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Expression of MicroRNA-141 in Peripheral Blood Mononuclear Cells from Non-small-cell Lung Cancer Patients

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ABSTRACT

MicroRNAs (miRs) play a crucial role in the pathogenesis, progression, and prognosis of cancer, including non-small-cell lung cancer. The purpose of this present study was to investigate the correlation between *MIR141* expression in peripheral blood mononuclear cells and serum levels of interleukins (IL-6 and IL-8) and CXCL10 in non-small-cell lung cancer patients.

Forty-six patients diagnosed with primary non-small-cell lung cancer and 30 age- and gender-matched healthy controls were recruited in this prospective cohort study. Two 3-mL samples of systemic blood were collected into tubes either containing or without an anticoagulant from all patients before treatment and from healthy controls. PBMCs were isolated, total RNA extracted, and microRNA expression measured using real-time quantitative polymerase chain reaction. Serum cytokine levels were measured by enzyme-linked immunosorbent assay.

MIR141 expression in peripheral blood mononuclear cells was significantly higher in non-small-cell lung cancer patients (4.124 [3.259–4.944]) compared to healthy controls (2.181 [1.036–2.946]). The area under the Receiver operating characteristic (ROC) curve, AUC for *MIR141,* was 0.695 (95% CI, 0.603–0.787), indicating statistically significant diagnostic performance. Serum levels of IL-6, IL-8, and *CXCL10* were also markedly elevated in non-small-cell lung cancer patients compared to healthy controls.

Increased expression of *MIR141* in peripheral blood mononuclear cells is associated with non-small-cell lung cancer and elevated systemic inflammatory mediators. These findings suggest that peripheral blood *MIR141* may serve as a promising non-invasive biomarker for the diagnosis of non-small-cell lung cancer.

Keywords: Cytokines; Immune system; *MIR141*; Non-small-cell lung carcinoma

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INTRODUCTION

Lung cancer (LC) is the most common cause of cancer-related mortality worldwide. In 2018, there was a significant rise in both incidence and mortality rates linked to lung cancer, highlighting its severe impact on global health.[1,2] Lung cancer is classified into small-cell lung cancer (SCLC, approximately 15% of the cases) and non-small-cell lung cancer (NSCLC, approximately 85% of the cases). NSCLCs include adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.[1] Among the histological types of NSCLC, lung adenocarcinoma is the most common.[3] Approximately 70% of NSCLC patients who present with locally advanced or metastatic disease have a poor prognosis, with an expected 5-year survival rate of <5%.[4,5]

Despite various combinations of surgery, radiotherapy, and chemotherapy,[4] overall survival rates for NSCLC patients remain poor.[4] Although early detection of lung cancer is critical,[1,6] its etiology is multifactorial, and its pathogenesis is incompletely understood.[1] The poor prognosis is due to various factors, including diagnosis at advanced disease stages, tumor heterogeneity, and a relatively limited understanding of lung cancer biology.[7] The immune system plays a key role in the development and progression of cancers[7] and is critical in cancer progression by releasing pro- or anti-tumorigenic factors.[8] Proinflammatory cytokines play an active role in reducing tumor growth, metastasis, apoptosis, and angiogenesis.[8] Thus, a better understanding of the key factors that evaluate lung cancer molecular mechanisms can provide a basis for identifying new biomarkers and developing effective therapies.[4] MicroRNAs (miRs), which are 21–25 nucleotides in length, play a crucial role in the pathogenesis, progression, treatment, and prognosis of NSCLC, primarily through targeting and regulating mRNA expression.[9] There is increasing evidence that miRNA dysregulation plays a role in the pathogenesis and development of various human cancers[10,11] by modulating immune responses.[12] In particular, human *MIR141*, a member of the miR-200 family located on chromosome 12,[13] has been associated with various human malignancies.[14] *MIR141* is upregulated in ovarian cancer[15] and colorectal cancer,[16] but downregulated in gastric cancer,[17] hepatocellular carcinoma,[18] and prostate cancer,[19] indicating different regulatory effects of *MIR141* in various cancers. These findings suggest that *MIR141* could be a potential biomarker for cancer, including NSCLC.

