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Original Article

Systematic analysis using a bioinformatics strategy identifies SFTA1P and LINC00519 as potential prognostic biomarkers for lung squamous cell carcinoma

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Abstract: Lung cancer has high incidence and mortality rates, in which lung squamous cell carcinoma (LUSC) is a primary type of non-small cell lung carcinoma (NSCLC). The aim of our study was to discover long non-coding RNAs (lncRNAs) associated with diagnose and prognosis for LUSC. RNA sequencing data obtained from LUSC samples were extracted from The Cancer Genome Atlas database (TCGA). Two prognosis-associated lncRNAs (including SFTA1P and LINC00519) were selected from LUSC samples, and the expression levels were also verified to be associated abnormal in LUSC clinical samples. Our findings demonstrate that lncRNAs SFTA1P and LINC00519 exert important functions in human LUSC and may serve as new targets for LUSC diagnosis and therapy.

Keywords: LUSC, SFTA1P, LINC00519, diagnosis, prognosis

Introduction

Lung cancer is the leading cause of cancer death world-wide, responsible for 27% of cancer deaths in male patients and about 22% in female patients [1]. Annually, the estimated new cases of lung and bronchus cancer number more than 25,000 globally, ranking second across all cancer types [2], and the five-year survival percentage is only 18.5% [3]. Lung squamous cell carcinoma (LUSC), a type of cancer that originates in squamous cells, is generally found in the tissue that forms the lining of the respiratory tract; LUSC accounts for about 30% of non-small cell lung cancer (NSCLC) cases [4, 5]. Therefore, LUSC is one of the primary pathological subtypes of lung cancer, constituting a vast proportion and poor prognosis of diagnosed cases.

Usually, patients with LUSC are diagnosed in the late stage, and most of the available treatment methods can not be implemented in time [6]. In addition, the sensitivity of patients with LUSC to radiotherapy and chemotherapy is far less than that of patients with small cell carcinoma (SCC) [7]. LUSC cancer cells usually show different shapes, which makes it impossible to clearly distinguish the scope from surrounding normal adjacent tissues [8-10]. This leads to a high recurrence rate of LUSC, making the prognosis more difficult to assess [11]. At

present, accurate prognosis and timely surgical resection are the key to improve the survival rate of patients with LUSC.

In recent years, researchers have carried out a series of in-depth studies on the methodology and/or markers of lung cancer based on the principle of early diagnosis and early treatment of cancer, and made significant progress in early diagnosis and prognosis prediction [12-14]. In recent years, the development and progress of LUSC have been deeply studied at the molecular level [18-20], it has been confirmed that the occurrence of LUSC is closely related to the expression of many oncogenes and the deletion of tumor suppressor genes or the structural abnormalities of their products [15-17]. In addition to studying the genes involved in the diagnosis and treatment of LUSC, researchers have found that the key pathways of gene and cell signaling pathways that can be used to evaluate or predict the prognosis of LUSC are also very important [21-23]. Some genes and proteins related to LUSC have been identified. Among them, some related genes have been used to evaluate lung cancer sections by immunohistochemical staining. The expression of these genes (e.g., SFTA3, TMC5, CALML3, and MLPH) can be used to distinguish between LUSC and lung adenocarcinoma (LUAD) [24-26]. In addition, studies on biomarker identification have also confirmed that some genes, including c-erbB-2, can be used as potential prognostic indicators, while squamous differentiation genes and pathway related genes (such as KEAP1 and NFE2L2) can be used as potential therapeutic targets for LUSC [27-30].

Long non-coding RNAs (lncRNAs) are RNA transcripts with a length of more than 200 nucleotides and do not encode proteins [34-36]. They are involved in a variety of biological processes, such as differentiation, cell proliferation, epigenetic regulation, transcription, chromosome reconstruction, and post-transcriptional modification [37-39]. In recent years, lncRNAs have been proved to be involved in the regulation of a variety of human diseases, including tumors, which has attracted more and more attention [31-33]. Studies have shown that lncRNAs play an important role in cancer biology, and the expression level or mutation of specific lncRNAs genes are closely related to the development and progress of cancer [40-43]. In addition, a large number of lncRNAs are abnormally expressed in a variety of tumors, including hepatocellular carcinoma, breast cancer, lung cancer, colorectal cancer and malignant glioma, which indicate that they may be effective biomarkers for diagnosis and prognosis, or as potential cancer treatment targets [44-47].

In this study, we downloaded and analyzed data from TCGA and Gene Expression Omnibus (GEO) databases to screen differentially expressed lncRNAs and analyze the diagnostic and prognostic value of these key lncRNAs in LUSC.

Materials and methods

Tissue samples and ethics statement

Fresh frozen samples were collected from LUSC patients undergoing surgical resection between 2010 and 2016 at Shanghai Tenth People's Hospital, Tongji University School of Medicine, which included 10 paired adjacent non-cancerous tissues and LUSC tumor. The study was approved by the Ethical Committee of Shanghai Tenth People's Hospital, Tongji University School of Medicine (SHSY-IEC-Paper-16-18).

