

# THOTTIP is Associated with Prognosis of Lung Cancer in the Chinese Population

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## Research

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## Abstract

**Background:** Lung cancer is a prevent malignancy with high mortality. Long noncoding RNAs (lncRNAs) have been reported to play important roles in tumorigenesis. The purpose of this study was to explore the prognostic value of lncRNA *HOTTIP* in lung cancer.

**Methods:** The expression of *HOTTIP* in lung cancer tissues was measured by quantitative real-time PCR (qRT-PCR). Chi-square test was applied to assess the correlation of *HOTTIP* with clinicopathological features. Overall survival curve was built by Kaplan-Meier method with log rank test. Cox regression analysis was used to explore the prognostic value of *HOTTIP* in lung cancer.

**Results:** The expression of *HOTTIP* was significantly increased in lung cancer samples compared with paired noncancerous samples ( $P<0.001$ ). Moreover, its expression patterns were correlated with lymph node metastasis ( $P=0.039$ ) and TNM stage ( $P=0.007$ ). Survival curve demonstrated that lung cancer patients with high level of *HOTTIP* had poor survival rate (log-rank  $P=0.011$ ). *HOTTIP* might be an independent prognostic factor for lung cancer ( $HR=1.916$ , 95%CI=1.133-3.238,  $P=0.015$ ).

**Conclusions:** *HOTTIP* is up-regulated in lung cancer, and associated with aggressive tumor progression. *HOTTIP* may be a potential prognostic biomarker for lung cancer.

## Background

Lung cancer is one of the most serious health problem worldwide. It is one of the leading cause of cancer related deaths around the world [1]. Unfortunately, evidences reveal that the incidence and mortality of lung cancer have been on the rise [2]. Based on the pathological characteristics, lung cancer can be classified into two types: non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). NSCLC accounts the major lung cancer cases [3, 4]. So far, there are some effective therapeutic strategies for patients suffering from lung cancer, such as surgical strategy, chemotherapy and radiotherapy, but the 5-year survival rate of lung cancer still remains unsatisfactory [5, 6]. Early relapse and metastasis are the major reasons for poor prognosis [7]. Thus, identification of novel biomarkers to predict tumor progression may be a promising approach to improve treatment of lung cancer.

Long noncoding RNAs (lncRNAs) are a class of noncoding RNA transcripts with exceed 200 nt in length [8, 9]. Up to now, there are thousands of lncRNAs have been discovered in human genome. Growing evidences suggest that lncRNAs play important roles in regulation of gene transcription and translation, cell growth, development, differentiation and death [10, 11]. Aberrant expression of specific lncRNAs has also been proved to be involved in development and progression of human cancers, such as hepatocellular carcinoma, gastric cancer and lung cancer [12-14]. LncRNAs may play pivotal roles in development and progression of lung cancer that can provide a new insight to the pathogenesis of the cancer [15].

HOXA transcript at the distal tip (*HOTTIP*) gene, located on in the 7p15.2 gene desert region, is a newly identified lncRNA [16]. Up-regulation of *HOTTIP* was observed in various malignancies, including prostate cancer, gastric cancer, and colorectal cancer [17–19]. The over-expression of *HOTTIP* could promote aggressive development and progression of tumors, suggesting its was an oncogene in malignancy. The oncogenic action of *HOTTIP* in lung cancer was also reported. Deng and colleagues reported that *HOTTIP* could regulate proliferation and apoptosis of lung cancer cells, thus contributing to tumor growth [20]. However, the prognostic value of *HOTTIP* in lung cancer remained unclear.

In this study, we aimed to investigate the prognostic performance of *HOTTIP* in lung cancer. The expression profiles of *HOTTIP* in lung cancer tissues were detected, as well as its association with clinical characteristics. In addition, we estimated the effects of *HOTTIP* expression on overall survival and prognosis of lung cancer patients.

## Methods

### Patients and specimens collection

The protocols and clinical materials used in our study were all approved by the ethics committee of Cangzhou Central Hospital. The written informed consent were obtained from all the patients before the surgery.

