

Tumor-Educated Platelets IncRNA-STAR4-AS1 and ELOA-AS1 as Potential Novel Biomarkers for the Early Diagnosis of Non-Small Cell Lung Cancer

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Purpose: (Tumor-educated platelets) TEPs have emerged as active players in all steps of tumorigenesis, confrontation of platelets with tumor cells via transfer of tumor-associated biomolecules and results in the sequestration of such biomolecules. The current study was aimed to examine whether TEPs IncRNA-STAR4-AS1 and ELOA-AS1 might be potential biomarkers for NSCLC.

Materials and Methods: TEPs were obtained by low-speed centrifugation. Quantitative real-time PCR was used to determine the expression level of TEPs-STAR4-AS1, ELOA-AS1 in the training cohort and the validation cohort. ROC curve was generated to evaluate their diagnostic value. Correlations between TEPs-STAR4-AS1, ELOA-AS1 and clinical parameters were further analyzed.

Results: Our results showed that the level of TEPs-STAR4-AS1 and ELOA-AS1 significantly upregulated in patients with NSCLC compared with healthy controls in the two cohorts. By ROC analysis, we found that TEPs-STAR4-AS1, ELOA-AS1 could offer valuable diagnostic performance for NSCLC patients ($AUC_{STAR4-AS1} = 0.800/0.774$, and $AUC_{ELOA-AS1} = 0.754/0.718$ for diagnosing adenocarcinoma and squamous cell carcinoma cases from controls, respectively). The combination of TEP-STAR4-AS1 and ELOA-AS1 improved the diagnostic efficiency of NSCLC. Clinicopathological analysis further revealed that TEPs-STAR4-AS1 level significantly correlated with tumor-node-metastasis (TNM) stage ($p = 0.011$), while TEPs-ELOA-AS1 expression significantly correlated with tumor-node-metastasis (TNM) stage and ($p = 0.019$) distant metastasis ($p = 0.004$).

Conclusion: Our data suggested that TEPs-STAR4-AS1 and ELOA-AS1 are promising non-invasive circulating diagnostic markers for NSCLC.

Keywords: tumor-educated platelets, STAR4-AS1, ELOA-AS1, diagnosis, NSCLC

Introduction

Non-small cell lung cancer (NSCLC), mainly divided into adenocarcinoma (LUAD) and squamous cell carcinoma (SCC), accounts for more than 80% of all lung cancers,¹ has the highest incidence and ranks first in cancer-related mortality worldwide.² Despite significant progress has been made in the treatment of lung cancer in recent years, the 5-year survival rate for NSCLC patients is only 5–20%,^{3,4} mainly due to the lack of effective early diagnostic methods. At present, the gold standard for tumor diagnosis is still tissue biopsy and pathologic diagnosis, but it has limitations in the assessment of cancer development, genotyping and prognosis, due to tumor evolution and heterogeneity.⁵ And it has been found that many patients refuse to undergo puncture surgery, considering its invasive procedure. Therefore, there is an urgent need to discover sensitive, specific, especially noninvasive biomarkers for early detection of NSCLC. In recent years, many clinicians and scientists have tried to use blood-based liquid biopsies as a potential alternative diagnostic method for NSCLC.

Liquid biopsies, including tumor-educated blood platelets (TEPs), exosomes, circulating cell-free tumor DNA, and circulating tumor cells, might offer earlier and more convenient diagnosis for patients with cancer.^{6,7} Additionally, these techniques are less invasive and might provide a more comprehensive characterization for cancer.

Platelets, as a type of abundant blood cells, are circulating anucleated cell fragments that originate from megakaryocytes in bone marrow and are traditionally known for their role in hemostasis and initiation of wound healing.⁸ More recently, TEPs have emerged as active players in all steps of tumorigenesis including tumor growth, tumor cell extravasation, and metastasis, confrontation of platelets with tumor cells via transfer of tumor-associated biomolecules including RNA transcripts and proteins, as well as altering their spliced RNA profiles and results in the sequestration of such biomolecules.^{9,10} Additionally, it has been reported that biomolecules in TEPs might be more stable and could offer high sensitivity for the detection of cancer, while tumor-associated biomolecules released into the plasma are susceptible to degradation.¹¹ Therefore, TEPs have emerged as a promising source of biomarkers for liquid biopsy.^{12–14} Numerous studies have indicated that the transcriptomic and proteomic profile of platelets undergo alterations in response to the presence of cancer, emphasizing their potential utility as a biomarker for the diagnosis and prognosis of tumor.^{15–18}

