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Clinicopathological and Prognostic Significance of Hypoxia-inducible Factor-1 alpha in Lung Cancer: a Systematic Review with Meta-analysis

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Summary: Hypoxia-inducible factor-1 alpha (HIF-1α) plays a vital role in the initiation, evaluation and prognosis in lung cancer. The prognostic value of HIF-1α reported in diverse study remains disputable. Accordingly, a meta-analysis was implemented to further understand the prognostic role of HIF-1α in lung cancer. The relationship between HIF-1α and the clinicopathological characteristics and prognosis of lung cancer were investigated by a meta-analysis. PubMed and Embase were searched from their inception to January 2015 for observational studies. Fixed-effects or random-effects meta-analyses were used to calculate odds ratios and 95% confidence intervals of different comparisons. A total of 20 studies met the criteria. The results showed that HIF-1α expression in lung cancer tissues was significantly higher than that in normal lung tissues. Expression of HIF-1α in patients with squamous cell carcinoma was significantly higher than that of patients with adenocarcinomas. Similarly, non-small cell lung cancer (NSCLC) patients had higher HIF-1α expression than small cell lung cancer (SCLC) patients. Moreover, lymph node metastasized tissues had higher HIF-1α expression than non-lymph node metastasized tissues. A high level HIF-1α expression was well correlated with the expression of vascular endothelial growth factor and epidermal growth factor receptor in the NSCLC. Notably, NSCLC or SCLC patients with positive HIF-1α expression in tumor tissues had lower overall survival rate than patients with negative HIF-1α expression. It was suggested that HIF-1α expression may be a prognostic biomarker and a potential therapeutic target for lung cancer.

Key words: non-small cell lung cancer; small cell lung cancer; hypoxia-inducible factor-1 alpha; vascular endothelial growth factor; epidermal growth factor receptor

In humans, lung cancer is the leading cause of death from cancer. It has an aggressive malignancy, which is characterized by early metastasis, frequent relapse and poor response to chemotherapy[1]. All these characteristics contribute to a poor prognosis of lung cancer[2]. To develop effective prevention and treatment plans for lung cancer patients, it is necessary to identify clinically relevant markers that can accurately predict the metastasis, recurrence and prognosis of lung cancer.

In 1999, the first study investigating the expression of hypoxia-inducible factor-1 alpha (HIF-1α) in human cancer tissues was reported[3]. Since then, more researchers have studied the relationship between HIF-1α expression and clinicopathological characteristics and prognosis of lung cancer, but their results are inconsistent and sometimes conflicting[4–23]. Some studies have demonstrated that in lung cancer cell lines, cell proliferation and angiogenesis were promoted and drug resistance was enhanced by elevated HIF-1α expression[24]. In contrast, metastasis of lung cancer cells and angiogenesis were prohibited when HIF-1α expression was down-regulated[25]. Therefore, high HIF-1α expression may be associated with poor prognosis and high risk of metastasis in lung cancer patients. However, other studies have shown that patients with HIF-positive lung carcinomas had a significantly longer median survival than patients with HIF-negative lung carcinomas[4, 25].

To resolve these conflicting notions, we conducted a systematic review with meta-analysis of these reports. In this study, we investigated the relationship between HIF-1α expression and the clinicopathological characteristics and prognosis of lung cancer.

1 MATERIALS AND METHODS

1.1 Search Strategy for Literatures

We followed The Meta-Analysis of Observational Studies in Epidemiology Guideline to perform the present meta-analysis[26]. PubMed and Embase were searched in January 2015 using the following terms: (1) synonyms of cancer, i.e. cancer, tumour, tumor, neoplasm, neoplasia, carcinoma, and malignancy; (2) synonyms of lung, i.e. lung and respiratory tract; (3) hypoxia-inducible factor 1, HIF-1, HIF-1α, hypoxia-inducible factors, or hypoxia-inducible factor. The references cited in the resulting articles or reviews were also searched for potential studies relevant to HIF-1α expression and lung cancer.

