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# PINK1 Expression Is Associated with Poor Prognosis in Lung Adenocarcinoma

**Guannan Chang,[1] Wenqing Zhang,[2] Yun Ma[3] and Qiang Wen[4]**

[1]Department of Cardiology, Yidu Central Hospital, Weifang, China
[2]Department of Geriatrics, Yidu Central Hospital, Weifang, China
[3]Department of Intensive Care Unit, Yidu Central Hospital, Weifang, China
[4]Department of Internal Medicine, Eastern District of Linyi Peoples' Hospital, Linyi, China

PTEN-induced putative kinase protein 1 (PINK1) is a serine/threonine-protein kinase that phosphorylates mitochondrial proteins and is involved in mitophagy. Thus, PINK1 may protect cancer cells against mitochondrial dysfunction during cellular stress. However, the role of PINK1 in lung cancer was rarely explored. In this study, we immunohistochemically analyzed the expression of PINK1 in 256 patients with non-small-cell lung cancer, consisting of 137 patients with adenocarcinoma (AC) and 119 patients with squamous cell carcinoma (SCC). In particular, we focused on the difference in diagnostic or prognostic value of PINK1 expression between AC patients and SCC patients. The patients with AC or SCC were divided into high or low PINK1 expression group, according to the immunohistochemical score that was based on the percentage of PINK1 positive cells and staining intensity. Among the 137 AC specimens, 52 specimens (37.96%) were judged as high PINK1 expression, and likewise, among 119 SCC specimens, 42 specimens (35.29%) were judged as high PINK1 expression. Importantly, high PINK1 expression was significantly associated with postoperative chemoresistance of AC, but not in case of SCC. Moreover, high PINK1 expression was identified as a poor prognostic factor for AC, but not for SCC. These results may reflect the biological difference between AC and SCC. In conclusion, high PINK1 expression is correlated with poor response to chemotherapy and is an independent prognostic factor for AC, but not for SCC. Our findings suggest that PINK1 detection could help stratify patients who may have poor response to chemotherapy and guide the individual treatment.

**Keywords:** adenocarcinoma; non-small-cell lung carcinoma; PTEN-induced putative kinase protein 1; prognosis; squamous carcinoma
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## Introduction

Lung cancer is one of the most common and deadly cancers worldwide (Siegel et al. 2014). Approximately about 220,000 new cases are diagnosed with lung cancer with 150,000 deaths every year in USA (Siegel et al. 2014). Lung cancer is well identified to originate from the gene-environment interactions. In developing countries such as China, air pollution and haze are more and more severe, leading to the increase of morbidity of lung cancer. The treatment choices and adjuvant therapies have been dramatically improved during the past decades, but the overall 5-year survival rate of lung cancer is still very unsatisfactory, remaining 10%-15% (Siegel et al. 2014). Histologically, lung cancer is mainly comprised of small-cell lung cancer and non-small-cell lung cancer (NSCLC) because of their different treatment strategies and prognoses. NSCLC accounts for about 80% of all cases of lung cancers (Chen et al. 2014), and are further divided into adenocarcinoma (AC) and squamous cell carcinoma (SCC). AC and SCC account for approximately 40% and 25%-30% of all lung cancers, respectively (Zhan et al. 2016). Although both SCC and AC are included into NSCLC with similar treatment strategy, their biological features and clinical manifestations are obviously different (Hirsch et al. 2016). For example, SCC frequently arises in the proximal bronchi, whereas most ACs are localized to the periphery of the lung (Hirsch et al. 2008). Moreover, smoking had stronger correlation with SCC compared with AC (Saito et al. 2017). Recently, large-scale gene expression profiling revealed the difference between AC and SCC from whole genome to single biomarker exploration (Zhang et al. 2015). Based on this breakthrough in high-throughput screening, the verification of new biomarkers of SCC or AC must be investigated separately because of their difference biological feature.