In the present study, we recruited 132 lung cancer patients, who were diagnosed in Cangzhou Central Hospital. 132 pairs lung cancer tissue and noncancerous samples were collected from the patients and immediately stored in liquid nitrogen at -80°C for further use. All the patients were followed up by telephone call rang from 6 months to 60 months. The clinicopathological characteristics of lung cancer patients, including age, gender, tumor size, differentiation, histology, lymph node metastasis and TNM stage, were recorded in the present study and summarized in Table 1.

**Table 1**  
**Association of *HOTTIP* with the clinicopathological data of lung cancer patients**

| Features                | No.<br>n = 132 | <i>HOTTIP</i> expression |              | <i>P</i> values |
|-------------------------|----------------|--------------------------|--------------|-----------------|
|                         |                | High (n = 72)            | Low (n = 60) |                 |
| Age (years)             |                |                          |              | 0.697           |
| ≤ 60                    | 53             | 30                       | 23           |                 |
| > 60                    | 79             | 42                       | 37           |                 |
| Gender                  |                |                          |              | 0.898           |
| Male                    | 74             | 40                       | 34           |                 |
| Female                  | 58             | 32                       | 26           |                 |
| Tumor size (cm)         |                |                          |              | 0.823           |
| ≤ 3                     | 58             | 31                       | 27           |                 |
| > 3                     | 74             | 41                       | 33           |                 |
| Differentiation         |                |                          |              | 0.921           |
| Well; Moderate          | 49             | 27                       | 22           |                 |
| Poor                    | 83             | 45                       | 38           |                 |
| Histology               |                |                          |              | 0.841           |
| Adenocarcinoma          | 87             | 48                       | 39           |                 |
| Squamous cell carcinoma | 45             | 24                       | 21           |                 |
| Lymph node metastasis   |                |                          |              | 0.039           |
| Positive                | 68             | 43                       | 25           |                 |
| Negative                | 64             | 29                       | 35           |                 |
| TNM stage               |                |                          |              | 0.007           |
| I-II                    | 71             | 31                       | 40           |                 |
| III-IV                  | 61             | 41                       | 20           |                 |

RNA extraction and quantitative real-time polymerase chain reaction (qRT-PCR)

Total RNAs were extracted from tissue samples with TRIzol reagent (Invitrogen, Carlsbad, CA, USA). The purity and concentration of RNA were calculated with the NanoDrop ND-1000 spectrophotometer (NanoDrop, DE, USA). Only the RNA with OD A260/A280 ratio close 2.0 was used in the further experiments.

We applied qRT-PCR to examine the expression level of *HOTTIP* in both lung cancer samples and noncancerous samples. The cDNA was obtained by RNA reverse transcription with the AMV reverse transcription system (Promega, USA). QRT-PCR reaction was performed with the SYBR Green PCR master mix (Applied Biosystems, USA) on 7300 Real-Time PCR System (Applied Biosystems, USA). *GAPDH* gene was employed as endogenous control in this reaction. All the primers were as follows: *HOTTIP* forward: 5'-CACACTCACATTCGCACACT-3', reverse: 5'-TCCAGAACTAAGCCAGCCATA-3'; *GAPDH* forward: 5'-GTCAACGGATTGGTCTGTATT-3', reverse: 5'-AGTCTTCTGGGTGGCAGTGAT-3'. The expression level of *HOTTIP* was calculated with the method of  $2^{-\Delta\Delta Ct}$  and normalized by expression of *GAPDH*.

## Statistical analysis

The data were expressed as mean  $\pm$  SD. The different expression of *HOTTIP* between lung cancer tissue and paired noncancerous samples was analyzed by Student's *t* test. To examine the relationship between *HOTTIP* and the clinicopathological data of lung cancer patients, Chi-square test was applied in our study. Overall survival curves were constructed with Kaplan-Meier method with log rank test. In order to investigate the prognostic accuracy of *HOTTIP* expression in lung cancer patients, cox regression analysis was carried out. Only the results with *P* value of  $< 0.05$  were considered statistically significant. All statistical analyses were performed in SPSS 18.0 software (SPSS, Chicago, IL, USA).