Long non-coding RNA (LncRNA) is a group of RNA molecules with a transcript length of more than 200 nucleotides that widely exists in eukaryotic cells, but it does not encode protein itself. The mechanism of action of lncRNA is diverse, it regulates the expression level of genes through epigenetic regulation, splicing, imprinting, transcriptional regulation, and subcellular transport, and it plays important roles in tumorigenesis and tumor progression, virus replication, inflammatory injury, and other pathological processes.^{19,20} For example, Ji et al first discovered and reported MALAT1 in 2003, it is closely related to early metastasis and prognosis of lung adenocarcinoma,²¹ and acts as an inflammatory regulator, modulating the expression of inflammatory mediators such as TNF- α and IL-6 in endothelial cells;²² Yi Liao et al also found that lncRNAs such as MALAT1 and NEAT1 possess a high accuracy in the diagnosis of sepsis and the determination of 28-day mortality in patients with sepsis.²³ Yongdong Wang et al found that lncRNAs such as H19, APOA1-AS, IFNG-AS1, RMRP, and lnc-EGFR exhibit considerable sensitivity and specificity in diagnosing MS but also in forecasting its progression and assessing disease severity.²⁴ Additionally, Ping Lin et al showed that lncRNAs, especially lncRNA H19, FAM201A and HOTAIR, can induce cancer radio resistance by regulating cell death-related signaling pathways, which could be considered as a predictive therapeutic biomarker to evaluate radiotherapy response.²⁵ These data indicated that lncRNAs play important roles in cancer pathogenesis, which could provide new insight into the biology of this disease.

In the present study, 2 lncRNAs were selected based on $p < 0.0001$ and \log_2 (fold change) > 14.8 from the result of Illumina high-throughput RNA sequencing between 1 LUAD sample and 1 healthy sample. Next, we investigated the expression pattern and diagnostic value of 2 lncRNAs from platelets in patients with NSCLC to explore whether TEPs could enable NSCLC diagnostic and identify NSCLC types.

Materials and Methods

Illumina High-Throughput RNA Sequencing

One early-stage LUAD sample and 1 healthy sample were obtained from The People's Hospital of Guangxi Zhuang Autonomous Region. The samples were proceeded for Illumina high-throughput RNA sequencing in the company of Novogene. Upregulated lncRNAs (STARD4-AS1, ELOA-AS1) were selected based on $p < 0.001$ and \log_2 (fold change) > 14.8 .

Sample Collection and Platelet Isolation

Whole blood samples of NSCLC patients and healthy controls, which then were divided into the training cohort (20 LUAD, 15 SCC and 15 healthy controls) and the validation cohort (81 LUAD, 59 SCC and 45 healthy controls), obtained from The People's Hospital of Guangxi Zhuang Autonomous Region from 2022 to 2024. Platelets were isolated using low-speed centrifugation as previously described.^{9,10} Plasma samples were collected and then centrifuged for 20 min at 120 g to remove cells and debris. The platelet-rich plasma was centrifuged at 360 g for 20 min to pellet platelets, which then collected in 300 μ l DEPC and stored at -80°C . The study complied with the Declaration of Helsinki and was approved by the Ethics Committee of The People's Hospital of Guangxi Zhuang Autonomous Region (No: KY-KJT-2021-79 and KY-KJT-2022-100). Informed consent was obtained from all individual participants included in the study.

RT-qPCR for lncRNAs

RT-qPCR was determined on the Bio-Rad CFX96 (Bio-Rad Laboratories, Inc, Hercules, CA, USA) using TB Green Premix EX Taq™ Fast qPCR (CN830S, Takara, Japan) after platelets RNA was isolated using a Liquid Total RNA Isolation Kit (RP4002, BioTeke, China) and reverse transcribed to cDNA using PrimeScript™ Fast RT reagent Kit with gDNA Erase (RR092s, Takara, Japan). The GAPDH was used as the endogenous control and was amplified simultaneously with target genes. The synthesized RT-qPCR primers were listed in Table 1. The relative gene expression level was calculated using the comparative Ct (Cycle threshold) method formula $2^{-\Delta Ct}$, while CT value is the number of cycles when the fluorescence signal in each reaction tube reaches a set threshold and $\Delta Ct = CT_{\text{lncRNA}} - CT_{\text{GAPDH}}$.

