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Original Article

Expression characteristics of AXL and YAP in non-small cell lung cancer and prognostic importance

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Abstract: Lung cancer has some of the highest morbidity and mortality. It is an urgent task to illuminate the exact mechanism of tumorigenesis of lung cancer. Previous studies suggested that receptor tyrosine kinase family member AXL and Hippo signal pathway co-activator YAP may be important signal molecules in tumorigenesis. In this paper we detect AXL and YAP expression in 81 non-small cell lung cancer cases that received surgery, and we discuss the relationship between the expression of AXL and YAP and tissue type, pathological staging, and degree of differentiation. We found that in NSCLC tissues $AXL^{Low}YAP^{Low}$ was 29.63%, $AXL^{High}YAP^{Low}$ was 13.58%, $AXL^{Low}YAP^{High}$ was 25.93% and $AXL^{High}YAP^{High}$ was 30.86%. The expression pattern of AXL and YAP was related to the degree of differentiation, T stage and pathological stage. Based on clinical follow-up data, we assessed the prognostic significance of AXL and YAP combined, with respect to recurrence and long-term survival. NSCLC tended to show AXL and YAP high expression, and high expression of AXL and YAP in NSCLC tissues suggested worse prognosis. Combined detection of AXL and YAP may be a new index to predict NSCLC patients' prognosis.

Keywords: Non-small cell lung cancer (NSCLC), immunohistochemistry, AXL, YAP, expression characteristics, prognosis

Introduction

At present, the morbidity and mortality rate of lung cancer has occupied the first place among cancer in China, and disappointingly, new cases have been increasing year by year [1]. Epidemiological investigation has shown that around 75% of lung cancer is non-small cell lung cancer (NSCLC), whose prognosis is slightly better than small cell lung cancer. However, the five-year survival rate of advanced NSCLC patients is still very low [2]. Therefore, "early detection, early diagnosis and early treatment" has become the top priority to prolong life. As for early detection of tumorigenesis, tumor markers may show special advantages in the early diagnosis of lung cancer and also have great value in prediction of patients' prognosis. However, existing tumor markers in lung cancer are still not satisfactory. It is an urgent task to find tumor markers for NSCLC with high specificity and high sensitivity.

AXL (Anexelekto) belongs to the family of receptor tyrosine kinase that was first successfully cloned from chronic myelogenous leukemia by O'Bryan [3] and others. It is a transmembrane molecule located in chromosome 19q13.1 whose size is around 140 kD. The interaction between AXL and its ligand Gas6 can activate its own tyrosine kinase activity and then activate the downstream signal transduction pathway. AXL also takes part in the regulation of multiple vital activities such as cell adhension, cell proliferation, anti-apoptosis, and cell transformation.

YAP is an important transcriptional co-activator in the Hippo signaling pathway, which can regulate the balance between cell proliferation and apoptosis, so that it is believed that YAP plays an important role in the genesis of multiple cancers. Abnormal expression and subcellular location of YAP is believed to be related to the appearance and invasive growth of tumors, which may indicate poor prognosis. (e. g. breast cancer [4], colon cancer [5]). Recent studies have found that activated YAP may facilitate the expression of AXL. When the expression of

Table 1. Expression of AXL in NSCLC and paracancerous lung issues

TIssue source	*n*	AXL		χ^2	*P*
		High	Low		
NSCLC tissue	81	36 (44.44)	45 (55.56)	9.87	0.0017
Paracancerous lung tissue	23	2 (8.70)	21 (91.30)		