In NSCLC cells, such as A549 and H1299, *MIR141* is reported to promote proliferation.[20] The expression of *MIR141* in lung cancer tissue is elevated and is correlated with overall survival rates, suggesting its potential role as a powerful prognostic marker in lung cancer.[20] However, the role of *MIR141* expression level in peripheral blood mononuclear cells (PBMCs) in the diagnosis and prognosis of NSCLC patients remains unclear. The present study aimed to elucidate whether the pattern of *MIR141* expression in PBMCs could help follow cancer pathogenesis and progression. We hypothesize that relative levels of peripheral blood *MIR141* expression may be used to diagnose NSCLC. We, therefore, evaluated *MIR141* expression in PBMCs and correlated this with serum cytokine levels in NSCLC patients.

MATERIALS AND METHODS

Ethical Consideration

This study was conducted following the principles outlined in the Declaration of Helsinki. It was approved by the Institutional Review Committee of Shahid Beheshti University of Medical Sciences, in collaboration with the Local Ethics Committee of Masih Daneshvari Hospital, Tehran, Iran. All patients and healthy controls provided written informed consent (Ethics committee approval number: IR.SBMU.NRITLD.REC.1402.082).

Study Participants

Forty-six new lung cancer patients (mean age, 59.67 years) were recruited at Masih Daneshvari Hospital in Tehran, Iran, between September 2022 and September 2023. NSCLC was confirmed by imaging, including computed tomography (CT) scans, and by pathology and clinical parameter analysis by specialists. Patients were all new cases and had no history of other cancers or lung inflammatory diseases. Thirty age- and sex-matched volunteer healthy controls were recruited in this study (Table 1).

Sampling Procedure

Two 3-mL blood samples were collected from each participant: one in a tube containing anticoagulant for PBMC isolation, and one in a tube without anticoagulant for serum cytokine analysis. Whole blood samples from

healthy controls and patients were collected into separate tubes containing blood clot-activating gel for obtaining serum to cytokines assay, and heparin tubes for PBMC isolation. Three milliliters of blood collected in heparin tubes were used to assess *MIR141* expression from isolated PBMCs. Serum tubes were allowed to stand at room temperature for 1 hour before being centrifuged at 300*g* for 10 minutes at 4°C. The supernatants were subsequently collected and further centrifuged at 300*g* for 10 minutes at 4°C. The supernatants were then stored at −80°C.

PBMCs Isolation

Whole blood was collected in heparin-containing tubes, and PBMCs were isolated using density gradient centrifugation by the Ficoll procedure. In brief, the blood was diluted with an equal volume of phosphate-buffered saline (PBS) buffer and then slowly added to a 3-mL lymphocyte separation medium (Ficoll-Paque, BAG Health Care GmbH, Germany, Cat No: 70125). After centrifugation at 1000*g* at 4°C for 22 minutes with the brake off, PBMCs were harvested gently and then washed with cold PBS. After one more wash and centrifugation, the supernatant was removed, and 500 µL TRIzol (Invitrogen, CA, USA, 16096014) was added to the cell pellet, which was stored at −80°C until used for the isolation of total RNA, as described below.

RNA Isolation and cDNA Synthesis

Total RNA was extracted with TRIzol according to the manufacturer's protocol. Briefly, total RNA was extracted from isolated PBMCs. Cells containing TRIzol were treated with chloroform (Merck KGaA, Darmstadt, Germany). After the addition of isopropanol (Merck KGaA, Darmstadt, Germany) to precipitate the RNA, centrifugation and ethanol washing were performed. The total RNA was then diluted in sterile DEPC-treated water. The concentration and purity of the isolated total RNA were determined using a NanoDrop 2000 spectrophotometer (NanoDrop Technologies Inc., Wilmington, DE, USA). Absorbance at 260 nm was used to determine the total RNA concentration in the samples. The absorption ratios of 260/280 nm (1.8–2) and 260/230 nm (1.8–2.2) were used to assess RNA purity. Extracted RNA (20 ng) was reverse transcribed using the BON-miR miRNA 1st-Strand cDNA Synthesis Kit (Stem Cell Technology Research Center, Tehran, Iran, BON209001) based on the Poly (A)-Tailed Universal Reverse Transcription method using poly (A) polymerase according to the manufacturer's instructions.