Statistical Analysis

Statistical analyses were performed using SPSS version 23.0 (SPSS, Chicago, IL, USA) or Prism7 (GraphPad software, La Jolla, CA). The Shapiro–Wilk test was carried out to check the normality of the distribution. The non-normally distributed variable was analyzed by Mann–Whitney test. Chi-square test was used to analyze the categorical variables. Statistical differences were set at * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$. $p < 0.05$ was considered statistically significant. ROC curve analysis was used to estimate the diagnostic value of the lncRNAs.

Results

Establishment the Detection Method of TEPs-LncRNAs

A total of 1457 upregulated and 1004 downregulated lncRNAs were screened according to the result of Illumina high-throughput RNA sequencing, we finally selected upregulated lncRNA-STAR4-AS1, ELOA-AS1 based on $p < 0.001$ and \log_2 (fold change) > 14.8 (Figure 1A). Next, we evaluated the TEPs that isolated from the certain volume of plasma are suitable for the detection of STAR4-AS1 and ELOA-AS1, our data showed that the abundances of 2 lncRNAs were proportionally increased as the volume of collected plasma increased (Figure 1B). Finally, we found TEPs, which are isolated from 600 μL volume of plasma is enough for the detection. The amplification Curve (Figure 1C) of TEPs-LncRNAs isolated from 600 μL plasma showed that the 600 μL plasma is enough for TEPs isolation and 2 lncRNAs detection, the Melt Curve (Figure 1D) of 2 lncRNAs isolated from 600 μL volume showed that the specificity of Primer is also good.

Upregulated of NSCLC TEPs-LncRNAs in Two Different Cohorts

The training cohort consisted of small samples including 20 LUAD patients, 15 SCC patients and 15 healthy controls. We initially explored the expression level of TEPs-TARD4-AS1 and ELOA-AS1 in the training cohort after the detection method establishment. As shown in Figure 2A and B, compared with healthy controls, TEPs-STAR4-AS1 and ELOA-AS1 notably upregulated in both LUAD and SCC patients. In order to confirm the expression level of 2 lncRNAs, we collected more samples including 81 LUAD patients, 59 SCC patients and 45 healthy controls as the validation cohort considering the small samples in the training cohort. In our validation cohort, the data show that the expression of 2 lncRNAs was highly consistent with the data of the training cohort (Figure 2C and D), which indicated the potential of TEPs-STAR4-AS1 and ELOA-AS1 as non-invasive circulating diagnostic markers for NSCLC.

Table 1 Primers Used for RT-qPCR

Primer Name	Sequence (5'-3')
STAR4-AS1-F	GCACAAGAACTCAGGCCAA
STAR4-AS1-R	GCGGCGGATCAGTAGTCAC
ELOA-AS1-F	TCAGCATTCTCCTCGACAAGTG
ELOA-AS1-R	GTTTCCCATCCAACCAGACGA
GAPDH-F	GGAGTCCACTGGCGTCTTCA
GAPDH-R	GTCATGAGTCCTCCACGATACC

