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RESEARCH

Decreased Expression of SOX7 is Correlated with Poor Prognosis in Lung Adenocarcinoma Patients

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Abstract Lung adenocarcinoma is the most frequently histologic subtype and the most histologically heterogeneous form of lung cancer. De-regulation of Wnt/β-catenin signaling pathway is implicated in lung carcinogenesis. SOX7, as a member of high mobility group (HMG) transcription factor family, plays a role in the modulation of the Wnt/β-catenin signaling pathway. However, the expression pattern and clinicopathological significance of SOX7 in patients with lung adenocarcinoma is still unclear. To address this problem, the SOX7 mRNA expression was detected by quantitative real-time reverse transcription polymerase chain reaction (qRT-PCR). Immunohistochemical studies were performed on 288 pairs of adjacent normal lung and lung adenocarcinoma tissues with complete follow-up records. Association of SOX7 protein expression with clinical outcomes was evaluated using the Kaplan-Meier method and a multivariate Cox proportional hazards regression model. SOX7 mRNA expression was significantly down-regulated in lung adenocarcinoma compared with matched adjacent normal tissues ($P<0.001$). SOX7 protein was expressed in the cytoplasm of lung adenocarcinoma cells in 106/288 (36.8 %) of cases, whereas its immunoreactivities were predominantly located in the cytoplasm of the adjacent normal tissues. The reduced SOX7 expression was correlated with poor differentiation ($P=0.002$), lymph node metastasis ($P=0.011$) and advanced TNM stage ($P=0.006$). Regarding patient survival, the overall survival and the disease-free survival rates were both significantly lower in patients with SOX7-negative tumors than in those with SOX7-positive tumors ($P=0.018$ and 0.013, respectively). Multivariate analysis using a Cox proportional-hazards model demonstrated that SOX7 expression status was an independent prognostic factor predicting the overall survival and the disease-free survival of patients with lung adenocarcinoma ($P=0.021$ and 0.016, respectively).Our data suggest that the decreased expression of SOX7 is an important feature of lung adenocarcinoma. The expression level of SOX protein may be a useful prognostic marker for patients with lung adenocarcinoma.

Keywords Lung adenocarcinoma · SOX7 · Immunohistochemistry · Quantitative real-time reverse transcription polymerase chain reaction · Prognosis

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Introduction

Lung adenocarcinoma is the most frequently histologic subtype and the most histologically heterogeneous form of lung

cancer, which is the leading cause of cancer death worldwide [1]. According to the 2004 World Health Organization (WHO) classification [2], lung tumors include four architectural growth patterns: bronchioloalveolar, acinar, papillary, and solid. In 2011, a new classification has been developed by an international multidisciplinary expert panel sponsored by the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society [3]. It addresses both resection specimens and small biopsies/cytology, and has already been validated in a North American series of 514 stage I lung adenocarcinomas. In this new classification, the terms bronchioloalveolar carcinoma and mixed subtype adenocarcinoma are no longer used [3]. Similar with other human malignancies, a variety of positive and negative factors are involved in the process of tumorigenesis and tumor progression of lung adenocarcinoma. Understanding the genetic changes and molecular events during the development of this disease is very important to identify mechanisms on tumor aggressiveness and develop effective new strategies for the prediction, diagnosis and treatment of lung adenocarcinoma.

SOX gene family belongs to the high mobility group (HMG) superfamily. SOXs were first identified through homology of the HMG domain to the testis-determining factor, SRY [4]. These genes are conserved across species and show tissue-specific expression patterns. It has been demonstrated that SOXs play important roles in embryonic development, sex differentiation, regulation of germ layer formation and nervous system development [5]. According to the degree of homology inside the HMG domain and the presence of conserved motifs outside the HMG box, SOX genes were divided into nine subgroups. SOX7, together with SOX17 and SOX18, belongs to SOX subgroup F. It was first identified in Xenopus and in mouse. SOX7 shares several homologous motifs with SOX17 and SOX18 [6]. The SOX7 gene encodes a transcription factor that can both enhance and inhibit transcription. It has been implicated in parietal endoderm differentiation [7]. The SOX7 protein contains a DxxEFDQYL motif that is evolutionarily conserved [8]. Recent studies have observed the de-regulation of SOX7 in different cancer cells. For example, SOX7 was shown to be up-regulated in pancreatic cancer cell lines [9] and primary gastric cancer cases [9], but down-regulated in primary colorectal tumors [10], prostate cancer [11] and breast cancer [9], implicating that SOX7 might play a role in these cancers. De-regulation of Wnt/β-catenin signaling pathway is implicated in lung carcinogenesis [12–15]. The central player in this signaling cascade is a cytoplasmic protein called β-catenin. The DxxEFDQYL motif in SOX7 protein mediates the interaction of SOX7 with β-catenin and SOX7 is involved in the modulation of the Wnt/β-catenin signaling pathway [16].

