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ORIGINAL ARTICLE

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An axis involving TPX2/hsa-let--7b-5p/TMPO-AS1 promotes lung adenocarcinoma in smokers

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Oncology in Clinical Practice
DOI: 10.5603/ocp.100751

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

Introduction. Lung cancer, a disease with the highest morbidity and mortality rates, is associated with smoking, which highlights the need for a better understanding of prognosis-related mRNA/miRNA/lncRNA-ceRNA networks.
Material and methods. To look at *TPX2*/miRNA and LncRNA expression in lung cancer tumors and healthy tissues, the study used such databases as UALCAN, OncoDB, ENCORI, KM Plotter, miRNet, and CancerMIRNome.
Results. In lung cancer cells, the *TPX2* gene is overexpressed and linked to lung squamous cell carcinoma. High *TPX2* expression is significantly associated with adenocarcinoma patients (HR = 1.88; CI 1.58–2.33; p = 2.8e–13) and those with a smoking history (HR = 1.71; CI 1.32–2.22; p = 4e–05). miRNA hsa-let-7b-5p negatively correlated with *TPX2* expression (–0.371), while lncRNA TMPO-AS1 positively correlated with the *TPX2* axis (0.659).
Conclusions. Smokers with lung adenocarcinoma have poorer prognosis due to elevated levels of TPX2 and TMPO--AS1 and low levels of miRNA hsa-let-7b-5p, possibly due to the formation of TMPO-AS1 sponges. These factors contribute to aggressive growth and poor prognosis. Targeting these factors and increasing miRNA hsa-let-7b-5p could potentially improve patient prognosis by inhibiting these factors and reducing aggressive cancer growth. Further research and clinical trials are needed to validate this targeted therapy.
Keywords: lung adenocarcinoma, *TPX2*, ceRNA network, prognosis, smoking

Oncol Clin Pract

Highlights

- Poor prognosis is associated with increased *TPX2* expression in lung adenocarcinoma and smoking.
- The ceRNA network reveals negative correlations between miRNA hsa-let-7b-5p and *TPX2* as well as positive associations between lncRNA TMPO-AS1 and *TPX2*.
- The combination of *TPX2*/hsa-let-7b-5p/TMPO-AS1 with lung adenocarcinoma and smoking holds promise as a prognostic biomarker.
- Lung adenocarcinoma (LUAD) cellular invasion, proliferation, metastasis, and epithelial-mesenchymal transition are associated with *TPX2* gene expression.

Introduction

The two most common subtypes of lung cancer are LUAD and lung squamous cell carcinoma (LUSC); both are the leading cause of cancer-related death. Previously, they were classified as non-small cell lung cancer (NSCLC) [1], but the evidence suggests they should be classified and treated as distinct cancers

Received: 18.05.2024 Accepted: 17.06.2024 Early publication: 10.07.2024

despite their similarities [2]. Non-small-cell lung cancer (NSCLC) accounts for 85% of all deaths worldwide [3] with LUAD representing 50–60% and LUSC 20–30% of all cases [4]. Personalized therapy in lung cancer has made significant progress, but a better understanding of clinical features of LUAD and LUSC is needed to improve treatment and prevention [5]. Lung adenocarcinoma accounts for 40% of all lung cancers and has distinct epidemiological, clinicopathological, and molecular properties [6]. Biomarkers for early detection, predicting high relapse and death rates, and target or immunological therapies are still insufficient.

Lung cancer ranks first among all The Cancer Genome Atlas (TCGA) cancers [7, 8]. Recent progress in genomics and transcriptomics has allowed us to look at the molecular and regulatory processes that cause lung cancer, helping us find new target molecules that can improve outcomes for lung cancer patients. High-throughput technologies have led to the discovery of new biomarkers, primarily for non-coding RNAs (ncRNAs) such as long ncRNAs (lncRNAs) and microRNAs (miRNAs) [9]. These ncRNAs play a crucial role in cell differentiation, cancer proliferation, and metastasis. Dysregulation of downstream tumor-suppressor genes or oncogenes controlled by aggressive miRNAs leads to cancer development when the miRNA arm-imbalance mechanism breaks [10].