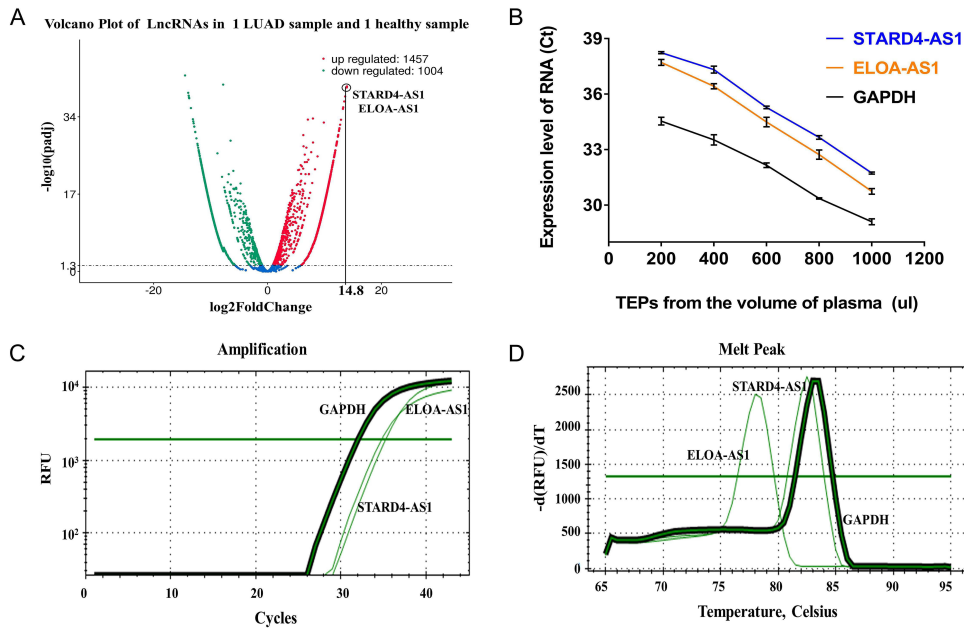


Figure 1 (A) Volcano plots compared the expression fold-change of lncRNAs in LUAD and Healthy control. (B) The CT value of lncRNAs in TEPs isolated from different volume of plasma. (C) The amplification Curve of 2 lncRNAs isolated from 600μL volume. (D) The Melt Curve of 2 lncRNAs isolated from 600 μL volume.

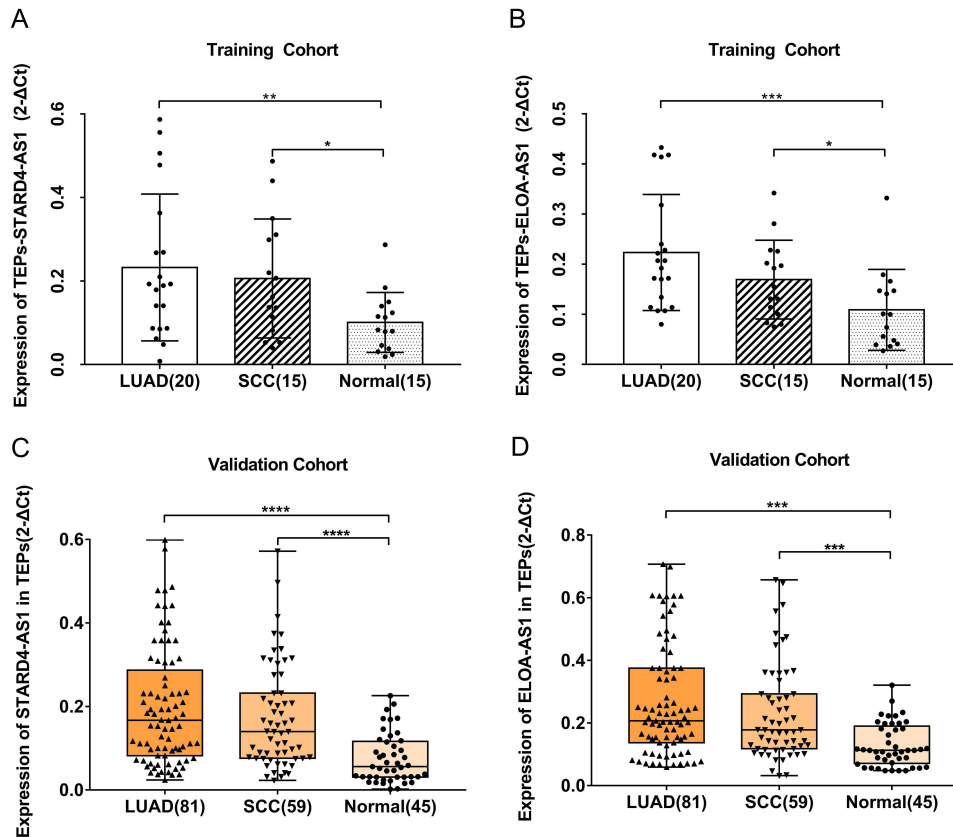


Figure 2 TEPs-STARD4-AS1 and ELOA-AS1 level was upregulated in NSCLC (A) TEPs-STARD4-AS1 was upregulated in LUAD (***) and SCC (*) in the training cohort. (B) TEPs-ELOA-AS1 was upregulated in LUAD (***) and SCC (*) in the training cohort. (C) TEPs-STARD4-AS1 was upregulated in LUAD (****) and SCC (****) in the validation cohort. (D) TEPs- ELOA-AS1 was upregulated in LUAD (****) and SCC (****) in the validation cohort. *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001.

