Clinical Research

Investigation of miRNA-339-3p and miRNA-155-5p expression levels in Non-Small Cell Lung Cancer (NSCLC)

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ABSTRACT

Objective: Lung cancers are malignant neoplasms arising from lung tissues, with Non-Small Cell Lung Cancer (NSCLC) being the prevalent subtype. miRNA-155 is markedly upregulated in lung cancer cases, facilitating tumor progression. In contrast, findings regarding miRNA-339 levels in lung cancer are inconsistent. In our study, we sought to analyze the serum expression levels of miRNA-155-5p and miRNA-339-3p in patients diagnosed with NSCLC and healthy controls.
Material and Method: miRNAs obtained from serum samples were converted into cDNA. miRNA-339-3p and miRNA-155-5p expression analyses were performed using SYBR GREEN kit.
Results: In the patient group, serum levels of miRNA 339-3p were found to be reduced compared to those in the control group, whereas miRNA 155-5p levels were significantly higher in the patient group than in the controls.
Conclusion: The serum levels of miRNA-155-5p and miRNA-339-3p, which showed significant statistical differences between the patient group and control groups, suggest that these miRNAs may serve as potential biomarkers for the diagnosis of NSCLC.

Keywords: *Lung Cancer, miRNA-339-3p, miRNA-155-5p, NSCLC.*

ÖZ

Küçük Hücreli Dışı Akciğer Kanserlerinde (KHDAK) miRNA-339-3p ve miRNA-155-5p Ekspresyon Düzeylerinin Araştırılması
Amaç: Akciğer kanserleri, akciğer dokularından kaynaklanan malign neoplazmlardır ve Küçük Hücreli Dışı Akciğer Kanseri (KHDAK) olarak bilinen türü en yaygın olarak bulunur. miRNA-155, akciğer kanseri vakalarında belirgin şekilde yukarı regüle olup, tümör ilerlemesini kolaylaştıran bir miRNA'dır. Ancak buna karşılık, literatürde miRNA-339 seviyeleri ile ilgili bulgular akciğer kanserinde tutarsızdır. Çalışmamızda, Küçük Hücreli Dışı Akciğer Kanseri tanısı konmuş hastalarda ve sağlıklı kontrol gruplarında miRNA-155-5p ve miRNA-339-3p'nin serum ekspresyon seviyelerini analiz etmeyi amaçladık.
Gereç ve Yöntem: Serum örneklerinden elde edilen miRNA'lar cDNA'ya dönüştürüldü. miRNA-339-3p ve miRNA-155-5p ekspresyon analizleri SYBR GREEN kiti kullanılarak gerçekleştirildi.
Bulgular: Hasta grubunda, kontrol grubuna kıyasla miRNA 339-3p serum seviyelerinin azaldığı, buna karşılık miRNA 155-5p seviyelerinin ise kontrol grubuna göre hasta grubunda önemli ölçüde daha yüksek olduğu bulundu.
Sonuç: Hasta grubu ile kontrol grupları arasında istatistiksel olarak anlamlı farklılıklar gösteren miRNA-339-3p ve miRNA-155-5p serum seviyeleri, bu miRNA'ların NSCLC tanısında potansiyel biyomarker olarak hizmet edebileceğini önermektedir.

Anahtar Sözcükler: *Akciğer Kanseri, miRNA-339-3p, miRNA-155-5p, KHDAK.*

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Recognized as the leading contributor to cancer-related deaths worldwide, lung cancer remains a predominant health concern and is pathologically categorized into two primary subtypes: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) (1, 2). NSCLC constitutes the majority of lung cancer cases, with risk factors including tobacco use, family history, exposure to carcinogenic chemicals and some heavy metals (3). The high lung cancer mortality rate is primarily linked to the stage at treatment initiation. When diagnosed at an early stage, patients with localized disease exhibit a 5-year survival rate of 52%. Conversely, over 52% of patients diagnosed with distant metastasis have a markedly lower 5-year survival rate

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of merely 3.6% (4). Consequently, the development of a readily accessible and minimally invasive diagnostic method, compared to traditional diagnostic approaches, has emerged as a critical focus of contemporary research in clinical practice.

MicroRNAs (miRNAs), which are the focus of our study in relation to various molecular mechanisms associated with lung cancer, are small non-coding RNAs ranging from 19 to 25 nucleotides in length and play pivotal roles in the regulation of gene expression (5, 6). miRNAs exert their regulatory effects by attaching to the 3' untranslated regions (UTRs) of messenger RNAs (mRNAs), thus critically influencing post-transcriptional gene regulation (7). This regulation can manifest itself as either upregulation or downregulation, influencing molecular mechanisms that affect lung cancer prognosis. This condition may contribute to favorable outcomes by inhibiting proliferation or inducing apoptosis, or conversely, may negatively impact prognosis by promoting proliferation and metastasis (8, 9).

