Nature and Science of Sleep

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

MiR-142-3p as an Indicator of OSA Severity Predicts Prognosis in Lung Adenocarcinoma with OSA

Ting Yang[1], Fang He[1], Mingxiang Zhang[2], Li Ai[1], Meng He[3], Xin Liu[3], Yongxia Li[1]

[1]Department of Respiratory, The Second Affiliated Hospital of Kunming Medical University, Yunnan, 650000, People's Republic of China; [2]Department of Cardiothoracic Surgery, Children's Hospital affiliated to Kunming Medical University, Yunnan, 650000, People's Republic of China; [3]Department of Thoracic Surgery, The Second Affiliated Hospital of Kunming Medical University, Yunnan, 650000, People's Republic of China

Correspondence: Yongxia Li, Department of Respiratory, The Second Affiliated Hospital of Kunming Medical University, Yunnan, 650000, People's Republic of China, Email liyongxia@kmmu.edu.cn

Nature and Science of Sleep downloaded from https://www.dovepress.com/
For personal use only.

Purpose: The aim was to explore the correlation between Obstructive sleep apnea (OSA) and Lung adenocarcinoma malignant prognosis and evaluate the miR-142-3p was used as an OSA severity indicator to predict the prognosis of Lung adenocarcinoma patients.

Methods: This study comprised of 21 diagnosed lung adenocarcinoma patients with or without OSA. The sleep-related variables and tumor pathology were recorded. Hypoxia-inducible factor-1α (HIF1α) and ki67 expression were analyzed by immunohistochemistry in tumor samples. Quantitative real-time polymerase chain reaction (qRT-PCR) was performed to assess the level of miR-142-3p.

Results: Lung adenocarcinoma with OSA showed higher apnea-hypopnea index (AHI), oxygen desaturation index (ODI), and the lower lowest pulse oxygen saturation (LS_PO_2) compared to Lung adenocarcinoma without OSA (P<0.05), and patients with severer OSA have an advanced TNM stage (P=0.004) and metastasis rate (p=0.032). In addition, OSA may down-regulate the miR-142-3p expression in patients with Lung adenocarcinoma, and the patients with low miR-142-3p expression exhibited severe OSA. MiR-142-3p levels significantly decreased in the advanced TNM stage (p=0.015), and the expression of miR-142-3p was negatively associated with AHI (r= −0.505, p=0.020), ODI (r= −0.513, p=0.017).

Conclusion: OSA severity may increase Lung adenocarcinoma malignant prognosis. OSA may down-regulate the expression of miR-42-3p. The expression of miR-142-3p was inversely correlated with AHI and ODI as a surrogate of OSA severity. Additionally, the low miR-142-3p expression level was significantly associated with advanced TNM stage in Lung adenocarcinoma patients.

Keywords: obstructive sleep apnea, lung adenocarcinoma, miR-142-3p, HIF1α, prognosis

Introduction

OSA is characterized by the collapse of the upper airway during sleep that results in recurrent oxyhemoglobin desaturation, and systemic inflammation leads to chronic intermittent hypoxia (IH), which can result in a complex series of pathophysiological changes,[1] such as the increased risk for hypertension,[2] coronary heart disease,[3] stroke,[4] as well as cognitive impairment[5] and even increased cancer incidence and mortality,[6] especially in lung cancer[7,8] and breast cancer.[9,10] As a marker of OSA, IH could be a vital factor in driving tumorigenesis and death.[1] Some clinical sleep parameters are linked with the mortality of lung cancer patients with OSA. Previous studies have investigated cancer-related mortality in patients with OSA, and there was a dose-response relationship between OSA severity as measured by AHI and percentage of time spent with oxygen saturation below 90%(CT90) and cancer mortality.[11] Severe OSA is associated with an increased risk of cancer mortality in III–IV stage lung cancer patients, and AHI was positively related to hypoxia-inducible factor 1(HIF1α).[7]

IH is a hallmark manifestation of OSA that could causally modify cancer-related biological processes to promote cancer malignant progression, mediated mainly by the activated HIFs.[12] The vital role of HIF1a in tumor malignant progression and chemoresistance is now well established.[13,14] Studies have demonstrated that hypoxia-repressed miR-142-3p by targets HIF1α, which provides therapeutic possibilities.[15] Accumulating evidence also has shown that miR-

Received: 16 August 2022
Accepted: 25 October 2022
Published: 9 November 2022

© 2022 Yang et al. This work is published and licensed by Dove Medical Press Limited. The full terms of this license are available at https://www.dovepress.com/terms.php and incorporate the Creative Commons Attribution – Non Commercial (unported, v3.0) License (http://creativecommons.org/licenses/by-nc/3.0/). By accessing the work you hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. For permission for commercial use of this work, please see paragraphs 4.2 and 5 of our Terms (https://www.dovepress.com/terms.php).