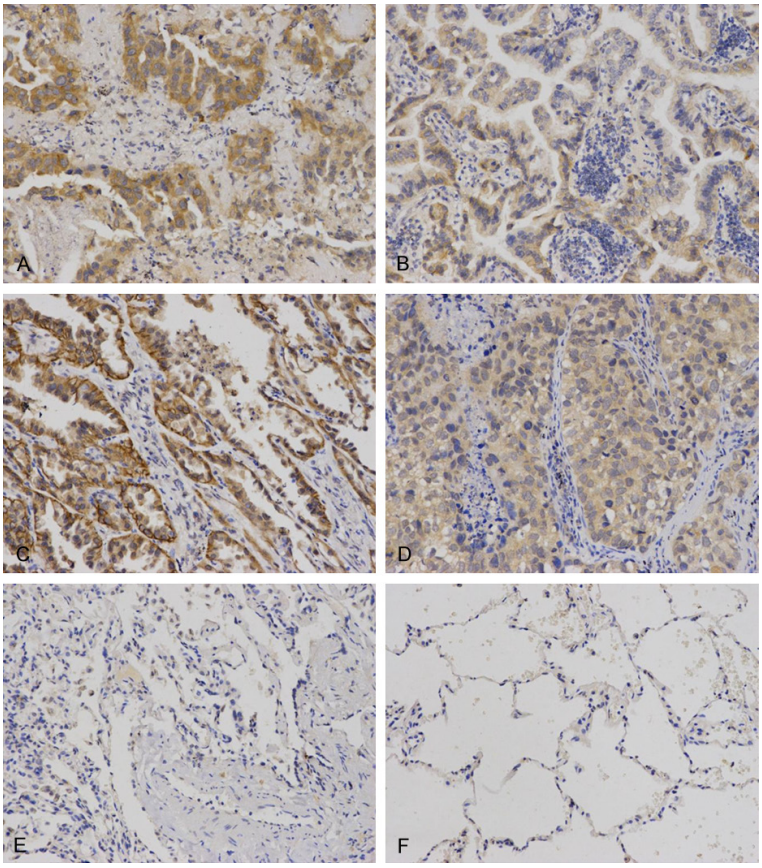

Figure 1. Expression of AXL in NSCLC and paracancerous lung tissue. A: Medium to well differentiated lung adenocarcinoma, AXL^{High}, 200×; B: Medium to welldifferentiated lung squamous cell carcinoma, AXL^{High}, 200×; C: Poorly differentiated lung adenocarcinoma, AXL^{High}, 200×; D: Poorly differentiated lung squamous cell carcinoma, AXL^{High}, 200×; E: Medium to welldifferentiated lung squamous cell carcinoma, AXL^{Low}, 200×; F: Paracancerous tissue, AXL^{Low}, 200×.

YAP was inhibited in lung cancer, the expression of AXL as well as its downstream molecules ERK1/2 and AKt were also down-regulated, and the invasive and transforming potential of tumor cells also dramatically decreased. Conversely, the overexpression of YAP in normal lung cells could result in an increase of AXL protein level and induce malignant transformation [6].

However, more research is needed into the exact relationship between AXL and YAP. We also need more evidence to confirm the clinical significance of AXL and YAP in NSCLC tissues. In this study, the correlation between AXL and YAP expression in NSCLC tissues was analyzed. We also observe the relationship between the AXL and YAP expression level and NSCLC tissue type, pathological stage, and degree of differentiation. We further discuss the clinical value of AXL and YAP expression in prognosis.

Materials and methods

Clinical features

Tissues were collected from 81 cases of non-small cell lung cancer and 23 cases of the paracancer lung tissues (5 centimeters away from the tumor lesions) removed from the lung cancer patients in the Department of Thoracic Surgery of Lishui Central Hospital during the period of 2007 to 2009, among which 60 cases were male, and 21 cases were female. The patients' age range was 36 to 81 and the median age was 60. All cases did not experience radiation therapy or chemotherapy before operation. According to the pathological morphology, they were divided into 42 cases of squamous cell carcinoma, and 39 cases of adenocarcinoma. According to the degree of differentiation, they were divided into 38 cases of medium-high and 43 cases of low differentiation cancer. According to the Union for International Cancer Control (UICC)'s seventh lung cancer pathological staging standard in 2010 (pathological tumor, nodes, metastasis-classification, pTNM): there were 35 cases in Stage I, 11 cases on Stage II, 35 cases in Stage III and no case in Stage IV. All the specimens were fixed in 10% neutral formalin and then desiccated and embedded. After 5 μm paraffin sectioning continuously and HE

Table 2. Expression of YAP in NSCLC and paracancerous lung tissue

Tissue source	*n*	YAP		X^2	*P*
		High	Low		
NSCLC tissue	81	46 (56.79)	35 (43.21)	13.76	< 0.0001
Paracancerous lung tissue	23	3 (13.04)	20 (86.96)		

