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Downregulation of the LINC01111 / DUSP1 Axis via miR-3924 Upregulation Promotes Metastasis and Aggressive Phenotypes in Lung Adenocarcinoma

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Abstract

Background: Lung Adenocarcinoma (LUAD) is one of the leading causes of cancer-related mortality. The putative LINC01111 / miR-3924/dual specificity phosphatase 1 (DUSP1) regulatory network has been implicated in epithelial malignancies.

Methods: This cross-sectional analytical study examined paired tumor samples and adjacent normal margin tissue samples from 50 patients. The relative expression Levels of LINC01111, miR-3924, and DUSP1 were determined by quantitative real-time PCR (qRT-PCR) via the $2^{-\Delta\Delta CT}$ method. Their diagnostic value was assessed using Receiver operating characteristic (ROC) curve analysis.

Results: miR-3924 was expressed at higher levels in tumor tissue than in adjacent normal margins of resection (P = 0.045), and DUSP1 was expressed at lower levels in tumor tissue than in adjacent normal margins of resection (P = 0.0115). Although LINC01111 expression was generally lower in tumor tissues than in their paired adjacent normal tissues, this difference did not reach statistical significance (P = 0.0818). Correlation analysis indicated a weak inverse association between DUSP1 and miR-3924. Higher miR-3924 expression and lower DUSP1 expression were significantly associated with adverse clinical parameters (P < 0.05). The individual receiver operating characteristic (ROC) curves for miR-3924 and DUSP1 demonstrated limited diagnostic discriminatory ability, with an area under the curve (AUC) of 0.58.

Conclusion: This study demonstrated a dysregulated LINC01111 / miR-3924 / DUSP1 axis in LUAD. Although the individual components of this axis demonstrate limited standalone diagnostic performance, significant associations with metastatic progression support their potential clinical utility as prognostic biomarkers and therapeutic targets.

Keywords: Adenocarcinoma of Lung, Long Noncoding RNA *LINC01111*, Biomarkers, *MicroRNA-3924*, *Dual Specificity Phosphatase 1*.

Introduction

Lung cancer is recognized as one of the fundamental challenges facing health systems worldwide and is the leading cause of cancer-related death. Non-small cell lung cancer (NSCLC) accounts for nearly 85% of all lung cancer cases (1). Global epidemiological statistics indicate that this malignancy had the highest global incidence rate in 2022, with roughly 2.5 million new cases reported. This figure represented 12.4% of all malignancies diagnosed that year, meaning that approximately one in every eight cancer cases worldwide was lung cancer. Lung cancer was also the leading cause of cancer-related death, responsible for an estimated 1.8 million deaths

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(18.7%) (2, 3). NSCLC includes lung adenocarcinoma (LUAD), the most common histologic subtype, which has distinct molecular profiles and varied responses to treatment (4). Despite advances in targeted therapy and immunotherapy, the five-year survival rate for patients with late-stage LUAD remains poor, partly because of delays in diagnosis and the multifaceted biological mechanisms underlying tumor growth and metastasis (5). Identifying novel biomarkers and understanding the molecular mechanisms and networks involved in cancer development and progression are essential for improving diagnostic and treatment strategies (6). The molecular biology of lung cancer is strongly influenced by dynamic regulatory layers, such as long non-coding RNAs (lncRNAs), which are transcripts longer than 200 nucleotides that, although not translated, are key regulators of cancer progression (7, 8). Dysregulation of these factors drives aggressive oncogenic phenotypes characterized by unbridled proliferation, chemoresistance, and metastatic dissemination (9, 10). Mechanistically, lncRNAs act as multifunctional scaffolds that regulate chromatin structure and transcription. Through their sponge-like interactions with miRNAs, a mechanism known as competing endogenous RNA (ceRNA) activity, lncRNAs influence the stoichiometric balance of gene networks in cancer cells (11, 12). Furthermore, the abnormal expression of several lncRNAs has been reported to correlate with increased growth and invasiveness of lung cancer cells (13). LINC01111 has received considerable attention for its potential tumor-suppressive role in several types of cancer; however, limited information is available regarding its expression level in LUAD and how LINC01111 exerts its effects on the pathophysiology of LUAD (14). The ceRNA hypothesis states that lncRNAs regulate target mRNA expression by interacting with and competing for miRNA binding, thereby acting as molecular sponges. miRNAs are small non-coding RNA molecules that regulate gene expression post-transcriptionally by promoting mRNA degradation or repressing mRNA translation (15). Computational predictions have identified miR-3924 as a potential target of LINC01111; however, its biological role in LUAD progression requires further investigation (14). A potential downstream effector of this regulatory mechanism is dual-specificity phosphatase 1 (DUSP1), a critical negative regulator of the mitogen-activated protein kinase (MAPK) signaling pathway. DUSP1 dephosphorylates and inactivates MAP kinases, including ERK, JNK, and p38, thereby affecting essential cellular processes such as survival, apoptosis, and inflammation. Bioinformatic analyses have identified potential binding sites for miR-3924 within LINC01111 and the 3′ untranslated region (UTR) of DUSP1, suggesting that LINC01111 may function as a molecular sponge for miR-3924 and regulate DUSP1 expression (16). This study will empirically examine this regulatory axis by assessing the expression levels of LINC01111, miR-3924, and DUSP1 in specimens from patients clinically diagnosed with LUAD. Additionally, the study will evaluate the associations between the expression levels of these three molecules and relevant clinical parameters to determine their potential utility as diagnostic biomarkers for lung adenocarcinoma and to improve our understanding of their roles in LUAD pathophysiology.