Numerous investigations have demonstrated that miRNAs are implicated in cancer metastasis by a) modulating angiogenesis in tumor cells; b) modulating the transcriptional activity of oncogenes, tumor suppressor genes or genes related to tumor metastasis; c) inhibiting enzymes involved in DNA methylation of tumor cells or d) regulating epithelial-mesenchymal transition (10).

miRNA-339 has been identified as a microRNA capable of inhibiting cell proliferation and metastasis in several cancer types (11, 12). In lung cancer patients, elevated miRNA-339 expression is linked to improved NSCLC prognosis by inhibiting proliferation and suppressing invasion and migration in adenocarcinoma (13). Research on over 600 miRNAs in adenocarcinoma highlighted their potential as diagnostic biomarkers in NSCLC, and miRNA-339-5p has been reported to inhibit migration and invasion, suggesting its potential as a biomarker for this cancer type (14, 15).

miRNA-155-5p is a key oncogenic miRNA that is upregulated in various cancer types and contributes to cell growth, migration, invasion, angiogenesis, genomic instability, and drug resistance (16,17). miRNA-155-5p has been reported to be upregulated in NSCLC, with disease progression linked to the suppression of key tumor suppressor genes mediated by this miRNA (5). The overexpression of miRNA-155-5p has emerged as a standalone prognostic indicator in adenocarcinoma and serves as a potential diagnostic biomarker in lung cancer (18-20). Inhibition of miRNA-155-5p may promote apoptosis and hinder cancer progression, with its targeted inhibition and modulation of autophagy proposed as a potential approach for future NSCLC therapies (17, 21).

In this research, we intended to assess the concurrent serum expression patterns of miRNA-339-3p and miRNA-155-5p, which have been reported in the literature to exhibit variable expression patterns in lung cancer cases. Although some evidence suggests that these miRNAs could function as potential biomarkers in NSCLC development, there is a paucity of studies exploring their expression levels together. We foresee that our findings will provide significant insights into the potential applications of miRNA-339-3p and miRNA-155-5p as biomarkers for the diagnosis and therapeutic management of NSCLC. Additionally, we hope that the findings will pave the way for novel diagnostic and therapeutic approaches for lung cancer.

MATERIAL AND METHOD

Study Group

This study included 51 volunteers, consisting of 26 adult patients diagnosed with NSCLC and 25 completely healthy controls. The determination of the study's sample size was achieved through a power analysis performed using G*Power software version 3.1. Individuals with a different type of cancer or who had previously undergone surgical procedures for cancer were excluded from the study. The control group comprised healthy adults over 18 years of age who had undergone comprehensive health screenings. The study received ethical approval from the Hitit University Non-invasive Clinical Research Ethics Committee (Approval No: 2024-13) and adhered strictly to the guidelines of the Declaration of Helsinki. All participants provided written informed consent before taking part in the study. Demographic data of the patients were extracted from their medical records.

miRNA Isolation

Serum samples from both patients and the control group were stored at -80°C in sterile tubes until miRNA experiments were performed. The isolation of miRNAs was carried out using Qiagen's miRNeasy Serum Plasma Kit (Qiagen, Hilden, Germany, Cat. No. / ID: 217184) according to the manufacturer’s instructions. The purity and concentration of the isolated miRNAs were measured using a NanoDrop2000 spectrophotometer (Thermo Scientific, Waltham, MA, USA).

cDNA Synthesis

cDNA synthesis was performed using the miRCURY LNA RT Kit (Cat. No. / ID: 339340-Qiagen) to the manufacturer's instructions. The amount of cDNA was quantified using the Qubit miRNA Assay Kit on a Qubit 3.0 Fluorometer (Thermo Scientific).

miRNA339-3p and miRNA155-5p Expression Analysis

cDNA serum samples were used for expression analysis. After quantifying the sample concentrations, Real-time PCR analysis was carried out using ROTOR-GENE device for miRNA339-3p (lot:201705190083-Qiagen-Germany) and miRNA155-5p (lot:21002552-1-Qiagen-Germany) gene and U6 control gene (housekeeping assay, RNU6-lot:20800469-1-Qiagen-Germany). miRNA-339-3p, miRNA-155-5p, U6 were dissolved in appropriate quantity of RNAse-free water before use.