TPX2, a protein involved in mitotic egg extracts, is crucial for the correct assembly of the mitotic spindle and in humans is located on chromosome 20q11.1 [11]. Overexpressed in various cancers, TPX2 is associated with poor prognosis [12–15]. Increased TPX2 expression improves proliferative, invasive, and migratory abilities in colorectal and cervical cancers [16, 17]. However, TPX2 downregulation in hepatocellular tumors could suppress these abilities via the PI3K/AKT/mTOR pathway [18]. The exact role of TPX2 in lung cancer development is unclear, and the molecular mechanisms behind its dysregulation remain vague despite extensive study. In this study, author examined the expression of *TPX2*, hsa-let-7b-5p (miRNA), and TMPO-AS1 (lncRNA) in lung adenocarcinoma and healthy tissue. The study elucidated cancer's regulatory mechanisms behind *TPX2* gene expression, highlighting the regulation of mRNA and ncRNAs, particularly hsa-let-7b-5p (miRNA) and TMPO-AS1 (lncRNA).

Material and methods

Expression analysis TPX2

The study utilized the UALCAN [19] and ENCORI [20] databases to analyze the expression of the TPX2 gene across TCGA cancers, comparing tumor and normal tissues in both LUAD and LUSC.

Survival analysis

The author of this article utilized the Kaplan-Meier (KM) plotter [21] for survival analysis of lung cancer datasets, focusing on the gene symbol *TPX2*, a key factor in the disease. The analysis included the histological subtypes adenocarcinoma and squamous cell carcinoma, as well as their associations with a history of smoking ("Gene symbol, Affy id: *TPX2*, 210052_s_at").

The study focused on competitive endogenous RNA (ceRNA) regulatory network analysis

The study used the ENCORI and miRNet [22] databases to analyze the miRNA/lncRNA network associated with *TPX2*. The ENCORI database verified the correlation between *TPX2* and miRNA and evaluated the correlations between miRNA and transcriptional factors. The author of this article evaluated the prognostic significance of *TPX2*-associated miRNA using the KM plotter. We used the Enrichr [23] and UALCAN databases to identify lncRNA associated with *TPX2* and validated the co-relation values using ENCORI.

Statistical analysis

The author of this article analyzed *TPX2* gene expression using t-tests and online database models to compare tumors and tissues. The author of this article examined the relationship between *TPX2* gene expression and prognosis. A log-rank test was used to compare survival rates, and the significance level was $p < 0.05$.

Results

The pan-cancer analysis highlights the prognostic significance of TPX2

The OncoMX database showed that *TPX2* was overexpressed in lung cancer with a fold change of 4.25, as listed in Table 1. More research using the UALCAN databases showed that *TPX2* was overexpressed in LUAD and LUSC, as shown in Figure 1A. Next, the author of this article analyzed the differential expression of *TPX2* in LUAD and LUSC using the UALCAN database. The results showed that *TPX2* was significantly overexpressed in both subtypes, LUAD and LUSC, with a fold change of 8.7 and 9.5, respectively, as shown in Figures 1B, C. Figure 2D, G shows a consistent pattern of overexpression using two different databases, OncoDB and ENCORI, in both LUAD and LUSC.