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Correopondence: Qiang Wen, Department of Internal Medicine, Eastern District of Linyi People's Hospital, 27 Jiefang Road, Linyi, Shandong 276000, China.
e-mail: awm562081@163.com

Mitophagy is a kind of selective autophagy, mediating the clearance of damaged mitochondria. The sustaining activation of tumor cell mitophagy can improve the ability of tumor cells to survive in extreme environments, leading to chemoresistance and poor prognosis (Villa et al. 2017). Phosphatase and tensin homolog (PTEN)-induced kinase 1 (PINK1) is a critical protein involved in mitophagy. PINK1 functions as a serine/threonine-protein kinase by phosphorylating mitochondrial proteins and protect against mitochondrial dysfunction during cellular stress (Kane et al. 2014). PINK1 was also proved to be involved in processes of cancer cell biology, including cell survival, mitochondrial homeostasis, stress resistance, and cell cycle (Murata et al. 2011; O'Flanagan et al. 2015).

As an essential mediator of mitochondria-dependent apoptosis, PINK1 is a widely expressed protein and has an average expression in lungs compared with other organs (https://www.proteinatlas.org/). PINK1 is involved in the normal function of lungs; namely, the altered expression was observed in several lung diseases. For example, PINK1 deficiency could promote lung fibrosis by impairing mitochondrial homeostasis (Bueno et al. 2015), and PINK1 expression was demonstrated to be lower in the lungs of patients with idiopathic pulmonary fibrosis than in healthy controls with Western blotting and qPCR analyses (Yu et al. 2018). PINK1-knockout mice exhibit deformed mitochondria and are more susceptible to pulmonary fibrosis than wild-type mice. A previous study indicated that NSCLC tissues showed higher levels of PINK1 protein compared with adjacent tissues, and demonstrated that PINK1 could promote proliferation of NSCLC (Zhang et al. 2017). However, the role and prognostic value of PINK1 in AC or SCC should be discussed separately because of their different biological features (Hirsch et al. 2016).

In the present study, we immunohistochemically analyzed PINK1 expression in the cancer specimens obtained from 256 patients with NSCLC, consisting of 137 AC and 119 SCC cases. The correlation between PINK1 expression and clinicopathological factors in AC or SCC was analyzed with Chi-Square test. With univariate and multivariate analyses, we further evaluated the prognostic significance of PINK1 expression in NSCLC, AC and SCC.

## Materials and Patients

*Patients and follow-up*

The study was approved and supervised by Ethical Committees of Yidu Central Hospital and Linyi People's Hospital. A total of 635 patients who underwent the resection of NSCLC in Yidu Central Hospital or Linyi People's Hospital from 2006-2016 comprised the primary cohort, and 256 patients with NSCLC were selected as follows: (1) available for follow-up; (2) available samples for immunohistochemistry (IHC); (3) radical section of the tumor; and (4) no preoperative adjuvant therapy. The 256 patients constituted the test cohort, with the average age as 59.4 years old and the average follow-up for 34.2 months. There were 137 patients with AC and 119 patients with SCC. Among the 256 NSCLC specimens, the seemingly normal lung tissues adjacent to AC or SCC were available from 32 specimens (20 AC cases and 12 SCC cases). PINK1 expression was analyzed with IHC. The pathologic tumor-node-metastasis (TNM) classification was based on the 7th International Union Against Cancer (2009).

*Immunohistochemistry and evaluation*

The expression of PINK1 was detected by IHC with a streptavidin-biotin immunoperoxidase method. In brief, the formalin-fixed and paraffin-embedded NSCLC samples were deparaffinized in xylene and graded ethanol firstly, followed by antigen retrieval in citrate buffer for 30 minutes and inactivation of endogenous peroxidase enzyme in 3% $H_2O_2$ for 20 minutes. Specimens were incubated with primary antibody against PINK1 (ProSci Inc., Poway, CA, United States) at dilution of 1:100 at 4°C overnight, and rinsed 3 times with phosphate buffer saline. Then the slides were incubated in the corresponding secondary antibody (Sangon Biotech, Shanghai, China) and streptavidin-peroxidase complex (Sangon Biotech, Shanghai, China) at 37°C for 30 minutes and visualized by incubation of 3,3′-diaminobenzidine solution (Sangon Biotech, Shanghai, China).