Data source

High-throughput data from RNA sequencing of patients diagnosed with LUSC were downloaded from TCGA [48]. These RNA sequencing data were from the Illumina HiSeq RNASeq platform and included 504 LUSC and 49 adjacent non-cancerous lung tissues. Additionally, data of LUSC patients from GEO database (http://www.ncbi.nlm.nih.gov/geo) were used to validate TCGA results. Independent sample *t* tests were used to statistically analyze the differential expression level of the selected lncRNAs between paracarcinoma lung tissues and LUSC samples. Receiver operating characteristic (ROC) curve analysis was used to validate the diagnostic value of the lncRNAs for LUSC patients based on GEO dataset GSE30219.

We also evaluated the differing lncRNAs expression levels between para-noncancerous tissues and cancer tissues with the assistance of Gene Expression Profiling Interactive Analysis (GEPIA) (http://gepia.cancerpku.cn), which analyzes the RNA sequencing data of 23

types of normal samples and cancers from TCGA.

Exploration of the diff-lncRNAs in LUSC

The RNA-Seq data of LUSC samples with 60,483 mRNAs covered 7,589 lncRNAs, as described by Ensembl (http://asia.ensembl.org/) or NCBI (https://www.ncbi.nlm.nih.gov/). The R language package DESeq [49] was subsequently used to calculate differentially expressed lncRNAs (the absolute $\log_2$ fold change (FC) ≥ 2 and adjusted $P < 0.05$). The lncRNAs with an expression of less than one in more than 15% of samples were excluded, and the lncRNA expression level was $\log_2$ transformed for following analysis.

The receiver operating characteristic (ROC) curve was available to analyze the diagnostic role of differentially expressed lncRNAs, and the top 10 lncRNAs were then selected for further evaluation.

RNA extraction and RNA sequencing analysis

RNA was purified using the QIAGEN RNA Kit (Qiagen, CA, USA) according to the manufacturer's instructions [50, 51]. Specimens from 10 paired adjacent non-cancerous tissues and tumor samples were obtained for RNA sequencing analysis [52]. Sequencing was performed on the Illumina Nextseq 500 platform according to the manufacturer's instructions [53]. Clean reads were mapped to reference *Homo sapiens* transcriptome sequences from the University of California Santa Cruz genome bioinformatics website (hg19) using Bowtie 2 and TopHat 2.0.1 software [54].

Statistical analysis

The statistical analyses were performed with SPSS statistics for Windows, Version 22.0 (IBM Corp.; Armonk, NY, USA). Data were presented as the mean and standard deviation (SD). The different expression was assessed by Student's *t* test. The Pearson correlation test (SPSS Inc., Chicago, IL, USA) was performed for the expression levels of differentially expressed lncRNAs that differed between normal and LUSC tissues. The prognostic roles of differentially expressed lncRNAs were analyzed using the Kaplan-Meier method to contradistinguish survival time and results were compared with a log-rank test. The univariate and multivariate Cox analyses for these lncRNAs were also performed. A *P*-value < 0.05 was considered statistical significance.

Results

Differentially expressed lncRNAs in LUSC based on TCGA data

The lncRNA expression level transformed with log2 was calculated by DESeq R software. In this study, we found 884 differentially expressed lncRNAs from LUSC samples, in which 669 highly expressed and 215 lowly expressed (**Figure 1A**). Then, all the differentially expressed lncRNAs were selected for ROC analysis, and there were 75 lncRNAs with an area under the ROC curve (AUC) over 0.95. Therefore, these lncRNAs had potentially high diagnostic value for LUSC patients.

Clinical value of the top ten aberrantly down- and upregulated lncRNAs in LUSC

The top ten differentially downregulated and upregulated lncRNAs were selected for further analysis, including downregulated SFTA1P, LINC00968, LINC01314, MIR3945HG, RP1-78O14.1, FENDRR, RP11-613D13.8, RP11-43-4D9.1, AC018647.3, and AC109642.1 (**Figure 1B**, **1D**), and upregulated RP11-244M2.1, AC068831.16, AC005537.2, RP11-796E10.1, LINC00519, RP11-776H12.1, RP11-161I6.2, RP13-463N16.6, CTD-2527I21.15, and CASC9 (**Figure 1C**, **1D**). All of these twenty differentially expressed lncRNAs showed high diagnostic values for distinguishing LUSC from non-cancerous lung tissues, and all had AUCs greater than 0.95 (**Figure 1E**).

Survival analyses showed that SFTA1P, LINC00968, RP11-613D13.8, LINC00519, and CTD-2626G11.2 were significantly involved in the overall survival (OS) time of LUSC patients, while LINC01197 and LINC00519 were significantly involved in the disease-free survival (DFS) time of LUSC patients (**Figure 2**).

Concerning the relationship between these twenty lncRNAs and LUSC progression, some differentially expressed lncRNAs were significantly related to clinical parameters of LUSC (**Figure 3**). In particular, the level of SFTA1P, AC109642.1, LINC01314, LINC00968, AC0-18647.3, and CASC9 was able to distinguish the LUSC patients in the early and middle stage