Prognostic significance of TPX2

The study then determined *TPX2*'s prognostic significance using the KM plotter database. Results showed that

Table 1 . *TPX2* gene expression in pan-cancer analysis

UniProtKB/ /SwissProt	Gene symbol	Log2 fold change	p-value	Adjusted p-value	Signifi-cant	Expression trend	TCGA study	Patient frequency	Source
Q9ULW0	*TPX2*	0.38	0.0175	0.0327	Yes	Up	Thyroid cancer	33	TCGA
		2.19	3.42E–34	1.83E–31	Yes	Up	Stomach cancer	24	
		2.12	1.96E–32	1.30E–30	Yes	Up	Liver cancer	29	
		3.83	3.20E–96	4.58E–93	Yes	Up	Uterine cancer	16	
		2.38	2.67E–20	3.83E–18	Yes	Up	Bladder cancer	13	
		1.73	1.79E–45	4.09E–43	Yes	Up	Head_and_neck cancer	36	
		4.25	1.33E–291	5.88E–288	Yes	Up	Lung cancer	78	
		2.4	1.31E–21	2.50E–18	Yes	Up	Esophageal cancer	7	
		1.87	2.60E–81	5.08E–79	Yes	Up	Colorectal cancer	45	
		1.48	2.61E–17	4.72E–16	Yes	Up	Prostate cancer	42	
		2.43	8.76E–86	6.87E–84	Yes	Up	Kidney cancer	82	
		3.55	3.01E–216	5.05E–213	Yes	Up	Breast cancer	97	

TCGA — The Cancer Genome Atlas

overexpression of *TPX2* was significantly associated with poor prognosis in lung cancer patients. The overall survival (OS) rate [hazard ratio (HR) = 1.79; confidence interval (CI) = 1.58–2.02; p < 1e–16] was 95.07 months in the low-expression cohort and 43.83 months in the high-expression cohort. Next, when the author of this article analyzed OS in LUAD patients (HR = 1.88; CI 1.58–2.23; p = 2.8e–13). The low-expression cohort had OS of 117.33 months and the high-expression cohort 48 months. It was suggested that *TPX2* overexpression was significantly associated with poor prognosis, but when we examined OS in LUSC patients, we found its expression is less significantly correlated with poor prognosis (HR = 1.19; CI = 0.96–1.48; p = 0.11), as shown in Figure 2A–C. However, overexpression of *TPX2* in LUAD patients with a history of smoking predicted significantly poorer survival (HR = 1.71; CI = 1.32–2.22; p = 4e–05), The low-expression cohort had OS of 116 months and the high-expression cohort 59 months, compared to patients with squamous cell carcinoma and a history of smoking (HR = 1.29; CI = 0.76–2.19; p = 0.35), among whom the low-expression cohort had OS of 93 months and the high-expression cohort 62 months, as shown in Figures 2D, E. Interestingly, the author of this article also checked *TPX2* expression with smoking status in males (HR = 1.7; CI = 1.02–2.4; p = 0.0025) and females (HR = 1.72; CI = 1.16–2.55; p = 0.0063), and the author of this article found that both sexes are significantly associated with poor prognosis, as shown in Figures 2F, G. These results suggest that *TPX2* is a poor prognostic marker for all LUAD patients who have a history of smoking.

Competitive endogenous RNA regulatory network

mRNA dysregulation of *TPX2*, linked to poor prognosis, tumor progression, and metastases, is influenced by microRNAs. A miRNA-mRNA network was created using the miRNet database to explore these microRNAs, and the study showed 12 miRNAs functioning in LUAD as shown in Figure 3A (*TPX2*, TMPO-AS1, hsa-let-7b-5p, hsa-mir-193b-3p, hsa-mir-26a-5p, hsa-mir-26b-5p, hsa-mir-335-5p, hsa-mir-34a-5p, hsa-mir-7-5p, hsa-mir-1-3p, hsa-mir-126-3p, hsa-mir-138-5p, hsa-mir-155-5p, hsa-mir-16-5p, hsa-mir-203a-3p, hsa-mir-20a-5p, and hsa-let-7g-5p). The miRNet topology, set to "concentric circle," was found to be most suitable for miRNA associated with the *TPX2*, with hsa-let-7b-5p being in proximity with TMPO-AS1. The study utilized the CancerMIRNome database and KM plotter to examine the usefulness of miRNA expression for prognostic purposes. We found that hsa-let-7b-5p is significantly under-expressed in lung cancer, and its downregulation is also associated with good survival, as shown in Figures 3B, C. Next, the author of this article also analyzed TMPO-AS1 using the UALCAN database and KM plotter. The work were explored how *TPX2*, hsa-let-7b-5p, and associated lncRNA interact with miRNA stability and regulation to determine their sponge effect. TMPO-AS1 was found to have consistent