The evaluation of IHC results was performed by two senior pathologists who were aware of the clinical data. According to previous studies (Xu et al. 2014), the final IHC score was calculated by the score of staining intensity multiplied by the score of positive cells percentage, ranging from 0 to 9 in our study. The score of staining intensity was defined as: 0 for negative staining; 1 for weak staining; 2 for moderate staining; and 3 for strong staining. The score of positive cell percentage was defined as follows: 0 for 10% positive cells; 1 for 10%-30% positive cells; 2 for 30%-50% positive cells; and 3 for 50% or more positive cells. The cut-off value was defined with receiver operating characteristic (ROC) curve. In ROC curve, the point with the highest sensitivity and specificity was set as the cut-off and divided the cohort into patients with high PINK1 expression and low PINK1 expression. In our study, patients with IHC score $\geq 6$ were defined as the group with high PINK1 expression and patients with IHC score $< 6$ were defined as the low PINK1 expression.

*Statistical analysis*

All the data in our study were analyzed with SPSS 22.0 software (SPSS, Inc., Chicago, IL, USA). The correlation between PINK1 expression and the clinicopathological factors was calculated with Chi-Square test. The survival curves were exhibited with Kaplan-Meier method and statistical significance of survival was analyzed with the log-rank test. The independent prognostic factors were identified with the Cox regression hazard model. $P < 0.05$ was considered to be statistically significant.

## Results

*Basic information of the patients*

Among the 256 patients with NSCLC, there were 137 patients with AC (53.52%) and 119 patients with SCC (46.48%). Our cohort was comprised of 167 male patients and 89 female patients (Table 1). PINK1 expression was analyzed with IHC in all the 256 NSCLCs, including 20 pairs of AC tissues and adjacent tissues and 12 pairs of SCC tissues and adjacent tissues. The expression of PINK1 in NSCLCs and adjacent tissues was semi-quantified with IHC

Table 1. Basic information of patients with NSCLC.

| Characters | NSCLC | | AC | | SCC | |
|---|---|---|---|---|---|---|
| | number | percentage | number | percentage | number | percentage |
| Sex | | | | | | |
| Male | 167 | 65.23% | 94 | 68.61% | 73 | 61.34% |
| Female | 89 | 34.77% | 43 | 31.39% | 46 | 38.66% |
| Age | | | | | | |
| < 60 | 108 | 42.19% | 25 | 18.25% | 83 | 69.75% |
| ≥ 60 | 148 | 57.81% | 112 | 81.75% | 36 | 30.25% |
| Tumor diameter (cm) | | | | | | |
| ≤ 3 | 101 | 39.45% | 43 | 31.39% | 58 | 48.74% |
| > 3 | 155 | 60.55% | 94 | 68.61% | 61 | 51.26% |
| Differentiation | | | | | | |
| Poor | 120 | 46.88% | 67 | 48.91% | 53 | 44.54% |
| Moderate | 77 | 30.08% | 53 | 38.69% | 24 | 20.17% |
| Good | 59 | 23.05% | 17 | 12.41% | 42 | 35.29% |
| Lymph invasion | | | | | | |
| No | 143 | 55.86% | 57 | 41.61% | 86 | 72.27% |
| Yes | 113 | 44.14% | 80 | 58.39% | 33 | 27.73% |
| Chemoresistance | | | | | | |
| No | 139 | 54.30% | 68 | 49.64% | 75 | 63.03% |
| Yes | 117 | 45.70% | 69 | 50.36% | 44 | 36.97% |
| TNM stage | | | | | | |
| I + II | 141 | 55.08% | 51 | 37.23% | 90 | 75.63% |
| III – IV | 115 | 44.92% | 86 | 62.77% | 29 | 24.37% |
| Smoking | | | | | | |
| Yes | 94 | 36.72% | 62 | 45.26% | 32 | 26.89% |
| No | 162 | 63.28% | 75 | 54.74% | 87 | 73.11% |
| PINK1 | | | | | | |
| Low | 161 | 62.89% | 85 | 62.04% | 77 | 64.71% |
| High | 95 | 37.11% | 52 | 37.96% | 42 | 35.29% |