Materials and Methods

Study Population and Clinical Sample Collection

In this analytical cross-sectional study, we characterized the expression profiles of LINC01111, miR-3924, and DUSP1 in LUAD tumor tissues and compared them with those in paired adjacent non-tumor tissues. The study was conducted at the Department of Surgery, Imam Reza Hospital, Tabriz University of Medical Sciences, Iran, between March and July 2025. During surgical procedures, 100 tissue samples were obtained, comprising 50 LUAD tumor samples and 50 paired adjacent non-tumor tissue samples. Patients were eligible if they had histopathological confirmation of NSCLC (adenocarcinoma

subtype), had not received chemotherapy or radiotherapy before sample collection, resided in Northwestern Iran, and provided written informed consent. Patients were excluded if the extracted RNA was of inadequate quality or quantity, if they had concurrent neoplastic conditions, or if they had been diagnosed with other genetic disorders. The demographic and clinical characteristics of the study population are presented in Table 1. The Ethics Committee of Tabriz University of Medical Sciences approved the study protocol (IR.TBZMED.REC.1403.495) on September 23, 2024. All participants provided written informed consent regarding the purpose of the study, the sample-selection process, and the protection of their personal data. All aspects of the research were conducted in accordance with the ethical standards outlined in the Declaration of Helsinki, including the protection of participants' identities and the integrity of the research findings.

Tissue Collection, Preservation, RNA Extraction, and cDNA Synthesis

During surgical resection, paired tumor and adjacent non-tumor margin tissues were collected under carefully maintained sterile conditions. All samples were confirmed to be suitable for pathological examination. To ensure RNA integrity and minimize potential confounding effects of prior therapy, only patients who had not received chemotherapy were included in the sampling process. Immediately after collection, the tissues were snap-frozen in liquid nitrogen and stored at −80 °C until RNA isolation. Total RNA was extracted using the RNeasy Mini Kit (Qiagen, Germany), according to the manufacturer's protocol. RNA quality and quantity were evaluated by measuring the 260/280-nm absorbance ratio using a NanoDrop spectrophotometer (Thermo Fisher Scientific, USA). cDNA synthesis was performed using the BioFACT cDNA Synthesis Kit (BioFACT, Korea). For accurate reverse transcription of miR-3924, a stem-loop-based specific primer system was used.

Table 1. Demographic and Clinical Characteristics of Patients (n=50).

Variable	Category	Frequency n (%)
Gender	Male	33 (66)
	Female	17 (34)
Age (years)	Mean ± SD	62.14 ± 8.32
Smoking History	Yes	26 (52)
	No	24 (48)
Distant Metastasis	Present	13 (26)
	Absent	37 (74)
TNM Stage	I – II	21 (42)
	III	29 (58)
Lymph Node Involvement	Positive	20 (40)
	Negative	30 (60)
Cellular Differentiation	Well/Moderate	35(70)
	Poorly	15(30)

Quantitative Real-Time PCR (qRT-PCR)

Expression levels of genes were determined by quantitative real-time PCR with a StepOnePlus™ system (Applied Biosystems), where each reaction contained a final volume of 20 µL with a master mix containing SYBR green (BioFact, South Korea) and specific primers that were designed using primer3 and Oligo Analyzer with the reference sequence of the National Center for Biotechnology Information (NCBI) database to be specific to LINC01111, DUSP1 and miR-3924. All primers were further validated by BLAST analysis (Table 2). Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was used as the internal reference gene for both LINC01111 and DUSP1, whereas U6 small nuclear RNA (snRNA) was the internal reference gene for miR-3924. All reactions were run in triplicate. Thermal cycling conditions consisted of an initial denaturation step followed by an amplification cycle with steps consisting of denaturation, annealing and extension. Gene expression relative to GAPDH or U6 snRNA was determined by the 2^(-ΔΔCt) method.

