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Evaluation of PI3K Levels and miRNA124-5p Expression Levels in Serum Samples from Patients With Lung Cancer

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Abstract

Background/Aim: Lung cancers are malignant neoplasms located in the lung tissues. miRNAs are short non-coding RNAs. It is known that miRNA-124 prevents metastasis in lung cancers. The phosphatidylinositol 3-kinases (PI3K) signaling pathway, a basic signaling pathway interconnected with other pathways, is activated during cancer development. This study aimed to compare miRNA-124-5p and PI3K serum levels in patient and control groups.
Materials and Methods: miRNA isolated from patient and control serum samples were converted into cDNA. miRNA-124-5p expression was determined using Real-Time PCR and a SYBR GREEN kit. PI3K serum level was determined using the Enzyme-Linked Immunosorbent Assay.
Results: While miRNA-124-5p serum level was statistically significantly lower in the patient group ($p>0.02$), serum PI3K level was higher in the patient group than in the control group but the difference was not statistically significant ($p>0.11$).
Conclusion: Lower serum levels of miRNA-124-5p and high PI3K levels observed in the patient group, compared to the control group, may be associated with a poor disease prognosis.

Keywords: Lung cancer, miRNA124, Real Time PCR, PI3K.

Introduction

Lung cancer is the most common form of cancer and a leading cause of cancer-related death in men. It is divided into two main types based on its histological features: small cell lung cancer (SCLC) and the comparatively less aggressive non-small cell lung cancer (NSCLC) (1). NSCLC is further divided into three subtypes: squamous cell carcinoma, adenocarcinoma and large cell carcinoma (2). While tobacco use is a well-established risk factor, approximately 10% of patients with lung cancer are non-smokers. Exposure to substances such as radon, asbestos,

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and silica also poses a significant additional risk (3, 4). The potential role of familial predisposition in lung cancer development has also been studied, with research suggesting a significantly higher risk in families of those diagnosed at an early age (5). At the molecular level, numerous mechanisms are closely related to lung cancer prognosis and have attracted considerable research interest (6, 7).

MicroRNAs (miRNAs) have emerged as key players in cancer development. These small non-coding RNA molecules have been extensively studied for their utility as biomarkers, with a growing body of literature highlighting their importance in cancer development (8, 9). miRNA-124, in particular, is expressed in the brain, thymus, lymph nodes, bone marrow, and peripheral blood mononuclear cells (10), and increasing evidence suggests that it has anti-tumor properties. miRNA expression in human cancer cells is often downregulated and triggers the progression of cancer pathology. There are two important mechanisms: In one of them, miR-124 transcription is repressed by methylation of CpG islands in the genomic region encoding pri-miR-124. In the second one, miR-124 is adsorbed and removed by circular RNAs and long non-coding RNAs with sequences complementary to miR-124 thus, removal of miRNA124 creates a suitable environment for tumor development (11). The over-expression of miRNA-124 has been shown to inhibit proliferation and migration in lung adenocarcinoma and to limit proliferation in NSCLC through pathways involving CD164 and cadherin-2 signaling (12). Furthermore, low levels miRNA-124 expression has been considered a marker of increased metastatic potential in several cancer types (13). The PI3K/AKT signaling pathway, a cornerstone of carcinogenesis, is tightly regulated by miRNAs (14). miRNA-124-3p inhibits lung cancer progression, in part by influencing the intracellular dynamics within the PI3K/AKT pathway (15).