Diagnostic Value of TEPs-LncRNAs Analysis in NSCLC

ROC curve analysis was used to evaluate the diagnosis value of TEPs-lncRNAs for NSCLC. ROC was constructed 3 models just using the data of validation cohort: LUAD vs controls, SCC vs controls, NSCLC vs controls. The AUC of TEP-STAR4-AS1 was 0.800 with 72.8% sensitivity and 71.1% specificity in LUAD, 0.774 with 89.8% sensitivity and 51.1% specificity in SCC, 0.789 with 70.1% sensitivity and 71.1% specificity in NSCLC (Figure 3A). The AUC of TEP-ELOA-AS1 was 0.754 with 77.8% sensitivity and 64.4% specificity in LUAD, 0.718 with 72.8% sensitivity and 64.3% specificity in SCC, 0.739 with 75.7% sensitivity and 64.5% specificity in NSCLC (Figure 3B). ROC curves revealed that the TEP-STAR4-AS1 and ELOA-AS1 expression was both able to discriminate NSCLC patients from healthy controls; however, TEP-STAR4-AS1 showed better AUC, moderate sensitivity and specificity. Next, we proceed a combined diagnosis of the 2 lncRNAs, 0.869 with 65.4% sensitivity and 95.6% specificity in LUAD, 0.825 with 78.0% sensitivity and 75.5% specificity in SCC, 0.851 with 60.7% sensitivity and 95.6% specificity in NSCLC (Figure 3C), the combined diagnosis for NSCLC show better AUC than that for STAR4-AS1 and ELOA-AS1 alone though the sensitivity was lower. More importantly, the combination of 2 lncRNAs improved the specificity to 95.6%, which provided compelling evidences that combination of 2 lncRNAs acted as relatively high diagnostic value for NSCLC. All AUCs are shown in Table 2.

Correlation Between the Expression Level of TEPs-LncRNAs and Clinical Parameters of NSCLC

According to the median value of relative TEPs-lncRNAs expression in the validation cohort, 140 NSCLC patients were correspondently classified into two groups; relative high group: expression ratio \geq median, relative low group: expression ratio $<$ median. As presented in Table 3 and Figure 3D–F, the result show that the TEPs-STAR4-AS1 expression significantly correlated with tumor-node-metastasis (TNM) stage ($p = 0.011$), the TEPs-ELOA-AS1 expression significantly correlated with tumor-node-metastasis (TNM) stage ($p = 0.019$) and distant metastasis ($p = 0.004$), while there were no significant correlations between TEP lncRNAs and other parameters.