1.2 Study Selection

Studies meeting the following criteria were selected: (1) examining the relationship between HIF-1α expres-

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sion and the clinicopathological characteristics or prognosis of lung cancer; (2) utilizing immunohistochemistry to detect the expression of HIF-1α in paraffin-embedded lung cancer specimens; (3) providing sufficient data to estimate an odds ratio (OR) with 95% confidence interval (CI); (4) using appropriate statistical methodology; and (5) written in English. Case reports, letters, reviews, and editorial articles were excluded. Studies in which required data were not provided or could not be calculated were also excluded.

1.3 Data Extraction

Two investigators (S. Yang and Q. Ren) independently extracted data from eligible studies, and disagreements were resolved by discussing with a third investigator (J. Hu). For each study, the first author, publication year, number of eligible patients, analytical methods, and other required data were recorded.

1.4 Statistical Analysis

The meta-analysis was performed by the statistical software STATA version 12.0 (StataCorp LP, College Station, USA). For numerical data, OR and 95 % CI were computed. Heterogeneity of the data from eligible studies was evaluated by using the *Q* statistics, with a significance level at $P<0.10$. The *I*-square value, which is a quantitative measure of inconsistency across different studies[27], was also calculated. *I*-square values typically range from 0% (no observed heterogeneity) to 100% (maximal heterogeneity), and an *I*-square value ≥50% is considered to represent substantial heterogeneity. The absence of heterogeneity across studies was identified, then the fixed-effects model. Otherwise, the random-effects model (DerSimonian–Laird method) was used[28]. Statistical significance was defined as a *P*-value less than 0.05.

2 RESULTS

2.1 Study Selection

Initially, we retrieved 927 unique articles from PubMed and Embase that were published prior to January 2015. The majority of these articles were excluded after the first screening of titles and abstracts. The excluded articles were reviews, case reports, letters, editorial articles, or research articles that did not report the expression of HIF-1α in lung cancer. After examining the remaining 22 articles, 2 of them were excluded because there were insufficient data presented to compute the ORs and 95% CI[3, 29, 30]. Finally, 20 studies were included in our meta-analysis[4–23]. Figure 1 shows the process of selecting the eligible studies.

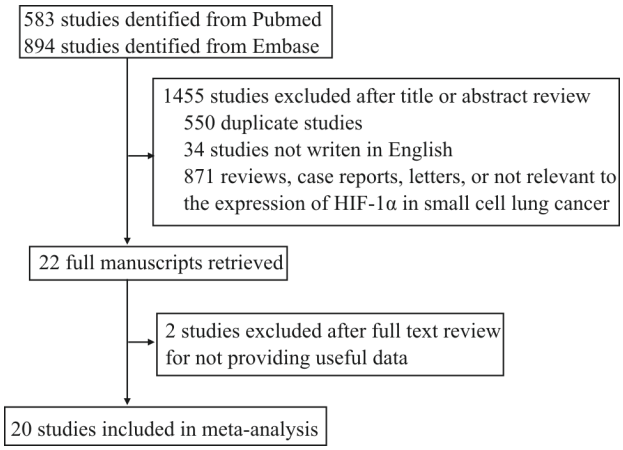

Fig. 1 Flowchart of selection of studies included in the meta-analysis

2.2 Characteristics of the Included Studies

A total of 20 studies met the criteria for this review[4–23]. These studies were published from 2000 to 2013, involving a total of 2056 patients with lung cancer, and have investigated HIF-1α expression in lung cancer tissues (table 1). Twelve out of the 20 studies were conducted in Asian countries including China, Japan and Korea, and the rest of them were carried out in the USA or European countries. In all of these studies, immunohistochemistry was used to examine the HIF-1α expression in the lung cancer specimens. In 2 studies, polymerase-chain reaction (PCR) was also used to quantitate the HIF-1α expression[15, 23]. The definition of positive HIF-1α staining differed among the included studies, and the cut-off values of positive HIF-1α expression ranged from 5% to 30% of total stained cells.