The molecular mechanisms driving lung cancer are complex, involving signaling pathways, epigenetic regulation, genetic mutations, and the inhibition of tumor suppressor pathways (16). Mutations in key oncogenes such as *KRAS* and *EGFR* have been identified as major contributors to lung cancer development (17). PI3K catalyzes the production of phosphatidylinositol-3,4,5-trisphosphate. Additionally, PI3K plays an important role in the pathways that govern cell survival, gene expression regulation, metabolic processing, and cytoskeletal organization. The dysregulation of the PI3K pathway has been associated with several diseases, including diabetes and cancer, highlighting that this pathway is a promising target for therapeutic intervention (18). Several studies have reported that the PI3K pathway is dysregulated particularly in solid tumors. The dysregulation of PI3K activity is well established in many malignancies, including lung cancer, where it plays an important role in tumorigenesis. Furthermore, AKT, a downstream effector of PI3K, is essential for the malignant transformation of cells (19). The PI3K/AKT pathway has also been shown to play a role in promoting cancer cell proliferation and metastasis (20). This pathway not only supports the survival of lung cancer cells but also intersects with other oncogenic pathways (21). Given the central role of PI3K/AKT signaling in cancer development, several PI3K-targeted inhibitors are being investigated as potential therapeutic agents for a variety of cancers (22).

In our study, to gain a deeper understanding of the interplay between miR-124-5p and the PI3K signaling pathway we aimed to simultaneously assess the expression levels of miRNA-124-5p and PI3K in serum samples collected from patients with lung cancer and healthy volunteer controls. In addition, we aimed to examine correlations between these expression levels and various demographic characteristics of the patients, such as age, sex, smoking, and family history.

Materials and Methods

Study population and clinical procedures. The current case-control study encompassed 25 patients with lung cancer who underwent clinical examinations and 25 healthy volunteer controls. The Ethics Committee decision for this study was obtained on 31/10/2024 (Hitit University) with file number 2024-303 and decision number 2024-22.

Table I. *Evaluation of groups in terms of age and sex.*

		Patient	Control	*p*-Value
Age Avr±SS (median) (Min-Max)		59.92±9.92 (60) (42-78)	40.36±4.86 (41) (32-48)	0.001*[1]
Sex n (%)	Male	21 (%84)	11 (%44)	0.008*[2]
	Female	4 (%16)	14 (%56)	

[1]Mann–Whitney *U*-Test. [2]Continuity (yates) correction. *$p<0.05$.

Demographic and clinical characteristics of the patients were collected from medical records.

miRNA isolation. In this study, serum samples previously isolated from peripheral blood samples and stored in portions at –80˚C were used. On the day of the study, serums were brought to room temperature and miRNA isolations were performed using the miRNeasy Serum/Plasma Kit (Cat. No./ID: 217184, Qiagen, Hilden, Germany), according to the instructions of the manufacturer. The purity and concentration of the isolated miRNAs were assessed using a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA).

cDNA synthesis. miRNAs were converted into cDNA using miRCURY LNA RT Kit (Cat. No./ID: 339340 – Qiagen) in accordance with the kit instructions and stored at –80˚C until miRNA-124-5p analysis.

Determination of miRNA levels using fluorometry. The miRNA concentration of the transcribed samples was determined using the Qubit miRNA Assay Kit's standard protocol on the Qubit 3.0 Fluorometer (Thermo Fisher Scientific). Following the concentration measurements, appropriate dilutions were made.

miRNA expression analysis. Expression levels of microRNA-124-5p (miRCURY 124, Qiagen) were determined by real-time polymerase chain reaction (RT-PCR) in Rotor-Gene using the miRCURY LNA SYBR Green PCR Kit (Cat. No./ID: 339346; Qiagen).

The internal control (housekeeping assay = RNU6-lot:20800469-1 Qiagen) was used to normalize the ΔCT values and calculate the fold change of miRNA expression levels. To determine miRNA levels, the Livak formula ($2^{-\Delta\Delta CT}$) was applied. 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 ($2^{-\Delta\Delta CT}$) (23).

PI3K analysis. The levels of PI3K were determined using the Human PI3K ELISA Kit (ABT Human PIK3Cβ ELISA Kit-Phosphoinositide-3-Kinase Catalytic Beta Polypeptide-Cat: ABT1571Hu-Atlasbio, Çankaya, Ankara, Turkey).