score. As a protein mediating mitophagy, PINK1 was mainly observed in the cytoplasm in both tumor tissues and the tumor adjacent tissues (Fig. 1A-F). Among all the NSCLCs, cases with low PINK1 expression and high PINK1 expression accounted for 62.89% and 37.11%, respectively (Table 1). There was no significant difference in the percentage of high PINK1 expression between AC (37.96%) and SCC (35.29%). The average IHC score of PINK1 expression in normal lung tissues was significantly lower than in AC tissues (P = 0.005) (Fig. 1G), but such a difference was not observed in SCC (P = 0.688) (Fig. 1H). However, no significant difference was detected in the IHC scores between AC and SCC and between AC adjacent tissues and SCC adjacent tissues (Fig. 1I, J). These findings support the recognized conclusion that AC and SCC have different biological features.

*Correlation between PINK1 and the clinicopathological factors*

The correlation between PINK1 and each of the clinicopathological factors in NSCLC was evaluated with Chi-Square test (Table 2). In NSCLC, high PINK1 expression was significantly associated with postoperative chemoresistance (P = 0.018), indicating that PINK1 may be involved in the processes of resistance to chemotherapy. This could be explained by the fact that PINK1 is involved in mitophagy, which plays a key role in tumor cell survival and chemoresistance. We further classified NSCLC to AC and SCC because they have different biological features. Importantly, AC patients with high PINK1 expression were more predisposed to chemoresistance (P = 0.006), whereas SCC patients did not show such tendency (P = 0.846). Moreover, AC patients with high PINK1 expression tended to be more susceptible to lymphatic invasion, although the difference was not significant (P = 0.074). In case of SCC, smokers had high PINK1 compared with non-smokers (P = 0.004), indicating that smoking may contribute to high expression of PINK1.

*Correlation between PINK1 expression and the overall survival rate*

The prognostic values of PINK1 expression and the other clinicopathological factors were evaluated by univariate analysis with Kaplan-Meier method first (Table 3).