Table 2. Primer sequences used for real-time PCR.

Gene name	NCBI Accession No.	Primer Seq		Tm (°C)	Product size (bp)
DUSP-1	NM_004417.4	F	GCGAAGGACATTTGGGCTGTG	59	161
		R	CGAGGAAAAGCTAGACCCCCG		
LNC-01111	NR_105006	F	ATCCTGGGATACATGTGCAGA	59	167
		R	TGATCCAAGGGCCTTTTCAGG		
GAPDH	NM_002046.7	F	CAAGATCATCAGCAATGCCTCC	59	135
		R	GCCATCACGCCACAGTTTCC		
U6	NR_004394.1	F	GCTTCGGCAGCACATATACTAAAAT	60	70
		R	CGCTTCACGAATTTGCGTGTCAT		
MiR-3924-5p	100500834	F	ATATGTATATGTGACTGCTACT	57	70
		R	CCAGTGCAGGGTCCGAGGT		

Statistical Analysis

Data were analyzed using GraphPad Prism (v9.5.1). To determine the appropriate statistical test, the normality of the data distribution was first examined using the Shapiro–Wilk test. Then, gene expression in paired tissues was compared using parametric (paired t-test) or nonparametric (Wilcoxon signed-rank) tests. To examine the diagnostic power of the studied genes, Receiver Operating Characteristic (ROC) curve analysis was used, and area under the curve (AUC), sensitivity and specificity values were calculated. Correlation between gene expression levels was determined using Pearson or Spearman tests. The association with clinicopathological characteristics was also analyzed using appropriate statistical tests. A *P*-value < 0.05 was considered statistically significant. The sample size was estimated using Cochran's formula.

Results

The Study cohort consisted of 50 patients with an average age of 62.14 ± 8.32 years. Males accounted for 66% of the cohort, and 52% of patients reported a history of smoking. According to the TNM tumor-staging classification, 58% of patients were classified as having stage III disease. Lymph-node involvement was observed in 40% of the cohort. The demographic and clinical characteristics of the participants are presented in Table 3.

Table 3. Correlation between Gene Expression Levels and Clinical Pathological Features in Lung Adenocarcinoma Patients.

Clinical Characteristic	P-value		
	miR-3924	*DUSP1*	*LINC01111*
Gender	0.21	0.056	0.087
Age	0.19	0.076	0.075
Distant Metastasis (M Stage)	0.015*	0.001**	0.067
Tumor Stage (TNM)	0.051	0.035*	0.053
Smoking History	0.061	0.052	0.062
Lymph Node Involvement	0.0011**	0.021*	0.053
Cellular Differentiation	0.047*	0.046*	0.071

Differential Expression of miR-3924, LINC01111, and DUSP1 in Lung Adenocarcinoma

A considerable increase in miR-3924 expression was observed in tumor samples ($P = 0.045$), suggesting its potential involvement in molecular pathways associated with lung adenocarcinoma development. This finding may support the oncogenic role of miR-3924. In addition, DUSP1 expression levels were significantly lower in tumor tissues than in adjacent margin tissues ($P = 0.0115$). DUSP1 is a well- documented inhibitor of the MAPK and SAPK signaling pathways; therefore, its downregulation may enhance cellular proliferation, migration, and metastasis. Although LINC01111 expression was relatively lower in tumor tissues than in adjacent margin tissues, this difference did not reach statistical significance ($P = 0.0818$). Nevertheless, further studies with larger sample sizes and greater statistical power are needed to better characterize the relationship between miR-3924 and DUSP1 and the associated regulatory mechanisms (Fig. 1).