Statistical analysis. The IBM SPSS Statistics 22 program was used for statistical analysis. The Shapiro Wilks test was used to examine normal distribution; it was determined that the parameters did not show a normal distribution. In addition to descriptive statistical methods (minimum, maximum, mean, standard deviation, median, frequency), Mann–Whitney *U*-test was used to make comparisons between two groups regarding quantitative data. Continuity (Yates) correction was used to compare qualitative data. Spearman's rho correlation test was used to examine the correlations between parameters. The most appropriate cut-off point was selected based on ROC curve analysis. Significance was evaluated at the $p<0.05$ level.

Results

The study included 50 cases, of which 32 (64%) were male and 18 (36%) were female, aged between 32 and 78 years. The mean age was 55.14±12.55 and the median age was 46. The study evaluated two groups: "Patient" (n=25) and "Control" (n=25) (Table I). The male case rate in the

Table II. *Evaluation of groups in terms of PI3K and miRNA124-5p ($2^{-\Delta\Delta CT}$).*

	Patient	Control	
	Ave.±SS (median) (Min-Max)	Ave.±SS (median) (Min-Max)	*p*-Value
PI3K	1.88±2.16 (1.08) (0.23-8.02)	0.98±1.25 (0.47) (0.23-4.19)	0.114
miRNA124-5p ($2^{-\Delta\Delta CT}$)	0.97±1.53 (0.17) (0.002-5.8)	1.48±1.41 (1) (0.02-4.98)	0.026*

Mann–Whitney *U*-Test. *$p<0.05$.

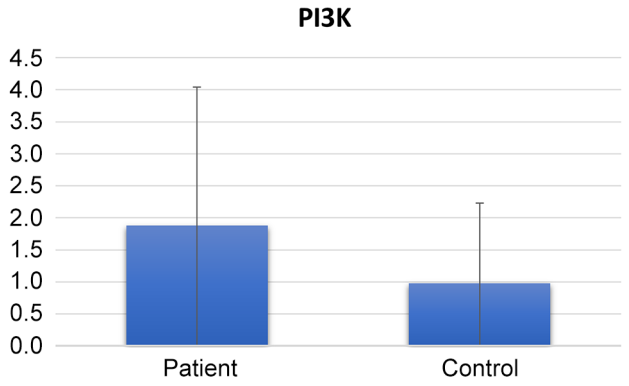

Figure 1. *The serum PI3K levels in the study groups. There was no statistically significant difference between the groups in terms of PI3K levels (p>0.05).*

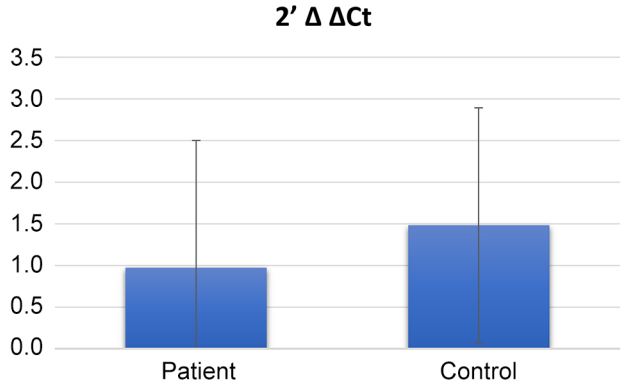

Figure 2. *Comparison of miRNA-124-5p expression levels between lung cancer and control groups. Differences between two groups were analyzed using the Mann-Whitney U-test. *p-value <0.05. miRNA124-5p ($2^{-\Delta\Delta CT}$) levels in the patient group were statistically significantly lower than those in the control group (p=0.026; p<0.05).*