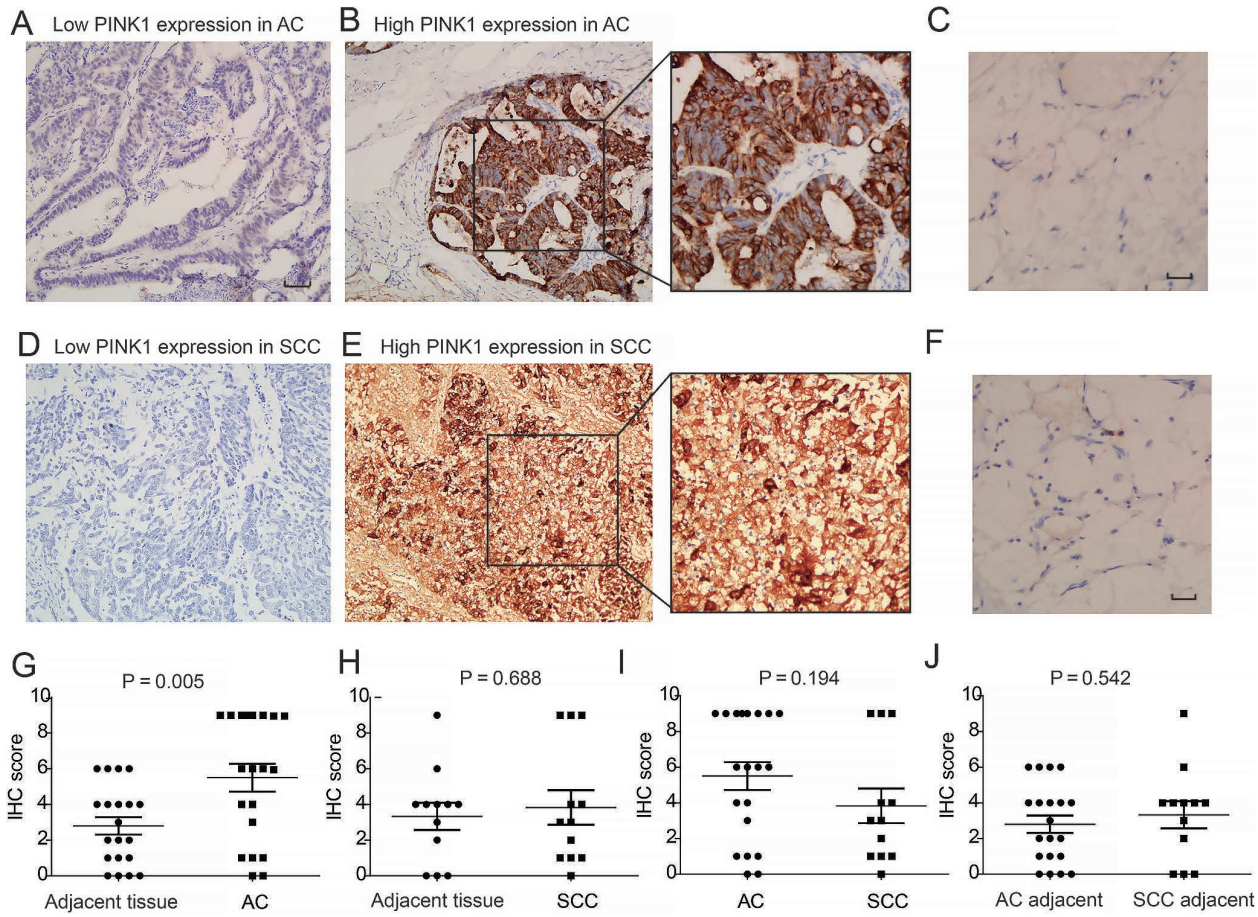


Fig. 1. PINK1 expression in AC, SCC, and adjacent lung tissues.
A. The image of an AC specimen, defined as low PINK1 expression. The total IHC score was 3. Scale bar: 100 $\mu$m.
B. The image of an AC specimen, defined as high PINK1 expression. The total IHC score was 9, and an enlarged image is shown at right panel.
C. The image of PINK1 expression in the adjacent tissue to AC (B) of the same patient. The IHC score was defined as 2. Scale bar: 50 $\mu$m.
D. The representative image of a SCC specimen, defined as low PINK1 expression. The total IHC score was 0.
E. The representative image of a SCC specimen, defined as high PINK1 expression. The total IHC score was 9, and an enlarged image is shown at right panel.
F. The representative image of PINK1 expression in the adjacent tissue to SCC (E) of the same patient. The IHC score was defined as 3. Scale bar: 50 $\mu$m.
G. The expression of PINK1 in 20 cases of ACs was significantly higher than in adjacent tissues.
H. IHC scores of PINK1 expression in 12 pairs of SCCs and adjacent tissues had no significant difference.
I and J. In the 20 cases of ACs, 12 cases of SCCs and their corresponding adjacent tissues, the IHC scores of PINK1 expression between ACs and SCCs (P = 0.194) (I), between AC adjacent tissues and SCC adjacent tissues (P = 0.542) (J) had no significant statistical difference.