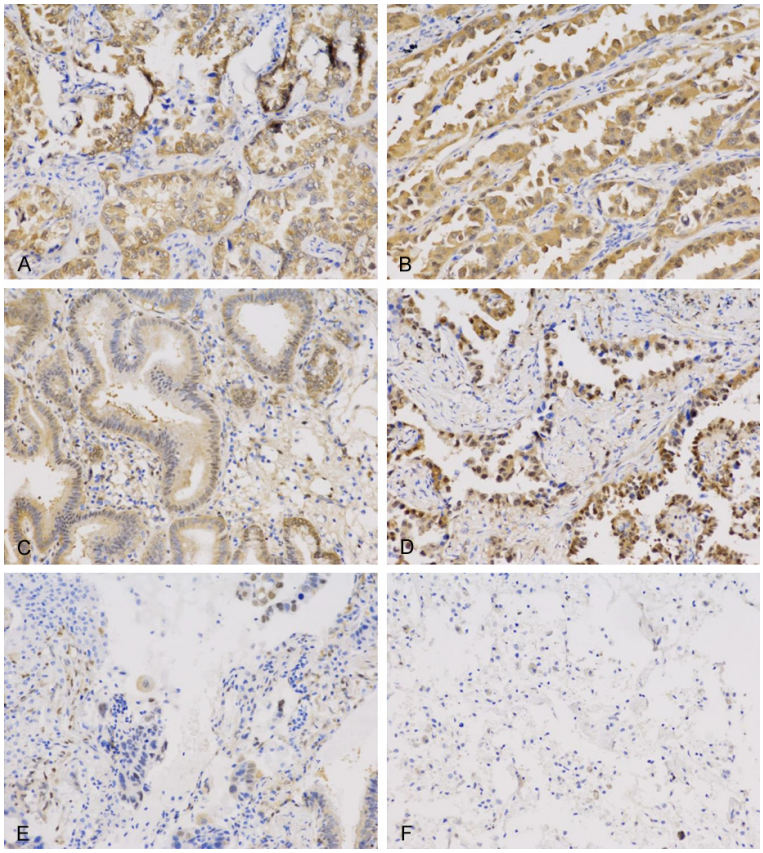

Figure 2. Expression of YAP in NSCLC and paracancerous lung tissue. A: Medium to well differentiated lung adenocarcinoma, YAP^{High}, 200×; B: Medium to well differentiated lung squamous cell carcinoma, YAP^{High}, 200×; C: Poorly differentiated lung adenocarcinoma, YAP^{High}, 200×; D: Poorly differentiated lung squamous cell carcinoma, YAP^{High}, 200×; E: Medium to welldifferentiated lung squamous cell carcinoma, YAP^{Low}, 200×; F: Paracancerous tissue, AXL^{Low}, 200×.

staining, every pathological section was confirmed by two pathologists.

The positive judgment standard

High expression of AXL or YAP in NSCLC tissues was shown by pale brown or chocolate brown particles in cytoplasm and membrane of tumor cells. The parenchymal area of tumors was selected by 100× light microscope in which five views were randomly picked. According to the staining intensity: negative = 0, weak positive = 1, medium positive = 2, strong positive = 3. The numbers of positive staining cells were divided into: ≤ 10% (positive = 0), 11%-30% (weak positive = 1), 31%-50% (medium positive = 2), > 50% (strong positive = 3). When the score sum of these two was ≥ 3, it was judged to be AXL or YAP high expression (AXL^{High}, YAP^{High}); when the sum was < 3, it was AXL or YAP low expression (AXL^{Low}, YAP^{Low}).

Statistical analysis

The SPSS 20.0 software package was used for statistical analysis. In addition, X^2 test was used to make a significant test of the relationship between AXL/YAP high expression and histological types, gender, age, the degree of differentiation, and tumor pathological stag. $P < 0.05$ indicated statistical significance. Log-rank was conducted to analyze the relationship between AXL, YAP expression and prognosis, and Kaplan-Meier was used to make survival curve analysis.

Results

Expression of AXL in NSCLC tissues and paracancer lung tissues

There were 36 AXL high expression cases among 81 NSCLC cases at the rate of 44.44%; there were only 2 AXL high expression cases among 23 paracancer lung tissues at the rate of 8.70%. Comparing these two types, it was revealed that the expression of AXL between NSCLC tissues and paracancer tissues had a significant difference ($P = 0.0017$) (**Table 1** and **Figure 1**).