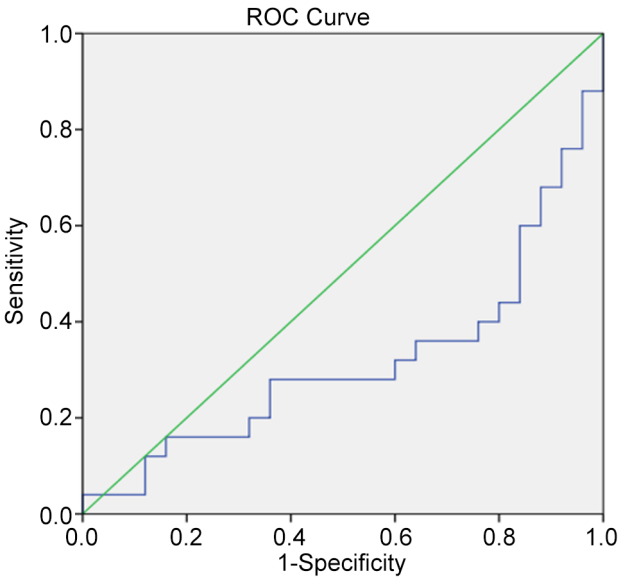

Figure 3. *Receiver operating characteristics (ROC) plot for miRNA-124-5p ($2^{-\Delta\Delta CT}$). miRNA-124-5p expression levels in the control and lung cancer groups. *p<0.05. The diagnostic potential of miRNA-124-5p as a biomarker for lung cancer was evaluated through the application of ROC curve analysis.*

patient group (84%) was higher than that of the control group (44%).

In this study the serum miRNA124-5p expression levels were statistically significantly lower in the patient group than the controls (p=0.02). Additionally, PI3K serum levels were found to be higher in the patient group compared to the control group, although not statistically significant (Table II, Figure 1, Figure 2). miRNA-124 is widely known as a tumor suppressor in various types of cancer. Regulation of PI3K/Akt pathway by miRNA-124 inhibits the proliferation and migration of cancer cells.

Receiver operating characteristic (ROC) curve analysis was performed and the area under the ROC curve was calculated to investigate the usefulness of miRNA-124-5p as a diagnostic performance for lung cancer. The ROC curve for $2^{-\Delta\Delta CT}$ levels was analyzed in the context of lung cancer diagnosis. The area under the curve (AUC) was determined to be 0.683, with a standard error of 0.08. This value was significantly greater than 0.5, indicating diagnostic relevance (p=0.020; p<0.05). Our results

Table III. *ROC analysis results for miRNA124-5p ($2^{-\Delta\Delta CT}$).*

	AUC	SE	95%CI	*p*-Value	Cut off point	Sensitivity	Specificity
miRNA124-5p $2^{-\Delta\Delta CT}$	0.683	0.08	0.536-0.807	0.020*	≤0.192	56.0	84.0

*$p<0.05$.

demonstrate that miRNA-124-5p could be a candidate biomarker for the diagnosis of lung cancer (Figure 3). The optimal cut-off value for $2^{-\Delta\Delta CT}$ levels in lung cancer diagnosis was established as ≤0.192. At this threshold, the sensitivity was calculated at 56%, while the specificity reached 84% (Table III).

No statistically significant relationship was detected between the demographic information of the patient group and PI3K levels. Additionally, no statistically significant relationship was detected between the demographic information of the patient group and miRNA-124-5p levels.

Discussion

miRNAs play an important role in cancer development (8). Throughout this process, the PI3K/AKT signaling pathway is tightly regulated by miRNAs (14). It has been shown that high miR-124 expression inhibits cancer cell proliferation in different cancer types (24). A recent study demonstrated that the over-expression of miR-124 effectively inhibited proliferation and invasion in NSCLC cell lines *in vitro* while preventing epithelial-mesenchymal transition (EMT) (25). According to one study, patients exhibiting upregulation of miR-124a in response to chemotherapy achieved the longest overall survival (OS) and disease-free survival (DFS). In the same study, patients with low miR-124 expression were reported to exhibit significantly shorter 5-year overall survival (OS) (26).

