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*Research article*

# Expression of autophagy-related factor p62 for lung cancer diagnosis and prognosis: A systematic review and meta-analysis

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**Abstract:** p62/SQSTM1 is the scaffold protein implicated in selective autophagy, which is induced by cellular stress. Research has shown that p62 is highly expressed in cancer. Moreover, p62 can easily promote tumor metastasis. However, studies have not reached a consensus on the relationship of p62 expression with the diagnosis and prognosis of lung cancer. We conducted a systematic review and meta-analysis of studies on p62 expression in the prognosis and clinical-pathological parameters of lung cancer patients. Literature search was performed with PubMed, Web of Science, EMBASE, Cochrane Library, and SpringerLink databases. Fixed-effects and random-effects models were used to study the relationship of p62 expression with patients' overall survival (OS) and clinical-pathological parameters. I2 was used to test for heterogeneity. Egger's test was used to assess publication bias. The meta-analysis collected and considered 13 articles, which included 1393 lung cancer patients. The studies show that the high expression of p62 is associated with poor OS in lung cancer patients. The clinical-pathological parameters of patients show that p62 is more highly expressed in high TNM stage (II + III + IV VS. I), Lymph node metastasis (N1 VS. N0), and distant metastases (D1 VS. D0). However, there is no correlation between the p62 expression and the Beclin 1 and LC3B in lung cancer patients. In conclusion, the over-expression of p62 is associated with poor OS in lung cancer patients and can be used as a biomarker for lung cancer diagnosis and prognosis.

**Keywords:** lung cancer; autophagy; p62; overall survival; diagnosis; prognosis

## 1. Introduction

Lung cancer is a common cancer in both men and women. In the past 50 years, lung cancer morbidity and mortality have risen rapidly all over the world, especially in developed countries [1,2]. Lung cancer is currently the leading cause of cancer deaths in humans [3].

Studies have shown that autophagy is related to the occurrence and development of lung cancer [4,5]. Autophagy is crucial in maintaining the cellular homeostasis of healthy cells, and has roles in cell metabolism, internal organelle renewal, and antitumor responses [6]. Dysfunctional autophagy can lead to the occurrence and development of tumors [7]. Autophagy can also provide nutrients and energy for increased tumor metabolism. After radiotherapy and chemotherapy treatments, tumor cells produce numerous damaged organelles, damaged proteins, and other harmful components. At this time, autophagy can be activated for the timely removal of these harmful substances to provide sufficient time and necessary conditions for the repair of damaged DNA [7]. p62/SQSTM1 is classically known as the scaffold protein that is implicated in selective autophagy, which is induced by cellular stress [8]. p62 comprises various protein interaction domains that can bind and degrade poly-ubiquitin proteins. Moreover, p62 is crucial in signal transduction pathways [9]. Studies suggest that p62 dysregulation is associated with the development of various cancers, such as lung cancer [4], gastric cancer [10], breast cancer [11], and esophageal adenocarcinoma [12]. The over-expression of p62 is correlated with distant metastasis in melanoma [13], lung cancer [5], pancreatic cancer [14], and colorectal cancer [15]. Studies have shown that p62 is involved in the regulation of RhoA, Ras, Raf, MAPK, and NF-KB signaling pathways, which can promote tumor proliferation and migration [16–20].

Some studies have also reported that p62 is expressed in lung cancer cells and tissues. James A. et al. found that tumor-associated antigens (TAAs), such as c-myc, cyclin B1, IMP1, Koc, p53, p62, and survivin, are expressed in the sera of lung cancer patients [21]. They found that the combination of p62 with multiple antigen miniarrays is an accurate and valuable tool for lung cancer detection and diagnosis. Daisuke Inoue et al. used immunohistochemistry (IHC) to investigate 109 non-small-cell lung cancer (NSCLC) cases. Moreover, they conducted multivariate analysis, which revealed that the positive immunoreactivity of p62 is an independent factor of poor lung cancer-specific survival ($P < 0.05$) [4]. Using a mini-array of TAAs (c-myc, p53, cyclin B1, p62, Koc, IMP1, and survivin), William N Rom et al. found a significantly increased frequency of positive immune reactivity to TAAs in lung carcinoma [22].

Although p62 expression in lung cancer has been reported, its expression trends in lung cancer remain unclear. Its influence on clinical–pathological parameters and prognosis of patients are likewise indefinite. Thus, we conducted a systematic review and meta-analysis to describe the role of p62 in lung cancer.

## 2. Materials and method

### *2.1. Search strategy*

A comprehensive electronic literature search was conducted with the following English-language databases: PubMed, Web of Science, EMBASE, Cochrane Library, and SpringerLink. The literature search strategy adopted was as follows: “p62 or SQSTM1 or autophagic

factor" [All Fields] and "lung cancer or lung carcinoma or lung tumor" [All Fields] and/or "diagnosis or prognosis or follow-up or outcome or survival" [All Fields]. The literature search ended on June 20, 2019. A total of thirteen articles, which were internationally published in English between 2003 and 2019, were collected. The details of the search procedures are provided in Figure 1.