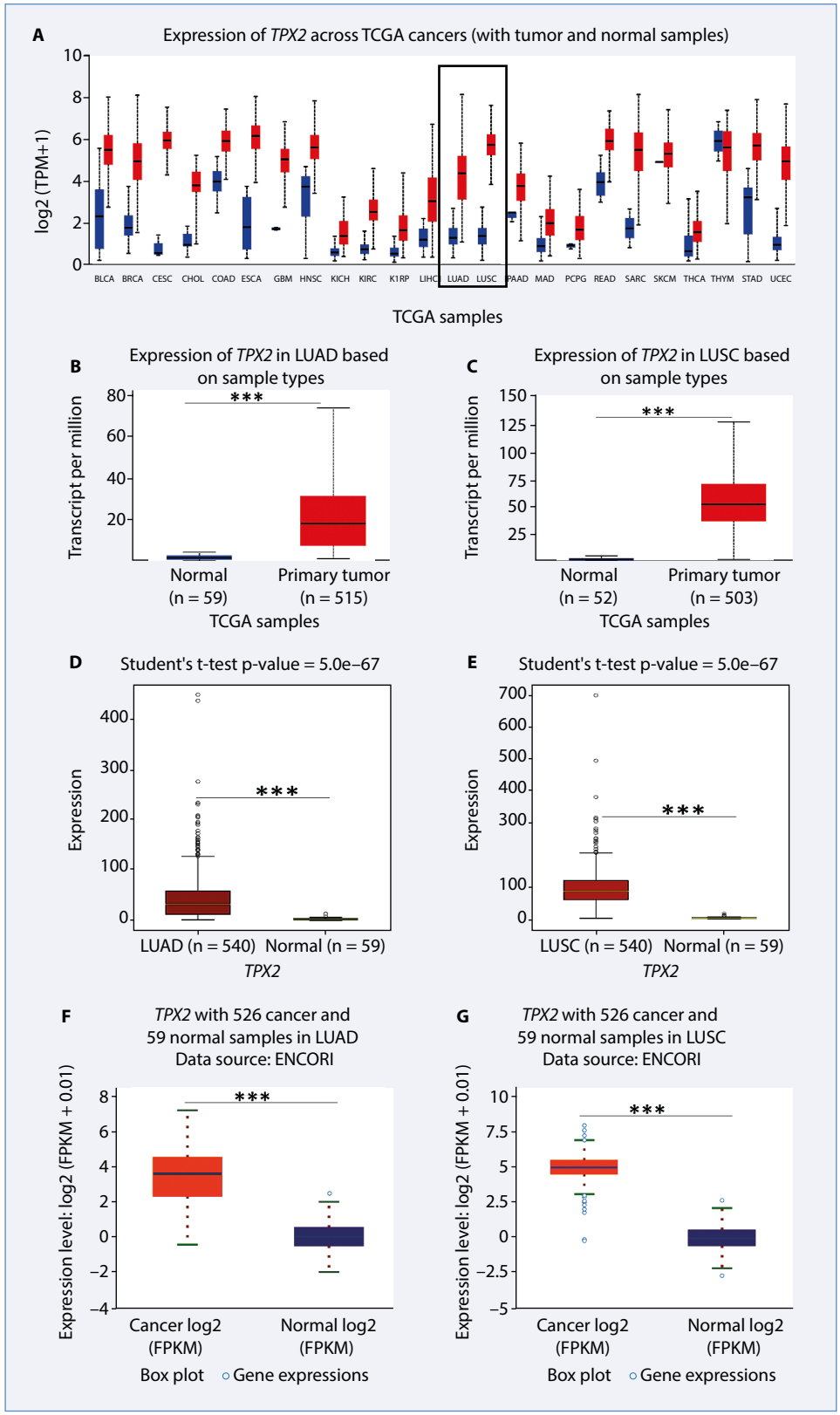

Figure 1. Expression pattern of *TPX2* across The Cancer Genome Atlas (TCGA) cancers; A. The UALCAN database determined the expression profile of *TPX2*, with red boxes indicating its expression level in cancer and blue boxes indicating its expression level in normal tissues. Differential expression of *TPX2* in lung cancer (**B**) lung adenocarcinoma (LUAD) (normal n = 59, tumor n = 515), (**C**) lung squamous cell carcinoma (LUSC) (normal n = 52, tumor n = 503), OncoDB (**D**) LUAD (normal n = 59, tumor n = 540), and (**E**) LUSC (normal n = 51, tumor n = 503), and ENCORI, LUAD (**F**) (normal n = 59, tumor n = 526), and (**G**) LUSC (normal n = 49, tumor n = 501)