Expression of YAP in NSCLC tissue and paracancer lung tissue

There were 46 cases with YAP high expression among 81 NSCLC cases at the rate of 56.79%;

Table 3. Combined detection of AXL and YAP expression in NSCLC and paracancerous tissue

Tissue source	*n*	YAP^{Low}		YAP^{High}		*P*
		Axl^{Low}	Axl^{High}	Axl^{Low}	Axl^{High}	
NSCLC tissue	81	24 (29.63)	11 (13.58)	21 (25.93)	25 (30.86)	< 0.0001
Paracanerous lung tissue	23	18 (78.26)	2 (8.70)	3 (13.04)	0 (0.00)	

Table 4. Correlation analysis of AXL and YAP expression in NSCLC tissues

Expression level	YAP		Total	χ^2	*P*
	YAP^{Low}	YAP^{High}			
AXL^{Low}	24	21	45		
AXL^{High}	11	25	36	4.229	0.04
Total	35	46	81		

there were only 3 YAP high expression cases among 23 paracancer lung tissues at the rate of 13.04%. Expression of YAP had significant differences between NSCLC tissues and paracancer tissues (**Table 2** and **Figure 2**).

Combined detection of AXL and YAP expression in NSCLC tissue and paracancer lung tissue

There were 24 $AXL^{Low}YAP^{Low}$ cases, 11 $AXL^{High}YAP^{Low}$ cases, 21 $AXL^{Low}YAP^{High}$ cases, and 25 $AXL^{High}YAP^{High}$ cases among 81 NSCLC cases respectively at the rate of 29.63%, 13.58%, 25.93% and 30.86%; there were 18 $AXL^{Low}YAP^{Low}$ cases, 2 $AXL^{High}YAP^{Low}$ cases, 3 $AXL^{Low}YAP^{High}$ cases, and 0 $AXL^{High}YAP^{High}$ cases among 23 paracancer lung tissues respectively at the rate of 78.26%, 8.70%, 13.04% and 0%. Comparing these two types, it was revealed that there were statistical differences (P < 0.0001) (**Table 3**).

Correlation analysis of AXL and YAP expression in NSCLC

There were 24 $AXL^{Low}YAP^{Low}$ cases, 11 $AXL^{High}YAP^{Low}$ cases, 21 $AXL^{Low}YAP^{High}$ cases, and 25 $AXL^{High}YAP^{High}$ cases among 81 NSCLC tissues. Correlation analysis indicateda significant correlation between AXL expression and YAP expression in NSCLC (P = 0.04) (**Table 4**). We believed that there may be an interaction between AXL and YAP, which may have a synergistic effect on tumorigenesis. However, further studies are needed to demonstrate the exact regulation mechanism between AXL and YAP.

The association between AXL expression in NSCLC tissues and clinical features

The relationship between AXL expression in NSCLC tissues and clinical features is shown in **Table 5**. Based on statistical analysis, AXL expression was not associated with patients age, gender, and histological type. However, it was significantly associated with degree of differentiation, T stage, and pathological TNM stage ($P < 0.05$). The rate of medium-well differentiated NSCLC among AXL high expression tissues was 27.78% (10/36), and that of poor differentiation was 72.22% (26/36). AXL high expression was associated with degree of differentiation ($P < 0.01$); poorly differentiated NSCLC tissues tended to have AXL high expression. In addition, among AXL high expression tissues, the rate of Stage T1 NSCLC tissues was 8.33% (3/36); that of Stage T2 was 44.44% (16/36), that of Stage T3 was 33.33% (12/36), and that of Stage T4 was 13.89% (5/36). There were statistical differences among different stages ($P < 0.01$); a higher AXL expression level may indicate a higher T stage. Also, 16.67% (6/36) of the AXL high expression tissues were in Stage I, 16.67% (6/36) were in Stage II, and 66.67% (24/36) were in Stage III. These were significant differences ($P < 0.01$) (**Table 5**).

