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Original Article

Insulin-like growth factor receptor 1 (IGF1R) expression and survival in non-small cell lung cancer patients: a meta-analysis

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Abstract: The insulin-like growth factor receptor-1 (IGF1R) plays an important role in cancer progression. Previous studies have been controversial with respect to the associations between IGF1R expression and non small cell lung cancer (NSCLC) prognosis. Thus, we performed a meta-analysis to investigate the prognostic value of IGF1R expression in NSCLC patients and the relationship between the expression of IGF1R and clinical characteristics. Two independent reviewers searched PubMed, Embase, Ovid Medline and CNKI to identify eligible studies. Overall survival (OS), disease free survival (DFS) and clinicopathological characteristics were collected from included studies. Pooled hazard ratios (HRs) or odds ratios (ORs) with 95% confidence interval (95% CI) were calculated to estimate the effect. 17 studies comprising 3,294 patients were included in this meta-analysis. The results showed IGF1R positive expression was associated with an unfavorable DFS in NSCLC patients on univariate analysis (HR = 1.26, 95% CI: 1.09-1.46, *P* = 0.002) and multivariate analysis (HR = 1.49, 95% CI: 1.01-2.20, p = 0.045), but the relationship between IGF1R expression and OS have no significant difference on univariate analysis (HR = 0.91, 95% CI: 0.82-1.01, *P* = 0.157) and multivariate analysis (HR = 0.79, 95% CI: 0.45-1.41, *P* = 0.427). Ever smoking and smaller tumor size (T1 or T2) were associated with IGF1R positive expression: pooled OR 1.45 (1.13-1.85) and pooled OR 0.61 (0.60-0.95). Our results suggested IGF1R positive expression as an unfavorable factor for DFS in NSCLC patients, and IGF1R expression was associated with smoking status and tumor size.

Keywords: Insulin-like growth factor receptor-1 (IGF1R), non-small cell lung cancer (NSCLC), prognosis, disease free survival (DFS), overall survival (OS), meta-analysis

Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide. About 1.5 million new cases of lung cancer are diagnosed annually [1] with 85% being non small-cell lung cancers (NSCLCs) [2]. Novel therapeutic developments in NSCLC have resulted in only minor improvement of patient outcomes, its 5-year overall survival (OS) is still only about 17% [3]. During the last few years, several new agents targeting critical and specific pathways for lung cancer have been evaluated in both preclinical and clinical models.

The insulin-like growth factor (IGF) pathway was regulated by a family of six IGF binding proteins (IGFBP), which were structurally related. The extracellular pathway components had two ligands (IGF1 and IGF2), two cell membrane receptors (IGF1R and IGF2R) and their binding proteins (IGFBP1-6) [4, 5]. The insulin-like growth factor receptor-1 (IGF1R) is a transmembrane heterotetrameric protein encoded by a gene located on chromosome 15q25-26 [6]. It comprised two half-receptors, each consisting of one extracellular alpha-subunit and one transmembrane beta-subunit, which can possess tyrosine kinase activity [7]. By regulating its downstream signaling, IGF1R plays an important role in cancer cell growth, survival, metabolism and transformation [8-11]. Studies have demonstrated that IGF1R overexpression was associated with disease progression, poor prognosis and treatment resistance in breast cancer [12, 13], esophagus adenocarcinoma [14],

colorectal cancer [15], and the squamous cell carcinoma of head and neck [16]. In lung cancer, the plasma levels of IGF-1 have been associated with an increased risk of the disease and high plasma levels of IGFBP3 have been associated with reduced risk [17, 18]. A meta-analysis by Huang indicated the genetic variations of IGF1R may be associated with increased risk of lung, especially among Asian populations [14]. Nevertheless, there was no meta-analysis of IGF1R protein expression in patients with non small cell lung cancer.

Given the impact of IGF-1R signaling on the development and progression of several types of cancer, researchers have long studied the prognostic significance of IGF1R protein expression in patients with NSCLC. However, the results of different studies are controversial and the prognostic role of IGF1R expression in NSCLC still remains unclear. Thus, the objective of our meta-analysis was to evaluate the potential relationship of the IGF1R expression with the clinical characteristics, disease free survival and overall survival in NSCLC patients.

Subjects and methods

Publication selection

Relevant studies were screened by an electronic search in PubMed, Embase, Ovid Medline and CNKI database from 1946 to March 2014, with a key word from amongst one of the following words: “non small cell lung cancer”, “lung cancer”, “lung carcinoma” or “lung neoplasm”. These were combined with “insulin-like growth factor-1 receptor,” “insulin like growth factor receptor-1” OR “IGF-1R”. Published studies were sought with no language restrictions or the minimum number of patients. Titles and abstracts were evaluated to identify related studies, and then full texts were read carefully. The eligible studies for inclusion in this meta-analysis had to meet the following criteria: 1. Expression of IGF1R was measured by immunohistochemistry (IHC), quantitative reverse transcription polymerase chain reaction (qRT-PCR) or fluorescence in situ hybridization (FISH). 2. Diagnosis of NSCLC was proven by histopathological methods and complied with the diagnosis criteria of the World Health Organization (WHO). Small-cell lung cancer was not included in our study, due to its highly malignant and undifferentiated cancer with a distinct pathology from NSCLC. 3. The patients did not undergo adjuvant therapy before surgery, and the tissue specimens were obtained prior to any treatment. The samples were surgically resected lung cancer tissues, rather than body fluids such as peritoneal fluid, serum and sputum. 4. The studies offered sufficient data for estimating hazard ratios (HRs) and their 95% confidence intervals (95% CIs).