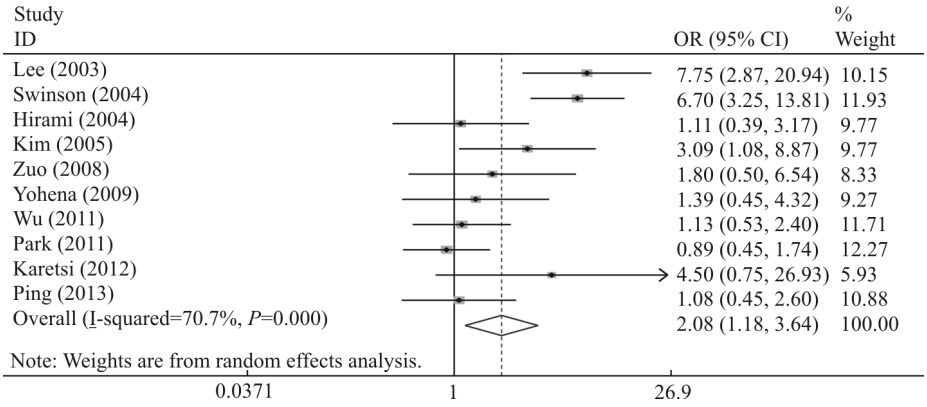

Fig. 2 Forest plot of OR to assess the association between HIF-1α expression and subtypes of NSCLC
The x-axis indicates OR. The horizontal lines show the 95% CIs of ORs from the included studies and the dots represent their averaged ORs. The vertical dash line indicates the weighted average OR of all the included studies and the diamond shape illustrates their CI.

Table 1 Characteristics of the included studies

Study (reference)	Year	Country	Sample size (M/F, *n*)	Mean/median age (years)	Classification of tumor	Survival analysis	Significant association between HIF-1α with adverse outcomes	Definition of positive HIF-1α expression
Volm *et al*[4]	2000	Germany	NR, 96	58	NSCLC	OS	No	Positive staining
Giatromanolaki *et al*[5]	2001	Greece	84/24, 108	63	NSCLC	OS	No	Score from 3 to 4★
Lee *et al*[6]	2003	Korea	NR, 84	NR	NSCLC	NR	NR	>1% nuclear staining
Hirami *et al*[7]	2004	Japan	54/26, 80	NR	NSCLC	OS	No	>1% nuclear staining
Swinson *et al*[8]	2004	United Kingdom	120/52, 172	65.9	NSCLC	OS	Yes	Stained ≥60% of cells
Kim *et al*[9]	2005	USA	NR, 74	67	NSCLC	DFS	Yes	Positive staining of ≥30% nuclei
Enatsu *et al*[10]	2006	Japan	36/42, 78	64	NSCLC	OS	Yes	Stained >10% of cells
Zuo *et al*[11]	2008	China	31/17, 48	NR	NSCLC	NR	NR	Score from 1 to 6▲
Chen *et al*[12]	2009	China	94/26, 120	61	NSCLC	NR	NR	Positive staining
Hung *et al*[13]	2009	Taiwan	69/18, 87	NR	NSCLC	OS and DFS	Yes	>50% nuclear staining
Ioannou *et al*[14]	2009	Greece	28/2, 30	64.3	SCLC	OS	No	Stained >10% of cells
Yohena *et al*[15]	2009	Japan	40/26, 66	NR	NSCLC	OS	Yes	>1% nuclear staining
Andersen *et al*[16]	2011	Norway	253/82, 335	NR	NSCLC	DFS	Yes	≥3 for HIF-1•
Park *et al*[17]	2011	Korea	111/46, 157	NR	NSCLC	OS	Yes	Positive staining of ≥10% nuclei
Wu *et al*[18]	2011	China	112/28, 140	60	NSCLC	OS	No	Scores of 3/4◆
Karetsi *et al*[19]	2012	Greece	52/3, 55	62.8	SCLC and NSCLC	NR	NR	>10% of cells staining
Lee *et al*[20]	2012	Korea	93/18, 111	65	SCLC	OS	Yes	Positive staining >10% nuclei
Persson *et al*[21]	2012	Sweden	NR, 44	NR	SCLC and NSCLC	NR	NR	Positive staining
Luan *et al*[22]	2013	China	36/9, 45	56.5	SCLC	OS	No	Stained >10% of cells
Ping *et al*[23]	2013	China	48/34, 82	58.5	NSCLC	DFS	Yes	Score from 3 to 7■

M, male; F, female; NR, not reported; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer

★score 2, tumors with moderate/strong cytoplasmic reactivity in a percentage of cancer cells lower than the mean value and no nuclear reactivity; ▲1: tumors with moderate/strong cytoplasmic reactivity in a percentage of cancer cells lower than the mean value and no nuclear reactivity; •0=negative, 1=weak, 2=intermediate, and 3=strong; ◆3: tumors with moderate/strong cytoplasmic reactivity in a percentage of cancer cells higher than the mean value; score 4: tumors with a clear nuclear reactivity with or without cytoplasmic reactivity regardless of the intensity; ■The staining intensity was rated as the following: 0=negative; 1=weak; 2=moderate; 3=strong staining intensity. The percentage of positive tumor cells was rated as follows: 1=1% to 10%; 2=11% to 50%; 3=51% to 80%; 4=81% to 100%. Points for staining intensity and percentage of positive tumor cells were added.