142-3p is downregulated in lung cancer.[16,17] Therefore, we suspect that miR-142-3p plays a critical role in OSA-related IH-induced lung cancer progression.

Most human studies to date have not yet explored the outcome of OSA in specific Lung adenocarcinoma sites. We analyzed the sleep parameters and characteristics of Lung adenocarcinoma patients with or without OSA to further evaluate the correlation between OSA and malignant tumor prognosis. Due to the biomarkers of OSA-related intermittent hypoxia not being fully evaluated, we assessed the correlation between the severity of OSA and the expression of miR-142-3p in Lung adenocarcinoma patients. In addition, we also analyzed the link between the miR-142-3p expression with cancer prognosis.

Materials and Methods

Study Population

Tumor and adjacent normal tissues from Lung adenocarcinoma patients who underwent surgery from January 2021 to September 2021 were collected from The Second Affiliated Hospital of Kunming Medical University. Inclusion criteria were as follows: (1) molecular biology and pathology certified the diagnosis of Lung adenocarcinoma. The tumor stage was evaluated according to the guidelines of the eighth edition American Joint Committee on Cancer (AJCC).[18] (2) Clinicopathological characteristics were collected after a median follow-up of nine months, the follow-up deadline was September 20, 2022. Due to the short-term follow-up, endpoint events were defined as recurrence, metastasis, or death during the follow-up period. (3) Patients were diagnosed with OSA by pre-or postoperative polysomnogram (PSG). With AHI ≥5 as a screening criterion for OSA, patients were divided into mild (5≤AHI<15), moderate (15≤AHI<30), and severe OSA (AHI≥30) according to the standard guideline.[19] Sleep parameters including the AHI, ODI, LS_PO_2, and CT90 were recorded. The study has been submitted for approval by the Ethics Committee of The Second Affiliated Hospital of Kunming Medical University (PJ-2021-65) and conducted in accordance with the Declaration of Helsinki.

Immunohistochemistry Staining

Lung adenocarcinoma tissues were dehydrated, embedded, sectioned, and baked, and slides were then counterstained with antigen retrieval; the sections were then blocked with 3% hydrogen peroxide and 5% goat serum (#SL038, Solarbio, China). Anti-HIF-1α antibody (#36169, 1:500, CST, USA) and anti-Ki67 antibody (#ab92742, 1:600, Abcam, UK) were incubated overnight at 4°C. Subsequently, the goat anti-rabbit antibody (#S0001, 1:5000, Affinity, USA) was incubated for 1 h at 37°C, followed by visualization with 3,3-diaminobenzidine. The stained slides were then examined and photographed using a microscope (BX43F, Olympus, Japan). The immunoreactivity of HIF1α and ki67 was categorized from negative (no staining), + (weak), ++ (moderate) and +++ (strong), and the percentage of staining was categorized as negative (≤ 5%), + (6–25%), ++ (26–50%), +++ (51–75%) and +++ (> 75%). The final score was determined by the intensity and percentage score, and the scoring was calculated by Image-Pro Plus 7.

Quantitative Real-Time Polymerase Chain Reaction (qRT-PCR)

MiRNA was isolated from tissues by RNAiso for small RNA (#9753A, Takara, Japan). The Mir-X miRNA First-Strand Synthesis Kit (#638315, Takara, Japan) was used for reverse transcription of miR-142-3p. According to the instructions for FastStart™ Universal SYBR® Green (#04913914001, Roche, Germany), amplification and quantification were performed on an ABI 7300/7500 system (Applied Biosystems). U6 was normalized to the reference genes for miR-142-3p. Data analysis was assessed to the $2^{-\Delta\Delta Ct}$ method. Primers are detailed in Table 1.

Statistical Analysis

Statistical calculations were performed using SPSS 23.0 software and GraphPad Prism 9.0. Between the two groups, the Mann–Whitney U (non-normal distribution) or Student's *t*-test (normal distribution) was used for comparing continuous data, the categorical data were compared using the chi-square test or Fisher exact test. The differences among multiple groups were identified with the One-way Analysis of Variance (ANOVA). The correlation analysis of parameters was performed using the Pearson test. P values < 0.05 were considered significant.