Considering the importance of Wnt/β-catenin signaling pathway in lung adenocarcinoma's tumorigenesis and the regulatory role of SOX7 in this signaling pathway, we performed clinical study on the expression of SOX7 in lung adenocarcinoma tissue samples. The purpose of this study is to investigate the role of SOX7 in lung adenocarcinoma. In addition, we wanted to determine whether the immunohistochemical expression of SOX7 could provide useful information as a novel prognostic option for treating lung adenocarcinoma.

Materials and Methods

Patients and Tissue Samples

This study was approved by the Research Ethics Committee of Xiangya Hospital, China. Written informed consent was obtained from all of the patients. All specimens were handled and made anonymous according to the ethical and legal standards.

Two-hundred eighty-eight lung adenocarcinoma patients who underwent surgery at the Department of Thoracic Surgery, Xiangya Hospital from March 1996 to February 2005 were included in this study. No preoperative chemotherapy or radiotherapy had been performed in any of these patients. Standard lobectomy and lymph node dissections were performed in every patient. The patients that had any other malignancy occurring before or after the primary lung adenocarcinoma were excluded from our study. The postoperative pathological staging was determined according to the 7th Edition of the TNM classification. The histological type and the grade of differentiation of the tumors were determined according to International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society International Multidisciplinary Classification of Lung Adenocarcinoma [3]. The clinical records, pathological reports and follow-up information were also obtained for all the patients. The clinical and pathologic parameters were obtained from the pathological reports and presented in Table 1.

Real-Time Quantitative Reverse Transcriptase Polymerase Chain Reaction

Real-time quantitative reverse transcriptase polymerase chain reaction (QRT-PCR) was used to examine the expression status of the SOX7 gene in 20 pairs of adjacent normal lung and lung adenocarcinoma tissues.

The cDNA templates for QRT-PCR were synthesized from RNA samples. The primers 5′- TGA GCC AGG TGG AAC TCC T -3′ and 5′- CTG GGA GAC CGG AAC ATG C -3′ were used to amplify 215-bp transcripts of SOX7, and the primers 5′- GGT GGC TTT TAG GAT GGC AAG -3′ and 5′- ACT GGA ACG GTG AAG GTG ACA G -3′ were used to amplify 202-bp transcripts of β-actin. Gene expression was

Table 1 Correlations of the SOX7 protein expression with the clinicopathological features of primary lung adenocarcinoma

Clinicopathological features	No. of cases (%)	SOX7		
		Positive (n, %)	Negative (n, %)	P
Age (years)	58.9±5.8	59.3±6.8	58.6±5.2	NS
Gender				
Male	178 (61.8)	63 (35.4)	115 (64.6)	NS
Female	110 (38.2)	43 (39.1)	67 (60.9)	
Smoking history (pack-years)	17.2±11.9	16.9±12.4	17.3±11.6	NS
Smoking status				
Never	92	33 (35.9)	59 (64.1)	NS
Former	140	52 (37.1)	88 (62.9)	
Current	56	21 (37.5)	35 (62.5)	
Tumor size	3.4±0.8	3.5±0.9	3.4±0.8	NS
Predominant histologic subtype				
Adenocarcinoma, predominantly invasive with some nonmucinous lepidic component	60 (20.8)	23 (38.3)	37 (61.7)	NS
Invasive mucinous adenocarcinoma	5 (1.7)	2 (40.0)	3 (60.0)	
Acinar	75 (26.0)	28 (37.3)	47 (62.7)	
Papillary	60 (20.8)	22 (36.7)	38 (63.3)	
Solid	88 (30.6)	31 (35.2)	57 (64.8)	
Differentiation grade				
Well	100 (34.7)	86 (86.0)	14 (14.0)	0.002
Moderate	80 (27.8)	18 (22.5)	62 (77.5)	
Poor	108 (37.5)	2 (1.9)	106 (98.1)	
Micropapillary component				
No	146 (50.7)	56 (38.4)	90 (61.6)	NS
Yes	142 (49.3)	50 (35.2)	92 (64.8)	
Pleural invasion				
No	160 (55.6)	60 (37.5)	100 (62.5)	NS
Yes	128 (44.4)	46 (35.9)	82 (64.1)	
Lymph node metastasis				
No	143 (49.7)	89 (62.2)	54 (37.8)	0.011
Yes	145 (50.3)	17 (11.7)	128 (88.3)	
Lymphovascular invasion				
No	151 (52.4)	58 (38.4)	93 (61.6)	NS
Yes	137 (47.6)	48 (35.0)	89 (65.0)	
TNM stage				
I	185 (64.2)	102 (55.1)	83 (44.9)	0.006
II~III	103 (35.8)	4 (3.9)	99 (96.1)	