2.3 Association of HIF-1α Expression and Histologic Types of Lung Cancer

The result showed that HIF-1α expression was significantly higher in patients with squamous cell carcinoma than in patients with adenocarcinoma, and the pooled OR was 2.08 (95% CI: 1.18 to 3.64) with substantial heterogeneity (*I*-square=70.7%, *P*=0.011) (fig. 2). Similarly, HIF-1α expression was significantly higher in patients with NSCLC than in patients with SCLC, and the OR was 2.66 (95% CI: 1.06–6.70) with low substan-

tial heterogeneity (*I*-square=0%, *P*=0.351).

2.4 Association of HIF-1α Expression and Gender in NSCLC

We investigated the relationship between HIF-1α expression in NSCLC and gender (male *vs*. female) based on 9 studies and found that the synthetical OR was 1.12 (95% CI: 0.80 to 1.58) with low heterogeneity (*I*-square=17.6%, *P*=0.286)[7, 10–13, 15, 17, 18, 23]. Thus, current evidence did not suggest that there is a significant effect of gender on HIF-1α expression in NSCLC.

2.5 Association of HIF-1α Expression and Lymph Node Metastasis of NSCLC

We investigated the association between HIF-1α expression and lymph node metastasis of NSCLC based on 11 studies and found that the synthetical OR was 1.35 (95% CI: 1.05 to 1.75) with moderate heterogeneity (*I*-square=44.8%, *P*=0.053)[6–12, 15, 17, 18, 23]. This result indicated that there is a significant association between HIF-1α expression and lymph node metastasis of NSCLC.

2.6 Association of HIF-1α Expression and Different Stages of NSCLC

We compared the expression of HIF-1α in NSCLC at different tumor stages (stage Ⅰ *vs*. stage Ⅱ-Ⅲ) based on 7 studies. The synthetical OR was 1.04 (95% CI: 0.62 to 1.74) with moderate heterogeneity (*I*-square=56.9%, *P*=0.031)[6, 8–10, 17, 18, 23]. Thus, current evidence did not show a significant association between HIF-1α expression and stage status of NSCLC.

2.7 Association of HIF-1α Expression and Differentiation Grading in NSCLC

We compared the expression of HIF-1α in NSCLC with different tumor differentiation grading (well and moderate *vs*. poor) in 4 included studies[11, 12, 18, 23]. The synthetical OR was 0.79 (95% CI: 0.44 to 1.42) with low heterogeneity (*I*-square=36.5%, *P*=0.193). Hence, the result did not support the assumption that there is a statistically significant difference in HIF-1α expression between poorly differentiated NSCLC and well and moderately differentiated NSCLC.

2.8 Association between the Expression of HIF-1α and Vascular Endothelial Growth Factor (VEGF) or Epidermal Growth Factor Receptor (EGFR) in NSCLC

Six studies have reported the expression of both HIF-1α and VEGF in NSCLC[5, 6, 9–11, 18]. We compared the expression of HIF-1α with that of VEGF and found that lung cancer with positive expression of VEGF was more likely to positively express HIF-1α (OR=2.74, 95% CI: 1.87 to 4.00, *I*-square=0.0%, *P*=0.882) (fig. 3A). Similarly, the meta-analysis of 4 studies indicated a substantial correlation between HIF-1α and EGFR expression in NSCLC, with an OR of 2.06 (95% CI: 1.41 to 3.01) and an insignificant heterogeneity (*I*-square=0.0%, *P*= 0.423) (fig. 3B)[5, 7, 8, 17].