Table 1 Primers Used for qRT-PCR

Gene	Primer Sequence
U6	Forward: 5'- CTCGCTTCGGCAGCACA - 3'
	Reverse: 5'- AACGCTTCACGAATTTGCGT - 3'
MiR-142-3p	5'- GCGCGTGTAGTGTTTCCTACTTTATGG - 3'

Results

Sleep Parameters and Clinical Characteristics of Lung Adenocarcinoma Patient

A total of 21 Lung adenocarcinoma patients were included in the study, and the baseline characteristics of patients were classified into three groups according to OSA severity as measured by AHI, shown in Table 2. Due to the small number of participants with moderate and severe OSA, moderate-to-severe OSA patients were established as a group. The result showed that female Lung adenocarcinoma patients have a lower prevalence of OSA. The age, body mass index (BMI), and CT90 did not significantly differ among the three groups (P>0.05). There were significant differences in three groups regarding AHI (p= 0.000), ODI (p= 0.000), and LS_PO_2 (p= 0.042). As expected, lung adenocarcinoma patient with severe OSA have a higher TNM stage (P=0.004) and metastasis rate (p=0.032). MiR-142-3p levels were lower in Group Lung adenocarcinoma with OSA than that in Lung adenocarcinoma, and the moderate to severe OSA (AHI≥15) group was lower than the mild OSA (5≤AHI<15) (Table 2).

We examined the correlation between sleep parameters and pathological characteristics in Lung adenocarcinoma patients (Table S1). The patients with advanced tumor stage had more severe OSA as messured by AHI and ODI (Figure 1). However, no significant correlation was observed between LS_PO_2 and tumor stage.

Immunohistochemical analysis of HIF1α and ki67 expression was performed in Lung adenocarcinoma samples shown in Figure 2. High expression of HIF1α and ki67 was observed in Lung adenocarcinoma patients with OSA. However, there is no dose relationship with OSA severity.

The Level of miR-142-3p and Patient Characteristics

The qRT-PCR was performed to analyze the expression of miR-142-3p in 21 sets of Lung adenocarcinoma samples. Patients were divided into two groups according to the level of miR-142-3p (Median=0.530). No statistical differences

Table 2 Clinical Characteristics of Lung Adenocarcinoma Patients

Characteristics	AHI<5 (n=7)	5≤AHI<15 (n=6)	AHI≥15 (n=8)	P value
Sex, female (%)	7 (100.00)	3 (50.00)	2(22.22)	0.011
Age (years)	52.57±9.76	57.83±14.36	66.13±9.88	0.090
BMI (kg/m^2)	23.48±2.70	23.64±3.90	26.04±4.77	0.389
AHI (events/h)	1.36±0.73	10.58±2.02	29.96±12.68	0.000
ODI (events/h)	5.83±2.05	12.20±4.14	23.41±10.42	0.000
CT90 (%)	0.73±1.28	7.63±10.04	18.31±30.72	0.146
LS_PO_2(%)	82.57±4.35	72.17±9.64	74.38±7.41	0.042
TNM stage				0.004
I	5(71.42)	1(16.67)	1(12.50)	
II	2(28.57)	2(33.33)	0	
III-IV	0	3(50.00)	7(87.50)	
Metastasis				0.032
NO	7 (100)	3(50.00)	3(37.50)	
YES	0 (0.00)	3(50.00)	5(62.50)	
MiR-142-3p level	0.85±0.66	0.57±0.22	0.21±0.28	0.033

Abbreviations: BMI, body mass index; AHI, apnea–hypopnea index; ODI, oxygen desaturation index; CT90, percentage of time spent with oxygen saturation below 90%; LS_PO_2, the lowest pulse oxygen saturation.

