cancer.¹³ Advancing age is associated with prolonged exposure to risk factors and reduced cellular repair capacity.¹⁴ The World Health Organization (WHO) reported that, of 34,783 lung cancer cases in Indonesia, 25,943 occurred in males, similar to this study, which found that 80% of patients were males, likely due to the higher prevalence of smoking among males.¹⁵

A significant difference in smoking status was found between groups, with lung cancer patients more likely to be current or former smokers. Smoking, which involves exposure to over 60 carcinogens, including polycyclic aromatic hydrocarbons and tobacco-specific nitrosamines, is a significant risk factor that promotes bronchial epithelial cell changes leading to cancer.¹⁶ Passive smoking also contributes, with a 15%

prevalence among patients and a 20-25% increased risk in nonsmokers.¹⁷

In this study, adenocarcinoma was the predominant histological type (80%), followed by squamous-cell carcinoma (20%). Globally, adenocarcinoma is the most common type of lung cancer in both smokers and nonsmokers, influenced by genetic factors such as EGFR mutations and environmental exposures. It accounts for 57% of cases in females and 39% in males, with incidence increasing in recent decades, particularly among females, due to changing smoking patterns and environmental factors.^{18,19}

In this study, most patients were diagnosed at an advanced stage (55% at stage IVA, 15% at stage IVB, and 5% at stage IIIA), which aligns with data from the American Lung Association, which reported that 47% of cases are detected at late stages.²⁰ Delayed diagnosis is influenced by socioeconomic factors, limited healthcare access, and delays in referral, all of which contribute to postponed treatment and higher mortality.²¹

Volatile organic compounds in exhaled breath have been extensively studied for the detection of lung cancer. They may arise from endogenous metabolism or environmental sources processed by the liver and kidneys. They are involved in intercellular signaling and tumorigenesis, with studies showing that cancer cells can upregulate VOCs, inducing morphological changes and apoptosis in neighboring normal cells within 48 hours.²²

Volatile organic compounds are exhaled through alveolar gas exchange, with common lung cancer biomarkers including propanol, isoprene, acetone, pentanal, hexanal, toluene, benzene, and ethylbenzene.³ Altered VOC profiles in lung cancer reflect tumor-associated metabolic changes. Lipid peroxidation by reactive oxygen species generates alkanes and aldehydes, while cancer cells show altered lipid metabolism, favoring longer saturated fatty acids to resist apoptosis. Elevated isoprene production from acetyl-CoA is also linked to increased cholesterol biosynthesis.²³

In this study, VOC analysis in exhaled breath was performed using the μ breath device, developed by Universitas Brawijaya, Malang. Breath samples were collected using special bags and analyzed for VOC components such as ethanol, formaldehyde, toluene, acetone, methylpentane, and methane.

The results demonstrated elevated levels of TVOC, ethanol, and methane in patients with lung cancer, although only TVOC and ethanol showed statistically significant differences. These findings are similar to the study by Oguma, *et al.* (2017) and are further corroborated by other studies, which reported significantly elevated levels of ethanol and toluene in patients with lung cancer.²⁴⁻²⁷ Conversely, acetone and hexane levels were lower in lung cancer patients, likely due to uncontrolled sampling sites, as VOC levels in breath may be affected by ambient air VOCs. Formaldehyde and toluene were undetectable in both groups, attributed to sensor malfunction in the μ breath analyzer.

Midkine, a member of the heparin-binding growth factor family (alongside pleiotrophin), plays a crucial role in cancer development and progression, including cancer cell proliferation, angiogenesis, invasion, and metastasis.^{28,29} In this study, urinary midkine levels were found to be elevated in lung cancer patients compared to controls, although the difference was not statistically significant. This differs from the study by Xia, *et al.* (2016), which reported significantly elevated midkine levels in NSCLC patients.³⁰ The discrepancy may be attributed to differences in sample size, subject characteristics, sample collection conditions, or analytical methods.