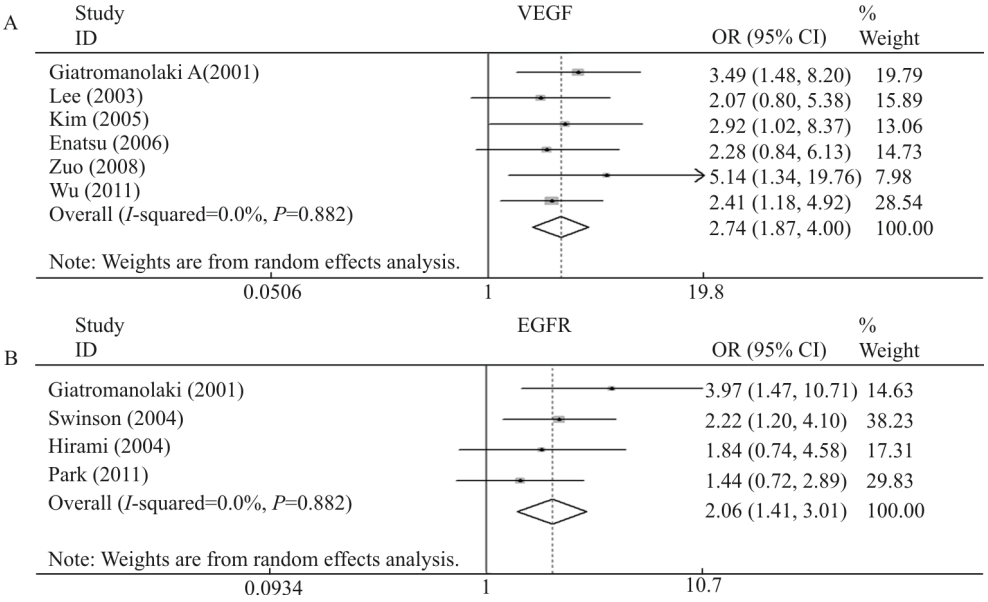

Fig. 3 Forest plot of OR to assess the association of HIF-1α expression and VEGF expression (A), as well as EGFR expression (B) in NSCLC

The x-axis indicates OR. The horizontal lines show the 95% CIs of ORs from the included studies and the dots represent their averaged ORs. The vertical dash line indicates the weighted average OR of all the included studies and the diamond shape illustrates their CI.

2.9 Association of HIF-1α Expression and Overall Survival in Patients with NSCLC or SCLC

Seven studies were included to analyze the association of HIF-1α expression and overall survival of patients with NSCLC[7, 8, 10, 13, 16–18]. Four studies found significant association between the two[8, 10, 13, 16], but the other 3 studies did not[7, 17, 18]. When these studies were combined for analysis, we found that the pooled hazard risk was 1.80 (95% CI: 1.17 to 2.77) with substantial heterogeneity (*I*-square=70.0%, *P*=0.003) (fig. 4A). Due to the great heterogeneity, a subgroup analyses stratified by ethnicity was conducted. The association between HIF-1α expression and overall survival was significant with small heterogeneity in patients from European countries, but no significant association was found in patients from the Asian countries. Thus, ethnicity may be responsible for the heterogeneity among the included studies. Similarly, a significant correlation has been found between the expression of HIF-1α in cancer tissues and the overall survival of SCLC patients. The pooled

hazard risk was 1.90 (95% CI: 1.17 to 3.1) with low heterogeneity (*I*-square=44.9%, *P*=0.163) (fig. 4B).