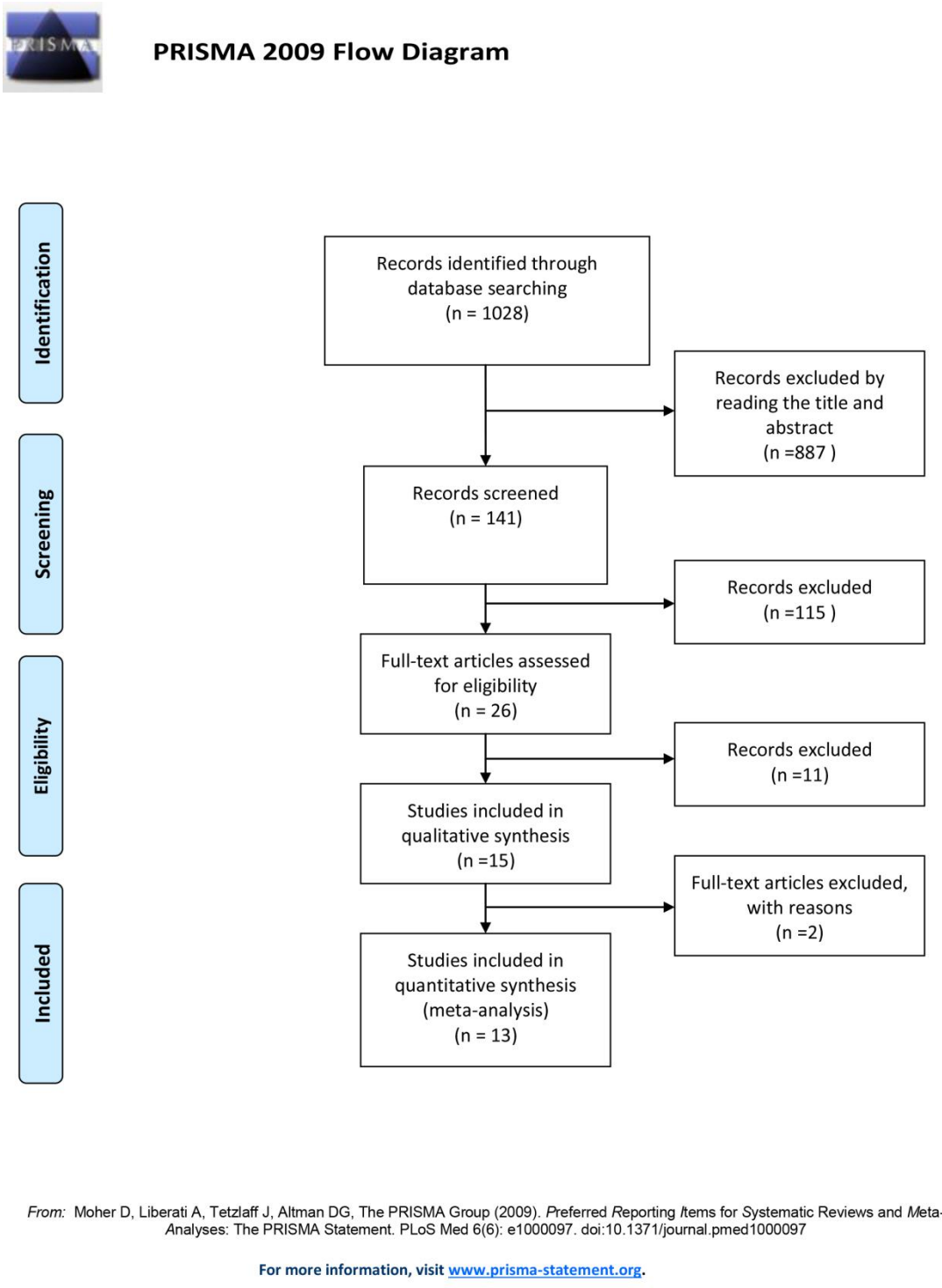


**Figure 1**. Literature inclusion process.

### *2.2. Inclusion and exclusion criteria*

The following inclusion criteria were adopted: (1) The studies are cohort and clinical randomized controlled trials. (2) The subjects of the study are lung cancer patients. (3) The studies examine p62 expression and/or its relationship with lung cancer prognosis. (4) The studies report the clinical–pathological parameters of lung cancer patients. The exclusion criteria included the following: (1) The full text of the study is unavailable, and only the title, abstract, reports, letters, or commentaries were provided. (2) The study utilizes cell and animal experiments for p62 expression; (3) The study investigates non-lung cancer tissues, e.g., only lung neoplasms, chronic obstructive pulmonary disease tissues, and normal lung tissues.

### *2.3. Data extraction and analysis*

Information was extracted from each study by two independent authors. The basic data of the studies are summarized in Table 1. We extracted the hazard ratio (HR) and 95% confidence interval (CI) to analyze the overall survival (OS) of the patients. All of the multivariate analysis results for the analysis of patient OS were available. Conflicts in data were resolved by discussion between the two authors.

### *2.4. Statistical analysis*

We calculated the expression of p62 in lung cancer patients for the meta-analysis. All of the data in the selected studies were analyzed by STATA 12.0 (STATA Corp., College Station, Texas, USA). We used HR and 95% CI to analyze the overall survival of patients. I2 was used to test for the heterogeneity of the articles. When I2 $\leq$ 50%, the results of the studies showed low heterogeneity. Thus, a fixed-effect model was used for the data analysis. When I2 >5 0%, we used the random-effects model to remove heterogeneity. When I2 = 0, no heterogeneity exists. We performed Egger's test to assess publication bias in the clinical-pathological parameters. Publication bias was assessed by Egger's test with funnel plots when the meta-analysis included 10 or more studies. However, only 3 studies were subjected to Egger's test. Therefore, we only describe publication bias in this paper instead of presenting the Egger's test results.

## 3. Results

### *3.1. Search results and study characteristics*

A total of 1028 articles were obtained through the search strategy mentioned above. A number of 141 studies left, by reading the title and abstract of the article. By reading the remaining 26 articles in full, and excluding 11 articles that do not meet the criteria. The remaining articles were analyzed in detail, and two articles that did not meet the inclusion criteria were excluded. Thus, 13 trials met the inclusion criteria and were summarized in the meta-analysis (Figure 1) [4,5,21–31].

We included 13 articles in this study on the basis of the inclusion criteria. Of the studies, 10 used IHC, 2 used ELISA, and one used Western blot to analyze p62 expression in 1393 lung cancer patients. The publication years of the articles ranged from 2003 to 2018.

### *3.2. Correlation between p62 expression and prognosis or clinicopathological features of lung cancer patients*

In the 13 articles, 5 articles [4,23,24,26,28] reported on the relationship between p62 expression and OS in the 1040 lung cancer patients. The results showed that the high expression of p62 indicated poor OS (I2 = 72.3%, P = 0.006; Z = 3.32, P = 0.001; Figure 2).