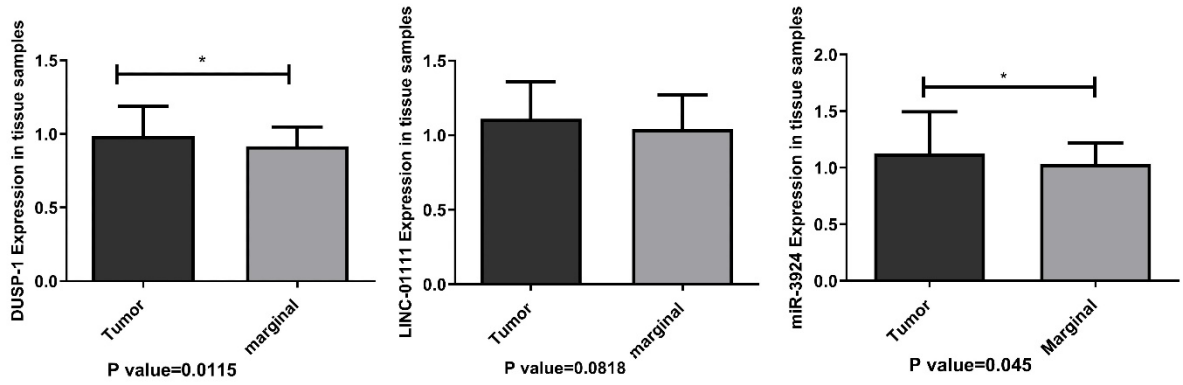

Fig. 1. Relative expression levels of DUSP-1, LINC-01111, and miR-3924 in lung adenocarcinoma tumor tissues compared to adjacent marginal tissues (n=50). The bar graphs illustrate the comparative quantitative real-time PCR (qRT-PCR) expression profiles for each target biomarker within the clinical cohort. Significant downregulation of the tumor suppressor DUSP-1 is observed in tumor tissues relative to non-cancerous marginal samples (P = 0.0115). LINC-01111 expression displays a downward trend in tumor tissues, reaching a near-significant borderline trajectory (P = 0.0818). Right panel: Significant tumor upregulation of oncogenic miR-3924 is demonstrated in comparison to matching marginal tissues (P = 0.045). Data are presented as mean ± standard error of the mean (SEM). Statistically significant differences between the tissue groups are denoted by asterisks (* P< 0.05).

Diagnostic Value Analysis (ROC Curve)

To evaluate the diagnostic performance of the biomarkers under study, receiver operating characteristic (ROC) curve analysis was performed to differentiate tumor tissues from non-tumor tissues. For DUSP1, the area under the curve (AUC) was 0.58 ($P = 0.085$), indicating limited diagnostic ability to distinguish tumor tissues from adjacent non-tumor tissues. Similarly, miR-3924 showed an AUC of 0.5235 ($P = 0.6198$), indicating limited predictive value when used alone; however, it may be more useful as part of a combined biomarker panel. LINC01111 also showed limited diagnostic performance, with an AUC of 0.5571 ($P = 0.2276$) (Fig. 2).

Correlation Analysis Among Target Genes

The intermolecular interactions within the LINC01111/miR-3924/DUSP1 regulatory network were evaluated using Pearson correlation analysis, and the results are presented in Table 3. Several notable trends were observed. Specifically, DUSP1 expression showed a weak positive correlation with miR-3924 ($P = 0.0665$), whereas LINC01111 exhibited weak negative correlations with both DUSP1 ($P = 0.1023$) and miR-3924 ($P = 0.1035$). Although these individual linear correlations did not reach statistical significance ($P < 0.05$), the observed trends highlight the complexity and potential nonlinearity of competing endogenous RNA (ceRNA)

regulatory networks. In such networks, expression patterns and transcript dynamics are not determined solely by binary interactions between molecules but are influenced by numerous tissue-specific regulatory factors that act in a coordinated and multilayered manner (Table 4).

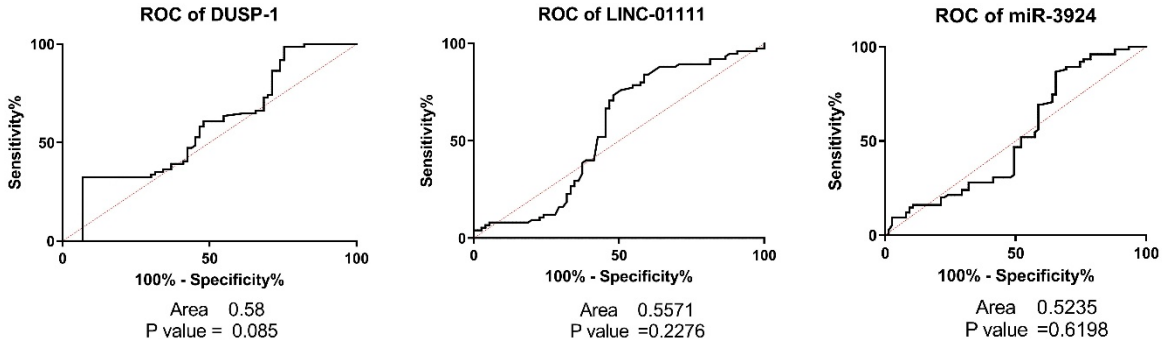

Fig. 2. Receiver Operating Characteristic (ROC) Curve Analysis of DUSP-1, LINC-01111, and miR-3924. Receiver operating characteristic (ROC) curves illustrating the diagnostic performance of DUSP-1, LINC-01111, and miR-3924 expression levels in distinguishing between the studied groups. The y-axis represents sensitivity (%) and the x-axis represents 100% − specificity (%). The area under the curve (AUC) was 0.58 for DUSP-1 (P = 0.085), 0.5571 for LINC-01111 (P = 0.226), and 0.5235 for miR-3924 (P = 0.6198). All three biomarkers demonstrated weak discriminatory ability, and none reached statistical significance.