Quantitative Real-time Polymerase Chain Reaction Analysis

MIR141 was detected by real-time polymerase chain reaction (PCR) assays by using the IQ SYBR Green Master Mix kit (BIO-RAD, CA, USA). miRNA primers were synthesized using a kit (Stem Cell Technology, Research Center, Tehran, Iran, Cat No: BON209001), and quantitative PCR was performed using a real-time PCR kit (Roche, Mannheim, Germany). A two-step real-time PCR protocol was employed, utilizing an initial denaturation step of 2 minutes at 95 °C, followed by 40 amplification cycles comprising a denaturation step (10 seconds at 95 °C) and an annealing step (30 seconds at 60 °C), as specified in the kit brochure. The melting curve was prepared for all the reactions to confirm the precision of each sample. The cycle threshold (Ct) values for the samples were normalized to U6 small nuclear RNA as an internal control, and results were then converted into fold change using the $2^{-\Delta\Delta Ct}$ method.

Cytokine Analysis

Three milliliters of whole blood in tubes without anticoagulants were harvested, and after isolation, the serum was stored at −80°C. The levels of the cytokines, including IL-6 (DY206), IL-8 (DY208), and the chemokine interferon-γ-induced protein (IP-10 or CXCL10) (DY266-05), were determined in the serum using an enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems, USA, Minneapolis, USA), according to the manufacturer's instructions. The sensitivity and specificity of these kits, as reported by the manufacturer, are as follows: IL-6: Sensitivity: 0.5 pg/mL, Specificity: 98%; IL-8: Sensitivity: 1 pg/mL, Specificity: 97%; CXCL10: Sensitivity: 0.2 pg/mL, Specificity: 95%. The optical density was read by an ELISA plate reader (Hiperion, Germany) at a wavelength of 450 nm with a reference wavelength of 545 nm. All assays were performed in duplicate on the same plate to facilitate comparison between groups.

Statistical Analysis

Quantitative real-time PCR analysis was performed in triplicate for each sample. Given the modest sample size and deviations from normality assessed by the Shapiro–Wilk test and Q–Q plots, all two-group comparisons were analyzed using the non-parametric

Mann–Whitney *U* test (2-tailed). Continuous variables are reported as median [interquartile range, IQR]. Receiver operating characteristic (ROC) analyses report areas under the curve (AUCs)s with 95% confidence intervals. Statistical analyses were performed in SPSS using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, NY, USA), and figures were prepared using GraphPad Prism (GraphPad Software, San Diego, CA, USA). A 2-sided $p \leq 0.05$ was considered statistically significant.

RESULTS

Characteristics of NSCLC Patients

Among the 46 NSCLC patients, 25 (54.3%) were≤60 years old and 21 (45.7%) were>60 years old. Twelve patients (26.1%) were female, and 34 (73.9%) were male. The majority of cases (67.4%) had adenocarcinoma, followed by squamous cell carcinoma in 12 patients (26.1%) and large cell carcinoma in 3 patients (6.5%). Detailed clinicopathological characteristics of the patients are summarized in Table 1.

Higher Expression of *MIR141* in PBMCs of NSCLC Patients

The expression levels of *MIR141* in PBMCs of NSCLC patients were increased (4.124 [3.259–4.944]) compared with healthy controls (2.181 [1.036–2.946]; $p<0.0001$; Figure 1). A ROC curve analysis was applied to evaluate the potential of *MIR141* as a diagnostic marker for NSCLC.