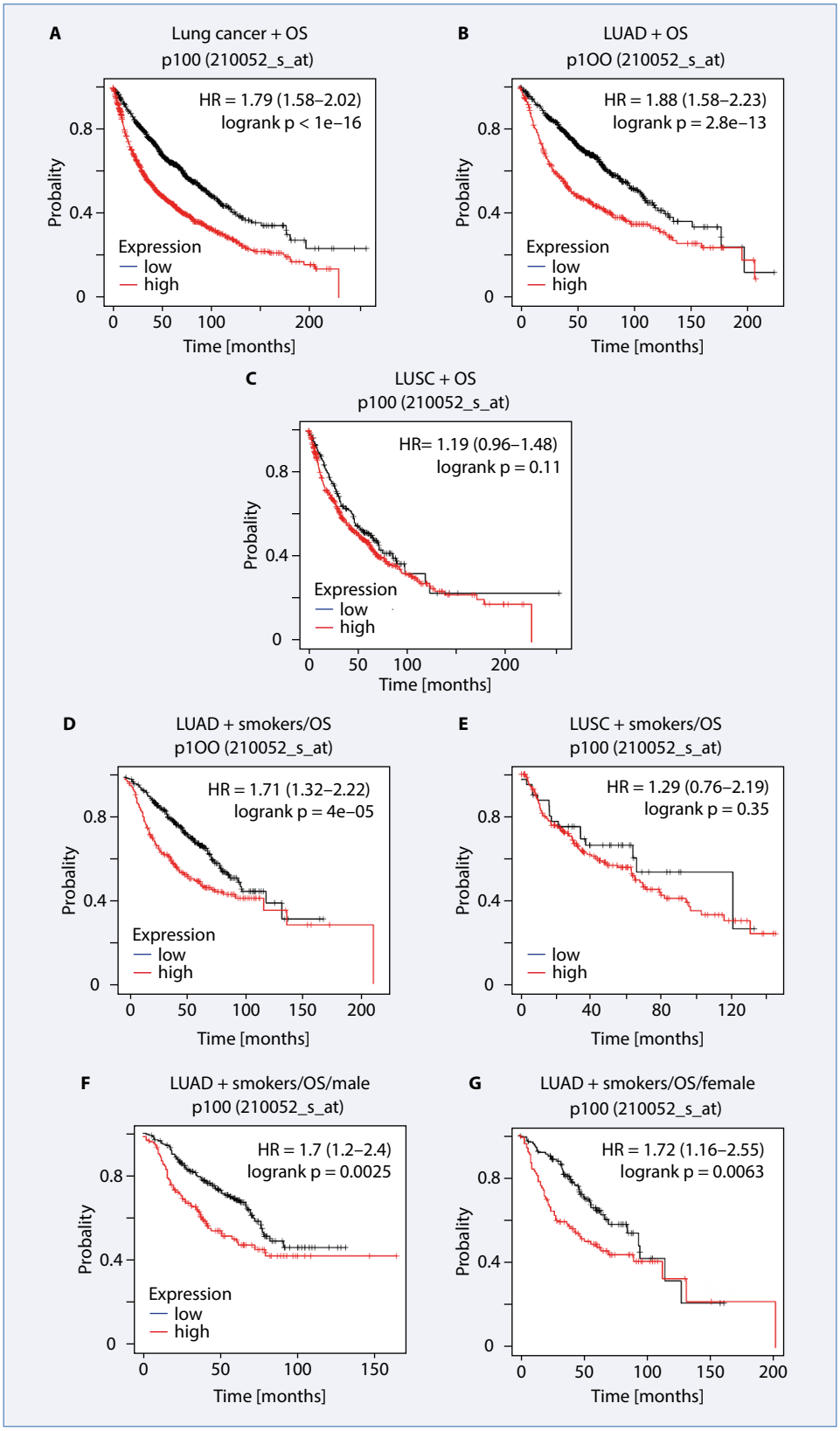

Figure 2. The study examined the prognostic role of mRNA expression of *TPX2* in lung cancer patients. The author of this article plotted Kaplan-Meier survival curves for (**A**) lung cancer with overall survival (OS) (n = 2166), (**B**) adenocarcinoma (LUAD) (n = 1161), (**C**) squamous cell carcinoma (LUSC) (n = 780), (**D**) adenocarcinoma + history of smoking (n = 546), and (**E**) squamous cell carcinoma + history of smoking (n = 244), (**F**) adenocarcinoma + history of smoking + male sex (n = 319), and (**G**) adenocarcinoma + history of smoking + female sex (n = 227)