Table 4. Correlation Analysis Between DUSP-1, LINC-01111, and miR-3924 Expression Levels.

Linear Correlation Metric	Inter-Transcript Axis	Pearson (r)	Significance (P)
Axis Matrix A	DUSP1 vs. miR-3924	+0.2160	0.0665 (ns)
Axis Matrix B	LINC01111 vs. miR-3924	+0.1895	0.1035 (ns)
Axis Matrix C	DUSP1 vs. LINC01111	-0.1927	0.1023 (ns)

*(ns) indicates non-significant linear correlations (P≥ 0.05).

Association with Clinicopathological Characteristics

Statistical analysis indicated that high miR-3924 expression was significantly associated with distant metastasis ($P = 0.015$), greater lymph-node involvement ($P = 0.0011$), and poor cellular differentiation ($P = 0.047$), suggesting that this molecule may contribute to tumor growth and an aggressive phenotype. Similarly, low DUSP1 expression was significantly associated with distant metastasis (P= 0.001), more advanced disease stages (P= 0.035), greater lymphatic spread (P= 0.021) and poor cellular differentiation (P= 0.046), supporting the potential tumour-suppressive role of this gene. The associations between LINC01111 expression and clinicopathological parameters did not reach statistical significance (P< 0.05); however, near-significant trends were observed for tumor stage (P= 0.053), lymph-node involvement (P= 0.053), and differentiation status (P= 0.071).

Discussion

In the present study, we assessed the diagnostic performance, expression profiles, molecular interactions, and clinicopathological relevance of the LINC01111/miR-3924/DUSP1 regulatory axis in LUAD. Our analysis showed that miR-3924 expression was significantly increased, whereas DUSP1 expression was significantly decreased, in LUAD tissues compared with paired adjacent non-tumor tissues. LINC01111 exhibited a reduced expression trend that approached statistical significance. Although none of the genes demonstrated sufficient diagnostic performance as independent biomarkers in the ROC curve analyses, their expression profiles

were strongly associated with disease aggressiveness. Specifically, upregulated miR-3924 expression was significantly associated with lymph-node involvement, distant metastasis, and poor tumor differentiation, whereas reduced DUSP1 expression was associated with advanced TNM stage, metastatic dissemination, lymphatic spread, and poor differentiation. The observed weak and non-significant linear correlations among LINC01111, miR-3924, and DUSP1 suggest that their interactions may occur within a complex regulatory network rather than through simple linear associations. Although the reduction in LINC01111 expression did not reach statistical significance, possibly because of the limited sample size, the observed expression pattern is consistent with the proposed ceRNA hypothesis. Based on these findings, we propose that, in normal lung tissue, LINC01111 sponges miR-3924, thereby supporting the tumor-suppressive function of DUSP1. In contrast, reduced LINC01111 expression during tumorigenesis may allow uncontrolled miR-3924 activity, resulting in decreased DUSP1 expression and potentially activating oncogenic signaling pathways. These findings extend previous mechanistic studies by demonstrating the potential clinical relevance of the LINC01111/miR-3924/DUSP1 axis in patients with LUAD. Whereas previous research has focused primarily on molecular interactions in in vitro models, our data suggest that disruption of this regulatory network is associated with clinical markers of disease invasiveness, particularly metastasis and lymphatic spread. Xu et al. previously predicted computationally and confirmed experimentally that the LINC01111/miR-3924/DUSP1 axis functions as a ceRNA network. They proposed that binding of LINC01111 to miR-3924 prevents DUSP1 degradation (19). Clinical data demonstrating the inverse relationship between increased miR-3924 and decreased DUSP1 expression in human NSCLC samples provide strong ex vivo validation of Xu's mechanism-based model. Additionally, Pan et al. identified LINC01111 as a potential tumor suppressor in pancreatic cancer and reported that increased LINC01111 expression inhibited cellular growth and metastasis through the miR-3924/DUSP1 axis, resulting in inactivation of the SAPK/JNK pathway. Our findings are consistent with studies from other countries, suggesting that the biological functions of the LINC01111/miR-3924/DUSP1 axis may be conserved across diverse populations and epithelial tumors. However, our cohort did not show statistically significant downregulation of LINC01111, which contrasts with previous findings. Similar to the results reported by Pan et al., we observed that LINC01111 was downregulated in lung adenocarcinoma and associated with aggressive clinicopathological features, including metastasis and poor differentiation (14). These observations suggest that the tumor-suppressive properties of LINC01111 may be conserved across epithelial cancers; however, its expression level may depend on tissue-specific cofactors. Li et al. demonstrated that inhibiting miR-3924 increased the expression of target genes such as WNT5A. Although the downstream target differs between studies (WNT5A versus DUSP1), the underlying role of miR-3924 as an oncomiR that promotes tumorigenesis appears to be consistent (20).