High PINK1 expression was significantly associated with lower survival rates among patients with NSCLC (P = 0.026) (Fig. 2A). Moreover, the lymphatic invasion, chemoresistance, and advanced TNM stage were all prognostic factors predicting unfavorable prognosis. Importantly, AC and SCC exhibited some different features in the univariate analysis. PINK1 expression still indicated the poor prognosis in AC (P = 0.002), but its prognostic value in SCC was almost vanished (P = 0.740). In AC, other prognostic factors included lymphatic invasion, chemoresistance and TNM stage. In SCC, only positive lymphatic invasion and advanced TNM stage were proved to be significantly correlated to poor prognosis.

*Independent prognostic factors in AC*

The independent prognostic significance was evaluated by multivariate analysis with the Cox-regression model (Table 4). The prognostic factors which were verified in univariate were all enrolled, including the chemoresistance, lymphatic invasion and PINK1 expression. TNM was excluded because it had obvious interaction with N stage, namely the lymphatic invasion in univariate analysis. In NSCLC, the lymph invasion (P = 0.018) and chemoresistance (P = 0.002) were identified as the independent prognostic

Table 2. Correlation between PINK1 and clinicopathologic parameters.

| Parameters | NSCLC | | | AC | | | SCC | | |
|---|---|---|---|---|---|---|---|---|---|
| | PINK1 | | | PINK1 | | | PINK1 | | |
| | Low | High | P* | Low | High | P* | Low | High | P* |
| Sex | | | | | | | | | |
| Male | 107 | 60 | 0.592 | 59 | 35 | 0.851 | 48 | 25 | 0.845 |
| Female | 54 | 35 | | 26 | 17 | | 29 | 17 | |
| Age | | | | | | | | | |
| < 60 | 66 | 42 | 0.615 | 15 | 10 | 0.823 | 51 | 32 | 0.301 |
| ≥ 60 | 95 | 53 | | 70 | 42 | | 26 | 10 | |
| Tumor diameter | | | | | | | | | |
| ≤ 3cm | 69 | 32 | 0.147 | 29 | 14 | 0.450 | 41 | 17 | 0.183 |
| > 3cm | 92 | 63 | | 56 | 38 | | 36 | 25 | |
| Differentiation | | | | | | | | | |
| Poor | 74 | 46 | 0.765 | 40 | 27 | 0.745 | 35 | 18 | 0.893 |
| Moderate | 51 | 26 | | 35 | 18 | | 16 | 8 | |
| Good | 36 | 23 | | 10 | 7 | | 26 | 16 | |
| Lymph invasion | | | | | | | | | |
| No | 96 | 48 | 0.156 | 41 | 17 | 0.074 | 56 | 30 | 0.880 |
| Yes | 65 | 47 | | 44 | 35 | | 21 | 12 | |
| Chemoresistance | | | | | | | | | |
| No | 99 | 44 | 0.018 | 50 | 18 | 0.006 | 49 | 26 | 0.846 |
| Yes | 62 | 51 | | 35 | 34 | | 28 | 16 | |
| TNM stage | | | | | | | | | |
| I + II | 94 | 47 | 0.166 | 37 | 14 | 0.068 | 58 | 32 | 0.916 |
| III – IV | 67 | 48 | | 48 | 38 | | 19 | 10 | |
| Smoking | | | | | | | | | |
| Yes | 52 | 42 | 0.056 | 39 | 23 | 0.862 | 14 | 18 | 0.004 |
| No | 109 | 53 | | 46 | 29 | | 63 | 24 | |

*Calculated by Chi-Square test.

factors. In AC, high expression of PINK1 was an independent factor predicting unfavorable prognosis (P = 0.006). Besides PINK1 expression, the lymphatic invasion was also demonstrated to be associated with prognosis independently (P = 0.023).