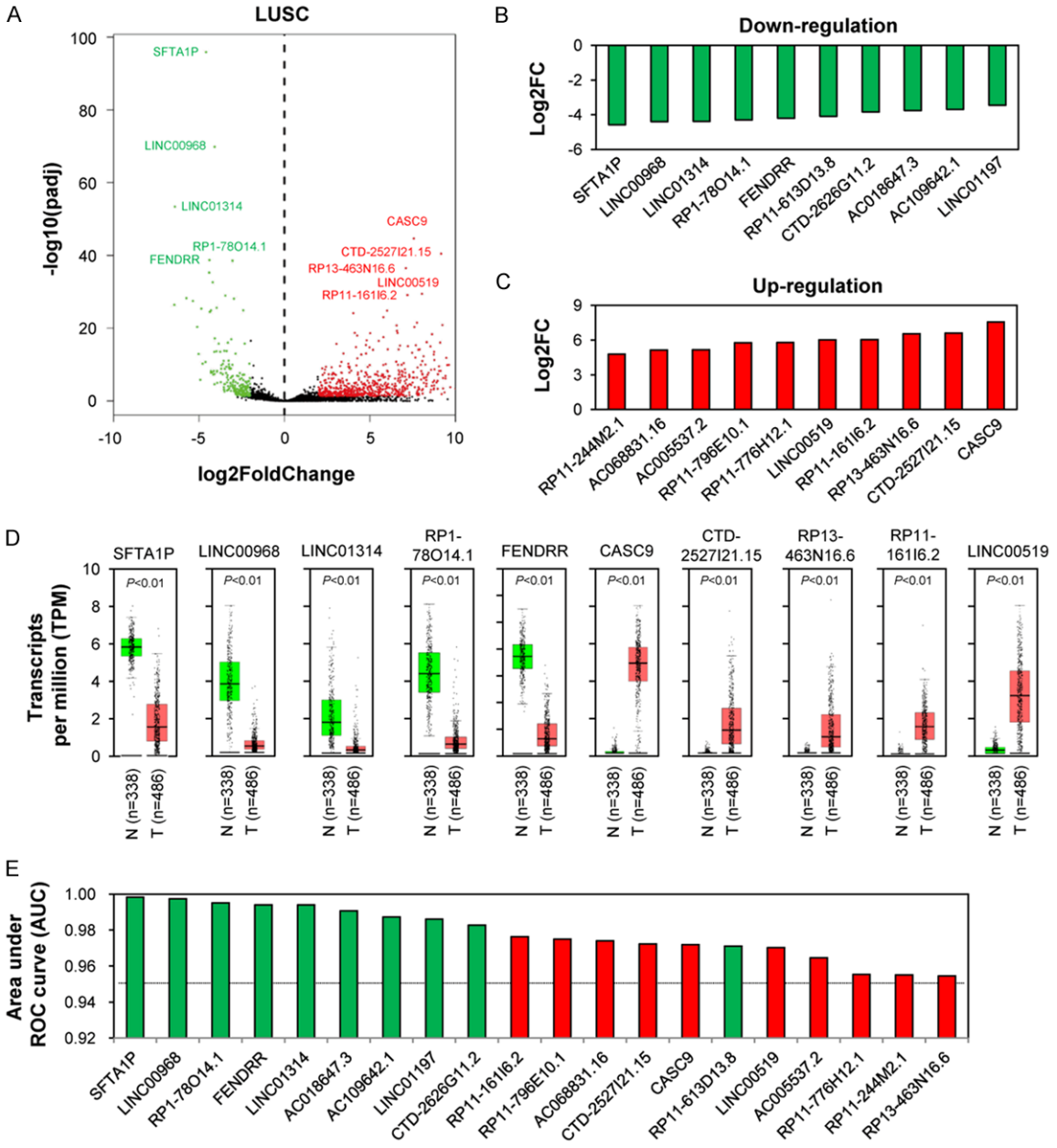

Figure 1. The differentially expressed lncRNAs between para-tumorous lung tissues and LUSC tissues. (A) Volcano plot of the all differentially expressed lncRNAs between para-tumorous lung tissues and LUSC tissues. Value of $\log_2$FC of the top ten aberrantly downregulated (B) and upregulated (C) lncRNAs in LUSC. (D) Differential expression of the top ten lncRNAs between LUSC and para-tumorous lung tissues. (E) AUC of the top 10 aberrantly upregulated lncRNAs.

from the patients in the advanced stage (**Table 1**).

Validation of expression and ROC value of three lncRNAs using GEO data

The expression levels of three key lncRNAs, LINC01197, SFTA1P, and LINC00519 were extracted from GEO dataset GSE30219. Among these, remarkably lower expression was observed for SFTA1P in LUSC tissues, while LUSC tissues showed predominantly higher expression of LINC00519 (**Figure 4A**).

Next, survival analyses of LUSC patients showed that SFTA1P and LINC00519 were significantly related to survival time of LUSC, while LINC00519 was significantly related to the disease-free time of LUSC patients (**Figure 4B**). Moreover, the ROC curves of two lncRNAs,