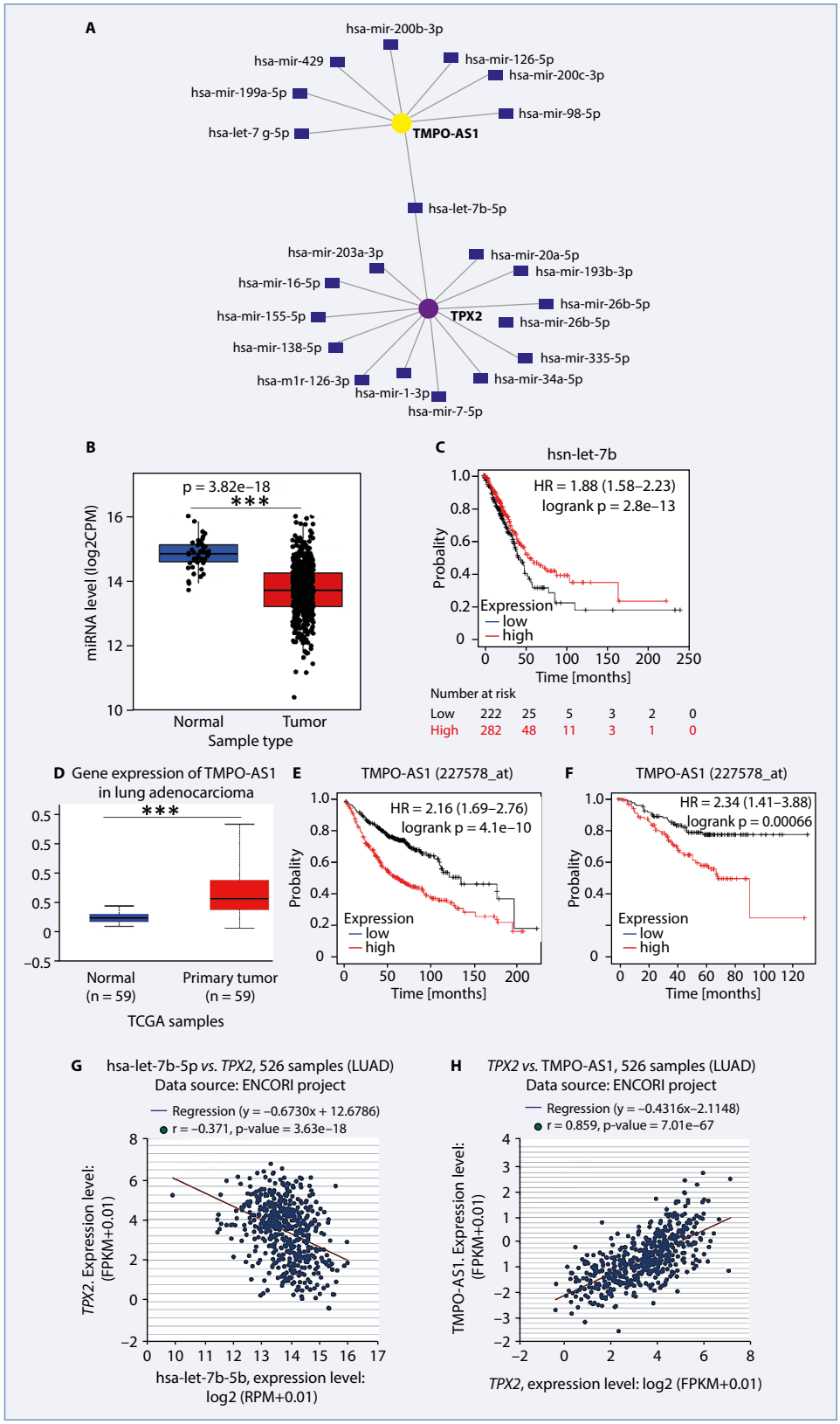

Figure 3. The study examined the correlation, expression, and survival status of miRNAs in tumor tissues from lung cancer patients using various databases. It conducted a network analysis between (**A**) *TPX2*, miRNAs (hsa-let-7b-5p) and TMPO-AS1, (**B**) analyzed the differential expression of hsa-let-7b-5p in lung adenocarcinoma patients using CancerMIRNome, (C) performed survival analysis using Kaplan Meier (KM) plotter, (D) analyzed the differential expression of TMPO-AS1 in lung adenocarcinoma patients using UALCAN, and (**E, F**) performed survival analysis using KM plotter for lung adenocarcinoma (LUAD) and history of smoking; HR — hazard ratio

overexpression in lung cancer, and the author of this article found a 9-fold change, as shown in Figure 3D. Surprisingly, we also found that TMPO-AS1 overexpression in LUAD patients predicted significantly poorer survival (HR = 2.16; CI = 1.69–2.7; p = 4.1e–10) compared to those with LUAD and smoking history (HR = 2.34; CI = 1.41–3.88; p = 0.00066), as shown in Figures 3E, F. Further, the author of this article correlated *TPX2*, TMPO-AS1, and hsa-let-7b-5p using the ENCORI database, and we found that TMPO-AS1 was positively correlated with *TPX2* in LUAD, while hsa-let-7b-5p was negatively correlated with *TPX2* in LUAD, as shown in Figures 3G–H. Based on the available data, we conclude that the TMPO-AS1/hsa-let-7b-5p/*TPX2* feedback loop may contribute to progression of lung adenocarcinoma in smokers.