## Discussion

Mitophagy is a fundamental process for clearance of damaged or excessive mitochondria by degradation in autophagosomes (Bernardini et al. 2016), which is essential for mitochondria quality control and could prevent excessive production of cytotoxic reactive oxygen species from damaged mitochondria. Generally, mitophagy is tumor suppressive during early tumorigenesis, but its role in advanced cancer has not received complete consensus (Zhong et al. 2016). Substantial evidence suggested the oncogenic role or tumor suppressive role of PINK1. For example, PINK1 was reported to inhibit apoptosis in breast cancer cell line and play an oncogenic role, but inhibit glioblastoma cell growth and act as a tumor suppressor (Berthier et al. 2011; Agnihotri et al. 2016).

In lung cancer, the oncogenic role of Parkin loss has been reported in a previous study (Veeriah et al. 2010), and the impaired autophagy resulted from Parkin loss was considered as the reason why Parkin loss led to the tumorigenesis of lung cancer. Compared with Parkin, the role of PINK1 in lung cancer attracted little interest of scientists. For the first time, we identified PINK1 as a correlator with chemoresistance and a predictor of poor prognosis of AC, but not in case of SCC. This is an important supplement to the roles of PINK1 and mitophagy in AC. Detecting PINK1 expression in AC may help identify the patients who may have poor prognosis and help guide the precise treatment to them.

As an essential process in cell survival in extreme environment, autophagy activation helps tumor cells survive during the chemotherapy. Several lines of evidence demonstrated the enhanced autophagy of tumor cells is associated with the positive resistance to chemotherapy and indicates inhibitors of autophagy as novel cancer therapeutic agents (Wang et al. 2016; Lei et al. 2017). In our study, the finding that overexpression of PINK1 was associated with chemoresistance was reported in several cancers such as esophageal squamous cell carcinoma (Yamashita et al. 2017). In NSCLC, a recent study demonstrated that PINK1 could enhance cell survival and mediate drug resistance in

Table 3. The correlation between clinicopathological factors and survival rates was analyzed with univariate analysis.

| Characters | NSCLC | | | AC | | | SCC | | |
|---|---|---|---|---|---|---|---|---|---|
| | n | 5-year OS | P* | n | 5-year OS | P* | n | 5-year OS | P* |
| Sex | | | | | | | | | |
| Male | 167 | 36.6 | 0.548 | 94 | 42.2 | 0.529 | 73 | 32.9 | 0.768 |
| Female | 89 | 41.2 | | 43 | 38.7 | | 46 | 45.9 | |
| Age | | | | | | | | | |
| < 60 | 108 | 34.8 | 0.592 | 25 | 30.2 | 0.946 | 83 | 36.2 | 0.291 |
| ≥ 60 | 148 | 39.5 | | 112 | 47.2 | | 36 | 29.7 | |
| Tumor diameter | | | | | | | | | |
| ≤ 3cm | 101 | 27.9 | 0.329 | 43 | 24.0 | 0.398 | 58 | 30.7 | |
| > 3cm | 155 | 45.5 | | 94 | 49.4 | | 61 | 39.9 | 0.687 |
| Differentiation | | | | | | | | | |
| Poor | 120 | 32.3 | | 67 | 27.0 | | 53 | 35.1 | |
| Moderate | 77 | 46.3 | 0.475 | 53 | 53.7 | 0.205 | 24 | 37.2 | 0.834 |
| Good | 59 | 34.8 | | 17 | 34.7 | | 42 | 34.0 | |
| Lymph invasion | | | | | | | | | |
| No | 143 | 38.8 | 0.011 | 57 | 47.1 | 0.010 | 86 | 33.3 | 0.125 |
| Yes | 113 | 43.2 | | 80 | 43.7 | | 33 | 39.5 | |
| Chemoresistance | | | | | | | | | |
| No | 139 | 44.0 | < 0.001 | 68 | 51.7 | 0.012 | 75 | 39.4 | 0.010 |
| Yes | 117 | 28.0 | | 69 | 22.4 | | 44 | 25.9 | |
| TNM stage | | | | | | | | | |
| I + II | 141 | 42.0 | 0.001 | 51 | 57.7 | < 0.001 | 90 | 39.1 | 0.034 |
| III – IV | 115 | 34.6 | | 86 | 26.1 | | 29 | 29.0 | |
| Smoking | | | | | | | | | |
| Yes | 94 | 41.8 | 0.724 | 62 | 44.9 | 0.267 | 32 | 47.8 | 0.508 |
| No | 162 | 34.9 | | 75 | 46.4 | | 87 | 29.6 | |
| PINK1 | | | | | | | | | |
| Low | 161 | 40.9 | 0.026 | 85 | 49.0 | 0.002 | 77 | 34.8 | 0.740 |
| High | 95 | 34.6 | | 52 | 20.8 | | 42 | 35.2 | |