ROC Curve Analysis of *MIR141* Level in the Prediction of NSCLC

The diagnostic performance of *MIR141* levels in PBMCs for NSCLC was evaluated using ROC curve analysis (Figure 2). Two cutoff values were considered: the exploratory threshold>0.260 was assessed for sensitivity, while the optimal cutoff >1.238, determined using Youden's index, provided the best balance between sensitivity (40.98%) and specificity (86.89%). AUC was 0.695 (95% CI, 0.603–0.787; $p=0.0002$), indicating a statistically significant result. The sensitivity and specificity of the optimal cutoff are summarized in Table 2 and illustrated in Figure 2.

Table 1. Clinical and pathological characteristics of non-small-cell lung cancer patients

Parameters	Lung cancer, n=46	n (%)
Age		
≤60	25	54.3%
>60	21	45.7%
Gender		
Female	12	26.1%
Male	34	73.9%
Histological subtype		
Adenocarcinoma	31	67.4%
Squamous cell carcinoma	12	26.1%
Large cell carcinoma	3	6.5%
Pathological differentiation		
Well to moderately differentiated	36	78.3%
Poorly differentiated	10	21.7%
Stage		
I or II	3	6.5%
III	9	19.6%
IV	34	73.9%
Smoking status		
Smoker	43	93.5%
Non-smoker	3	6.5%

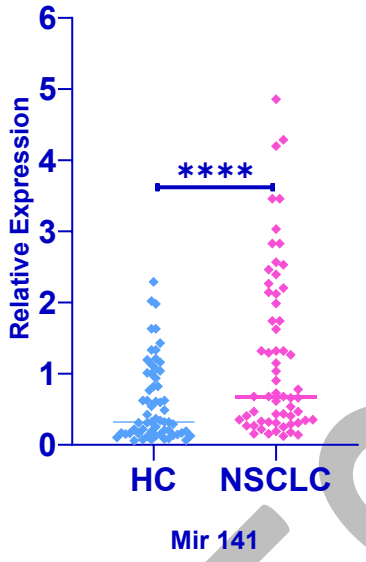

Figure 1. Expression of *MIR141* in peripheral blood mononuclear cells (PBMCs) of non-small-cell lung cancer (NSCLC) patients versus healthy controls. Box plots showing a significant upregulation of *MIR141* expression in PBMCs from NSCLC patients (n = 46) compared to age- and sex-matched healthy controls (n = 30). Data are represented as median with interquartile range. Statistical comparisons were performed using the Mann–Whitney *U* test; $p<0.0001$.

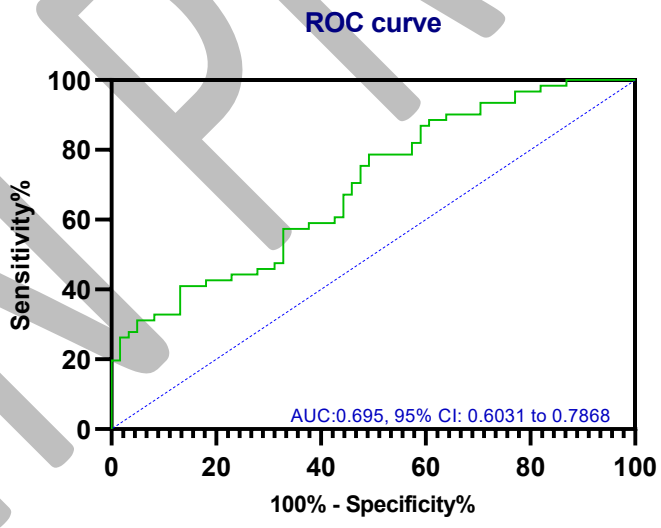

Figure 2. Receiver operating characteristic (ROC) curve of *MIR141* in peripheral blood mononuclear cells for non-small-cell lung cancer diagnosis. The area under the curve was 0.695 (95% CI, 0.603–0.787; $p=0.0002$), indicating a statistically significant result. Two cutoff values were considered: the exploratory threshold >0.260 (relative expression units) and the optimal cutoff>1.238 (relative expression units), determined using Youden's index, which yielded 40.98% sensitivity and 86.89% specificity.

Serum Levels of IL-6, IL-8, and CXCL10 in NSCLC Patients

Serum levels of IL-6, IL-8, and CXCL10 were significantly higher in NSCLC patients than in healthy controls (p<0.0001; Table 3; Figure 3).