Furthermore, the statistically significant association between high miR-3924 expression and lymph-node involvement in our cohort ($P= 0.001$) provides strong evidence that miR-3924 may contribute to invasive and metastatic processes in LUAD. Clinically, this association is important because lymph-node status is a key indicator of disease recurrence and survival in patients with NSCLC. Therefore, miR-3924 may be more useful as a molecular marker of metastatic potential than as a conventional diagnostic biomarker.

DUSP1 is a dual-specificity phosphatase that dephosphorylates and inactivates MAPKs (21). Acero-Riaguas et al. demonstrated that DUSP1 deletion results in JNK hyperactivation (22). Therefore, the significant reduction in DUSP1 expression observed in metastatic tumors provides additional support

for the hypothesis that loss of this regulatory brake on MAPK signaling contributes to more aggressive NSCLC phenotypes. The relationship between miR-3924 and DUSP1 showed a weak inverse correlation, whereas the relationship between LINC01111 and DUSP1 showed a weak direct correlation.

A strong linear relationship does not appear to exist, likely because of the complexity of the ceRNA network and the relative stoichiometry of competing RNA species within the cytoplasm (23). These weak correlations do not disprove the proposed ceRNA mechanism; rather, they highlight the complexity of biological regulatory systems, in which multiple miRNAs, lncRNAs, and signaling pathways simultaneously influence gene expression. This observation emphasizes the limitations of assessing ceRNA interactions solely through simple pairwise correlation analyses in patient tissues.

Regarding the utility of each gene for predicting disease outcomes, ROC curve analysis indicated that the individual genes had relatively low discriminatory power, with AUC values ranging from approximately 0.52 to 0.58. Although these findings demonstrate the limitations of ncRNAs as independent diagnostic indicators, they provide important insights into the underlying biological mechanisms. Consistent with existing evidence, single-molecule biomarkers are often insufficient for accurately diagnosing cancer because malignancy is multifactorial and rarely results from dysfunction of a single gene. Instead, cancer develops through complex interactions across molecular networks.

However, the associations of these molecules with prognostic factors, including metastasis and TNM stage, suggest that their primary value may lie in prognostic stratification and their inclusion in multimarker panels rather than their use as standalone diagnostic markers (14). These findings indicate that miR-3924 and DUSP1 are associated with clinically important outcomes. A biomarker signature comprising high miR-3924 and low DUSP1 expression may help identify patients at increased risk of distant metastasis who could potentially benefit from more intensive adjuvant treatment (25).

From a therapeutic perspective, increasing LINC01111 expression and/or inhibiting miR-3924 may help restore DUSP1 expression and thereby reduce MAPK signaling–mediated proliferative effects (26). In our cohort, 58% of patients were diagnosed with stage III disease, and 40% had lymph-node metastases. These high rates of advanced-stage disease are consistent with epidemiological data from Iranian and global lung cancer registries, which indicate that 50–70% of lung adenocarcinomas are diagnosed after local spread to regional lymph nodes or distant metastasis, partly because symptoms are often absent during the early stages of disease (27).

The relatively large proportion of patients with advanced disease provided sufficient variation to demonstrate a statistically significant association between miR-3924 expression and lymph-node metastasis. This finding supports the hypothesis that miR-3924 functions as an oncomiR by promoting epithelial–mesenchymal transition (EMT) and the invasive processes involved in cancer-cell dissemination through lymphatic vessels (29). Conversely, the high frequency of lymph-node involvement further emphasizes the potential need for biomarkers such as DUSP1, which was expressed at lower levels in patients with positive lymph nodes, to identify patients who may require more intensive adjuvant therapy after surgical resection (30).

A limitation of the present study is the lack of standardized data on individual disease duration, defined as the interval between symptom onset and surgical intervention. Because most patients presented with advanced-stage disease, clarifying the longitudinal relationship between disease duration and biomarker fluctuations remains an important goal for future prospective, multicenter studies involving larger cohorts. The limited sample size may also have contributed to the borderline statistical

significance of LINC01111 mRNA expression.