determined using SYBR Green PCR mix (Toyoko) and 10 μg of template. Real-time PCR was performed on a MyiQ.2 Two-Color Real-Time PCR Detection System (Bio-Rad), using the following amplification conditions: 5 min, 95 °C; followed by 40 cycles of 10 s 95 °C, 20 s 60 °C and 20 s 72 °C. All assays were carried out in triplicate. CT-values were determined using the IQ5 software (Bio-Rad). Gene expression in each sample was normalized with the housekeeping gene (β-actin) expression. Relative quantification of target gene expression was evaluated using the comparative cycle threshold (CT) method.

Immunohistochemistry Analysis

Immunohistochemical study was performed to examine the expression status of the SOX7 gene in 288 pairs of adjacent normal lung and lung adenocarcinoma tissues.

Briefly, following a brief proteolytic digestion and a peroxidase blocking of tissue slides, the slides were incubated with the primary antibody against SOX7 (1:50 dilution, goat polyclonal antibody, R&D Systems) overnight at 4 °C. The specificity of the primary antibody has been validated by the

previous studies [10, 11]. After washing, peroxidase labeled polymer and substrate-chromogen were then employed in order to visualize the staining of the interested proteins. In each immunohistochemistry run, negative controls were carried out by omitting the primary antibody, whereas SOX7 overexpression confirmed by western blotting was used as positive controls.

Following a hematoxylin counterstaining, immunostaining was scored by two independent experienced pathologists, who were blinded to the clinicopathological parameters and clinical outcomes of the patients. The scores of the two pathologists were compared and any discrepant scores were trained through re-examining the stainings by both pathologists to achieve a consensus score. The number of positive-staining cells showing immunoreactivity on the cytoplasm (for SOX7) in ten representative microscopic fields was counted and the percentage of positive cells was calculated. The percentage scoring of immunoreactive tumor cells was as follows: 0 (0 %), 1 (1–10 %), 2 (11–50 %) and 3 (>50 %). The staining intensity was visually scored and stratified as follows: 0 (negative), 1 (weak), 2 (moderate) and 3 (strong). A final score was obtained for each case by multiplying the percentage and the intensity score. Therefore, tumors with a multiplied score exceeding 3 (median of total scores for SOX7) were deemed to be positive expression of SOX7; all other scores were considered to be negative.

Statistical Analysis

The software of SPSS version13.0 for Windows (SPSS Inc, IL, USA) and SAS 9.1 (SAS Institute, Cary, NC) was used. Statistical analysis were performed with Fisher's exact test for any 2×2 tables, Pearson χ^2 test for non- 2×2 tables, chi-square trend test for ordinal datum. Regarding patient survival, overall survival was defined as the time from treatment initiation to date of death from any cause. Disease-free survival was defined as the time from the initial treatment to date of onset of local recurrence or distant metastasis. Kaplan-Meier and Cox Regression methods were used for the question of survival analysis. Differences were considered statistically significant when p was less than 0.05.

Results

Expression of the SOX7 Gene in Lung Adenocarcinoma Tissues

Total RNA of 20 pairs of adjacent normal lung and lung adenocarcinoma tissues were extracted and the expression of SOX7 gene was detected by QRT-PCR. The results showed that SOX7 mRNA expression was significantly down-regulated in lung adenocarcinoma compared with matched adjacent normal tissues ($P<0.001$, Fig. 1).

Expression and Localization of the SOX7 Protein in Lung Adenocarcinoma Tissues

The expression and localization of SOX7 in 288 pairs of adjacent normal lung and lung adenocarcinoma tissues were examined by immunohistochemically. SOX7 protein was expressed in the cytoplasm of lung adenocarcinoma cells in 106/288 (36.8 %) of cases (Fig. 2a), whereas its immunoreactivities were predominantly located in the cytoplasm of the adjacent normal tissues (Fig. 2b).