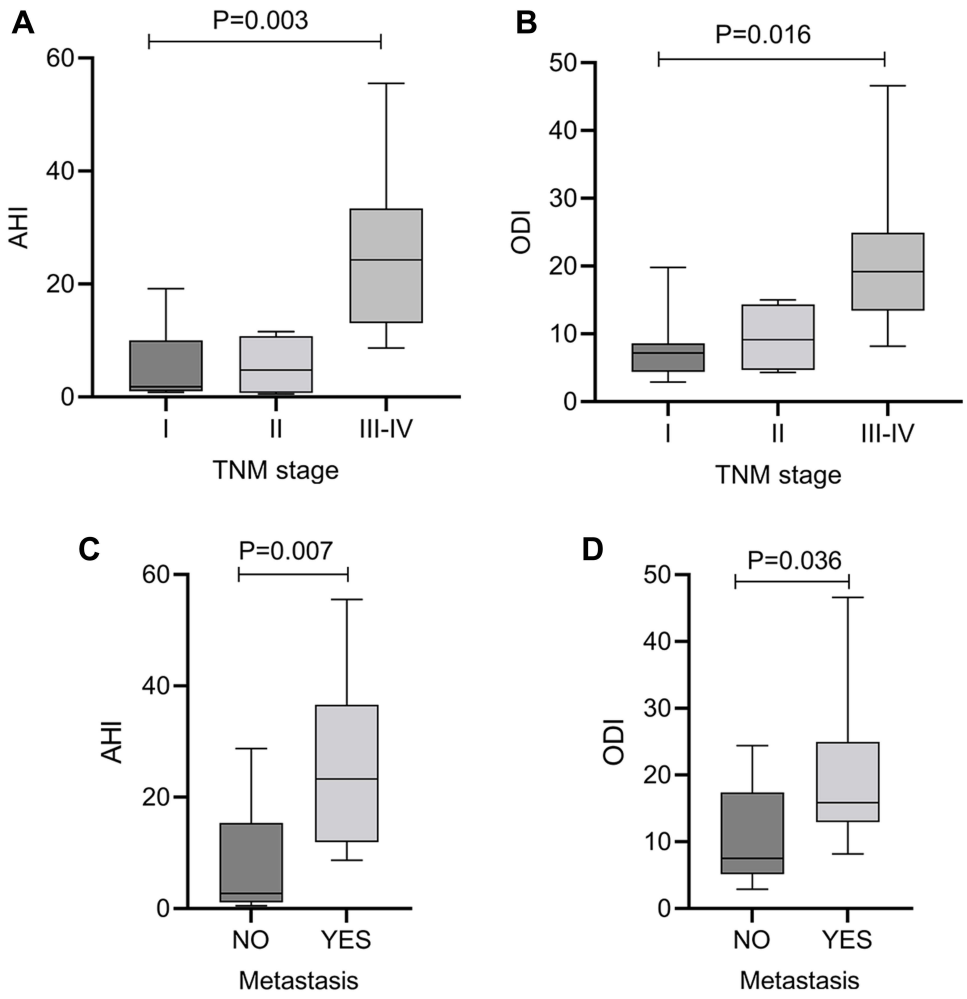

Figure 1 Correlation between sleep parameters and pathological characteristics. (**A-B**) Comparison of the OSA severity in the groups of lung adenocarcinoma patients and TNM stage. (**C-D**) Comparison of the OSA severity in the groups of lung adenocarcinoma patients, with and without metastases.
Abbreviations: AHI, apnea–hypopnea index; ODI, oxygen desaturation index.

were found in terms of gender, BMI, CT90, LS_PO_2 and metastasis rate between the two groups. While the patients with low miR-142-3p expression exhibited severe OSA, both AHI (7.35±6.36 VS 23.19±17.13, P= 0.018) and ODI (9.79 ±5.72 VS 19.36±11.82, P=0.027) were higher compared to another group. The patients with the low miR-142-3p expression group exhibited a higher TNM stage (P=0.012) (Table 3).

We further analyzed the correlation of miR-142-3p expression with pathological characteristics and sleep parameters (Tables S2 and S3). We discovered that the miR-142-3p expression level was significantly lower in the advanced TNM stage (Figure 3A), and there was a negatively correlated between miR-142-3p expression level with AHI (r= −0.505, p=0.020) and ODI (r= −0.513, p=0.017) (Figure 3B–C).

Discussion

Several studies are in favor of a link between the increasing severity of OSA and lung cancer incidence and mortality.[6,20,21] However, the association of the severity of OSA in specific Lung adenocarcinoma have not yet been fully elucidated. Firstly, lung adenocarcinoma patients were classified into three groups according to OSA severity as measured by AHI, and there was a significant difference in AHI, ODI, LS_PO_2, as well as TNM stage and Metastatic spreading. According to the analysis of the correlation between OSA values and lung cancer staging, AHI and ODI were significantly increased in advanced tumor stage, and as the severity of OSA worsens, it's poor prognosis, suggesting the OSA severity contributes to the tumor malignant prognosis. Similar results were reported by the Wisconsin Sleep Cohort