## Results

### *HOTTIP* expression level

In the current study, the expression of *HOTTIP* was assessed by qRT-PCR. The result revealed that the expression of *HOTTIP* was significantly up-regulated in lung cancer samples compared with the matched noncancerous samples ( $P < 0.001$ ) (Fig. 1).

### Association between *HOTTIP* and clinicopathological features of lung cancer patients

In order to investigate the relationship between expression of *HOTTIP* and clinicopathological features of lung cancer, Chi-square test was applied in our study. The patients were divided into high expression group ( $n = 72$ ) and low expression group ( $n = 60$ ), according to their average expression value of *HOTTIP*. From the results in Table 1, we found that the elevated expression of *HOTTIP* was remarkable correlated with positive lymph node metastasis ( $P = 0.039$ ) and advanced TNM stage ( $P = 0.007$ ). However, age, gender, tumor size, differentiation and histology did not show obvious association with the expression of *HOTTIP* (all  $P > 0.05$ ).

### The prognostic value of *HOTTIP* in patients with lung cancer

To assess the relationship between *HOTTIP* expression and the survival of lung cancer patients, Kaplan-Meier survival curves were constructed in our study. The curves suggested that the patients with low level of *HOTTIP* had higher survival rates than those with high level (log rank test,  $P = 0.011$ ) (Fig. 2).

Cox regression analysis was applied to evaluate the prognostic significance of *HOTTIP* and clinical parameters in lung cancer. Analysis results demonstrated that *HOTTIP* was an independent prognostic factor for lung cancer patients ( $HR = 1.916$ ,  $95\%CI = 1.133-3.238$ ,  $P = 0.015$ ) (Table 2).

Table 2  
Cox regression analysis for prognosis analysis in lung cancer patients

| Variables  | Univariate analysis |             |       | Multivariate analysis |             |       |
|--|---------------------|-------------|-------|-----------------------|-------------|-------|
|  | HR                  | 95%CI       | P     | HR                    | 95%CI       | P     |
| <i>HOTTIP</i><br>(high vs low)                           | 1.916               | 1.133-3.238 | 0.015 | 1.916                 | 1.133-3.238 | 0.015 |
| Age (year)<br>(> 60 vs ≤ 60)                             | 1.057               | 0.637-1.755 | 0.829 | -                     | -           | -     |
| Gender<br>(male vs female)                               | 1.171               | 0.717-1.913 | 0.528 | -                     | -           | -     |
| Tumor size (cm)<br>(> 3 vs ≤ 3)                          | 1.026               | 0.632-1.664 | 0.918 | -                     | -           | -     |
| Differentiation<br>(poor vs well + moderate)             | 1.196               | 0.713-2.005 | 0.497 | -                     | -           | -     |
| Histology<br>(adenocarcinoma vs squamous cell carcinoma) | 1.395               | 0.835-2.328 | 0.203 | -                     | -           | -     |
| Lymph node metastasis<br>(positive vs negative)          | 1.280               | 0.790-2.074 | 0.317 | -                     | -           | -     |
| TNM stage<br>(III-IV vs I-II)                            | 1.065               | 0.659-1.721 | 0.797 | -                     | -           | -     |

Note: HR: hazard ratio; CI: confidence interval; -: indicated no related data.

## Discussion

In China, lung cancer is considered as a lethal disease due to its high mortality [21]. Despite the advances in treatments of lung cancer, the outcomes of lung cancer are still not ideal [22]. The poor prognosis may be attributed to early relapse and metastasis [7]. The mechanisms for tumor metastasis remain unclear [23]. A variety of parameters are applied to predict tumor progression of lung cancer, such as

performance status, disease stage, and weight loss. However, the effects were far from satisfactory [24]. Thus, it is essential to explore novel biomarker for prognosis and treatment of lung cancer.