Expression analysis was performed as described in the instructions of the miRCURY LNA SYBR Green PCR Kit (Cat. No. / ID: 339346-Qiagen).

miRNA Calculation

The internal control (housekeeping assay=miR-U6) was used to normalize the ΔCT values and calculate the fold change of miRNA expression levels. To determine miRNA levels, the Livak formula (2^(-ΔΔCT)) was applied (22). The ΔΔCT value was calculated by subtracting the ΔCT of the target gene from the average ΔCT of the internal controls. The fold change was then calculated as 2^(-ΔΔCT).

Statistical Analysis

Statistical analysis of the data obtained in the study was performed using the SAS (Statistical Analysis System,) v9.4 program. The normality of the dependent and independent variables used in the study was first examined using the Kolmogorov-Smirnov test. For this purpose, skewness values were reviewed, and parametric tests were applied as the data followed a normal distribution. To evaluate the differences between the two groups, an independent sample t-test was performed. A paired sample t-test was performed to compare the miRNA-339-3p and miRNA-155-5p values. To determine the sensitivity and specificity, ROC analysis was performed. Throughout the study, a significant level of <0.05 was considered statistically significant.

RESULTS

The demographic characteristics of the patient cohort are detailed in table 1.

Table 1. *Demographic data of the patients.*

	n
Age, year	51.2±12.4
Sex, Male/Female	34 / 17
Never smoked, n (%)	3.8%
Ex Smoker, n (%)	69.2%
COPD, n (%)	48.0%
Family Cancer history, n (%)	24.0%
Cought, n (%)	26.9%
Shortness of breath, n (%)	19.2%

COPD: Chronic obstructive pulmonary disease.

The 26 patients (84.62% male, 15.38% female) had a mean age of 61.6±11.4 years. Of these, 3% had never smoked, 69.2% had quit smoking at various times, 48% were suffering from Chronic Obstructive Pulmonary Disease (COPD), and 24% had a family history of cancer. Complaints about cough and shortness of breath were reported at 26.9% and 19.2%, respectively.

In the comparative analysis of miRNA expression levels between patient and control groups, miRNA-339-3p expression was significantly downregulated in the patient group relative to the control group. Conversely, the expression of miRNA-155-5p was markedly upregulated in the patient group compared to the control group (Table 2).

Table 2. *Expression levels of miRNA-339-3p and miRNA-155-5p in patient and control groups.*

$2^{-\Delta\Delta Ct}$	**Patient (n =26)**	**Control (n =25)**	**p-value**
miRNA-339-3p	0.03 (0.09)	3.11 (5.20)	<.0001*
miRNA-155-5p	4.80 (4.79)	1.72 (1.57)	0.0151*

** t test p-value; p <0.05.*

The independent samples t-test yielded a p-value of <0.05, indicating that the observed differences in miRNA expression levels between the groups are statistically significant and unlikely to have occurred by chance.

Sensitivity and specificity calculations were performed for various $2^{-\Delta\Delta Ct}$ threshold values to predict disease status. The optimal $2^{-\Delta\Delta Ct}$ threshold and the corresponding sensitivity and specificity values are presented in table 3 and 4.

Table 3. *ROC analysis; miRNA-339-3p*

	Estimate	**95% Confidence Limits**	
PPV	0.95652	0.87318	1.03987
NPV	0.83333	0.68423	0.98244
Sensitivity	0.84615	0.70747	0.98484
Specificity	0.95238	0.86130	1.04346
AUC	0.9634	0.9200	1.0000
	cutoff	**prob**	**Youden**
2'deltadeltaCT	0.0128	0.89532	0.79853
	Somers' D	**Gamma**	**Tau-a**
	0.9267	0.9267	0.4681
True Positive	**True Negative**	**False Positive**	**False Negative**
22	20	1	4

PPV: Positive predictive value; NPV: negative predictive value; AUC: area under curve.

Table 4. *ROC analysis; miRNA-155-5p.*

	Estimate	**95% Confidence Limits**	
PPV	0.76471	0.56306	0.96635
NPV	0.70000	0.53601	0.86399
Sensitivity	0.59091	0.38545	0.79636
Specificity	0.84	0.69629	0.98371
AUC	0.7073	0.5511	0.8634
	cutoff	**prob**	**Youden**
2'deltadeltaCT	3.1813	0.50291	0.43091
	Somers' D	**Gamma**	**Tau-a**
	0.4145	0.4145	0.2109
True Positive	**True Negative**	**False Positive**	**False Negative**
13	21	4	9

PPV: Positive predictive value; NPV: negative predictive value; AUC: area under curve.