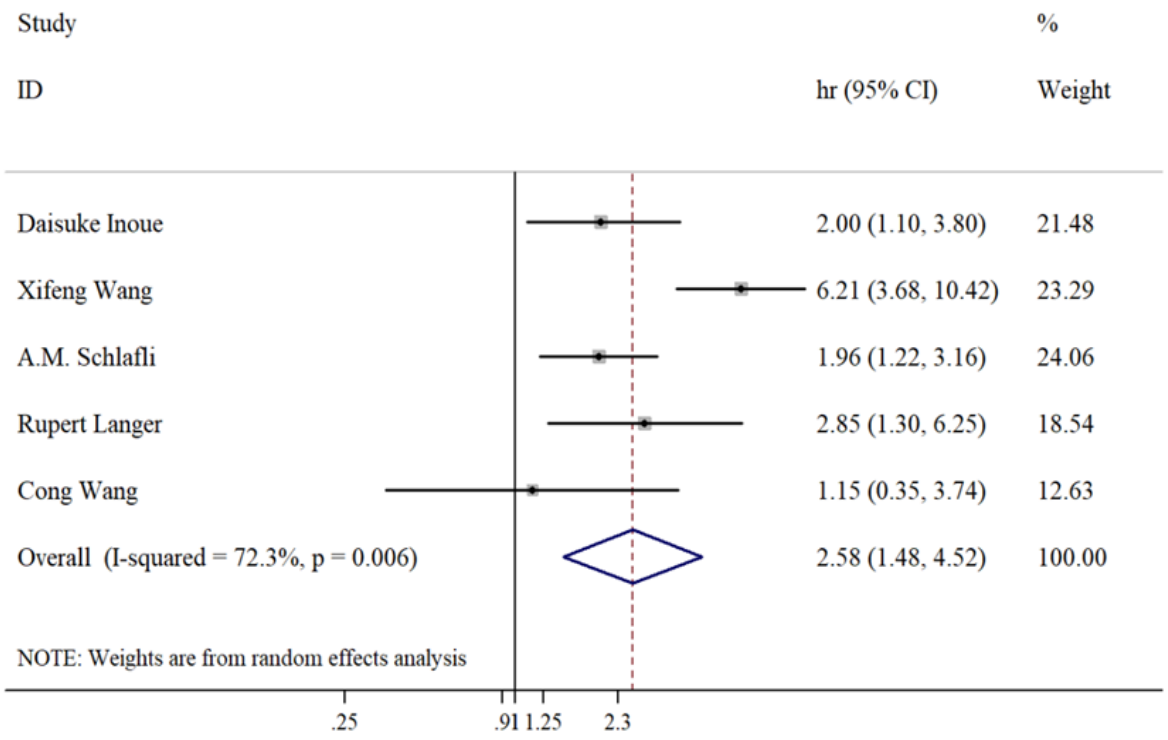


**Figure 2**. Forest plots of overall survival in lung cancer patients. Squares and horizontal lines correspond to the study-specific standard errors (ES) and 95% CI, respectively. The rhombus presents the summary of the ES and 95% CI.

We analyzed the following clinical–pathological parameters of lung cancer patients: gender, tumor-node-metastasis (TNM) stage, lymph node metastasis, and dastant metastases (Table 2). All the clinical-pathological parameters presented low heterogeneity (I2 ≤ 50%). We directly applied the fixed-effects model to detect heterogeneity. Furthermore, the advanced TNM stage (II, III, and IV) presented statistically significant higher p62 expression than a low level TNM stage (I) (I2 = 26.5%, P = 0.236; Z = 3.15, P = 0.002; Figure 3). Patients with positive lymph node metastasis also showed statistically significant higher p62 expression than patients with negative lymph node metastasis (Figure 3). This trend also appears from distant metastasis of tumors (D1 VS. D0) for p62 expression (Figure 3).

However, no statistical significance was found for age (≥ 60 VS < 60), gender (Male VS Female), histological type (ADC VS. SCC), and histological type differentiation (Well and Moderate VS. Poor; Figure 4).

**Table 1**. Basic information of the selected seven articles.

| N. | Author | Year | Patient | Methods | Antibody | Dilution | Staining Position | Follow-up time Mean time | range | Multivariate hazard ratio (95% CI; p62; + VS −) |
|---|---|---|---|---|---|---|---|---|---|---|
| **1** | Daisuke Inoue | 2012 | 109 | IHC | Abcam | NR | Cytoplasm | 1626D | 17–3366D | 2.0 (1.1–3.8) |
| **2** | Jin Gu Lee | 2015 | 5 | WB | Santa Cruz | NR | Cytoplasm+ nuclear | NR | NR | NR |
| **3** | Xifeng Wang | 2015 | 128 | IHC | Abcam | 1:200 | Cytoplasm | 48.5 M | 3–96.5 M | 6.211 (3.676–10.417) |
| **4** | A.M. Schläfli | 2016 | 466 | IHC | MBL | 1:8000 | Cytoplasm | 186 M | 119–252 | 1.962 (1.217–3.164) |
| **5** | A.M. Schläfli | 2015 | 20 | IHC | Sigma | 1:8000 | Cytoplasm | NR | NR | NR |
| **6** | James A | 2003 | 56 | ELISA | Boston, MA | 1:200 | NR | NR | NR | NR |
| **7** | William N Rom | 2010 | 22 | ELISA | QIAGEN | NR | NR | NR | NR | NR |
| **8** | Rupert Langer | 2018 | 271 | IHC | LabForce | 1:8000 | Cytoplasm | 86M | 74–98 | 2.854(1.303–6.251) |
| **9** | Yuan Chen | 2018 | 88 | IHC | Novus Biological | 1:1000 | Cytoplasm +Nuclear | NR | NR | NR |
| **10** | Cong Wang | 2018 | 66 | IHC | Cell Signaling Technology | 1:100 | Cytoplasm +Nuclear | 48.5 | 3–96.5 | 1.15(0.35–3.74) |
| **11** | Xue-li Sun | 2016 | 42 | IHC | Abcam | 1:250 | Cytoplasm +Nuclear | NR | NR | NR |
| **12** | Xiao-hui Liao | 2017 | 60 | IHC+Elisa | NR | | NR | NR | NR | NR |
| **13** | Gui-fang Yan | 2015 | 60 | IHC | PROTEINTECH GROUP, INC. | | NA | 62 | 40–78 | NR |

IHC: immunohistochemistry; WB: Western blot; MBL: Beijing B & Mbiotech Co., Ltd.; VS: versus; D: day; M: month; NR: not reported.