LncRNAs are a class of long non-coding RNAs, which have been reported to play regulatory roles in gene expression, ligand-receptor engagement and RNA splicing [25, 26]. Recently studies suggested that lncRNAs were involved the initiation, response to therapy and progression of a variety of human cancers [27, 28]. Meanwhile, some lncRNAs have ever been reported to take part in development and progression of lung cancer. *XIST* was an oncogenic lncRNA in NSCLC, and its elevated expression level represented shorter survival and poor prognosis [29]. LncRNA *GAS5-AS1* was down-regulated in NSCLC tissue specimens, and correlated with tumor size, TNM stage, and metastasis, suggesting its inhibitory roles in malignant development of the cancer [30]. Over-expression of lncRNA *HOTAIR* showed obvious link with pathological stage and lymph node metastasis of the patients that hold the potential to serve as a prognostic biomarker for lung cancer [23]. All the researches suggested that lncRNAs played pivotal roles in tumorigenesis of lung caner which might be employed as predictors for the cancer.

In this study, we investigated the expression of *HOTTIP* by qRT-PCR method. The results revealed that the expression of *HOTTIP* was significantly up-regulated in lung cancer tissue samples compared with the matched noncancerous tissue samples. Moreover, the increased *HOTTIP* expression showed significant associated with lymph node metastasis and TNM stage. All the data revealed that *HOTTIP* was an oncogenic lncRNA in lung cancer that promoted aggressive development and progression of the cancer. The conclusion was supported by the previous investigations. The study carried out by Sang et al. reported that *HOTTIP* was up-regulated in NSCLC tissues. Knockdown of *HOTTIP* could suppress cell proliferation, migration and invasion in vitro, suggesting its promoting roles in lung cancer progression [31]. However, the oncogenic mechanisms of *HOTTIP* in the carcinogenesis of lung cancer were far from being full elucidated. Further researches were still needed.

Given its functional roles in tumor progression, *HOTTIP* was proved to serve as a predictor for several cancers. Ye et al. suggested over-expression of *HOTTIP* could contribute to initiation and progression of gastric cancer which might be a potential prognostic biomarker for the cancer [18]. In colorectal cancer, up-regulation of *HOTTIP* presented poor prognosis for patients [19]. Additionally, the predictive function of *HOTTIP* was also reported in other types of malignancy, like osteosarcoma, tongue squamous cell carcinoma, and hepatocellular carcinoma [32–34]. Based on the previous investigations, we deduced that *HOTTIP* might be an effective indicator for lung cancer progression. In this study, survival curve was built based on the expression levels of *HOTTIP* among lung cancer patients. The curve demonstrated that lung cancer patients with low expression of *HOTTIP* had a longer survival than those with high expression. Cox regression analysis demonstrated that *HOTTIP* was an independent prognostic factor for lung cancer.

## Conclusions

In conclusion, over-expression of *HOTTIP* plays promoting roles in malignant development and progression of lung cancer. *HOTTIP* may be an independent biomarker for lung cancer.

## List of abbreviations

Long noncoding RNAs (lncRNAs)

quantitative real-time PCR (qRT-PCR)

non-small-cell lung cancer (NSCLC)

small-cell lung cancer (SCLC)

HOXA transcript at the distal tip (*HOTTIP*)

## Declarations

## Declarations

### Ethics approval and consent to participate

This study was supported by the Ethics Committee of Cangzhou Central Hospital and also has been carried out in accordance with the World Medical Association Declaration of Helsinki.

The subjects had been informed the objective. Certainly, written consents were signed by every subject in this study.

### Consent for publication

We obtained permission from participants to publish their data.

**Availability of data and materials** The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request. The authors declare that they have no competing interests. **Funding** Not applicable. **Authors' contributions** Y.Z. design of the work; X.K. the acquisition, analysis, H.W. interpretation of data; X.K. the creation of new software used in the work; Y.Z. have drafted the work or substantively revised it. All authors read and approved the final manuscript. **Acknowledgements** Not applicable.