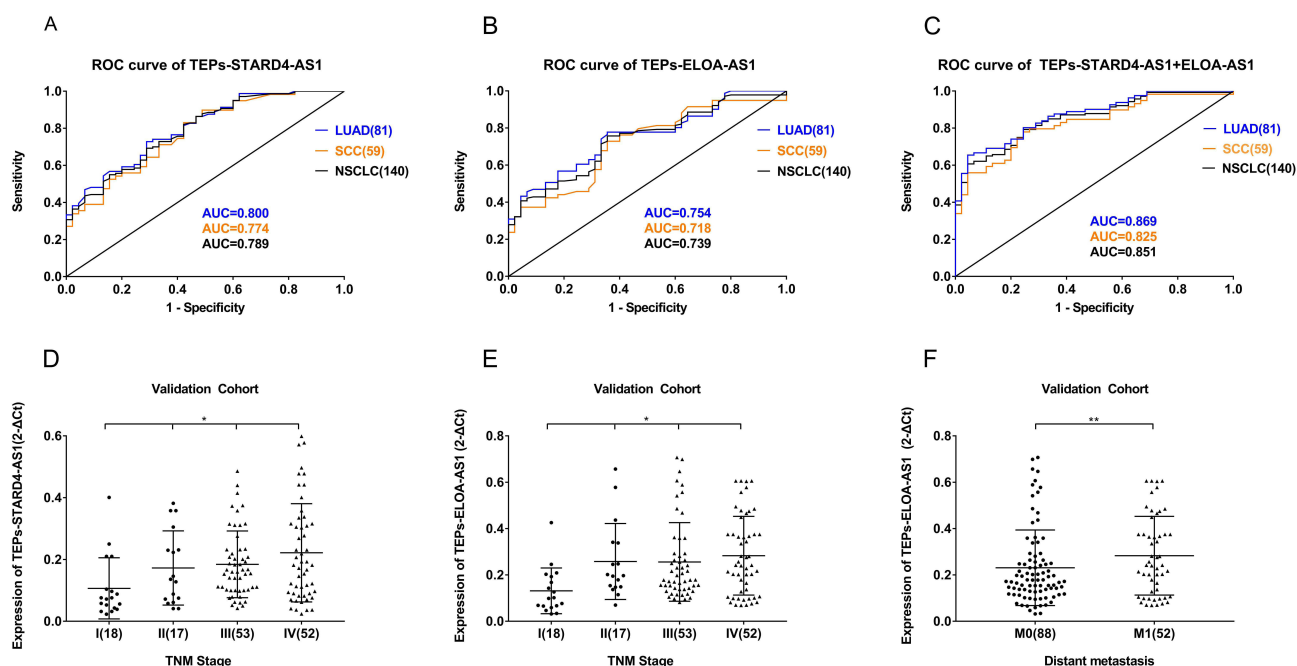


Figure 3 Diagnostic value of 2 lncRNAs in LUAD and SCC (A) The ROC curve of TEPs-STAR4-AS1 with LUAD (AUC = 0.800) and SCC (AUC = 0.774). (B) The ROC curve of TEPs-ELOA-AS1 with LUAD (AUC = 0.754) and SCC (AUC = 0.718). (C) The ROC curve of combination 2 lncRNAs with LUAD (AUC = 0.869) and SCC (AUC = 0.825). (D) Relative expression level of TEPs-STAR4-AS1 in T1–T4 stages (*). (E) Relative expression level of TEPs-ELOA-AS1 in T1–T4 stages (*). (F) Relative expression level of TEPs-ELOA-AS1 in M0 and M1 stages (**). * $p < 0.05$, ** $p < 0.01$.

Table 2 AUC of TEPs-STARD4-ASI and ELOA-ASI in All Subgroups

Group	LUAD					SCC					NSCLC				
	AUC	95% CI	P	Se (%)	Sp (%)	AUC	95% CI	P	Se (%)	Sp (%)	AUC	95% CI	P	Se (%)	Sp (%)
TEPs-STARD4-ASI	0.800	0.723–0.877	<0.0001	72.8	71.1	0.774	0.686–0.863	<0.0001	89.8	51.1	0.789	0.717–0.862	<0.0001	70.1	71.1
TEPs-ELOA-ASI	0.754	0.671–0.837	<0.0001	77.8	64.4	0.718	0.620–0.816	<0.0001	72.8	64.3	0.739	0.662–0.815	<0.0001	75.7	64.5
TEPs-STARD4-AS+ELOA-ASI	0.869	0.809–0.929	<0.0001	65.4	95.6	0.825	0.747–0.903	<0.0001	78.0	75.5	0.851	0.795–0.908	<0.0001	60.7	95.6

Table 3 Correlation Between TEPs-lncRNAs Level and Clinical Parameters of NSCLC

	Group	N	TEPs- STARD4-ASI		P	TEPs- ELOA-ASI		P
			Low	High		Low	High	
Histology	AD	81	39	42	0.608	35	46	0.137
	SCC	59	31	28		33	26	
Age	<60	57	26	31	0.390	23	34	0.107
	≥60	83	44	39		45	38	
Gender	Male	105	56	49	0.172	48	57	0.241
	Female	35	14	21		20	15	
Smoking	Negative	77	39	38	0.865	42	35	0.118
	Positive	63	31	32		26	37	
TNM stage	I-II	35	24	11	0.011*	23	12	0.019*
	III-IV	105	46	59		45	60	
Invasion	T1-T3	87	47	40	0.223	43	45	0.845
	T4	53	23	30		25	28	
Lymph-node metastasis	NO	54	31	23	0.165	27	27	0.789
	N1-N3	86	39	47		41	45	
Distant metastasis	MO	88	48	40	0.162	51	37	0.004**
	MI	52	22	30		17	35	

Note: * $p < 0.05$, ** $p < 0.01$.