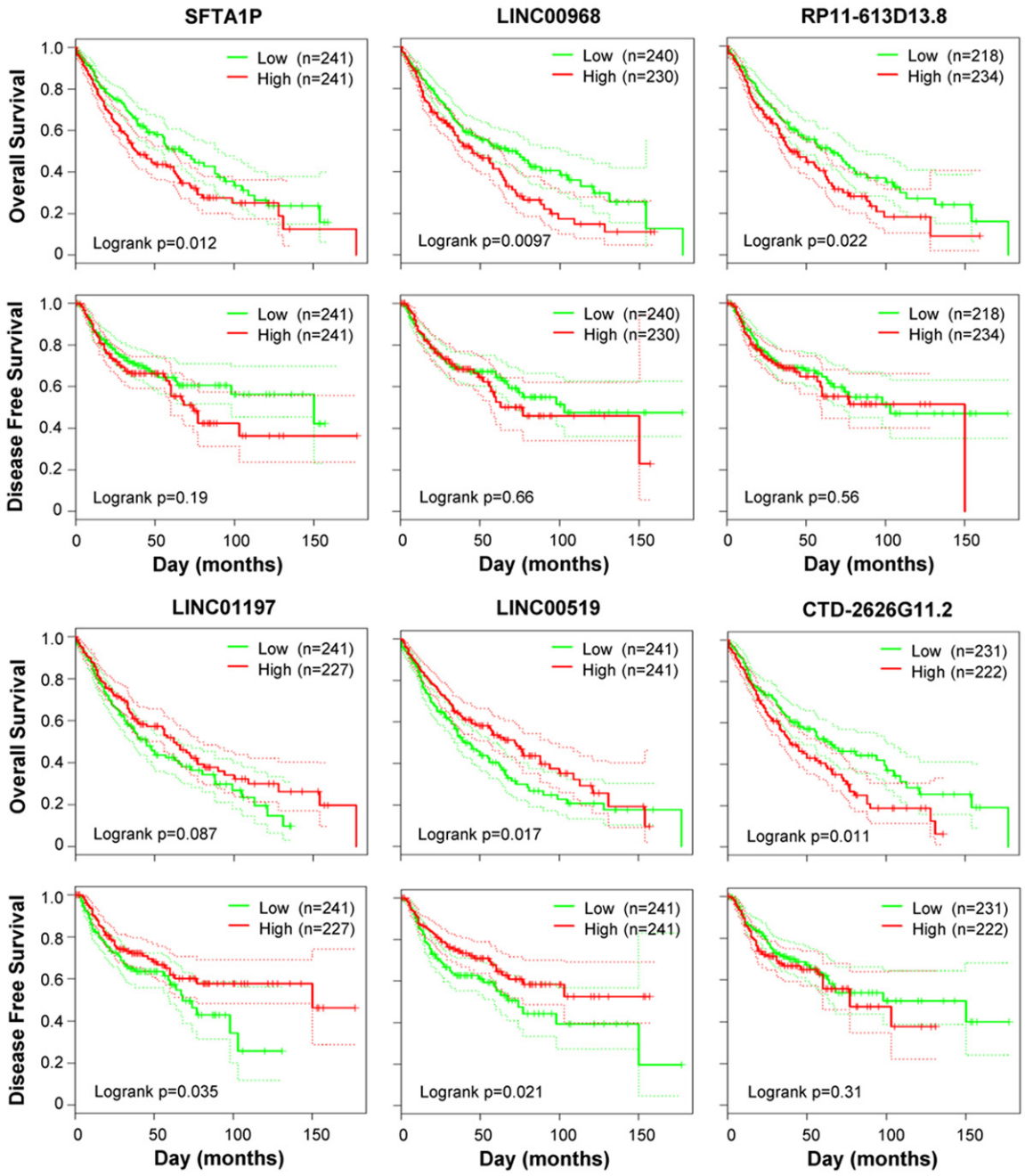

Figure 2. Kaplan-Meier curves of the top 10 aberrantly downregulated and upregulated lncRNAs in LUSC. The X-axis indicates overall survival and disease-free survival time (months), and the Y-axis indicates the survival rate.

SFTA1P (AUC = 0.92) and LINC00519 (AUC = 0.99), indicated favorable diagnostic value for LUSC (**Figure 4C**) (**Table 2**).

Validation based on LUSC clinical samples

We performed RNA sequencing to study lncRNA expression in the 10 paired clinical samples. The mean expression levels of SFTA1P, LINC00968, and LINC01197 were significantly lower in LUSC tissues than in those of non-cancerous normal lung sapmles ($P < 0.01$, **Figure 5A**). The expression level of LINC00519 was notably higher in LUSC tissues than in non-cancerous lung tissues ($P < 0.001$, **Figure 5A**).

SFTA1P expression levels were significantly lower in tissues from the 10 tumor biopsies than in the paired adjacent non-tumor tissues. However, LINC00519 expression levels were