There is a complex interaction between VOCs and biological processes. Rapidly proliferating normal cells may reach the oxygen diffusion limit and enter a hypoxic state, leading cancer cells to rely more heavily on glycolysis, a phenomenon known as the Warburg effect. This process produces volatile compounds, such as alkanes and methylated alkanes, which are excreted in the breath.³¹

Under hypoxia, energy production shifts from the Krebs cycle to glycolysis. Acetyl-CoA, a product of long-chain fatty acid oxidation, is used for ketogenesis, producing ketone bodies (acetone, acetoacetate, and beta-hydroxybutyrate). Consequently, elevated acetone levels may be observed. Lung cancer patients also show increased glycolysis byproducts such as acetate, acetaldehyde, and ethanol.³²

Midkine expression in lung cancer cells is regulated by hypoxia-inducible factor-1 α (HIF-1 α), a subunit of HIF-1, in response to hypoxia.⁹ Both midkine and VOCs may be elevated due to hypoxia in the tumor

microenvironment and contribute to cancer progression. However, there are no existing studies analyzing the relationship between midkine and VOCs in lung cancer. In this study, no significant correlation was found between urinary midkine and VOC levels.

The diagnostic analysis results in this study showed that the sensitivity and specificity of the ethanol and methane VOCs were 75% and 45%, respectively. These findings differ from a previous study, which reported higher sensitivity and specificity values using the e-Nose device, with sensitivity reaching 81% and specificity reaching 91%.⁸ The sensitivity and specificity values of urinary midkine levels in this study were relatively low (60%). This differs from the study by Xia, *et al.* (2016), which demonstrated that serum midkine had a sensitivity of 71.2% and a specificity of 88.1% in detecting NSCLC.³⁰ Furthermore, urinary midkine levels showed a significant correlation with serum midkine levels, with a Spearman's correlation coefficient (r) of 0.636 ($p < 0.001$), indicating a strong association between the two parameters.³⁰

In this study, ethanol showed higher diagnostic accuracy than urinary midkine, likely due to its direct association with tumor-related metabolic changes in the lung and detection through alveolar gas exchange. In contrast, urinary midkine is influenced by systemic factors and renal clearance.

CONCLUSION

This study identified significant differences in exhaled ethanol concentrations between patients with lung cancer and healthy controls using the μ breath device. These results suggest that ethanol may be a helpful non-invasive biomarker for lung cancer screening and diagnosis. Further assessment of environmental VOC levels and the establishment of standard calibration criteria for the μ breath device are required to ensure more reliable application.

Although elevated urinary midkine levels were observed in patients with lung cancer, the difference was not statistically significant. Nonetheless, these findings suggest its potential as a noninvasive biomarker for the early detection and diagnosis of lung cancer. Further studies on VOC levels and urinary midkine, using larger sample sizes, stricter criteria, and standardized calibration of the μ breath breath analyzer, are needed to validate clinical relevance.

LIMITATIONS OF THE STUDY

Several limitations may have affected the results of this study. The sample size was relatively small, with

heterogeneous subject characteristics, which might have influenced the overall results. The selection of control subjects was based solely on medical history (anamnesis) without confirmation by chest radiographic examination, potentially allowing undetected pulmonary conditions to be included in the control group. Volatile organic compound levels in exhaled breath may be affected by environmental VOC levels. In this study, the sampling locations were not controlled, as breath samples were collected randomly from both indoor and outdoor environments. This variation could have influenced the ambient VOC levels and, consequently, the measured breath. There were no standardized criteria for calibrating the μ breath device. Potential confounding factors were not fully controlled, such as medication use, dietary intake, and other comorbid conditions (e.g., infections or other diseases). Validation of the clinical relevance of VOC levels and urinary midkine warrants further studies with larger sample sizes, rigorous inclusion criteria, and standardized calibration of the μ breath analyzer.

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Conflict of Interest

The authors declared there is no conflict of interest.

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Authors' Contributions

Conceptualizing, designing: SM, UAS, RT, SD, AYPW, ASL. Collecting data and interpreting results: SM, UAS. Preparing manuscript and revising: SM, UAS, RZT, SDJ, DP, AYPW, ASL. All authors contributed and approved the final version of the manuscript.

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