Table 2. Receiver operating characteristic curve of peripheral blood mononuclear cells microRNA-141 level for risk of non-small-cell lung cancer

Cut-off value (relative expression units)	Sensitivity (%)	Specificity (%)	AUC (95% CI)	*p*
>0.260	84.43	41.96	0.695 (0.603–0.787)	0.0002
>1.238	40.98	86.89	0.695 (0.603–0.787)	0.0002

Two cutoff values for *MIR141* are presented. The value >0.260 (relative expression units) was evaluated as a lower exploratory threshold for sensitivity analysis, whereas >1.238 (relative expression units) was identified as the optimal cutoff based on Youden's index, providing the best balance between sensitivity (40.98%) and specificity (86.89%). The >1.238 value therefore represents the optimal diagnostic threshold. AUC: area under the curve; CI: confidence interval.

Table 3. Cytokine results in patients and control groups

Parameter	Patients (median [IQR])	Healthy controls (median [IQR])	*p*
IL-6, pg/mL	18.5 [10.2–35.6]	5.1 [3.0–7.8]	<0.0001
IL-8, pg/mL	42.0 [25.3–75.1]	6.8 [5.0–9.6]	<0.0001
CXCL10, pg/mL	95.0 [60.5–150.2]	6.0 [4.2–8.1]	<0.0001

Comparisons performed using the Mann-Whitney *U* test. CXCL: C-X-C motif chemokine ligand; IL: interleukin; IQR: interquartile range.

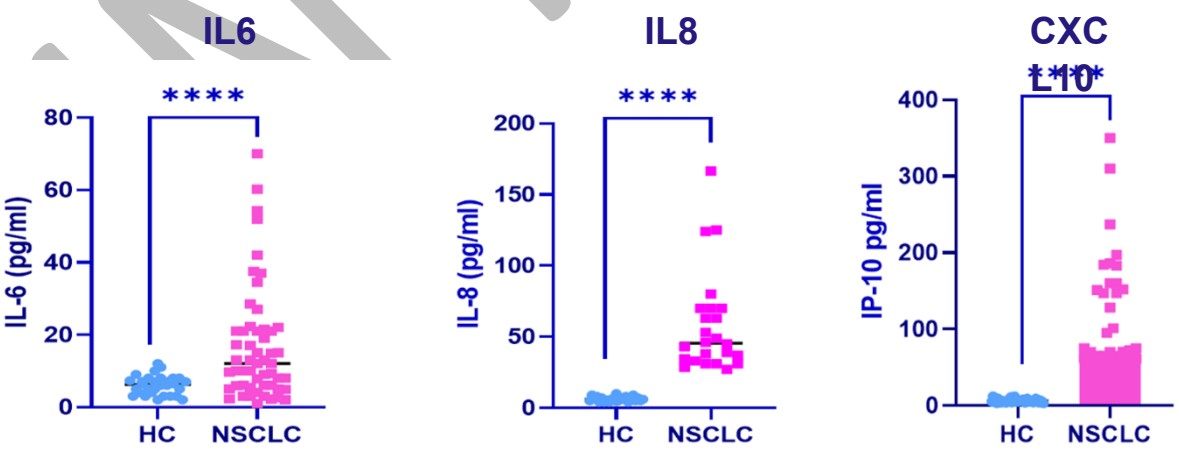

Figure 3. Serum cytokine levels of IL-6, IL-8, and CXCL10 in non-small-cell lung cancer (NSCLC) patients and healthy controls. Box plots showing significantly elevated serum cytokine levels in NSCLC patients (n=46) compared to healthy controls (n=30). Data are presented as median with interquartile range (IQR). Statistical comparisons were conducted using the Mann-Whitney *U* test; p<0.0001.

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DISCUSSION

In this study, we observed a significant overexpression of *MIR141* in PBMCs from 46 NSCLC patients compared to age- and sex-matched healthy controls. Additionally, serum levels of IL-6, IL-8, and CXCL10 were markedly elevated in NSCLC patients.