Additionally, based on these findings, an empirical ROC curve was generated using a non-parametric method in the SAS software, which is depicted in figures 1 and 2.

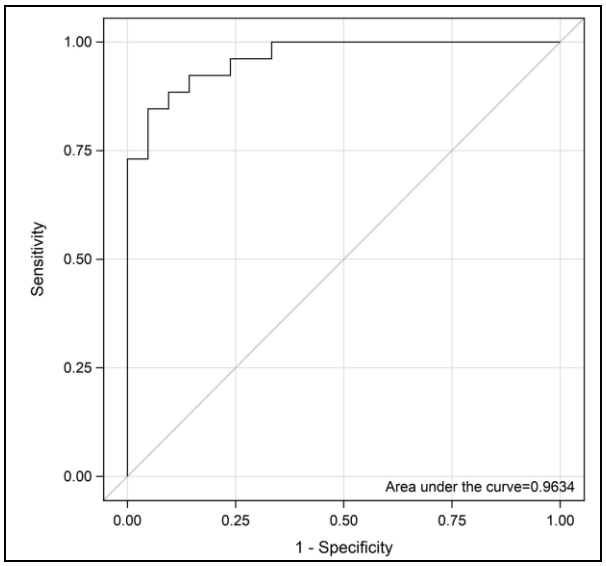

Figure 1. *ROC curve; miRNA-339-3p.*

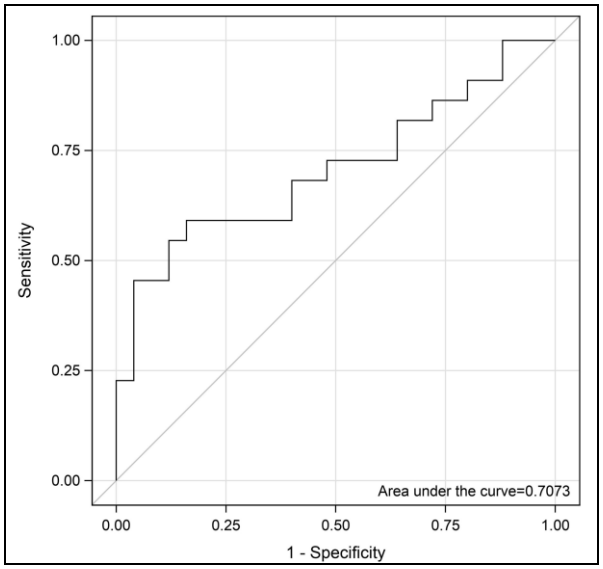

Figure 2. *ROC curve; miRNA-155-5p.*

These ROC curves and AUC values indicate that $2^{-\Delta\Delta Ct}$ values possess strong predictive power in distinguishing patients from healthy individuals.

To compare the miRNA-339-3p and miRNA-155-5p levels between individuals in patient and control groups, a paired sample t-test was performed. The results are presented in table 5 and figure 3.

Table 5. *Analysis of dependent variables.*

Grup	miRNA-339-3p	miRNA-155-5p	Difference	p
Patient Mean (SD)	0.03 (0.09)	4.80 (4.79)	-4.8 (4.80)	**0.0001**
All Mean (SD)	0.6 (1.46)	3.2 (3.78)	-2.6 (4.36)	**0.0004**

Paired sample t-test p-value <0.05.

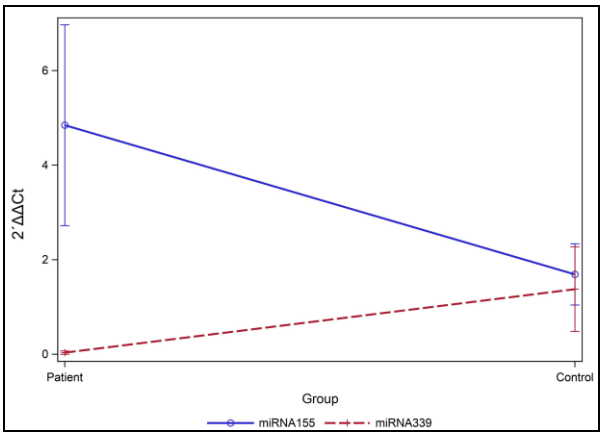

Figure 3. *Expression Levels of miRNA-339-3p and miRNA-155-5p in patient and control groups.*

A notable statistical difference was observed between the mean values of miRNA-339-3p and miRNA-155-5p in the patient group (p =0.0001). Additionally, the analysis conducted without distinguishing between the patient and control groups also revealed a statistically significant difference between the mean values of miRNA-339-3p and miRNA-155-5p.