Association between YAP expression in NSCLC and clinical features

YAP expression was not associated with patients age, gender,and histological type. However, it was associated with degree of tumor differentiation, T stage, and pathological TNM stage ($P < 0.05$). The rate of medium- well differentiated cancer among YAP high expression tissues was 26.09% (12/46), and that of poor differentiation was 73.91% (34/46). YAP high expression was associated with degree of differentiation ($P < 0.01$); poorly differentiated NSCLC tissues tended to have YAP high expression. In addition, among YAP high expression tissues, the rate of Stage T1 was 8.70% (3/46);

Table 5. Association between AXL expression in NSCLC tissues and clinical features

Clinicopathologic feature	*n*	AXL		χ^2	*P*
		Low	High		
Age				0.23	0.6353
< 60	27	14 (31.11%)	13 (36.11%)		
≥ 60	54	31 (68.89%)	23 (63.89%)		
Gender				0.46	0.4963
Male	60	32 (71.11%)	28 (77.78%)		
Female	21	13 (28.89%)	8 (22.22%)		
Differentiation				9.53	0.0020
Medium-well differentiated	38	28 (62.22%)	10 (27.78%)		
Poorly differentiated	43	17 (37.78%)	26 (72.22%)		
Histologic type				1.09	0.2964
Squamous carcinoma	42	21 (46.67%)	21 (58.33%)		
Adenocarcinoma	39	24 (53.33%)	15 (41.67%)		
T stage				2.84	0.0046
T1	12	9 (20.00%)	3 (8.33%)		
T2	44	28 (62.22%)	16 (44.44%)		
T3	18	6 (13.33%)	12 (33.33%)		
T4	7	2 (4.44%)	5 (13.89%)		
Pathological TNM stage				4.30	< .0001
I	35	29 (64.44%)	6 (16.67%)		
II	11	5 (11.11%)	6 (16.67%)		
III	35	11 (24.44%)	24 (66.67%)		
IV	0	0 (0.00%)	0 (0.00%)		

that of Stage T2 was 41.30% (19/46), that of Stage T3 was 34.78% (16/46), and that of Stage T4 was 15.22% (7/46). There were statistical differences among different T stages ($P < 0.01$). Also, among YAP high expression tissues, 10.87% (5/46) were in Stage I, 15.22% (7/46) were in Stage II, and 73.91% (34/46) were in Stage III. These were significant differences ($P < 0.01$) (**Table 6**).

Association between combined detection of AXL and YAP expression in 81 NSCLC tissues and paracancer lung tissues and its clinical features

The relationship between the combined detection of AXL and YAP expression in 81 NSCLC tissues and paracancer lung tissues and its clinical features was showed in **Table 6**. Based on statistical analysis, it was found: AXL and YAP expression were not associated with patients age, gender, or histological type. However, they was associated with the degree of differentiation, T stage, and pathological TNM stage (**Table 7**).

Association between AXL expression in NSCLC tissues and its prognosis

Among 81 patients, the shortest survival time was 8 months. There were 26 deaths in 36 NSCLC patient cases with AXL high expression; but there were only 11 deaths in 45 NSCLC patients with low expression. Comparing the two types, the statistical result showed AXL expression was related to NSCLC patients' prognosis (**Figure 3**).

The association between YAP expression in NSCLC tissues and its prognosis

There were 31 deaths in 46 NSCLC patient cases with YAP high expression; but there were only 6 deaths in 35 NSCLC patient cases with low expression. Comparing the two types, the statistical result showed YAP expression was related to NSCLC patients' prognosis (**Figure 4**).

Association between combined detection of AXL and YAP expression in NSCLC tissues and prognosis

There were 3 deaths in 24 NSCLC patient cases with $AXL^{Low}YAP^{Low}$; 3 deaths in 11 NSCLC patient cases with $AXL^{High}YAP^{Low}$; 8 deaths in 21 NSCLC patient cases with $AXL^{Low}YAP^{High}$; 23 deaths in 25NSCLC patient cases with AXL^{High} YAP^{High} whose prognosis was worse ($P < 0.0001$). Statistical results showed that combined detection of AXL and YAP had superior prognostic value for NSCLC patients (**Figure 5**).

Discussion

At present, China occupies first place in lung cancers in the whole world, and morbidity rate and mortality rate are No.1 among malignant tumors [1]. Among confirmed lung cancer cases, the non-small cell lung cancer (NSCLC) cases account for 85%. When diagnosed, most

Table 6. Association between YAP expression in NSCLC tissues and clinical features