Discussion

TPX2, a microtubule-associated protein, plays a crucial role in spindle apparatus assembly and DNA damage stress in various cancer tissues, including colon, esophagus, bladder, and liver cancer [24]. *TPX2* can upregulate the expression of the matrix metalloproteinases (*MMP*) family by activating the *PI3K/Akt* pathway in colon cancer, and inhibiting *TPX2* expression through downregulating *MMP*2 and *MMP*9 expression can inhibit liver cancer cell invasion [25]. A study found that *TPX2* expression was significantly higher in lung cancer tissue than in tumor-adjacent tissue, and downregulation can inhibit lung cancer cell proliferation, migration, and invasion [18, 25, 26]. *TPX2* is necessary for microtubule formation and regulates cell movement during important biological processes [27]. It has an oncogenic role in multiple malignancies, including gastric, colorectal, hepatocellular, and bladder cancers [28, 29]. A recent study suggested that *TPX2* may be a prognostic marker to stratify high-risk lung cancer patients. High expression of *TPX2* was significantly associated with poor overall survival in lung cancer patients with MYCN amplification [30]. Knockdown of *TPX2* suppressed proliferation and blocked cell cycle progression in lung cancer cell lines [25]. Targeting *TPX2* could potentially serve as a novel therapy for lung cancer, given the high incidence of lung cancer and poor treatment outcomes [31].

This study investigated the molecular mechanism behind *TPX2* dysregulation in lung adenocarcinoma as well as its potential use as a prognostic biomarker for lung cancer patients who have a history of smoking. Compared to LUAD, differential expression analysis of *TPX2* in both lung adenocarcinoma and lung squamous cell carcinoma suggested a close association between *TPX2* and lung squamous cell carcinoma. However, further survival analysis demonstrated a significant association between *TPX2* overexpression and poor prognosis in LUAD patients, particularly those with a history of smoking. We identified E2F1 as a potential transcriptional regulator of *TPX2*, elucidating its contribution to *TPX2* dysregulation in LUAD. The study also explored the role of microRNAs and long non-coding RNAs in regulating *TPX2* expression through the ceRNA network. Aggressive lung adenocarcinoma states, including invasion, proliferation, and metastasis, are associated with *TPX2* overexpression. This knowledge provides a better understanding of how to target *TPX2* in lung cancer treatments. The study analyzed the role of microRNAs and long non-coding RNAs in regulating *TPX2* expression through the ceRNA network. *TPX2* was associated with 12 miRNAs, with hsa-let-7b-5p being the key miRNA negatively correlated with *TPX2* expression. Downregulation of hsa-let-7b-5p was associated with a poor prognosis. The long noncoding RNA TMPO-AS1 had a positive relationship with *TPX2* expression and a negative relationship with hsa-let-7b-5p. This suggests that it may control *TPX2* expression in LUAD. This ceRNA network dysregulation was associated with adverse clinical outcomes, emphasizing its significance in lung adenocarcinoma and prognosis for smokers. Targeting *TPX2* in lung cancer treatments is crucial.

Conclusions

The study showed that lung cancer (LUAD) and smoking have poor prognosis due to increased *TPX2* expression, regulated by lncRNA TMPO-AS1 and negatively correlated with miRNA hsa-let-7b-5p. High miRNA hsa-let-7b-5p levels may lead to decreased *TPX2* expression, potentially improving prognosis in LUAD patients with a history of smoking. Molecular biology techniques such as RNA-protein binding assays and gene expression analysis could help understand this mechanism. Targeting miRNA hsa-let-7b-5p could potentially inhibit tumor growth and improve patient outcomes.

Article Information and Declarations

Data availability statement

The data that support the findings of this in silico analysis are available from the corresponding author upon request.

Ethics statement

This study did not require ethical approval.

Author contributions

R.N.: conception, study design, critical reading, intellectual assessment of the manuscript, and preparation of the manuscript.

Funding

R.N. would like to thank Manipal University Jaipur for the Enhanced Seed Grant under the Endowment Fund (No. E3/2023-24/QE-04-05).

Acknowledgments

R.N. would like to thank Manipal University Jaipur for the Enhanced Seed Grant under the Endowment Fund (No. E3/2023-24/QE-04-05).

Conflict of interest

The author declare that have no competing interests.

Supplementary material

None.

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