The results suggest that the expression levels of these two miRNAs may play a role in disease status and differ accordingly. Statistical significance indicates that this difference is not due to chance.

DISCUSSION

NSCLC is one of the most prevalent malignant tumors worldwide, with its management hindered by delayed diagnosis, drug resistance, high recurrence rates, and limited treatment options (23). Lung cancer progression is a multistage process involving genetic and molecular defects, with targeted molecular therapies showing promising results in improving patient quality of life (24). To improve lung cancer prognosis, minimally invasive biomarkers are crucial for facilitating early detection and guiding optimal treatments, leading to more precise, individualized therapies and better clinical outcomes.

Numerous studies have emphasized the significance of miRNA in the molecular mechanisms influencing cancer prognosis (13, 14, 19). Hence, this study specifically investigates the expression levels of miRNA-339-3p and miRNA-155-5p in lung cancer, both of which have been previously identified as exhibiting differential expression across various cancer types. There is substantial evidence indicating that miRNA-339 plays a pivotal role in suppressing cancer cell proliferation, migration, and invasion, as well as regulating genes that induce apoptosis. Moreover, miRNA-339-5p has been shown to prevent metastasis in lung, ovarian, and pancreatic cancers by regulating epithelial-mesenchymal transition (10, 12, 25). In the literature, miRNA-339-5p expression was significantly lower in the primary tissues of NSCLC patients compared to the surrounding normal tissues (15).

Furthermore, miRNA-339-3p's inhibitory effect on tumor cell invasion has been validated in various cancers, including its tumor-suppressive role in melanoma. Also, in gastric cancer (GC), miRNA-339-3p is downregulated, and its upregulation inhibits proliferation, migration, invasion, and enhances apoptosis, suggesting its role in suppressing GC development (26, 27). However, contrary to these findings, there is also a study that reports miRNA-339-3p to be upregulated in patients with NSCLC (28).

In our study, we found that miRNA-339-3p was significantly downregulated in patients diagnosed with lung cancer compared to the control group. The literature has shown that miRNA-339-3p suppresses cell proliferation in lung cancer by targeting the 3'-UTR of Skp2 mRNA (12). When considered alongside the existing literature, this suggests that miRNA-339-3p plays a role in inhibiting cancer cell growth.

miRNA 155 has been shown to be involved in the regulation of inflammatory processes (29). A meta-analysis highlighted that it may serve as a potential biomarker for the detection of lung cancer (30). Increased expression of miRNA-155 has been recognized as an independent prognostic factor associated with adverse outcomes in patients with adenocarcinoma. Additionally, it functions as a negative prognostic indicator in adenocarcinomas and a positive prognostic marker in SCC cases with lymph node metastasis (18, 31).

miRNA-155-5p is highly expressed in NSCLC, negatively affecting disease progression, patient prognosis, and survival rates. The inhibition of this miRNA has been proposed as a potential strategy to prevent NSCLC progression (5). Moreover, the transfection of AntimiR-155-5p significantly decreases miRNA-155-5p expression while simultaneously increasing the rate of apoptosis (17). These data underscore the prognostic role of miRNA-155 in various types of lung cancer and suggest that it may represent a promising approach for future NSCLC treatment strategies.

In our study, consistent with findings in the literature, we found that miRNA-155-5p expression levels were significantly higher in individuals diagnosed with lung cancer compared to healthy individuals. The elevated levels of miR-155-5p, particularly in NSCLC and other various cancer types, suggest that this miRNA plays a crucial role in cancer progression and tumor cell proliferation.

We believe that the potential of miRNA-339-3p and miRNA-155-5p as molecular biomarkers in NSCLC is supported by the findings of this study. However, a limitation of our current research is the relatively small sample size, which restricts the generalizability of the results. Therefore, it is crucial to emphasize that our findings should be validated through further studies involving larger lung cancer cohorts. Such large-scale investigations will provide more robust evidence for considering both miRNA-339-3p and miRNA-155-5p as significant biomarkers and potential therapeutic targets in the pathogenesis of lung cancer.

In conclusion, our findings regarding the serum levels of both miRNAs in patients diagnosed with NSCLC align with the prevailing consensus in the literature. Accordingly, we believe that miRNA-339-3p and miRNA-155-5p have potential as biomarkers in lung cancer and could serve as therapeutic targets, warranting further investigation in future studies.

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