MiRNAs play a role in the regulation of various molecules. For instance, miRNA-124, in conjunction with miRNA-137, has been reported to inhibit cell proliferation in glioblastoma by suppressing the cell cycle regulator CDK6. In lung cancers, the expression of miRNA-124 in cancerous tissues has been shown to be lower than in healthy tissues, and this reduction is associated with increased cell invasion. Similarly, studies conducted on hepatocellular cancer and healthy tissues have indicated that miRNA-124 expression levels are significantly lower in cancerous tissues. Moreover, it has been suggested that miRNA-124 could serve as a diagnostic biomarker for hepatocellular carcinoma and colorectal carcinoma (27-30).

Reduced expression of miR-124-3p has been identified as a key driver of metastasis in various tumor types (24). The down-regulation of miR-124-3p enhances the migratory capacity of NSCLC cells, facilitating metastasis. By modulating the PI3K/AKT pathway, miR-124-3p suppresses metastatic activity and inhibits lung cancer progression. However, its dysregulation disrupts this suppressive effect, increasing the metastatic potential of NSCLC (31).

The overactivation of the PI3K signaling pathway is associated with the initiation and progression of NSCLC (24, 32). The PI3K signaling pathway regulates essential cellular processes, including proliferation, motility, survival, and angiogenesis, all of which are fundamental to tumor growth and maintenance (33). A key target of the PI3K pathway is AKT, a serine/threonine kinase that mediates the majority of PI3K-driven signals. Aberrant activation of AKT has been implicated in lung carcinogenesis, underscoring its critical role in the pathophysiology of NSCLC (34).

In studies on cancer and miRNA-124 in the literature, the down-regulation of miRNA-124 has been associated with poor prognosis due to increased proliferation, migration and invasion. Our study demonstrated that serum PI3K activity was elevated in the patient group compared to the control group, and serum miRNA-124-5p levels were significantly lower than those observed in controls. According to the findings of our study, reduced levels of miRNA-124-5p expression, which has tumor suppressor properties, may lead to increased tumor formation and progression in the patient.

As demonstrated in a study showing that miRNA-124-3p can prevent cell metastasis in NSCLC through extracellular exosome transport and intracellular PI3K/AKT signaling pathway (15), our study showed low miRNA-124 level and high PI3K level in lung cancer cases. Additionally, the results of our study are compatible with the results of a similar study (35). Therefore, it can be said that miRNA124-5p exerts its tumor suppressor effect through regulation of the PI3K/Akt pathway.

As in many types of cancer, low expression of miRNA-124 in lung cancers is important for cancer prognosis considering its antiproliferative and antimetastatic effects. miRNA-124-5p will be promising for therapeutic studies, especially on metastasis. The significantly low level of miRNA-124-5p in patients suggests that it can be used as a diagnostic biomarker in lung cancer cases. Treatment approaches may be to increase miRNA-124-5p expression.

Conclusion

This study showed that miRNA-124-5p serum expression level was reduced in lung cancer, while PI3K level was increased in the same patients. Our results are consistent with those of several previous studies showing that low expression of miRNA-124-5p is associated with poor cancer prognosis. Therefore, low expression of miRNA-124-5p may be a candidate biomarker and prognostic factor for lung cancer diagnosis. Considering that the metastasis-inhibiting effect of high expression of miRNA124-5p is through the PI3K/AKT signaling pathway, simultaneous analysis of PI3K will be important in diagnosis.

Conflicts of Interest

All Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

All Authors contributed significantly to this study. The conceptualization of the study was carried out by F.T.A. and O.A. The formal analysis and investigation were undertaken by F.T.A., and O.A. while, F.T.A. and O.A. handled the methodology. Data curation was provided by S.A. Project management, visualization, and the original draft were prepared by F.T.A. Finally, F.T.A., and O.A. collaborated in reviewing, and editing the manuscript.

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