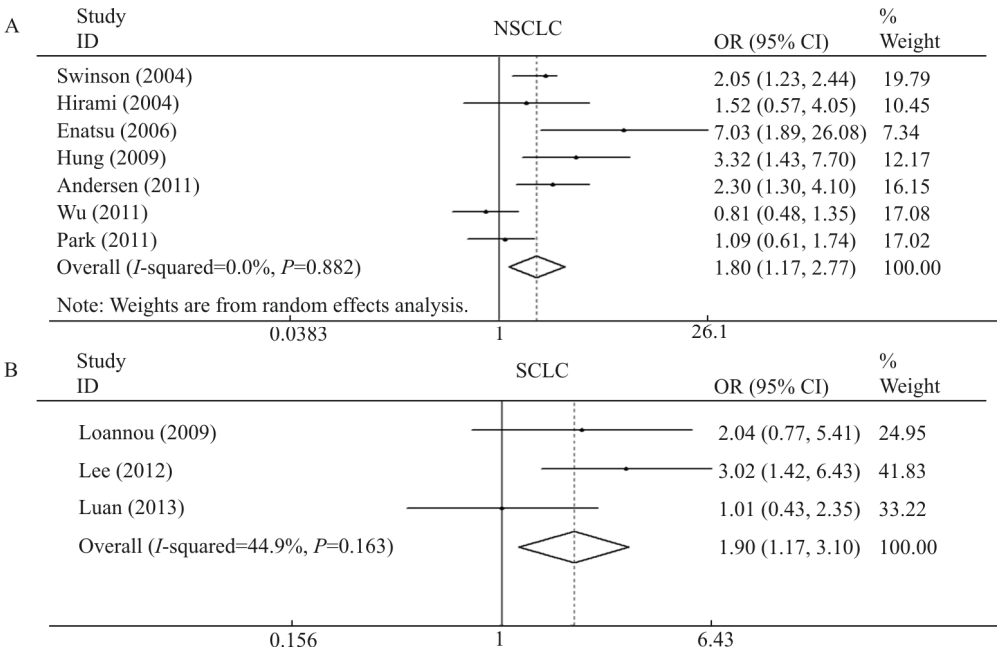

Fig. 4 The association between HIF-1α expression and overall survival of NSCLC patients (A) and SCLC patients (B)
The x-axis indicates OR. The horizontal lines show the 95% CIs of hazard ratios (HRs) from the included studies and the dots represent their averaged HRs. The vertical dash line indicates the weighted average HR of all the included studies and the diamond shape illustrates their CI.

2.10 Evaluation of Publication Bias on Overall Estimate in NSCLC

Publication bias was assessed by funnel plot and Egger's test. There was no indication of publication bias among the included studies (*P*=0.230) (fig. 5).

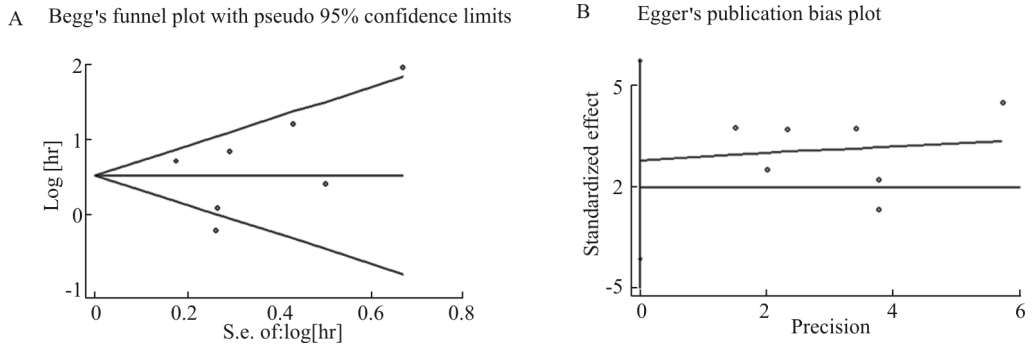

Fig. 5 Funnel plots of Begg's (A) and Egger's (B) to detect publication bias on overall estimate of NSCLC

3 DISCUSSION

HIF-1α often exists in solid tumors and plays a vital role in tumor formation, progression and metastasis though activating a set of genes that are involved in regulation of cell survival, metabolism, differentiation, angiogenesis, and resistance to radiation therapy[31]. Previous studies have shown that overexpression of HIF-1α is correlated with unfavorable outcomes in patients suffering from liver cancer[32], colorectal cancer[33], pancreatic cancer[34], etc. By far, many HIF-1α inhibitors, including known anticancer drugs and novel HIF-1α inhibitors, are in preclinical and clinical trials to treat solid tumors, and some of them have exhibited beneficial therapeutic effects[35]. To apply these inhibitors to treat lung cancer, we have to know the relationship between HIF-1α expression and lung cancer. Documenting such relationship, a number of relevant reports have been published, but we still cannot get a definite conclusion because these results are inconsistent or even conflicting[5–13, 15–20, 22]. So this study provides a systematic assessment of whether HIF-1α expression is associated with the characteristics of lung cancer, which may help clinical diagnosis and selection of effective therapy for lung cancer patients.