Association of the SOX7 Protein Expression with the Clinicopathological Characteristics

The association of SOX protein expression with the clinicopathological features of lung adenocarcinoma patients was shown in Table 1. A statistically significant association was found between the SOX7 protein expression and the differentiation grade of lung adenocarcinoma tissues. The SOX7 protein expression was more frequently detected in the well-differentiated adenocarcinomas than that in the moderately or poorly differentiated adenocarcinomas ($P=0.002$). The tumors with a negative SOX7 protein expression more frequently showed lymph node metastasis ($P=0.011$). The frequency of the SOX7 protein expression in the lung adenocarcinoma tissues with TNM stage I was significantly higher than that in those with TNM stage II~III ($P=0.006$). There was no significant association with age, gender, the smoking history (pack-years), the smoking status, tumor size, predominant histologic subtype, a micropapillary component, pleural invasion, or lymphovascular invasion (all $P>0.05$).

Prognostic Implications of the SOX7 Protein Expression in Lung Adenocarcinoma

Adequate The 5-year overall survival rate was 62.3 % (66/106) in patients with SOX7-positve tumors and 46.7 % (85/182) in those with SOX7-negative tumors. The overall survival was significantly lower in patients with SOX7-negative tumors than in those with SOX7-positve tumors ($P=0.018$, Fig. 3a). Turning to the disease-free survival, the 5-year disease-free survival rate was 58.5 % (62/106) in patients with SOX7-positve tumors and 40.1 % (73/182) in those with SOX7-negative tumors, which was significantly different ($P=0.013$, Fig. 3b). Multivariate analysis using a Cox proportional-hazards model demonstrated that SOX7 expression status was a significant independent factor predicting the overall survival and the disease-free survival of patients with lung adenocarcinoma ($P=0.021$ and 0.016, respectively, Table 2) as well as differentiation grade ($P=$