Discussion

Over the past decade, systematic empirical research specific on NSCLC have identified several biomarkers and prognostic factors.²⁶ However, the prognosis of NSCLC remains quite poor and the 5-year survival rate for NSCLC patients is still low, since most of the patients are diagnosed at a late stage of the disease. Recently, TEPs, as a promising source of biomarkers for liquid biopsy, is progressively proving a pivotal tool for screening and early detection of cancer.²⁷⁻²⁹

LncRNAs are a heterogeneous group of noncoding transcripts widely found in body fluids including TEPs. In recent years, aberrant TEPs lncRNA expression has been found to participate in NSCLC development and metastasis. For example, Xiaohan Dong et al found that downregulated TEPs SNORD55 possessed an AUC of 0.803 for NSCLC and an AUC of 0.803 for early NSCLC, they validated that it had the ability of acting as a promising biomarker for NSCLC.³⁰ Additionally, Xinyi Li et al found that downregulated TEP linc-GTF2H2-1, RP3-466P17.2 and upregulated lnc-ST8SIA4-12 in patients with lung cancer possessed AUCs of 0.781, 0.788, 0.725, which suggested that lncRNAs sequestered in TEPs enabled blood-based lung cancer diagnosis and progression prediction.³¹ However, there is few rearches on STARD4-ASI or ELOA-ASI in NSCLC.

In this study, we examined the potential of TEPs-STARD4-ASI and ELOA-ASI might as non-invasive circulating diagnostic markers for NSCLC. Firstly, upregulated lncRNA-STARD4-ASI and ELOA-ASI were selected based on log₂ (fold change) >14.8 according to the result of Illumina high-throughput RNA sequencing. Meanwhile, we found TEPs, which isolated from 600 μL volume of plasma, are enough for the detection of 2 lncRNAs; this suggests that only 2 mL of blood is needed for each patient and greatly facilitating clinical blood collection. Next, we explored the expression level of 2 lncRNAs in the training cohort and confirmed it in the validation cohort after the detection method establishment. The results show that TEPs-TARD4-ASI and ELOA-ASI were upregulated in the two cohorts, which is consistent with the data of Illumina high-throughput RNA sequencing. For STARD4-ASI, there are reports suggesting its upregulation might regulate the process of ferroptosis and could be used as a novel biomarker of oral squamous cell carcinoma,^{32,33} but the research in TEPs from NSCLC is rarely reported just like ELOA-ASI. It is the first time that TEPs-STARD4-ASI and ELOA-ASI were found to upregulate in NSCLC. We then evaluate the diagnosis value of 2 lncRNAs, we found they could offer valuable diagnostics information for NSCLC, both TEPs-STARD4-ASI (AUC 0.800 in LUAD and AUC 0.774 in SCC) and TEPs-STARD4-ASI (AUC 0.754 in LUAD and AUC 0.718 in SCC). Of

course, combination of 2 lncRNAs possessed a better ability to discriminate between NSCLC and controls (AUC 0.869 in LUAD and AUC 0.825 in SCC). More importantly, the combination of 2 lncRNAs improved the specificity to 95.6%, which indicated the potential as non-invasive circulating diagnostic markers for NSCLC. We also analyzed the correlation between the 2 lncRNAs level and the clinicopathological characteristics of the 140 NSCLC patients in the validation cohort, we found that the expression level of TEPs-STAR4-AS1 was positively correlated with TNM stage, while TEPs-ELOA-AS1 expression significantly correlated with TNM stage and distant metastasis, this might suggest they play a role similar to oncogene in the development and malignancy of NSCLC.

Despite the role of STAR4-AS1 and ELOA-AS1, we found in TEPs from NSCLC, and few studies have previously discussed. Nevertheless, there are several limitations in the present study, which should be carefully considered. First, our research included 175 NSCLC patients, and the total sample size was relatively small. Second, most of the subjects included in the study recruit in one hospital and are local residents, which may affect the accuracy of the conclusion. A previous study has already highlighted that differences in RNA expression in LUAD across races and differences in protein expression across race,³⁴ which demonstrated that enough research subjects from different district, country or race would provide compelling result. Last, we did not proceed ROC curve analysis, which combined TEPs-lncRNAs with a standard screening test marker such as CEA because of the data missing in some subjects.

Conclusion

Our data suggested that TEPs-STAR4-AS1 and ELOA-AS1 are promising non-invasive circulating diagnostic markers for NSCLC.

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Disclosure

The authors report no conflicts of interest in this work.

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