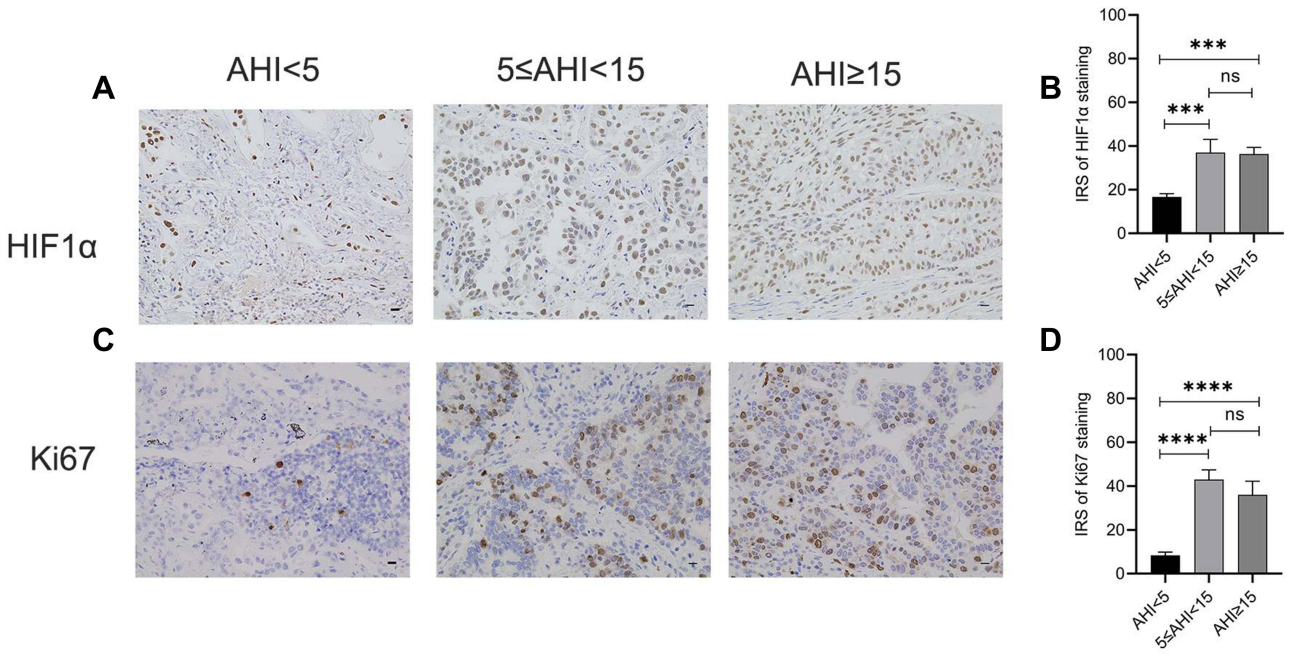

Figure 2 Immunohistochemistry pictures of HIF1α (**A** and **B**) and ki67(**C** and **D**) expression. Scale bars, 25um. Immunohistochemistry scores are shown (***P < 0.001, ****P< 0.0001, ns, P>0.05).

Abbreviations: IRS, immunoreactive score of Remmele and Stegner; AHI, apnea–hypopnea index.

and Spanish cohort study; OSA severity as measured by AHI is correlated to elevated malignant tumor neoplasms incidence and malignant mortality in a dose-response relationship.[22,23] A prospective cohort study also found that in lung cancer patients with stage III and IV, severe OSA was an independent predictor of cancer mortality, and higher AHI had increased overall cancer mortality.[7] A cross-sectional study validated that OSA increased the risk of colorectal cancer onset, and abnormal ODI value was associated to a higher lymph node metastasis.[24]

Several potential mechanisms implicated a relationship between OSA and lung cancer incidence and mortality. In particular, OSA-related IH exacerbates lung cancer proliferation, stem cell-like properties, epithelial-mesenchymal transition, and invasion.[25–28] It also has been elucidated the IH enhanced proliferative and migratory properties and

Table 3 Comparison of the Baseline Characteristics Between Groups with High and Low Expression of miR-142-3p

Characteristics	MiR-142-3p High	MiR-142-3p Low	P value
Sex, female (%)	7(63.6%)	5(50%)	0.670
Age (years)	51.28±9.99	68.00±7.63	0.000
BMI (kg/m^2)	23.64±3.54	25.45±4.32	0.307
AHI (events/h)	7.35±6.36	23.19±17.13	0.018
ODI (events/h)	9.79±5.72	19.36±11.82	0.027
CT90 (%)	2.30±3.15	17.21±27.95	0.067
LS_PO_2 (%)	78.73±6.34	74.00±9.70	0.198
TNM			0.012
I	6(54.55%)	1(10%)	
II	3(27.27%)	1(10%)	
III-IV	2(18.18%)	8(80%)	
Metastasis			0.080
NO	9(81.8%)	4(40%)	
YES	2(18.2%)	6(60%)	

Abbreviations: BMI, body mass index; AHI, apnea–hypopnea index; ODI, oxygen desaturation index; CT90, percentage of time spent with oxygen saturation below 90%; LS_PO_2, the lowest pulse oxygen saturation.