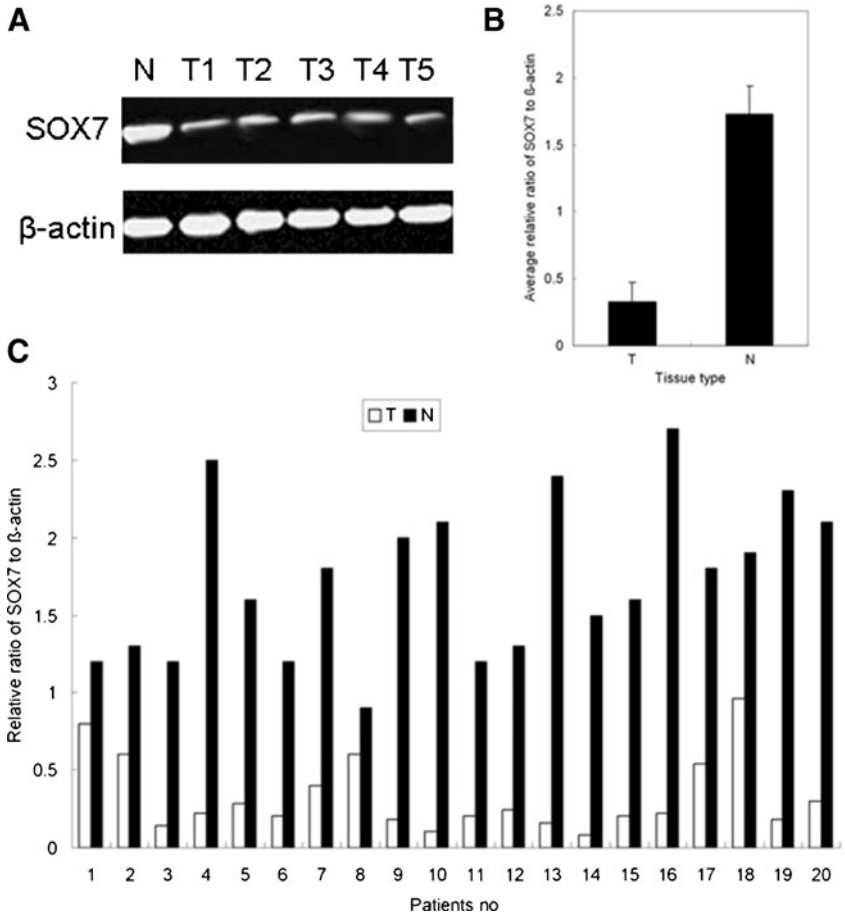

Fig. 1 Real time PCR analyses of SOX mRNA in adjacent normal lung and lung adenocarcinoma tissues. **a**, **b** Compared with adjacent normal lung tissue (N), SOX7 mRNA expression was significantly decreased in lung adenocarcinoma tissues (T1-T5) ($P<0.001$). **c** In each pair of adjacent normal lung (N) and lung adenocarcinoma (T) tissues, the SOX7 mRNA expression in the lung adenocarcinoma tissues was significantly lower than in corresponding adjacent normal lung tissues

0.022 and 0.018, respectively, Table 2), the status of lymph node metastasis ($P=0.033$ and 0.020, respectively, Table 2) and TNM stage ($P=0.011$ and 0.009, respectively, Table 2).

Discussion

Lung adenocarcinoma is the most frequent histologic type in women and nonsmokers, and is a very heterogeneous cancer. The oncogenesis of lung adenocarcinoma is linked to different molecular events. It is of great challenge to clinicians and basic scientists to find out the molecular markers associated with the progression and prognosis of this cancer. The data presented in this study shown the reduced expression of SOX7 in lung adenocarcinoma tissues, which may promote advance and metastasis of this cancer. To the best of our knowledge, this is the first study in which the relationship between the SOX7 expression and the clinicopathological features, with special attention given to the prognostic significance of lung adenocarcinoma, has been extensively investigated.

The Wnt/β-catenin signaling pathway is well known to have important roles in various malignancies, especially in lung cancers [12–15]. The SOX transcription factors are

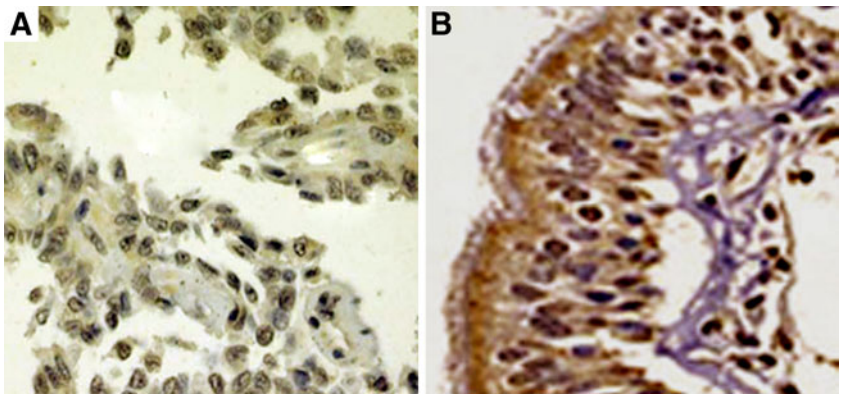

Fig. 2 Immunohistochemical expression for SOX7 protein in adjacent normal lung and lung adenocarcinoma tissues (×200). **a** SOX7 was weakly expressed in the cytoplasm of lung adenocarcinoma cells. **b** SOX7 was strongly expressed in the cytoplasm of adjacent normal lung tissues

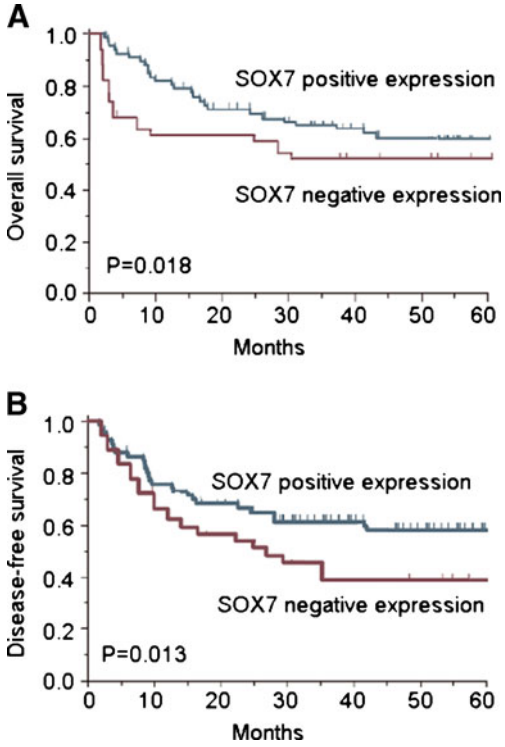

Fig. 3 Overall (**a**) and disease-free (**b**) survival of patients with primary lung adenocarcinoma stratified according to the SOX7 expression status. The patients with negative SOX7 expression tumor showed significantly poorer overall survival (P=0.018) and disease-free survival (P=0.013) rates than those with positive SOX7 expression