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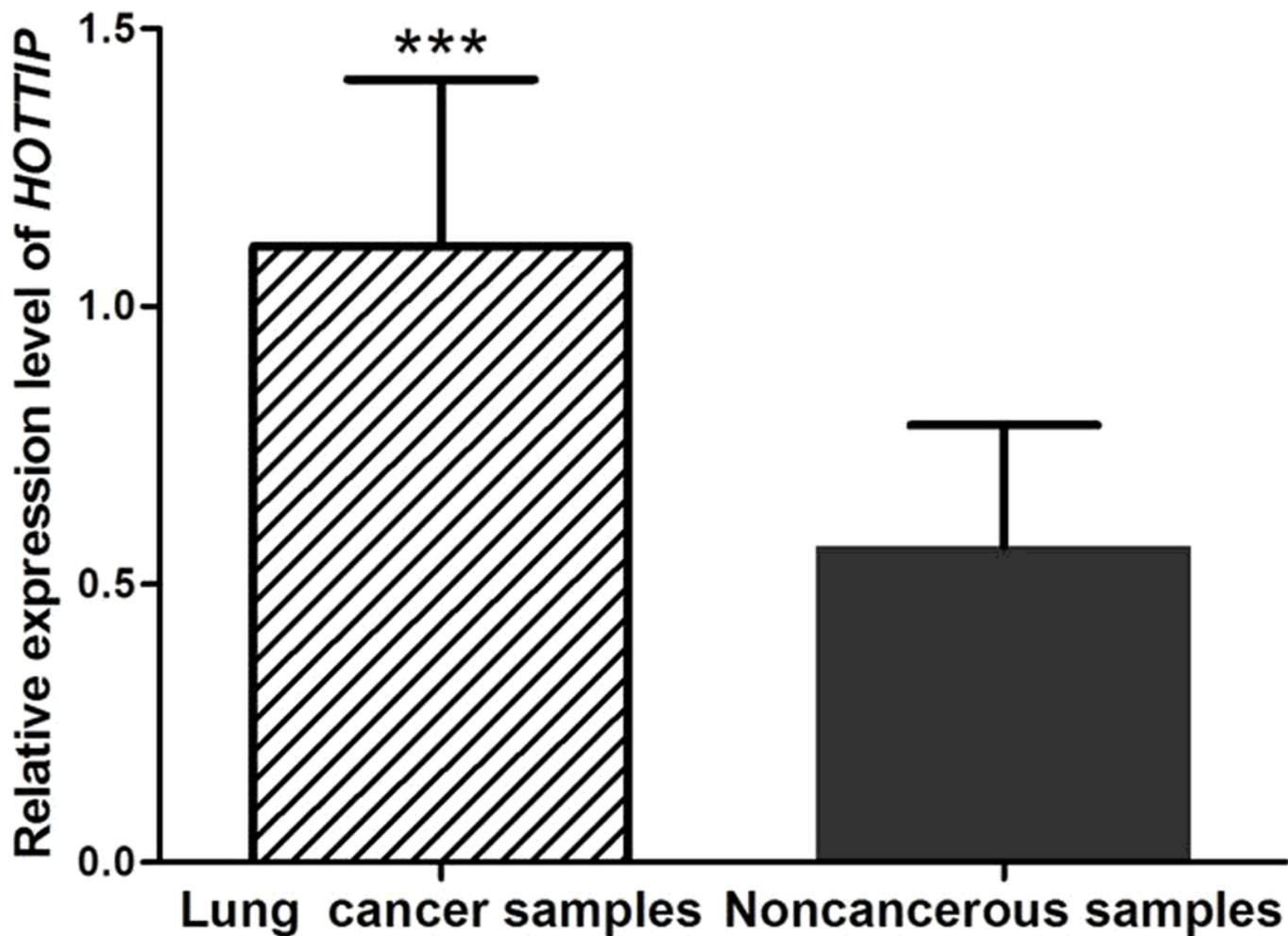
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## Figures



**Figure 1**

The expression of HOTTIP in lung cancer tissue samples and paired noncancerous samples. HOTTIP expression level was up-regulated in lung cancer tissues, compared with non-cancerous tissues. \*\*\*: suggested  $P < 0.001$ .