**Table 2**. Results of the pathological parameters in the patients.

| Outcome of parameter | Number of tissue samples | RR/WMD | 95% CI | Heterogeneity (%) | P | Z |
|---|---|---|---|---|---|---|
| Age (≥ 60 VS < 60) | E-p62 = 362<br>C-p62 = 330 | 0.94 | 0.56–1.66 | $I^2$ = 79.0, P = 0.009 | 0.824 | 0.22 |
| Gender (Male VS Female) | E-p62 = 897<br>C-p62 = 293 | 1.07 | 0.90–1.27 | $I^2$ = 0.00, P = 0.645 | 0.445 | 0.76 |
| Histological differentiation (Well and Moderate VS Poor) | E-p62 = 423<br>C-p62 = 181 | 1.03 | 0.65–1.62 | $I^2$ = 80.8, P = 0.000 | 0.12 | 0.901 |
| TNM Stage (I VS II, III, and IV) | E-p62 = 411<br>C-p62 = 366 | 0.69 | 0.54–0.87 | $I^2$ = 26.5, P = 0.236 | 0.002 | 3.15 |
| Lymph node metastasis (Positive VS Negative) | E-p62 = 267<br>C-p62 = 437 | 1.25 | 1.08–1.44 | $I^2$ = 48.3, P = 0.085 | 0.002 | 3.04 |
| Histological type (ADC VS SCC) | E-p62 = 409<br>C-p62 = 455 | 1.03 | 0.65–1.62 | $I^2$ = 80.8, P = 0.000 | 0. 12 | 0.901 |
| LC3B (+ VS. -) | E-p62 = 131<br>C-p62 = 146 | 1.06 | 0.27-4.17 | $I^2$ = 92.1, P = 0.000 | 0.08 | 0.934 |
| Beclin 1(+ VS. -) | E-p62 = 110<br>C-p62 = 96 | 0.86 | 0.43-1.58 | $I^2$ = 78.0, P = 0.000 | 0.58 | 0.561 |

TNM: tumor node metastasis; ADC: adenocarcinoma; SCC: squamous cell carcinoma; RR: risk ratio; WMD: weighted mean difference; 95% CI: 95% confidence interval; VS: versus; E-: experimental group; C-: control group.

**Table 3**. Basic patient information and experimental result interpretation.

| **Name** | **Year** | **Basic patient information and result interpretation** |
|---|---|---|
| 1.Daisuke Inoue | 2012 | Patients: Patients examined in this study did not receive radiotherapy or chemotherapy before surgery. Mean age: 65.6 years (range, 23–82 years).<br>IHC: More than 10% of carcinoma cells was regarded as positive. |
| 2. Jin Gu Lee | 2015 | Patients: 5 NSCLC patients (3 ADC and 2 SCC) were treated with chemotherapy.<br>5 NSCLC patients (2 ADC and 3 SCC) received neoadjuvant treatment before operation. |

*Continued on next page*

| Name | Year | Basic patient information and result interpretation |
|---|---|---|
| 3.Xifeng Wang | 2015 | Patients: All patients received no chemotherapy, radiotherapy, or adjuvant treatment before surgery. Patients recruited from October 2006 to December 2009.<br>IHC: Staining intensity was defined as the depth of the shade of the protein and graded as follows: 0 = no staining; 1 = mild staining; 2 = moderate staining; 3 = strong staining. Staining extent was defined as the percentage of the tumor cells with positive brown–red staining and graded as follows: 0 =< 10%; 1 = 10%–49%; 2 =≥ 50%. Total score: Sum index: high (≥4) or low (<4). |
| 4.A.M. Schläfli | 2016 | Patients: Median age was 67 years (range: 39–83 years). Exclusion criteria: lymph node metastases; neoadjuvant treatment; rare tumor types other than ADC, SCC, and LCC; and insufficient tumor tissue for further analysis.<br>IHC: Cytoplasmic p62 staining was scored as follows: 0, no or very faint staining; 1, weak staining; 2, moderate to strong. |
| 5.A.M. Schläfli | 2015 | Patients: Not provided.<br>IHC: Intensity score from 0–3 was used for quantitative evaluation: 0, no dots or barely visible dots in <5% of the cells; 1, detectable dots in 5%–25% of the cells; 2, readily detectable dots in 25%–75% of the cells; 3, dots in >75% of cells. Diffuse cytoplasmic staining: 0, absent or presenting only faint background staining; 1, weak; 2, strong. |
| 6. James A | 2003 | Patients: The serum bank of the tumor cell engineering laboratory of Xiamen University has a collection of sera from cancer patients, with sera from 56 lung cancer patients.<br>ELISA: Typically dichotomized by the selection of a threshold or cutoff absorbance value: positive reaction, an observed absorbance value above the threshold; negative reaction, below the threshold. Trees were initially constructed using preset cutoffs of normal means +3 SDs and normal means +2 SDs on all of the antibody assays. The input for each individual consisted of dichotomous variables "positive" or "negative" in each antibody assay, along with group membership (cancer cohort or normal). |
| 7.William N Rom | 2010 | Patients: Lung cancer cases were identified upon referral by a thoracic surgeon; phlebotomy was performed on the day of surgery, and stage and histology analyses were performed during the hospitalization.<br>Result analysis: The distributions of demographic and medical history characteristics were summarized for the five groups of subjects under study by using the frequency distributions of the categorical variables and summary statistics of the continuous variables. For each group of samples, descriptive summary statistics (mean, median, and standard deviation) were obtained. |
| 8.Rupert Langer | 2018 | p62 cytoplasmic staining was scored from 0 to 3 as follows: Score 0: no or faint staining, score 1: weak staining, score 2: moderate staining visible and score 3 strong staining. |