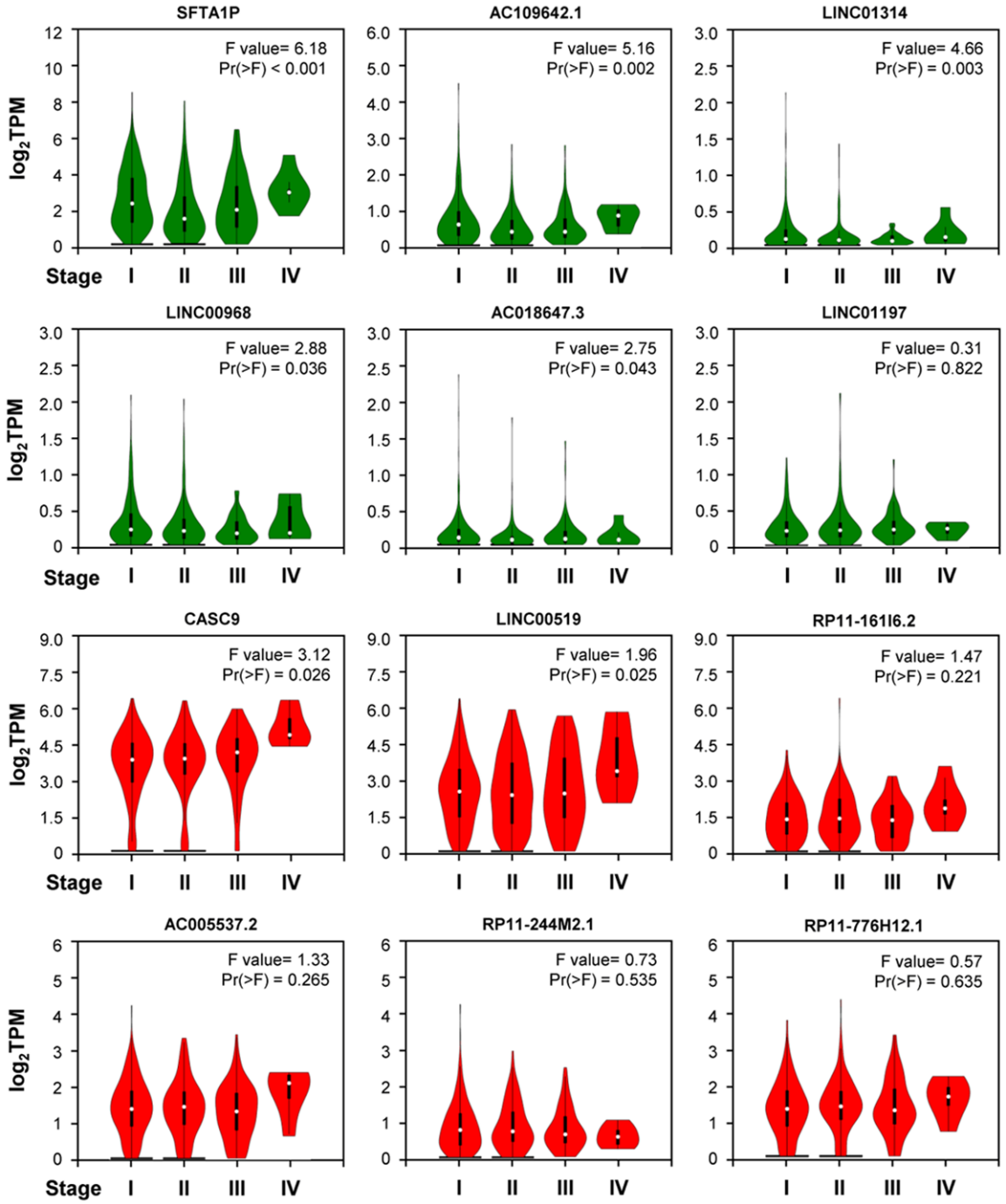

Figure 3. The relative expression of differentially expressed lncRNAs between different LUSC stages. Red violin plot indicates the expression of upregulated lncRNAs relative to different stages in LUSC; green violin plot indicates the relative expression of downregulated lncRNAs relative between different stages in LUSC.

significantly higher in tissues from the 10 tumor biopsies than in the paired adjacent non-tumor tissues. Next, we carried out the correction analysis and found a significant negative correlation between tumor biopsy tissue and paired adjacent non-tumor tissues for SFTA1P and LINC00519 expression (**Figure 5B**).

Survival analyses showed that the ROC curve of LINC00519 indicated favorable diagnostic value for LUSC (**Figure 5D**).

Table 1. Univariate and multivariate Cox analyses for six lncRNAs in LUSC

Variables	Univariate			Multivariate		
	P value	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI
LINC00519	0.002	1.875	1.264-2.317	0.006	1.811	1.211-2.158
SFTA1P	0.004	1.573	1.154-2.145	0.019	1.551	1.073-2.242
RP11-613D13.8	0.033	1.375	1.002-2.016	0.473	1.185	0.887-1.234
LINC00968	0.118	1.276	0.945-1.732			
LINC01197	0.468	1.025	0.898-1.543			
CTD-2626G11.2	0.605	0.968	0.756-1.322			