Clinicopathologic feature	*n*	AXL		χ^2	*P*
		Low	High		
Age				1.61	0.2045
< 60	27	9 (25.71%)	18 (39.13%)		
≥ 60	54	26 (74.29%)	28 (60.87%)		
Gender				1.13	0.2884
Male	60	28 (80.00%)	32 (69.57%)		
Female	21	7 (20.00%)	14 (30.43%)		
Differentiation				18.54	< .0001
Medium-well differentiated	38	26 (74.29%)	12 (26.09%)		
Poorly differentiated	43	9 (25.71%)	34 (73.91%)		
Histologic type				0.00	0.9470
Squamous carcinoma	42	18 (51.43%)	24 (52.17%)		
Adenocarcinoma	39	17 (48.57%)	22 (47.83%)		
T stage				4.08	< .0001
T1	12	8 (22.86%)	4 (8.70%)		
T2	44	25 (71.43%)	19 (41.30%)		
T3	18	2 (5.71%)	16 (34.78%)		
T4	7	0 (0.00%)	7 (15.22%)		
Pathological TNM stage				6.95	< .0001
I	35	30 (85.71%)	5 (10.87%)		
II	11	4 (11.43%)	7 (15.22%)		
III	35	1 (2.86%)	34 (73.91%)		
IV	0	0 (0.00%)	0 (0.00%)		

NSCLC patients already are mid-term and terminal stage, among which 16% are Stage IIIA, 8% are Stage IIIB, and 41% are Stage IV [7, 8]. Although multiple therapeutic options such as operation, radiation therapy, chemotherapy, neo-adjuvant therapy, and biological target therapy have made dramatic progress, the total therapeutic effect is still not satisfactory [2]. Therefore, "early detection, early diagnosis, early treatment" is the top priority to make lung cancer patients live longer. Because of the special advantages of tumor markers in early diagnosis and their practical value in patients' prognostic assessment, selecting new tumor markers with high specificity and high sensitivity is an urgent and important task for clinical and scientific research of lung cancer.

The appearance and development of NSCLC is a complicated process with many steps. A great number of genes play important roles in the development of NSCLC, which have clinical significance. Malignant transformation of normal tissues depends on insensitivity to cell inhibition factors, apoptosis resistance, and unlimited proliferation, which are all caused by the change of some specific cell factors and related abnormal signaling pathway regulation [9, 10]. Therefore, the detection of related genes in tumor tissues provides an experimental basis for early diagnosis of lung cancers and clinical therapy, further providing a theoretical foundation for judging prognosis.

AXL overexpression increased the invasive degree of tumors related to patients' poor prognoses. Hector's [11] research on 92 cases of esophageal adenocarcinoma revealed that AXL high expression was related to depth of invasion, lymph node metastasis, and T stage; andmedian survival of AXL high expression patients was much shorter than that of negative expression patients (P = 0.004), which was an independent factor for poor prognosis. In addition, AXL high expression was closely related to the transformation of esophageal Barrett mucosa to adenocarcinoma. Shieh [12] used immunohistochemistry to study AXL expression in 58 lung adenocarcinoma cases, finding that AXL expression was related to lymph node metastasis and clinical stage ($P < 0.001$). In this study, we found that AXL-high expression rate in NSCLC was much higher than that of paracancer lung tissues ($P < 0.01$). AXL high expression was related to the degree of differentiation, T stage and pathological stage, but AXL-high expression was not related to gender, age, or histological type. The shortest survival time of 81 cases was 8 months. There were 26 deaths in 36 AXL-high expression NSCLC patients; but only 11 deaths in 45 AXL-low expression NSCLC patients. These results also revealed that AXL-high expression probably indicated tumor progression and poor prognosis, consistent with previous studies.

Table 7. Association between combined detection of AXL and YAP expression in 81 NSCLC tissues and paracancer lung tissues and clinical features