*Continued on next page*

| Name | Year | Basic patient information and result interpretation |
|---|---|---|
| 9.Yuan Chen | 2018 | IHC was scored semiquantitatively as negative (<10% positively stained cells; score 0), weak (10–25% positively stained cells; score 1); moderate (26–50% positively stained cells; score 2), or strong (more than 50% positively stained cells; score 3). Low expression: 0–1; High expression: 2–3. |
| 10.Cong Wang | 2018 | Ten high-magnitude (400×) fields of view were randomly selected for each slice, and 100 cells were counted for each field of view. The results were judged according to the cell staining intensity × the proportion of positive cells. Dyeing intensity: 0 (no staining), 1 (light staining), 2 (moderate staining), and 3 (strong staining). The percentage of stained tumor cells, the scores were as follows: 0 (<10%), 1 (10%–49%), 2 (≥ 50%). Multiply the two scores to get the final result, positive (≥2) or negative (<2). |
| 11.Xue-li Sun | 2016 | The results of immunohistochemical evaluation were judged based on the staining intensity of cells and the proportion of positive cells. (1) Cell staining intensity score: no staining: 0, Light yellow: 1, Brownish yellow: 2 points, Sepia: 3 points. (2) According to the proportion of positive cells: <10%: 0 points, 0%–30%: 1 point, 31%–50%: 2 points, and >50%: 3 points. The results of the two were added together. The results of immunohistochemical results were 1-2 divided into low expression, 3–4 divided into moderate expression, and 5-6 divided into high expression; and the results were >2 divided into positive. |
| 12.Xiao-hui Liao | 2017 | The experimental data were expressed as Mean ± SD. The comparison between the two groups before and after treatment was performed by paired t test, and the count data were compared using $\chi 2$ test or Fisher exact probability method, $P < 0.05$ is statistically significant. |
| 13.Gui-fang Yan | 2015 | Five high-magnitude (400×) fields of view were randomly selected for each slice, and 100 cells were counted for each field of view. Judging criteria for dyeing degree: Basic non-staining: 0 points, Brownish yellow particles with lighter color in the cytoplasm or nucleus: 1 point, and brownish yellow particles with medium color: 2 points, and dark brownish yellow appears: 3 points. The staining degree score is multiplied by the number of stained positive cells in the counted cells to obtain an H value. H value 0 is divided into negative (-); $0 < H < l$ is weakly positive (+); $l < H < 2$ is moderately positive (++), and $2 < H < 3$ is strongly positive (+++). |

IHC: Immunohistochemistry; NSCLC: non-small-cell lung cancer; ADC: adenocarcinoma; SCC: squamous cell carcinoma; LCC: large-cell lung cancer; SD: standard deviation.

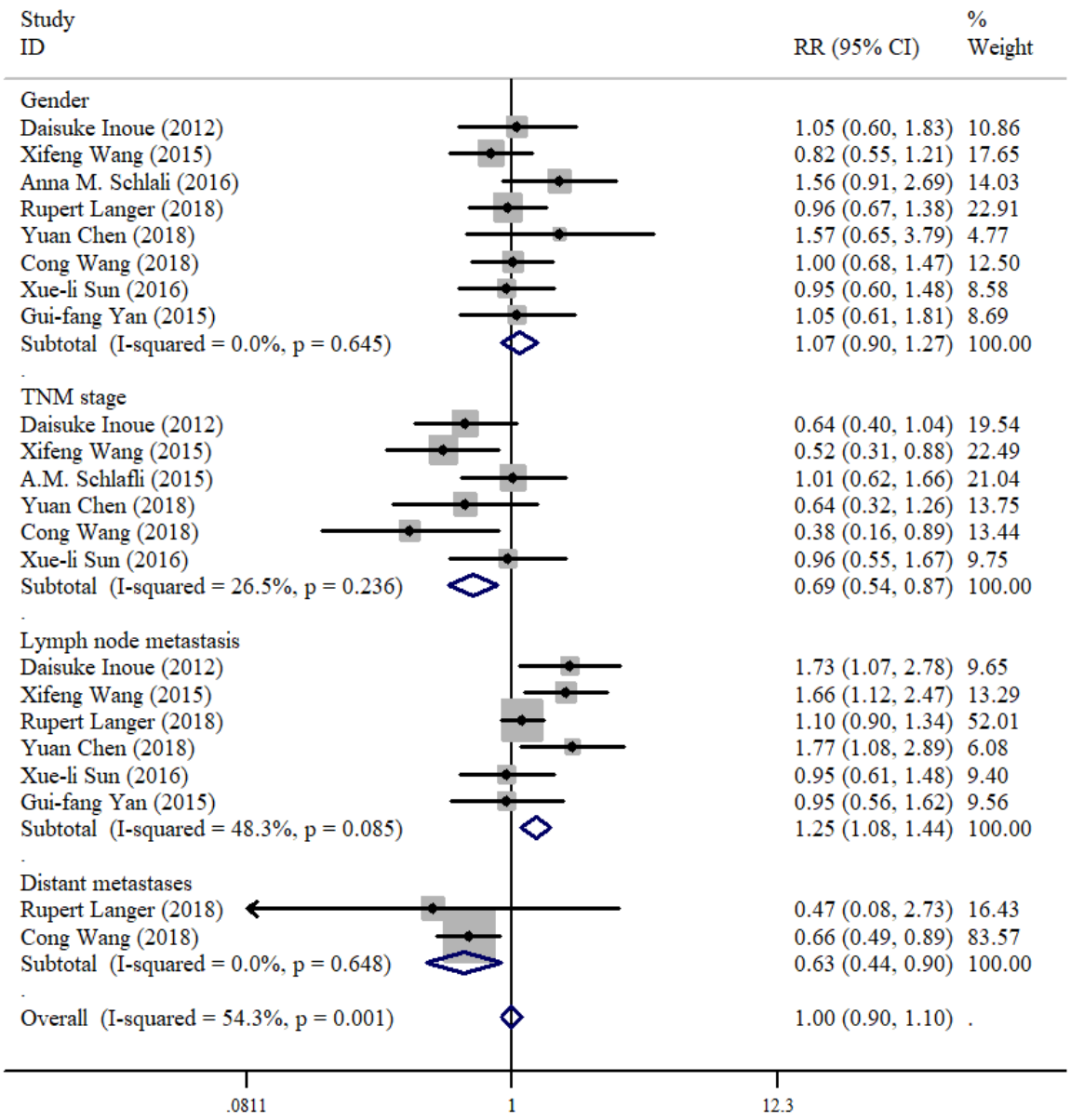


**Figure 3**. Forest plots of TNM stage, lymph node metastasis, and histological type. The squares and horizontal lines correspond to study-specific RR and 95% CI, respectively. RR: risk ratio.