*Calculated with Log-rank test.

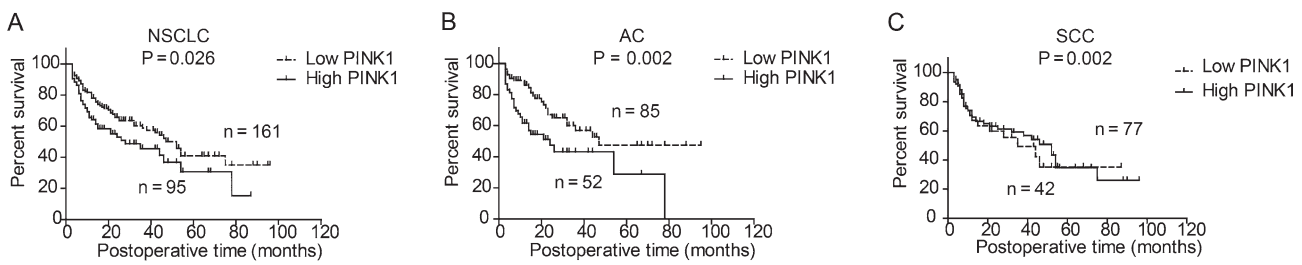


Fig. 2. Overall survival rates among patients with NSCLC.
A. Patients with high PINK1 expression showed lower survival rates compared with low PINK1 expression in NSCLC.
B. Patients with high PINK1 expression showed lower survival rates compared with low PINK1 expression in AC.
C. The difference between high or low expression of PINK1 was not significant in patients with SCC.

NSCLC cells (Zhang et al. 2017); however, they did not further stratify NSCLC into AC and SCC. Here, we showed the different features of AC and SCC.

In conclusion, we show that PINK1 is a prognostic biomarker for AC but not for SCC. Our findings could expand the understanding of difference between AC and SCC, and help identify the high-risk patients and guide individual treatment. Lastly, the PINK1-suppressing therapy may be effective in patients with chemoresistance.

## Conflict of Interest

The authors declare no conflict of interest.

Table 4. Independent prognostic factors are identified with multivariate analysis.

| | NSCLC | | | AC | | |
|---|---|---|---|---|---|---|
| Characters | HR | 95% CI | P* | HR | 95% CI | P* |
| Lymph invasion | | | | | | |
| No | 1 | | | 1 | | |
| Yes | 1.59 | 1.08-2.34 | 0.018 | 1.94 | 1.09-3.44 | 0.023 |
| Chemoresistance | | | | | | |
| No | 1 | | | 1 | | |
| Yes | 1.83 | 1.24-2.71 | 0.002 | 1.62 | 0.90-2.92 | 0.108 |
| PINK1 | | | | | | |
| low | 1 | | | 1 | | |
| high | 1.32 | 0.89-1.95 | 0.168 | 2.14 | 1.25-3.66 | 0.006 |

*Calculated with Cox-regression model.

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