Furthermore, this was an observational study of tissue expression. Future research should include functional experiments, such as knockdown and overexpression studies in lung cancer cell models, to evaluate the direct effects of this regulatory axis on cell proliferation and migration. Investigating the methylation status of the LINC01111 promoter region may also help identify epigenetic alterations associated with its reduced expression in lung cancer.

In summary, this research provides clinical evidence of a dysregulated LINC01111/miR-3924/DUSP1 pathway in lung adenocarcinoma. Downregulation of DUSP1, possibly resulting from elevated miR-3924 levels due to reduced LINC01111-mediated sponging, was associated with late-stage disease progression and/or the presence of metastases. These findings suggest that the three molecules may represent potential therapeutic targets for restoring cellular homeostasis in non-small cell lung cancer.

Authors' Contribution

R.S.: data analysis and interpretation, reviewing the manuscript; A.A.: writing the draft, reviewing the manuscript; M.A.: Study design, data collection, processing and reviewing the manuscript; H.S.J.: Data collection, writing the draft, data analysis and interpretation; M. SH.: Data collection and processing; H.Z.: Study design, data analysis and interpretation, reviewing the manuscript. All authors have read and approved the final manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval

This study was formally approved by the Organizational Ethics Committee of the Tabriz University of Medical Sciences (Ethics Committee Code: IR.TBZMED.REC.1403.495). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of Interest

The authors declare that they have no conflict of interest.

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References

1. Firoozi MR, Sadeghi-Mohammadi S, Asadi M, Shekari N, Seyed Nejad F, Alizade-Harakiyan M et al. Durvalumab and taxane family combination therapy enhances the antitumoral effects for NSCLC: An in vitro study. Cell Biochem Funct. 2024; 42(1):e3919.
2. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229-263.
3. Zhang L, Fan C, Shang H, Wang X, Zhang X, Qiao Q, Ni J, Wu S. Cross-Regional Transcriptome Data Reveal Transcriptional Abnormalities Associated with Lung Adenocarcinoma. Rep Biochem Mol Biol. 2025;14(1):102-113.
4. Fukuda H, Arai K, Mizuno H, Nishito Y, Motoi N, Arai Y et al. Molecular subtypes of lung adenocarcinoma present distinct immune