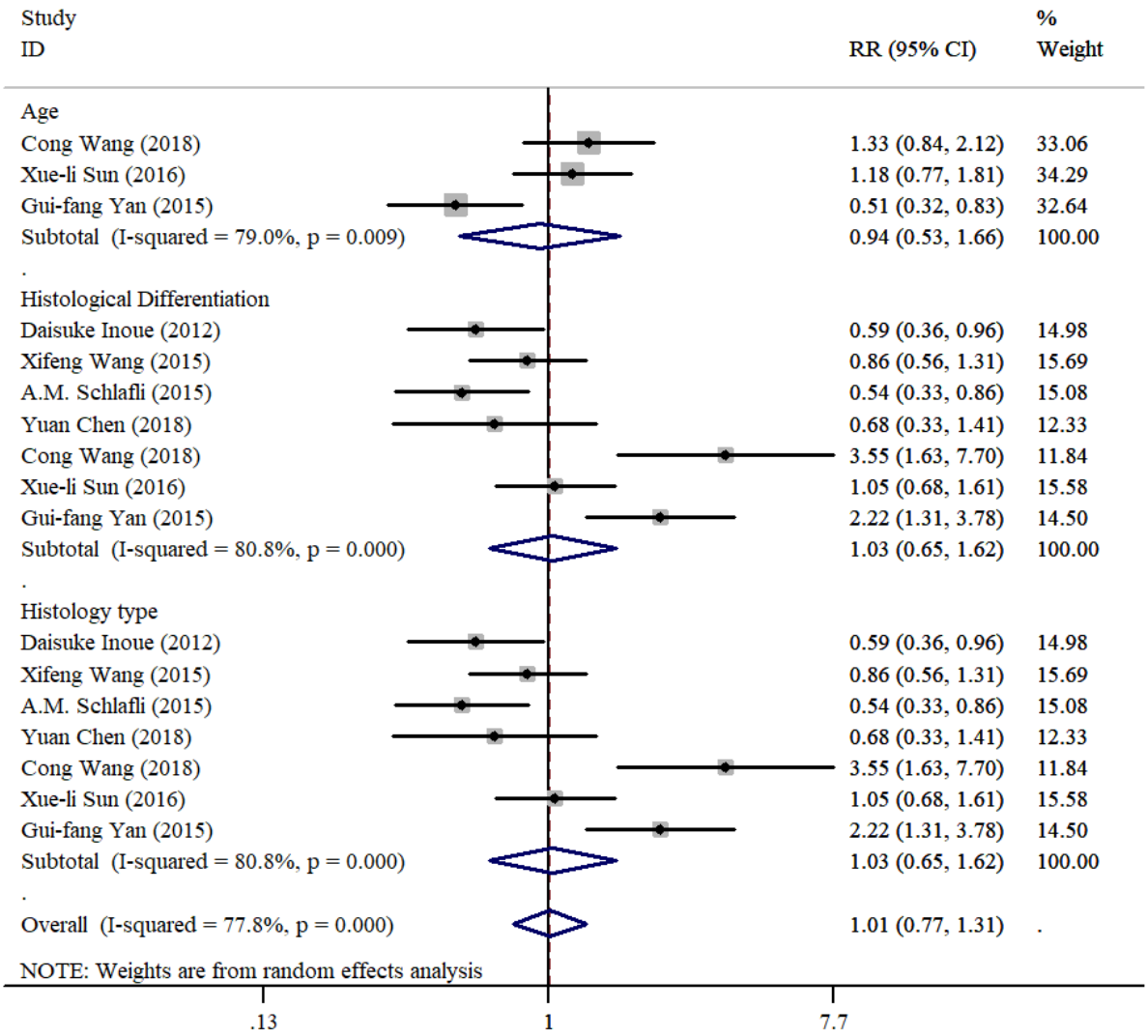


**Figure 4**. Forest plots of age, gender, and tumor differentiation in lung cancer.

### *3.3. Correlation between P62 and LC3 and Beclin 1*

There are three articles reporting the correlation between p62 expression and Beclin 1 and LC3. However, there is no correlation between the expression of p62 and these two factors in lung cancer patients (P values in both groups are greater than 0.05; Figure 5).

### *3.4. Publication bias*

We performed Egger's test to assess publication bias in the group with three studies. The results showed no evidence of publication bias for patient OS ("P>|t|" = 0.206; Figure 6, and Figure 7).