Clinicopathologic feature	n	YAP^{Low}		YAP^{High}		χ^2	*P*
		AXL^{Low}	AXL^{High}	AXL^{Low}	AXL^{High}		
Age						1.65	0.6490
< 60	27	6 (25.00%)	3 (27.27%)	8 (38.10%)	10 (40.00%)		
≥ 60	54	18 (75.00%)	8 (72.73%)	13 (61.90%)	15 (60.00%)		
Gender						1.02	0.2210
Male	60	20 (83.33%)	8 (72.73%)	12 (57.14%)	20 (80.00%)		
Female	21	4 (16.67%)	3 (27.27%)	9 (42.86%)	5 (20.00%)		
Differentiation						37.25	< .0001
Medium-well differentiated	38	20 (83.33%)	6 (54.55%)	8 (38.10%)	4 (16.00%)		
Poorly differentiated	43	4 (16.67%)	5 (45.45%)	13 (61.90%)	21 (84.00%)		
Histological type						1.41	0.7031
Squamous carcinoma	42	12 (50.00%)	6 (54.55%)	9 (42.86%)	15 (60.00%)		
Adenocarcinoma	39	12 (50.00%)	5 (45.45%)	12 (57.14%)	10 (40.00%)		
T stage						20.67	0.0001
T1	12	6 (25.00%)	2 (18.18%)	3 (14.29%)	1 (4.00%)		
T2	44	18 (75.00%)	7 (63.64%)	10 (47.62%)	9 (36.00%)		
T3	18	0 (0.00%)	2 (18.18%)	6 (28.57%)	10 (40.00%)		
T4	7	0 (0.00%)	0 (0.00%)	2 (9.52%)	5 (20.00%)		
Pathological TNM stage						56.17	< .0001
I	35	24 (100.00%)	6 (54.55%)	5 (23.81%)	0 (0.00%)		
II	11	0 (0.00%)	4 (36.36%)	5 (23.81%)	2 (8.00%)		
III	35	0 (0.00%)	1 (9.09%)	11 (52.38%)	23 (92.00%)		
IV	0	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)		

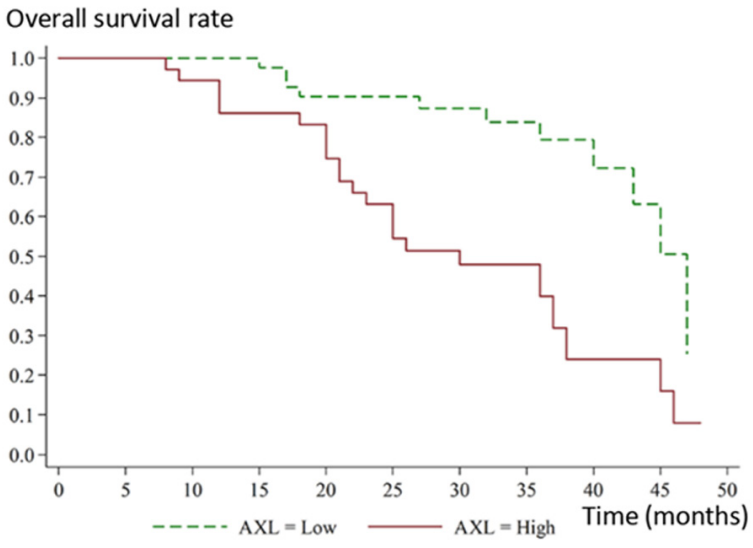

Figure 3. Association between AXL expression in NSCLC tissues and prognosis.

YAP has already been confirmed as a crucial effector in the Hippo signal transduction pathway that regulates the balance between cell growth and apoptosis as well as the occurrence of tumors. The abnormal expression and location of YAP are considered closely related to the appearance and invasive growth of tumors and an unfavorable prognosis [13, 14]. Zhao [15] used immunohistochemistry to detect expression of 115 lung cancer cases, showing that in 54% (63/115) lung cancer cells, YAP expression was positive and located in the nucleus; however, in 95% (40/42) of normal lung tissues, YAP expression was weak positive. YAP expression levels in normal and cancer tissues had statistical differences ($P < 0.001$), showing that the abnormal expression of YAP and the change of subcellular localization play important roles in the appearance and development of lung can-

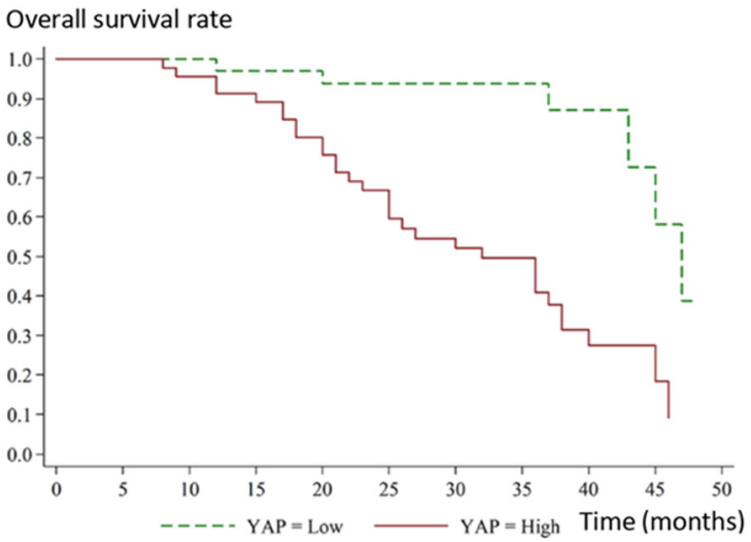

Figure 4. Association between YAP expression in NSCLC tissues and prognosis.