tumor microenvironments. Cancer Sci. 2024;115(6):1763-1777.
5. Huang Q, Li Y, Huang Y, Wu J, Bao W, Xue C, Li X, Dong S, Dong Z, Hu S. Advances in molecular pathology and therapy of non-small cell lung cancer. Signal Transduct Target Ther. 2025;10(1):186.
6. Fu C, Sun L, Zhang L, Zhou T, Bi Y. Identification of key biomarkers and potential therapeutic drugs in nasopharyngeal carcinoma based on comprehensive bioinformatics analysis. Discov Oncol. 2025;16(1):1189.
7. Asadi M, Sadeghi-Mohammadi S, Shekari N, Zafari V, Soleimani Z, Mert U, et al. Therapeutic Potential of Circular RNAs as Targets for Cancer Treatment. Adv Pharm Bull. 2025;15(3):533-551.
8. Tuna M, Mills GB, Amos CI. The role of long non-coding RNAs in lung cancer metastasis: Molecular mechanisms, pathogenesis and clinical implications. Clinical and Translational Medicine. 2025;15(8):e70429.
9. Ge X, Shen Z, Yin Y. Comprehensive review of LncRNA-mediated therapeutic resistance in non-small cell lung cancer. Cancer Cell Int. 2024;24(1):369. doi: 10.1186/s12935-024-03549-1.
10. Shalmashi H, Safaei S, Shanehbandi D, Asadi M, Bornehdeli S, Mehdi Navaz A. Evaluation of lncRNA FOXD2-AS1 Expression as a Diagnostic Biomarker in Colorectal Cancer. Rep Biochem Mol Biol. 2022;11(3):471-478.
11. Han Y, Li S, Oyang L, Cui S, Zhang W, Yang W et al. Novel insights into lncRNAs as key regulators of post-translational modifications in cancer: mechanisms and therapeutic potential. Cell Oncol. 2025;48(5):1219-1244. doi: 10.1007/s13402-025-01086-1.
12. Esfandi F, Fallah H, Arsang-Jang S, Taheri M, Ghafouri-Fard S. The Expression of *CCAT2, UCA1, PANDA* and *GHET1* Long Non-coding RNAs in Lung Cancer. Rep Biochem Mol Biol. 2019;8(1):36-41.
13. Wang J, Han X, Yuan Y, Gu H, Liao X, Jiang M. The Value of Dysregulated LncRNAs on Clinicopathology and Survival in Non-Small-Cell Lung *Cancer*: A Systematic Review and Meta-Analysis. Front Genet. 2022;13:821675.
14. Pan S, Shen M, Zhou M, Shi X, He R, Yin T, et al. Long noncoding RNA LINC01111 suppresses pancreatic cancer aggressiveness by regulating DUSP1 expression via microRNA-3924. Cell Death Dis. 2019;10(12):883.
15. Shanehbandi D, Asadi M, Seyedrezazadeh E, Zafari V, Shekari N, Akbari M, et al. MicroRNA-Based Biomarkers in Lung Cancer: Recent Advances and Potential Applications. Curr Mol Med. 2023;23(7):648-667.
16. Niture S, Mooers BHM, Wu DH, Hart M, Jaboin J, Seneviratne D. Dual-specificity protein phosphatase 1: A potential therapeutic target in cancer. iScience. 2025;28(11):113706.
17. Singh A, Ashok A, Pandey S, Lin Q. Editorial: Recent developments in clinical biomarkers for cancer prognosis, prediction, treatment, and their clinical utility. Front Genet. 2024;15:1437556.
18. Aftabi Y, Ansarin K, Shanehbandi D, Khalili M, Seyedrezazadeh E, Rahbarnia L, Asadi M, Amiri-Sadeghan A, Zafari V, Eyvazi S, Bakhtiyari N, Zarredar H. Long non-coding RNAs as potential biomarkers in the prognosis and diagnosis of lung cancer: A review and target analysis. IUBMB Life. 2021;73(2):307-327.
19. Xu J, Xu J, Liu X, Jiang J. The role of lncRNA-mediated ceRNA regulatory networks in pancreatic cancer. Cell Death Discov. 2022;8(1):287.
20. Li Y, Zhong H, Luo L, Gan M, Liang L, Que L, et al. Integrated analysis of the lncRNA-miRNA-mRNA ceRNA network in nasopharyngeal carcinoma. Transl Cancer Res. 2024;13(8):4372-4388.
21. Lang R, Raffi FAM. Dual-Specificity Phosphatases in Immunity and Infection: An Update. Int J Mol Sci. 2019;20(11):2710.
22. Acero-Riaguas L, Griso-Acevedo AB, SanLorenzo-Vaquero A, Ibáñez-Herrera B, Fernandez-Diaz SM, Mascaraque M. et al. DUSP1 and SOX2 expression determine squamous cell carcinoma of the salivary gland progression. Sci Rep. 2024;14(1):15007.

23. Raziq K, Cai M, Dong K, Wang P, Afrifa J, Fu S. Competitive endogenous network of lncRNA, miRNA, and mRNA in the chemoresistance of gastrointestinal tract adenocarcinomas. Biomed Pharmacother. 2020;130:110570.
24. Ala U. Competing Endogenous RNAs, Non-Coding RNAs and Diseases: An Intertwined Story. Cells. 2020;9(7):1574.
25. Li J, Hou S, Ye Z, Wang W, Hu X, Hang Q. Long Non-Coding RNAs in Pancreatic Cancer: Biologic Functions, Mechanisms, and Clinical Significance. Cancers (Basel). 2022;14(9):2115.
26. Xiong G, Pan S, Jin J, Wang X, He R, Peng F, Li X, Wang M, Zheng J, Zhu F, Qin R. Long Noncoding Competing Endogenous RNA Networks in Pancreatic Cancer. Front Oncol. 2021;11:765216.
27. Gridelli C, Rossi A, Carbone DP, Guarize J, Karachaliou N, Mok T, Petrella F, Spaggiari L, Rosell R. Non-small-cell lung cancer. Nat Rev Dis Primers. 2015;1:15009.
28. Zheng J, Zhong H, Quan E, Gao Z, Ying S. Prognostic value of lymph node ratio in patients with non-small cell lung cancer: a systematic review and meta-analysis. Front Oncol. 2025;15:1601575.
29. Díaz-López A, Moreno-Bueno G, Cano A. Role of microRNA in epithelial to mesenchymal transition and metastasis and clinical perspectives. Cancer Manag Res. 2014;6:205-16.
30. Rocco R, Hendriksen BS, Ortiz BA, Shen KR, Cassivi SD, Saddoughi S, et al. Impact of lymph node evaluation standard in patients undergoing lung resection for clinical stage IA pulmonary adenocarcinoma and squamous cell carcinoma. J Thorac Dis. 2024;16(11):7663-7674.