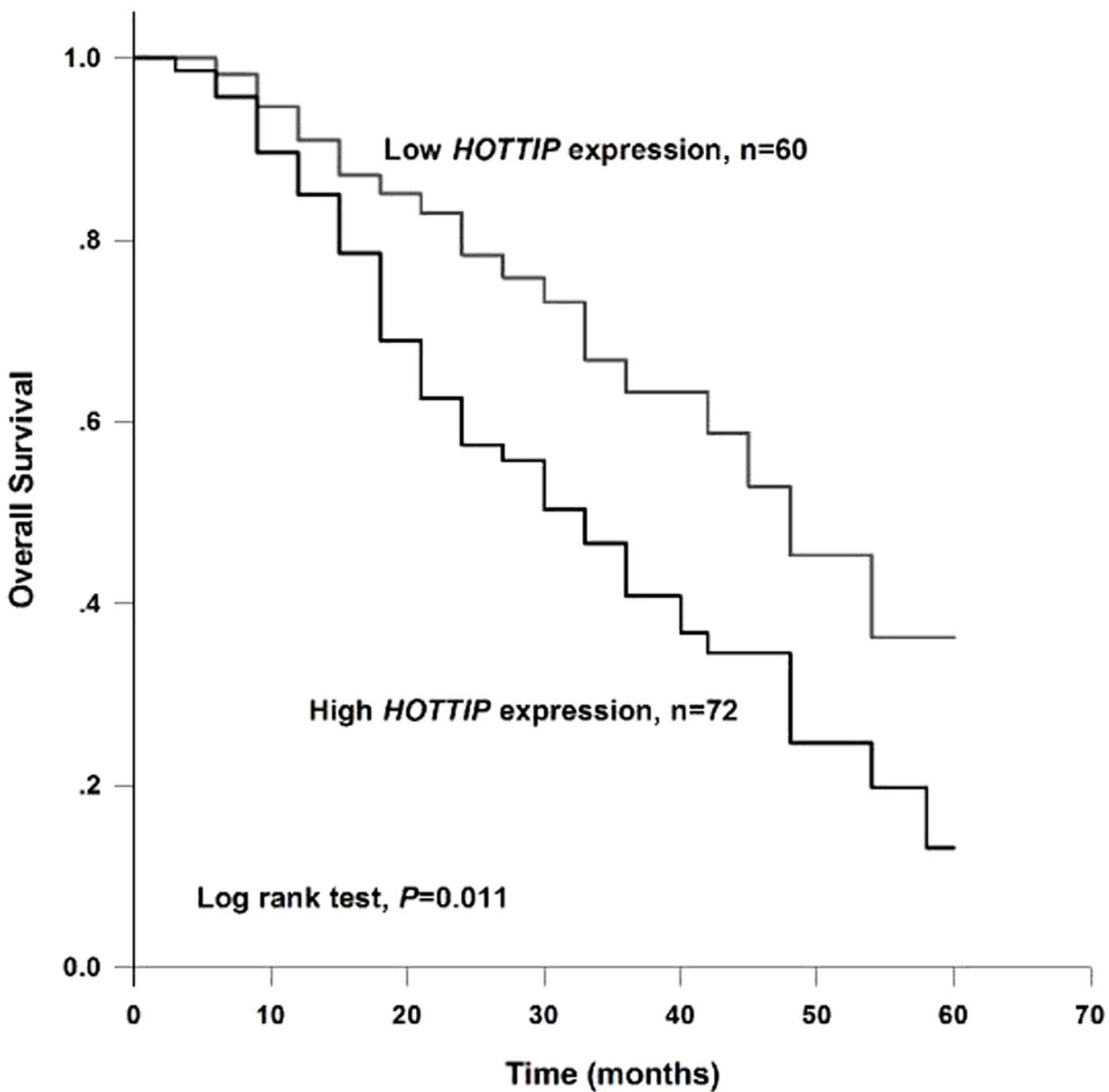


Figure 2

The Kaplan-Meier survival curves for lung cancer patients based on their expression of *HOTTIP*. The curve demonstrated that patients with high expression of *HOTTIP* had a shorted overall survival than those with low expression (log rank test,  $P=0.011$ ).