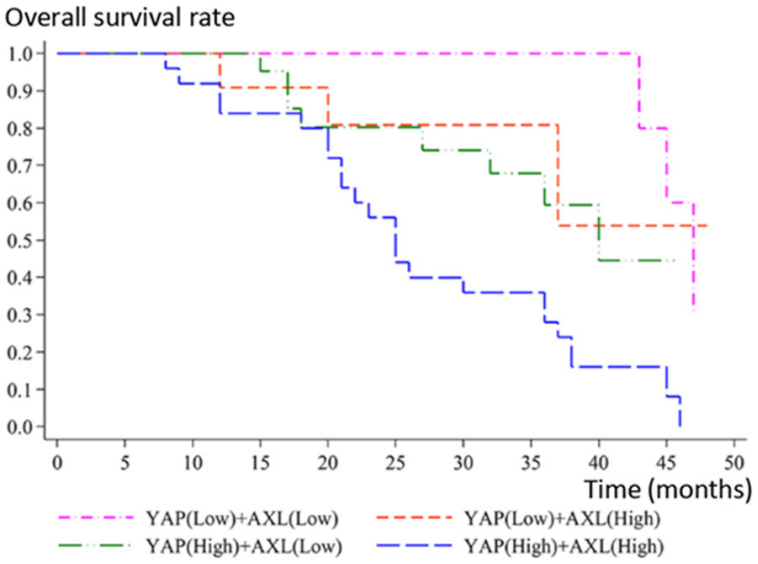

Figure 5. Association between combined detection of AXL and YAP expression in NSCLC tissues and prognosis.

cer. Lam-Himlin's group [16] studied YAP expression in 51 normal esophagus mucosa basal layer cases, 54 mature squamous metaplasia cases, 31 severe atypical hyperplasia cases, and 65 esophagus cancer cases by immunohistochemistry and tissue chip technology. The YAP expression rate in normal basal layer nuclei of hyperplastic mucosa was 45%, which was significantly higher than the cytoplasmic positive rate of 14% and mature squamous metaplasia nuclear expression of 20%. The expression in severe atypical hyperplasia and esophageal cancer nucleus and cytoplasm (32%, 38% and 45%, 48%) also were much higher than that of normal epithelial cells (20%, 20%).

In the current study, combined AXL and YAP expression characteristics were studied in NSCLC with regard to prognosis. There were 24 AXL^{Low} YAP^{Low} cases in 81 NSCLC tissues cases at the proportion of 29.63%; 11 $AXL^{High}YAP^{Low}$ cases at 13.58%; 21 AXL^{Low} YAP^{High} cases at 25.93%; and 25 $AXL^{High}YAP^{high}$ cases at 30.86%. In addition, there were 18 $AXL^{Low}YAP^{Low}$ cases in 23 paracancer lung cases at the proportion of 78.26%; 2 $AXL^{High}YAP^{Low}$ cases at 8.70%; 3 $AXL^{Low}YAP^{High}$ cases at 13.04%; 0 $AXL^{High}YAP^{High}$ case at 0%. The AXL and YAP expressions were related to degree of differentiation, T stage, and pathological stage ($P < 0.0001$, $P = 0.0001$, $P < 0.0001$), but they had no statistical significance regarding gender, age, and histological type. There were 3 deaths in 24 $AXL^{Low}YAP^{Low}$ NSCLC patients; 3 deaths in 11 AXL^{High} YAP^{Low} patients; 8 deaths in 21 $AXL^{Low}YAP^{High}$ patients; and 23 deaths in 25 $AXL^{High}YAP^{High}$ patients, whose prognosis was worst ($P < 0.0001$). Hence, we believe combined detection of AXL and YAP expression can better judge and assess NSCLC prognosis, and also could set a new standard for NSCLC prognosis assessment.

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Disclosure of conflict of interest

None.

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