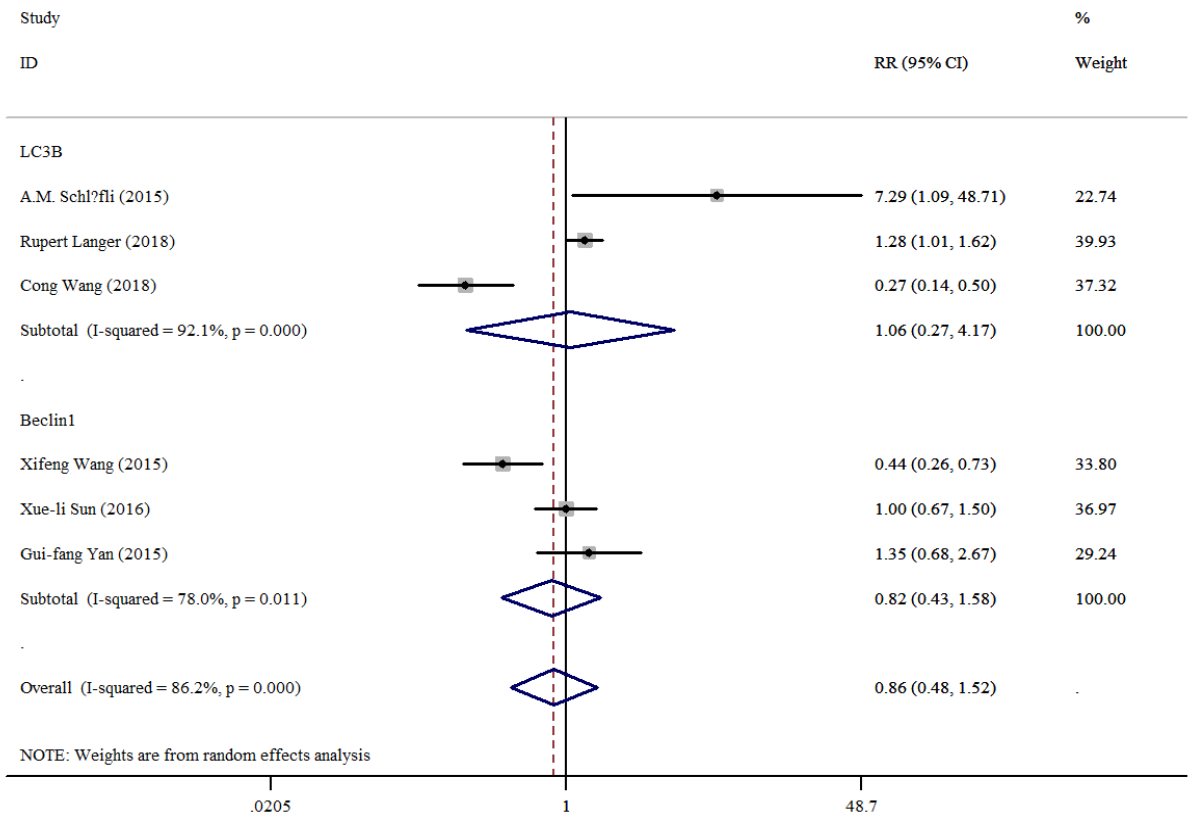


**Figure 5**. Correlation between P62 and LC3 and Beclin 1.

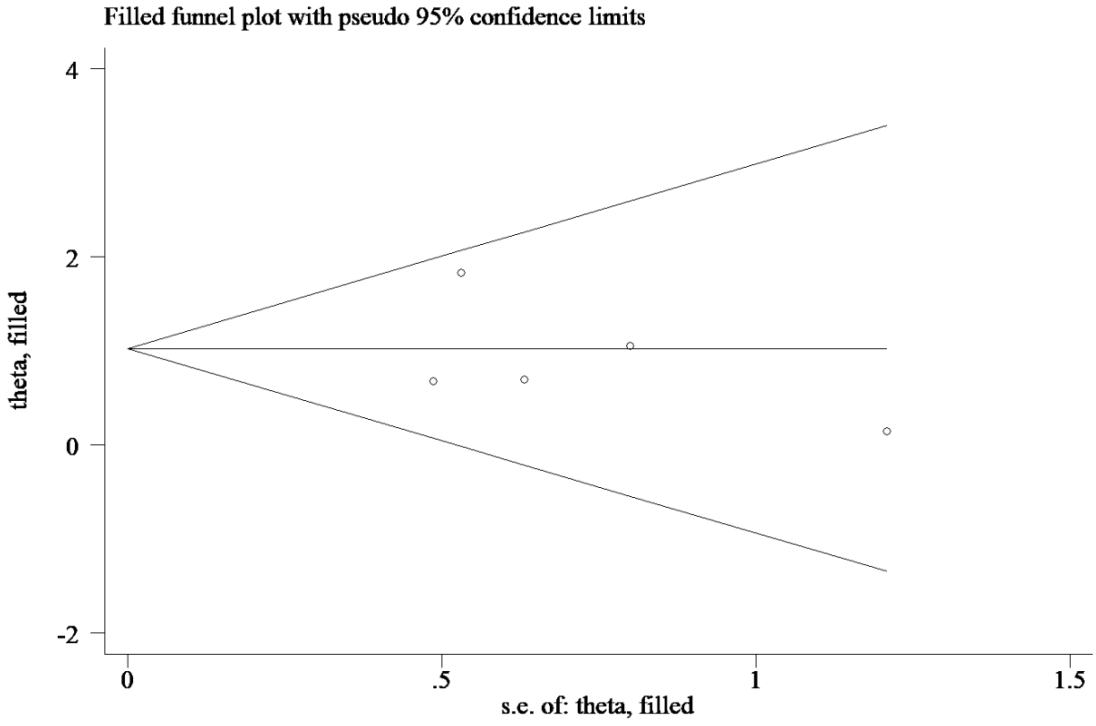


**Figure 6**. Funnel-plot of overall survival rate (OS) of patients.

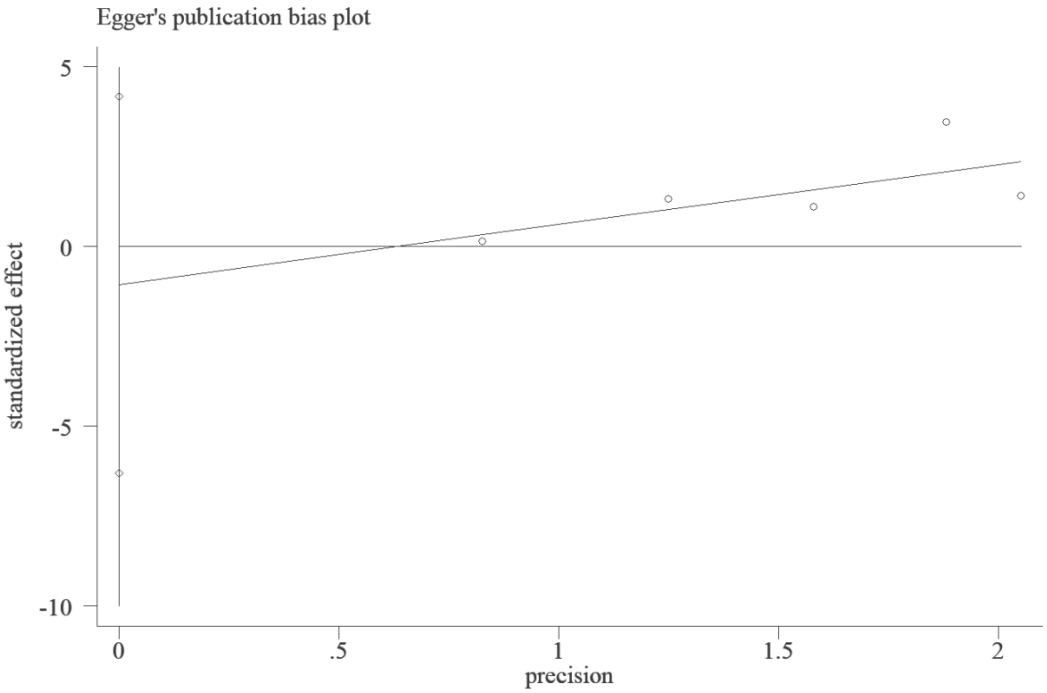


**Figure 7**. The publication bias plot of Egger's.

*3.5. Systematic review*

In one study, p62 expression was detected by IHC [25]. This study showed that p62 expression was higher in lung cancer tissue than in the corresponding non-lung cancer tissue. Thus, applying p62 tissue collection and IHC on single-tissue samples may be a valuable method for determining the impact of autophagy on human diseases when tissue-based analyses are demanded. In another study, p62 expression in 10 lung cancer patients was detected by Western blot [5]. The result showed that p62/sequestosome1 expression decreased in chemotherapy-treated tissue compared with chemo-naïve cancer tissue, thus implicating autophagy in acquired chemotherapy resistance in lung cancer. In two other studies, the sera from lung cancer patients were examined, and the following conclusions were drawn: p62 combined with multiple antigen miniarrays can provide accurate and valuable tools for lung cancer detection and diagnosis in patients [21,22], more details information show Table 3.