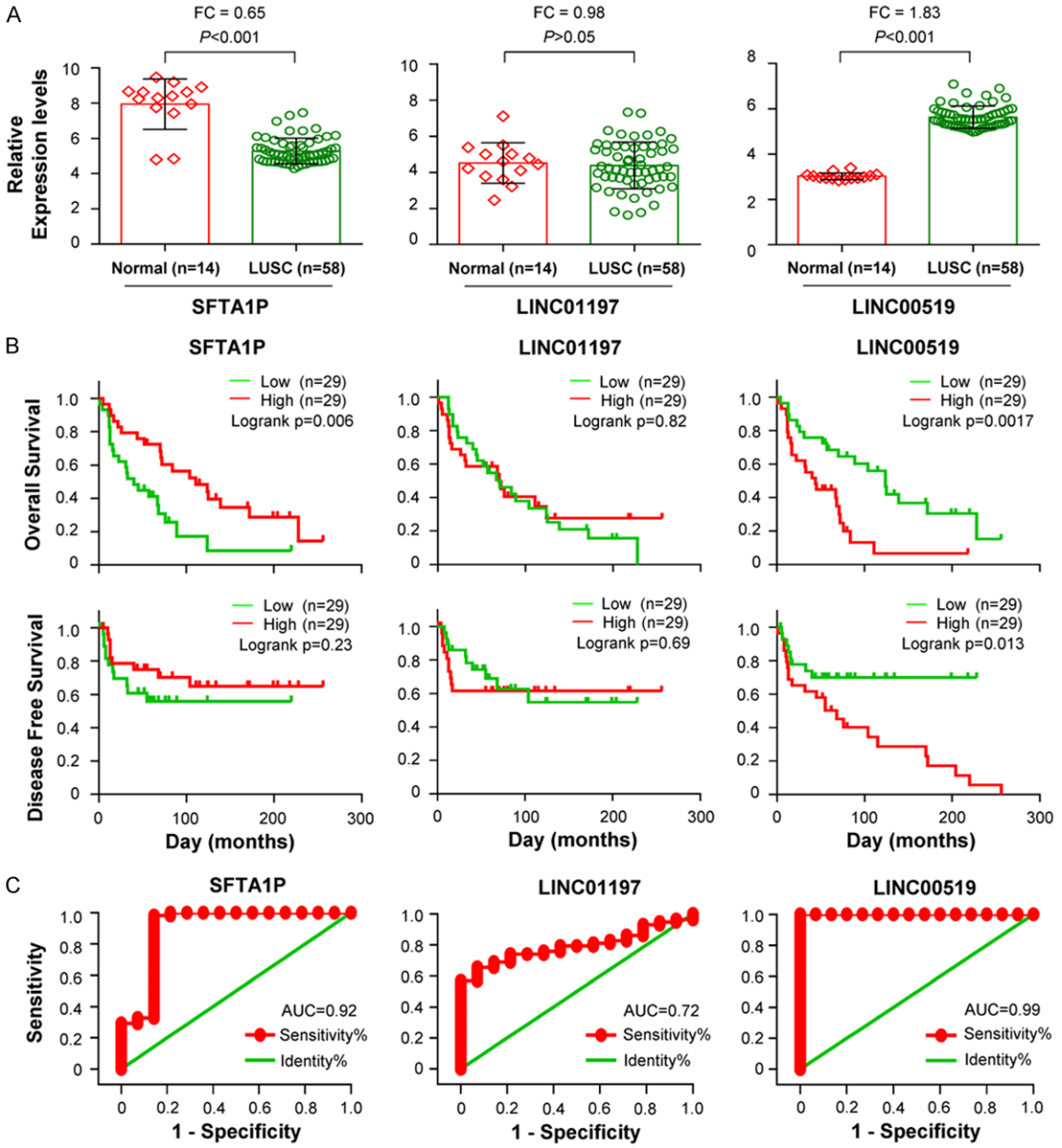

Figure 4. The expression levels and clinical significance of SFTA1P, LINC01197, and LINC00519 in LUSC based on GEO dataset GSE30219. A. The differing expression levels of SFTA1P, LINC01197, and LINC00519 between LUSC tissue and normal tissue based on GEO dataset GSE30219. B. Kaplan-Meier curves of SFTA1P, LINC01197, and

LINC00519 in LUSC based on GEO dataset GSE30219. C. ROC curves of SFTA1P, LINC01197, and LINC00519 in LUSC based on GEO dataset GSE30219.

Table 2. Univariate and multivariate Cox analyses for three lncRNAs in LUSC

Variables	Univariate			Multivariate		
	P value	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI
LINC00519	0.013	2.577	1.265-5.311	0.008	2.677	1.284-5.215
SFTA1P	0.036	0.684	0.521-1.005	0.042	0.625	0.511-0.926
LINC01197	0.269	1.237	0.662-2.314			