The results of our meta-analysis showed that there is an association between positive HIF-1α expression and different subtypes of lung cancer. The substantial heterogeneity of this association may be caused by the varied cutoff values of positive HIF-1α expression adopted by different studies. Our results indicated that the expression of HIF-1α may be controlled by different molecular mechanisms in different subtypes of lung cancer, but the precise mechanism is still not clear.

HIF-1α expression was also found to be associated with lymph node metastasis and the expression levels of VEGF and EGFR in NSCLC. But HIF-1α expression is not related to tumor differentiation status or tumor stage. VEGF plays an important role in tumor angiogenesis through promoting endothelial cell growth and migration[36]. Therefore, HIF-1α accelerates the development of lung cancer by promoting angiogenesis and lymph node metastasis of cancer cells.

It is well known that EGFR plays a key role in carcinogenesis, including promoting cell proliferation, decreasing apoptosis, and enhancing tumor cell motility and angiogenesis[37]. The results of this meta-analysis showed that there is an association between the expression levels of HIF-1α and EGFR in tumor tissues. EGFR may influence the level of HIF-1α expression in lung cancer by activating the PI-3K and/or p42/p44 MAPK pathways[38]. It is possible that increased EGFR signaling promotes lung cancer cell proliferation rapidly, which may lead to tumor hypoxia and elevated HIF-1α expression[39].

Among the 20 included studies, 10 of them provided information on overall survival of patients[7, 8, 10, 13, 14, 16–18, 20, 22], but only two of them collected data on disease-free survival rate[9, 13]. In half of the 10 studies that provided the data of overall survival, no significant association was found between the expression of HIF-1α protein level and overall survival of patients with lung cancer[7, 14, 17, 18, 22]. But the other 5 studies found opposite results which showed that elevated HIF-1α expression is associated with a poor prognosis in lung cancer patients[8, 10, 13, 16, 20]. Generally, lung cancer is divided into two major subtypes, NSCLC and SCLC. The two subtypes grow and spread in distinctive ways and are being treated differently. Therefore, these two subtypes were analyzed separately in our meta-analysis. When the overall survival data from all the relevant studies were combined, we found that the pooled hazard risk was 1.80 (95% CI: 1.17 to 2.77) with substantial heterogeneity for NSCLC. Subgroup analyses stratified by the ethnicities showed that only European NSCLC patients with higher HIF-1α protein expression had poor overall survival. Heterogeneity was low for subgroup analysis for Europeans. Therefore, race can be one of the main reasons that cause the heterogeneity. For SCLC, the association between overall survival and HIF-1α expression was only evaluated in a few studies. Three eligible studies were evaluated to generate the combined OR value of 1.90 (95% CI: 1.17 to 3.1) with low heterogeneity, which suggested that HIF-1α can be used as a biomarker to predict prognosis for patients with SCLC.

The design of this study has a few limitations. First, we only included literatures written in English and did not include those published in other languages, which may lead to bias in publication inclusion. Second, although the methods of immunohistochemical measurement of HIF-1α expression were similar among the included studies, different laboratories used antibodies from different manufacturers and set different criteria for positive HIF-1α expression[5–13, 15–20, 22]. For example, nuclear staining of HIF-1α was conducted in all included studies, but the thresholds for positive HIF-1α expression varied from 1% to 50% of total stained cells[5–13, 15–20, 22].

In sum, this meta-analysis found that HIF-1α expression varies in different subtypes of lung cancer (adenocarcinomas *vs*. squamous cell carcinoma or NSCLC *vs*. SCLC). Increased expression of HIF-1α is positively associated with lymph node metastasis whereas it is negatively correlated with the postoperative survival time of lung cancer patients. Expression of HIF-1α also positively correlates with the expression levels of VEGF and EGFR. Therefore, HIF-1α may serve as an important factor that influences the biological characteristics and prognosis of lung cancer and therefore, evaluation of HIF-1α expression may be important for clinical treatment and prognostic evaluation of lung cancer. Based on our discovery, large population-based multicenter prospective studies are needed to assess the efficacy of HIF-1α inhibitors in treating lung cancer patients.

Conflict of Interest Statement

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article

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