Our findings align with previous research, which indicates that *MIR141* expression is elevated in various cancers. For instance, a study demonstrated a 46-fold overexpression of *MIR141* in the serum of prostate cancer patients compared to healthy controls.[21] Similarly, elevated circulating *MIR141* levels have been identified as potential biomarkers for gall bladder cancer.[22] In the context of NSCLC, circulating *MIR141* has been proposed as a novel biomarker for diagnosis and prognosis, particularly in patients with lung adenocarcinoma.[13]

The role of *MIR141* in NSCLC has been further elucidated through its association with angiogenesis.[23] Overexpression of *MIR141* has been linked to increased secretion of vascular endothelial growth factor A (VEGF-A) through the downregulation of Krüppel-like factor 6 (*KLF6*), thereby promoting tumor angiogenesis.[24] Additionally, exosomal *MIR141* has been shown to enhance tumor angiogenesis by targeting *KLF12* in gastric cancer, suggesting a similar mechanism may be present in NSCLC.[23]

The significant elevation of IL-6, IL-8, and CXCL10 in our NSCLC cohort is consistent with their known roles in tumor progression and the inflammatory tumor microenvironment. IL-6 has been shown to promote epithelial-to-mesenchymal transition (EMT) and foster a tumor-promoting microenvironment.[25] IL-8 is associated with tumor invasiveness and metastasis through the upregulation of matrix metalloproteinases.[26] CXCL10 is critical in immune cell trafficking to inflammatory sites and has been proposed as an indicator of immune response.[27]

MIR141 modulates inflammatory responses indirectly by targeting upstream signaling molecules rather than directly binding to *IL6, IL8, or CXCL10* mRNAs. It influences cytokine levels, such as IL-6, by suppressing proinflammatory pathways, including the regulation of proteins like DAPK1 and HMGB1, and by affecting angiogenesis-related factors like VEGFA. While *MIR141* does not directly target these cytokines, its broader impact on inflammation and immune regulation plays a significant role in tumor progression.[28,29]

The integration of liquid biopsy techniques, such as the analysis of circulating microRNAs, offers a minimally invasive alternative to traditional tissue biopsies for cancer diagnosis and monitoring.[30] Liquid biopsies can detect cancer markers such as circulating tumor DNA or RNA, providing real-time insights into tumor dynamics.[31] In NSCLC, liquid biopsies have been utilized for early diagnosis, risk stratification, and monitoring of minimal residual disease.[32]

This study has several limitations. The relatively small sample size and the lack of multicenter validation and longitudinal follow-up limit the generalizability of the findings. Additionally, while *MIR141* expression was elevated in PBMCs from NSCLC patients, no direct analysis was performed on tumor tissue or exosomes, which could provide more specific insights into tumor origin and pathophysiology. Future research should include larger, multicenter cohorts, incorporate tumor tissue analysis, and utilize longitudinal follow-up to better validate *MIR141* as a potential liquid biopsy marker for NSCLC.

Our findings indicate that *MIR14*1 is overexpressed in PBMCs of NSCLC patients and is associated with increased serum levels of proinflammatory mediators. These results support the potential role of *MIR141* as a non-invasive biomarker for the diagnosis and monitoring of NSCLC, highlighting the promise of liquid biopsy approaches in clinical oncology.

STATEMENT OF ETHICS

This study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences, in collaboration with the Local Ethics Committee of Masih Daneshvari Hospital, Tehran, Iran (approval number: IR.SBMU.NRITLD.REC.1402.082). Written informed consent was obtained from all participants prior to enrollment.

The study protocol was reviewed and approved by the National Institutional Research Tuberculosis and lung disease (NRITLD) of 0f shahid Beheshti Medical University, Tehran, Iran.

FUNDING

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

Not applicable.

DATA AVAILABILITY

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request. Requests for access to the data can be made by contacting the corresponding author at the email address provided in this article.

AI ASSISTANCE DISCLOSURE

Artificial intelligence tools were used only for language editing. No artificial intelligence tools were used for data analysis or interpretation.

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