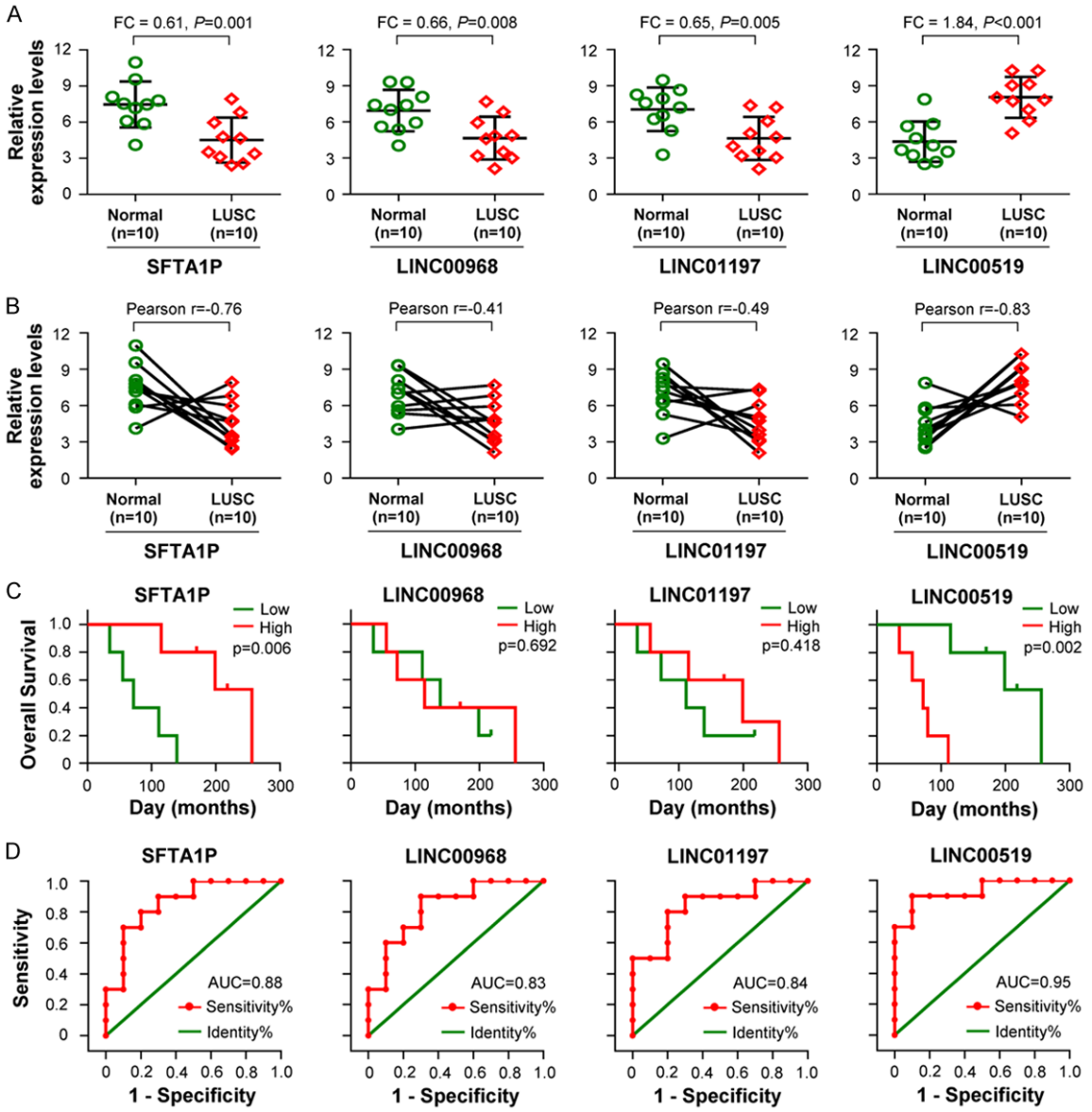

Figure 5. The expression levels and clinical significance of SFTA1P, LINC01197, and LINC00519 in 10 LUSC patients. The expression levels (A) and correlation analyses (B) of SFTA1P, LINC00519, LINC00968, and LINC01197 in paired LUSC tissues and non-cancerous lung tissues from 10 LUSC patients. (C) Kaplan-Meier curves of SFTA1P, LINC00519, LINC00968, and LINC01197 from LUSC clinical samples. (D) ROC curves of SFTA1P, LINC00519, LINC00968, and LINC01197 from LUSC clinical samples.