DNA-binding HMG domain proteins. They are found in all metazoans and regulate many of the same processes as Wnt/β-catenin signaling pathway including tissue specification, organ development, stem cell homeostasis, and cancer [17, 18]. Emerging evidence suggests that they have widespread and underappreciated roles in modulating Wnt/β-catenin signaling pathway in development and disease. For example, SOX proteins repress Wnt transcriptional responses; however, some SOX proteins appear to enhance Wnt-target gene expression. The expression of some SOX genes are also regulated by Wnts. Based on the interactions between SOXs and Wnt signaling pathway, we assume that SOXs might be involved in the carcinogenesis of lung cancers. Xiang et al. [19] found the up-regulation of SOX2 in lung cancer cells, which has an important role in maintaining stem cell properties and functions. Titulaer et al. [20] demonstrated that SOX antibodies are specific serological markers for small-cell lung cancer. Vural et al. [21] also found the frequent and stable presence of SOX Group B in small-cell lung cancer. The seroreactivity against SOX1 correlated with younger age, lower lactate dehydrogenase levels, and better response to initial therapy. Friedman et al. [22] detected the high and differential overexpression of SOX4 in primary small cell lung cancer, and they further demonstrated that the identification of naturally processed T cell and Ab epitopes from SOX4 provides valuable tools for the development of peptide-based vaccination strategies against lung cancer as well as to monitor SOX-4-specific responses in vaccinated patients. Regarding SOX7, a member of the SOXF subfamily of proteins, which also includes SOX17 and SOX18, a motifs in SOX7 protein enables SOX7 to bind to β-catenin. In 2002, Katoh et al. [9] investigated that SOX7 mRNA was significantly down-regulated in primary lung cancers, compared with normal lung tissues. Consistent with the previous study, we found the the expression levels of SOX7 mRNA and protein in primary lung adenocarcinoma were both significantly reduced. In addition to its differential expression, we also demonstrated that the reduced SOX7 expression was significantly correlated with poor differentiation (P=0.002), lymph node metastasis (P=0.011) and advanced TNM stage (P=0.006), supporting the notion that loss of SOX7 activity might critically contribute to the aggressiveness of lung adenocarcinoma.

We further investigated the prognostic value of SOX7 expression status in lung adenocarcinoma. Our results suggested that the negative expression of SOX7 is associated with poor prognosis in patients with lung adenocarcinoma. The overall survival and the disease-free survival were both

Table 2 Multivariate analysis of prognostic factors in patients with primary lung adenocarcinoma

Prognostic factors	Overall survival		Disease-free survival	
	Relative risk (95 % confidence interval)	P	Relative risk (95 % confidence interval)	P
Predominant histologic subtype	1.52 (0.73–3.67)	NS	1.68 (0.81–4.72)	NS
Differentiation grade	5.42 (2.36–12.28)	0.022	5.67 (2.54–12.48)	0.018
Micropapillary component	0.66 (0.39–1.11)	NS	1.13 (0.58–2.22)	NS
Pleural invasion	1.81 (0.86–3.46)	NS	1.93 (0.85–3.88)	NS
Lymph node metastasis	1.67 (0.80–3.61)	NS	1.69 (0.82–3.66)	NS
Lymphovascular invasion	1.20 (0.51–3.09)	NS	1.28 (0.53–3.60)	NS
TNM stage	3.12 (1.01–12.29)	0.031	3.31 (1.08–12.96)	0.029
SOX7 expression	3.62 (1.19–12.37)	0.021	4.86 (1.39–16.88)	0.016

shorter in patients with SOX7 negative cancers than in those with SOX7 positive cancers,suggesting that the reduced expression of SOX7 is a potential marker for identifying lung adenocarcinomas with poor prognosis.

In conclusion, our data suggest that the decreased expression of SOX7 is an important feature of lung adenocarcinoma. The expression level of SOX protein may be a useful prognostic marker for patients with lung adenocarcinoma. This is the first report to suggest a relationship between SOX7 expression and prognosis in patients with lung adenocarcinoma, and further prospective analysis would be worth doing.

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