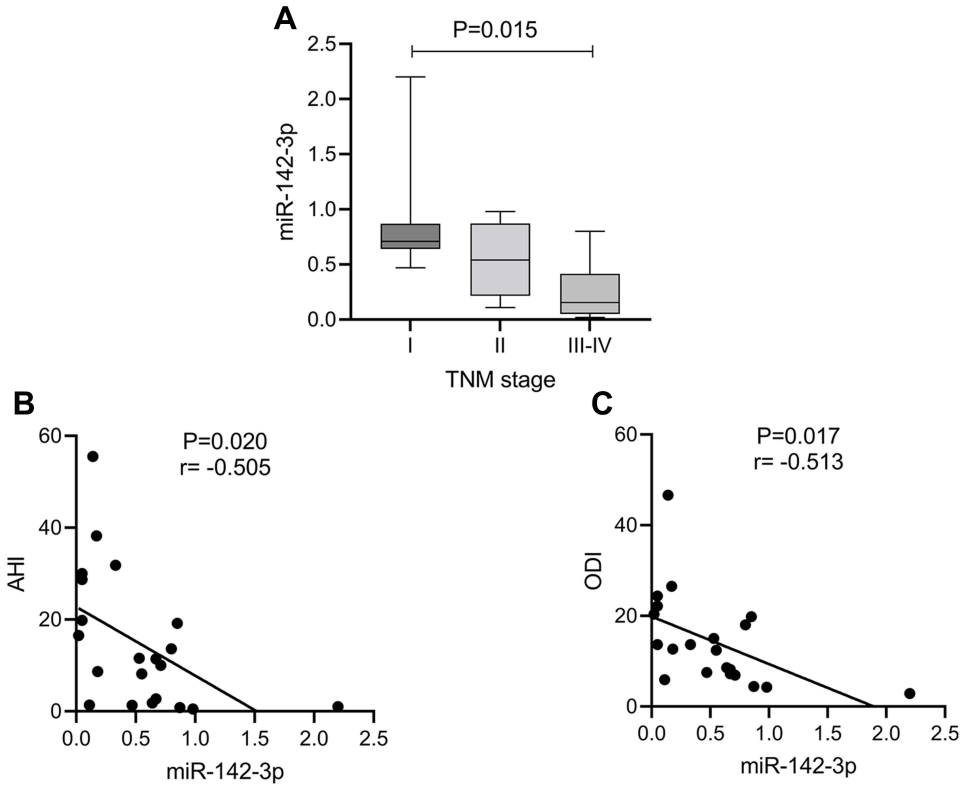

Figure 3 Relationship of miR-142-3p levels with pathological characteristics and sleep parameters. A There was a significant difference in miR-142-3p levels between TNM stage subgroups; B-C The level of miR-142-3p was inversely correlated with AHI and ODI (r, the Pearson correlation coefficient).

invasiveness of tumors in a mouse model of sleep apnea.[29,30] In response to hypoxia, cancer cells set off downstream genes by activating the HIF family, particularly HIF1α, which plays a crucial role in accelerating cancer progression.[31,32] Our findings confirmed that HIF1α was highly expressed in Lung adenocarcinoma patients with OSA but had no dose relationship with the AHI, which is inconsistent with reports that the expression of HIF1α was associated with the severity of OSA in lung cancer.[20] Due to the patients included in the cohort had more severe OSA (AHI >30, n=11, 59. ±20.8) comparing us (AHI >30, n=4, 38.9±11.6). The more severe the hypoxia, the higher the expression of HIF1α. We first found that Ki67 was highly expressed in lung adenocarcinoma with OSA compared with lung adenocarcinoma. This suggested that IH promotes tumor proliferation.

Emerging evidence suggests that hypoxia-repressed miR-142-3p targets HIF1α.[15,33] The function of miR-142-3p in inhibiting lung cancer progression, metastasis, invasion, and enhancing cell apoptosis has been validated.[16,17] However, no studies about the role of miR-142-3p in lung cancer with OSA that investigated the suppressive effects on intermittent hypoxia. Our study first demonstrated the downregulation of miR-142-3p in Lung adenocarcinoma patients with OSA compared to patients without OSA, and the patients with low miR-142-3p expression exhibited severe OSA. Second, the expression of miR-142-3p significantly decreased in the advanced TNM stage. Additionally, miR-142-3p expression was negatively correlated with AHI and ODI. Previous studies also have found that low miR-142-3p expression level was significantly associated with advanced FIGO stage, lymph node metastasis, and depth of cervical invasion and was also related to the advanced stage metastatic melanoma.[34,35] Based on these previous studies and our data, we proposed that miR-142-3p could be used as an OSA severity indicator to predict the prognosis of lung cancer patients, suggesting that miR-142-3p may be a novel therapeutic hypoxia target.

One of the limitations of this study is the short-term follow-up, and further long-term follow-up is needed to assess the cancer-related mortality to provide more conclusive evidence. Another limitation is that the sample size is too small, especially the sample of lung adenocarcinoma patients with moderate (15≤AHI<30) and severe (AHI≥30) OSA, we will conduct further research to confirm our hypothesis.

Conclusion

In this study, we demonstrated the correlation between OSA severity and malignant prognosis in lung adenocarcinoma patients. In addition, OSA may down-regulated the miR-142-3p expression in patients with Lung adenocarcinoma, and the expression of miR-142-3p was inversely correlated with AHI and ODI as a surrogate of OSA severity. Furthermore, low miR-142-3p expression level was significantly associated with the advanced TNM stage. The findings bring us to the attention that miR-142-3p may be an OSA severity indicator to predict the prognosis of lung cancer patients, implying that miR-142-3p is a potential hypoxia therapeutic target.

Ethics Statement

The study has been submitted for approval by the Ethics Committee of The Second Affiliated Hospital of Kunming Medical University (PJ-2021-65). All participating patients in the study have signed informed consent.