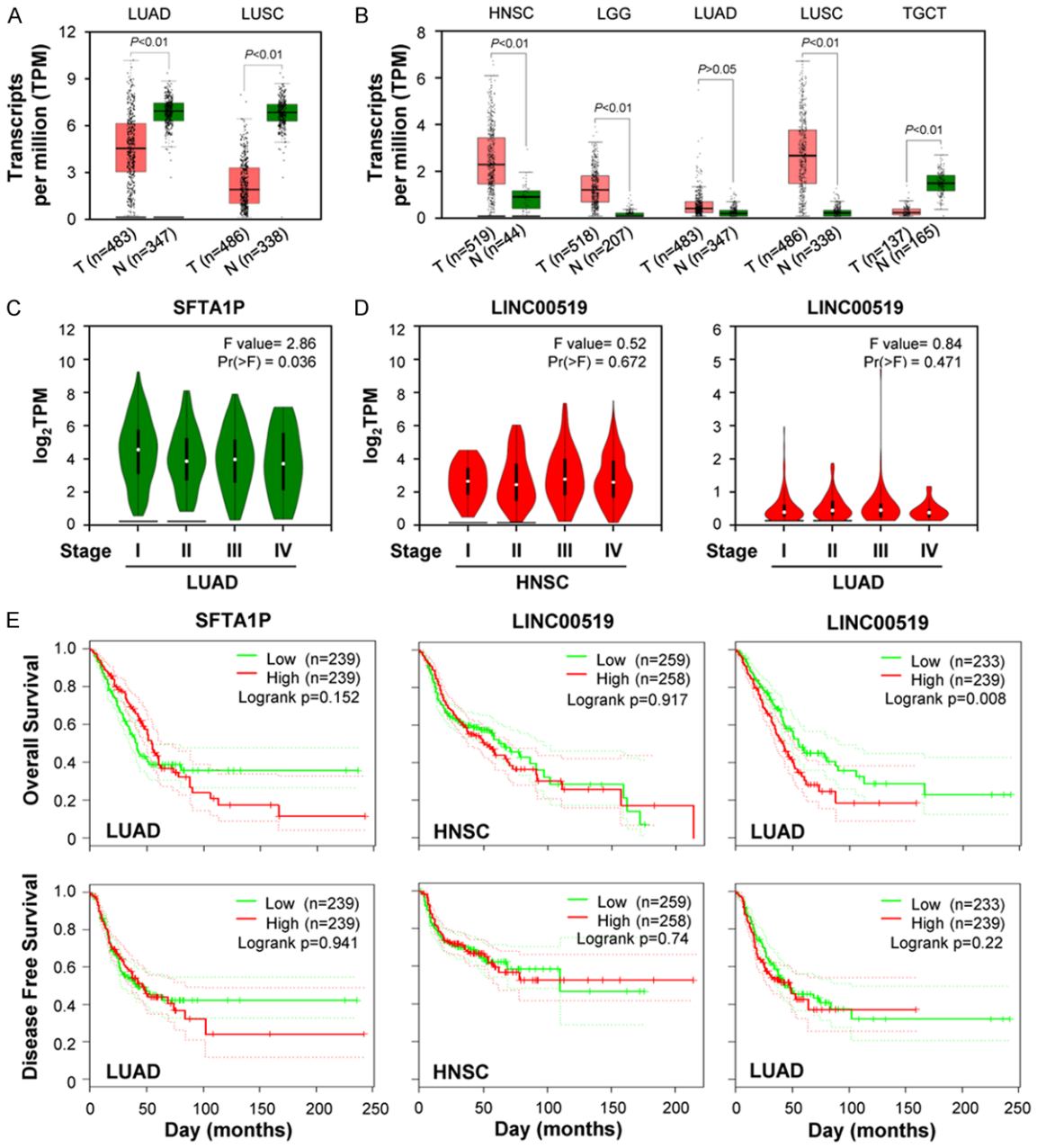

Figure 6. SFTA1P and LINC00519 expression levels in multiple tumors. A. SFTA1P relative expression level in LUAD and LUSC. B. LINC00519 relative expression level in multiple tumors. C. SFTA1P relative expression between different stages in LUAD. D. LINC00519 relative expression between different stages in HNSC and LUAD. E. Kaplan-Meier curves of SFTA1P in LUAD and LINC00519 in LUSC and HNSC.

Analysis of two key lncRNAs expression in 22 types of cancers using TCGA

Downregulation of SFTA1P was found in lung adenocarcinoma (LUAD) and LUSC tissues based on the results from GEPIA (**Figure 6A**). There was no significant difference in SFTA1P expression between cancer samples and paranoncancerous normal samples among other cancer types.

As shown in **Figure 6B**, consistent results were found in brain lower grade glioma (LGG), head and neck squamous cell carcinoma (HNSC), and LUSC, revealing that the LINC00519 level was significant higher in these cancer samples compared with that in paranoncancerous tissues, while the expression of LINC00519 was significantly downregulated in testicular germ cell tumors (TGCT). However, there was no significant difference of LINC-

00519 expression between LUAD samples and para-noncancerous normal lung tissues.

Concerning the relationship between SFTA1P and LUAD progression, SFTA1P was found to be closely related to LUAD clinical parameters (**Figure 6C**). Nevertheless, LINC00519 levels could not distinguish the LUAD or HNSC patients in the early stage from those in the advanced stage (**Figure 6D**).

Survival analyses showed that LINC00519 was significantly related to the LUAD survival time (**Figure 6E**). However, LINC00519 level was not related to the OS and DFS of HNSC. SFTA1P expression showed no significant effect on OS or DFS in LUAD.

Discussion

Genomics projects, such as TCGA, have yielded much information about alternative molecular pathways and genomic, transcriptomic, proteomic, and epigenetic alterations in many specific types of cancer [55-58]. Studies utilizing databases not only provide information on the matter of protein-coding genes but also can be used to study non-coding transcripts, which have been shown to be involved in the regulation of a diverse array of biological processes.

Few studies have examined how lncRNA participates in the invasion and metastasis of cancer [59-61]. Non-coding RNA HOX mimics antisense intergenic RNA (HOTAIR) and inhibits the translation of HOXD by recruiting PRC2, which acts as a scaffolding molecule [62]. It also involves PRC2 and the LSD1/CoREST/REST complex, influencing gene-specific histone modification changes, which in turn leads to cancer metastasis [63].

LncRNA is essentially a substitute in additional tissues [64-66]. Miscellaneous studies have shown that lncRNA has obvious tissue-specific expression [67-69]. Accurate analysis of the information from differentially expressed lncRNAs uploaded to the GEO database is important in bioinformatics technology [70]. Normal expression of the lncRNAs is limited in tumors and aberrant in normal tissues, and typical lncRNAs may play a streamlining role in regulating cancer occurrence, development, invasion, and metastasis [71-73].

LncRNAs that have been previously found to play a role in lung infection include MALAT1, HOTAIR, Gas5, and H19 [74-77]. Critically, these lncRNAs function in tumor progression, aggressiveness, and metastasis and reveal an important regulatory issue in lung disease cells [78-81].

Studies have found that SFTA1P is downregulated in gastric illness tissues compared to adjacent normal tissues [82]. SFTA1P could be a dangerous biomarker of gastric cancer in clinical settings because the downregulation of SFTA1P leads to poorer outcomes for patients with gastric cancer [83]. It should also be taken into consideration that overexpression of SFTA1P could lead to improvement both in vitro and in vivo, inhibit G1, promote apoptosis of gastric cancer cells, and stall the advance and invasion of gastric cancer [84-86]. Interestingly, SFTA1P also inhibits lung adenocarcinoma cell migration and invasion, but it does not inhibit LUAD cell proliferation [87]. However, the performance of LINC00519 in cancer has never been reported. More research is needed on the role of these aberrant lncRNAs in lung squamous cell carcinoma.

Conclusion

In conclusion, this study validated the association with LUSC prognosis of two lncRNAs, SFTA1P and LINC00519, and the associated abnormal expression levels were also verified in LUSC clinical samples. These findings demonstrated that lncRNAs SFTA1P and LINC00519 may be involved in the occurrence and progression of human LUSC and may serve as new targets for LUSC diagnosis and therapy.

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Disclosure of conflict of interest

None.

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