## 4. Discussion

Lung cancer is a leading cause of cancer deaths in humans. Current studies have shown that numerous pathogenic factors, such as smoking, genetic inheritance, environmental pollution, chemical or physical occupational exposure, and eating habits, can lead to the occurrence of lung cancer [1,3].

In recent years, autophagy dysfunction has been implicated in the occurrence and development of cancer [7]. Autophagy results in high metabolism and high nutritional requirements during cancer development. Thus, the inhibition of autophagy has become a novel method in cancer treatment. Wu

HM et al. found that the application of gemcitabine caused tumor autophagy, which consequently led to the tumor cells acquired resistance of chemotherapy [32]. They also found that the combined use of gemcitabine and an autophagic inhibitor induced the apoptosis of lung cancer cells. Eileen White et al. studied the effect of removing the autophagy gene ATG7 in NSCLC laboratory models [33]. Their results showed that switching off autophagy by deleting ATG7 is dramatically destructive to established NSCLC cells. Their study also demonstrated that NSCLC selectively requires autophagy for tumor development and that therapeutically targeting autophagy is a possible alternative to targeting Ras.

Studies have shown that the abnormal expression of autophagy-related factor p62 can cause the malignant transformation of cells [34,35]. In the process of autophagy, p62 binds to microtubule-associated protein 1-light chain3 (LC3) and to damaged organelles, which result in the incorrect folding or aggregation of proteins and some long-lived molecules, as well as the degradation of autophagy in the autolysosome [36]. p62 binds the ubiquitin protein and then binds the LC3-II protein to form a complex that is localized in the inner membrane of the autophagy body. Finally, autophagic degradation occurs in cells. Therefore, the p62 protein is constantly degraded in the cytoplasm when authophagy occurs. When autophagy is weakened and defective, p62 protein accumulates in the cytoplasm. Thus, p62 is a marker protein that reflects autophagic activity. Recent findings link p62 acts as a signaling hub through its ability to recruit and oligomerize important signaling molecules in cytosolic speckles to control cell survival. P62 is a key factor in the selective degradation process of autophagy in many proteins and mitochondria. And it also direction action with some apoptosis and survival pathway proteins which include caspase-8, TRAF6 and ERK [37]. Research further confirmation that caspase-8 can be degraded by the action of p62 in apoptosis [38,39]. There also has study show that in Atg7 knockout mice p62 loss lessens the liver damage caused by deficient autophagy. They think that it's based on the role of p62 in activating the caspase pathways. They suggest that liver toxicity associated with impaired autophagy leads to caspase activation and apoptosis. And p62 loss expression in Atg7-deficient livers could dampen caspase-activated apoptosis. This indicated that the livers of Atg7/p62 double knockout mice are healthier than those in mice deficient in Atg7 alone [39–41]. The above studies shown that p62 plays an significance role in the process of autophagy and apoptosis.

The functions of p62 and its association with pathological type, metastasis, and prognosis of lung cancer have also been studied. Daisuke Inoue et al. utilized IHC to detect p62 expression in 109 NSCLC cases [4]. They reported that p62 accumulation is detected in 37% of NSCLC patients. Moreover, p62 accumulation is correlated with the survival rate of patients. Studies have also shown that p62 may be an independent prognostic factor for NSCLC. Xifeng Wang et al. used a tissue microarray and IHC staining to determine p62 expression and prognosis in 104 NSCLC patients [23]. Their multivariate Cox regression analysis indicated that p62 is an independent risk factor that is related to the OS of NSCLC patients. Weihong Liu et al. asserted that the autoantibodies against TAAs are biomarkers for cancer immunodiagnosis [42]. They found that 12 out of 56 patients show p62 expression in their sera antibodies. Their results showed that p62 can be used as a biomarker in cancer immunodiagnosis.

In our meta-analysis, we considered 13 articles that reported p62 expression in lung cancer. Our results showed that p62 is highly expressed in lung cancer at advanced TNM stages (II, III, IV), thus implicating p62 in the malignant progression of lung cancer. The expression levels of p62 are inconsistent between distant metastasis and non-distant metastasis. p62 expression in the

lymph-node-positive group is higher than that in the negative group, further confirming that p62 is involved in the development of lung cancer. Analysis of sera from lung cancer patients showed that combining p62 with multiple antigen miniarrays can provide accurate and valuable tools for the detection and diagnosis of lung cancer in patients. Study show that p62 structure containing important interaction domains attests to the ability of this protein to regulate and modulate the activation of these signaling pathways during tumor formation and propagation. However, because of p62 protein is subject to complex regulation at both the transcriptional and post-translational levels, the measurement of p62 expression strictly as a marker of autophagic flux is still controversial and can be misinterpreted [8]. In a word, as an autophagic regulatory factor, p62 will be play an important role between in lung cancer and autophagy.

## 5. Conclusion

In conclusion, the meta-analysis suggests that high p62 expression increases the risk of lymph node metastasis, distant metastases, and advanced TNM stage in lung cancer. Furthermore, high expression of p62 show a poor overall survival in lung cancer patients. Moreover, p62 detection in the serum can be used for lung cancer detection and diagnosis. Thus, our study provides evidence that the autophagy-related factor p62 is a potential biomarker and good indicator for lung cancer diagnosis and prognosis in patients. However, more studies and patient samples are needed to support our conclusion.

## Conflict of interest

The authors declare that they have no conflict of interest.

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