Funding

This work was supported by The Yunnan Science and Technology Planning Project (201901B070066).

Disclosure

The authors have no conflict of interest to declare for this work.

References

1. Hunyor I, Cook KM. Models of intermittent hypoxia and obstructive sleep apnea: molecular pathways and their contribution to cancer. *Am J Physiol Regul Integr Comp Physiol*. 2018;315(4):R669–r87. doi:10.1152/ajpregu.00036.2018
2. Torres G, Sánchez-de-la-Torre M, Barbé F. Relationship between OSA and hypertension. *Chest*. 2015;148(3):824–832. doi:10.1378/chest.15-0136
3. Gonzaga C, Bertolami A, Bertolami M, Amodeo C, Calhoun D. Obstructive sleep apnea, hypertension and cardiovascular diseases. *J Hum Hypertens*. 2015;29(12):705–712. doi:10.1038/jhh.2015.15
4. Lyons OD, Ryan CM. Sleep apnea and stroke. *Can J Cardiol*. 2015;31(7):918–927. doi:10.1016/j.cjca.2015.03.014
5. Kerner NA, Roose SP. Obstructive sleep apnea is linked to depression and cognitive impairment: evidence and potential mechanisms. *Am J Geriatr Psychiatry*. 2016;24(6):496–508. doi:10.1016/j.jagp.2016.01.134
6. Justeau G, Gervès-Pinquié C, Le Vaillant M, et al. Association between nocturnal hypoxemia and cancer incidence in patients investigated for OSA: data from a large multicenter French cohort. *Chest*. 2020;158(6):2610–2620. doi:10.1016/j.chest.2020.06.055
7. Huang HY, Lin SW, Chuang LP, et al. Severe OSA associated with higher risk of mortality in stage III and IV lung cancer. *J Clin Sleep Med*. 2020;16(7):1091–1098. doi:10.5664/jcsm.8432
8. Liu W, Zhou L, Zhao D, et al. Development and validation of a prognostic nomogram in lung cancer with obstructive sleep apnea syndrome. *Front Med*. 2022;9:810907. doi:10.3389/fmed.2022.810907
9. Yap DWT, Tan NKW, Tan BKJ, et al. The Association of obstructive sleep apnea with breast cancer incidence and mortality: a systematic review and meta-analysis. *J Breast Cancer*. 2022;2022:25.
10. Choi JH, Lee JY, Han KD, Lim YC, Cho JH. Association between obstructive sleep apnoea and breast cancer: the Korean national health insurance service data 2007–2014. *Sci Rep*. 2019;9(1):19044. doi:10.1038/s41598-019-55551-7
11. Nieto FJ, Peppard PE, Young T, Finn L, Hla KM, Farré R. Sleep-disordered breathing and cancer mortality: results from the Wisconsin sleep cohort study. *Am J Respir Crit Care Med*. 2012;186(2):190–194. doi:10.1164/rccm.201201-0130OC
12. Hao S, Li F, Jiang P, Gao J. Effect of chronic intermittent hypoxia-induced HIF-1α/ATAD2 expression on lung cancer stemness. *Cell Mol Biol Lett*. 2022;27(1):44. doi:10.1186/s11658-022-00345-5
13. de Heer EC, Jalving M, Harris AL. HIFs, angiogenesis, and metabolism: elusive enemies in breast cancer. *J Clin Invest*. 2020;130(10):5074–5087. doi:10.1172/JCI137552
14. Liu J, Gao L, Zhan N, et al. Hypoxia induced ferritin light chain (FTL) promoted epithelia mesenchymal transition and chemoresistance of glioma. *J Exp Clin Cancer Res*. 2020;39(1):137. doi:10.1186/s13046-020-01641-8
15. Saatci O, Kaymak A, Raza U, et al. Targeting lysyl oxidase (LOX) overcomes chemotherapy resistance in triple negative breast cancer. *Nat Commun*. 2020;11(1):2416. doi:10.1038/s41467-020-16199-4
16. Jin C, Xiao L, Zhou Z, Zhu Y, Tian G, Ren S. MiR-142-3p suppresses the proliferation, migration and invasion through inhibition of NR2F6 in lung adenocarcinoma. *Hum Cell*. 2019;32(4):437–446. doi:10.1007/s13577-019-00258-0
17. Liu J, Tian W, Zhang W, et al. MicroRNA-142-3p/MALAT1 inhibits lung cancer progression through repressing β-catenin expression. *Biomed Pharmacother*. 2019;114:108847. doi:10.1016/j.biopha.2019.108847
18. Rami-Porta R, Asamura H, Travis WD, Rusch VW. Lung cancer - major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin*. 2017;67(2):138–155. doi:10.3322/caac.21390
19. Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. *Chest*. 2014;146(5):1387–1394. doi:10.1378/chest.14-0970
20. Huang HY, Shih-Wei L, Chuang LP, et al. Severe obstructive sleep apnea associated with higher risk of mortality in stage III and IV lung cancer. *J Clin Sleep Med*. 2020;2020:1.

21. Cheng L, Guo H, Zhang Z, Yao Y, Yao Q. Obstructive sleep apnea and incidence of malignant tumors: a meta-analysis. *Sleep Med*. 2021;84:195–204. doi:10.1016/j.sleep.2021.05.029
22. Martínez-García M, Campos-Rodriguez F, Barbé F. Cancer and OSA: current evidence from human studies. *Chest*. 2016;150(2):451–463. doi:10.1016/j.chest.2016.04.029
23. Campos-Rodriguez F, Martinez-Garcia MA, Martinez M, et al. Association between obstructive sleep apnea and cancer incidence in a large multicenter Spanish cohort. *Am J Respir Crit Care Med*. 2013;187(1):99–105. doi:10.1164/rccm.201209-1671OC
24. Xiong H, Lao M, Zhang S, et al. A cross-sectional study of obstructive sleep apnea in patients with colorectal cancer. *J Gastrointest Oncol*. 2022;13 (2):683–694. doi:10.21037/jgo-22-175
25. Gu X, Zhang J, Shi Y, et al. ESM1/HIF-1α pathway modulates chronic intermittent hypoxia-induced non-small-cell lung cancer proliferation, stemness and epithelial-mesenchymal transition. *Oncol Rep*. 2021;45(3):1226–1234. doi:10.3892/or.2020.7913
26. Hao S, Zhu X, Liu Z, et al. Chronic intermittent hypoxia promoted lung cancer stem cell-like properties via enhancing Bach1 expression. *Respir Res*. 2021;22(1):58. doi:10.1186/s12931-021-01655-6
27. Chao Y, Shang J, Ji W. ALKBH5-m(6)A-FOXM1 signaling axis promotes proliferation and invasion of lung adenocarcinoma cells under intermittent hypoxia. *Biochem Biophys Res Commun*. 2020;521(2):499–506. doi:10.1016/j.bbrc.2019.10.145
28. Li W, Huang K, Wen F, et al. Intermittent hypoxia-induced downregulation of microRNA-320b promotes lung cancer tumorigenesis by increasing CDT1 via USP37. *Mol Ther Nucleic Acids*. 2021;24:528–541. doi:10.1016/j.omtn.2020.12.023
29. Kang HS, Kwon HY, Kim IK, et al. Intermittent hypoxia exacerbates tumor progression in a mouse model of lung cancer. *Sci Rep*. 2020;10 (1):1854. doi:10.1038/s41598-020-58906-7
30. Almendros I, Wang Y, Becker L, et al. Intermittent hypoxia-induced changes in tumor-associated macrophages and tumor malignancy in a mouse model of sleep apnea. *Am J Respir Crit Care Med*. 2014;189(5):593–601. doi:10.1164/rccm.201310-1830OC
31. Hou P, Shi P, Jiang T, et al. DKC1 enhances angiogenesis by promoting HIF-1α transcription and facilitates metastasis in colorectal cancer. *Br J Cancer*. 2020;122(5):668–679. doi:10.1038/s41416-019-0695-z
32. Jögi A, Ehinger A, Hartman L, Alkner S. Expression of HIF-1α is related to a poor prognosis and tamoxifen resistance in contralateral breast cancer. *PLoS One*. 2019;14(12):e0226150. doi:10.1371/journal.pone.0226150
33. Ou ZL, Zhang M, Ji LD, et al. Long noncoding RNA FEZF1-AS1 predicts poor prognosis and modulates pancreatic cancer cell proliferation and invasion through miR-142/HIF-1α and miR-133a/EGFR upon hypoxia/normoxia. *J Cell Physiol*. 2019;234:15407–15419. doi:10.1002/jcp.28188
34. Li M, Li BY, Xia H, Jiang LL. Expression of microRNA-142-3p in cervical cancer and its correlation with prognosis. *Eur Rev Med Pharmacol Sci*. 2017;21(10):2346–2350.
35. Tembe V, Schramm SJ, Stark MS, et al. MicroRNA and mRNA expression profiling in metastatic melanoma reveal associations with BRAF mutation and patient prognosis. *Pigment Cell Melanoma Res*. 2015;28(3):254–266. doi:10.1111/pcmr.12343

Nature and Science of Sleep Dovepress

Publish your work in this journal

Nature and Science of Sleep is an international, peer-reviewed, open access journal covering all aspects of sleep science and sleep medicine, including the neurophysiology and functions of sleep, the genetics of sleep, sleep and society, biological rhythms, dreaming, sleep disorders and therapy, and strategies to optimize healthy sleep. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

Submit your manuscript here: https://www.dovepress.com/nature-and-science-of-sleep-journal