Methodological assessment

To evaluate the methodological quality of each study, two independent investigators read and scored all the articles according to the assessment of European Lung Cancer Working Party quality scale for biological prognostic factors for lung cancer, which has been used in other similar meta-analyses widely [19]. The following four main dimensions were evaluated: scientific design, laboratory methodology, generalizability and results analysis. Each dimension had a maximal score of ten, with an overall maximum score of 40. Each item scored two points if it is clearly defined in the article, one point if its description is incomplete or unclear and zero point if it is not mentioned or inadequate. The each investigator’s scores were compared and disagreements were discussed. Finally, a consensus was reached. The final scores was calculated in the total of four main dimensions, which were expressed as percentages (0%-100%), and higher values indicated better methodological quality.

Data extraction

Two reviewers evaluated the articles, extracted data and checked all potentially relevant studies independently. All disagreements between the findings of the two reviewers in the data extraction were resolved by discussion and consensus, and if necessary, were adjudicated by a third reviewer. The following information from each article were extracted: first author, year of publication, country, number of patients, follow-up period, disease stage, cut-off score, detection method, IGF-1R positive ratio and HR estimation. From some published researches, HR and 95% CI could be directly obtained by using survival analysis. Otherwise, for articles which didn’t provide HR and 95% CI directly, two reviewers independently digitized and extracted the data through the Kaplan-Meier curves by using GetData Graph Digitizer 2.24

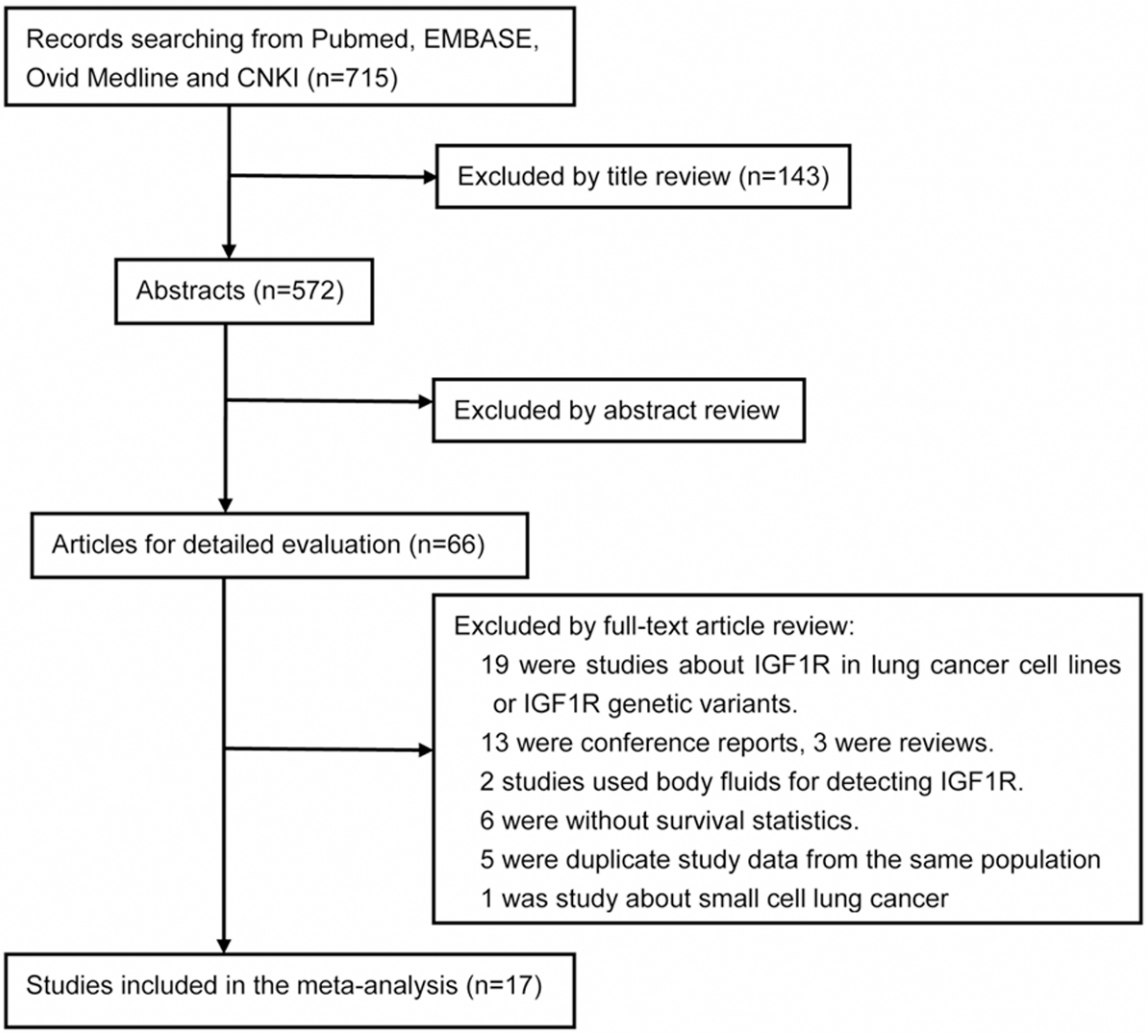

Figure 1. Flow chart of the literature search and selection of included studies.

(http://getdata-graph-digitizer.com) and then extracted data were utilized to reconstruct the HR and its variance according to previously described methods [20, 21].

Statistical methods

STATA 12.0 software (STATA Corp., College Station, TX) and Revman 5.2 software (Cochrane Collaboration, Copenhagen) were used to perform statistical analysis [22]. The associations between IGF1R expression and survival were described as HRs, and the strength of association between IGF1R and clinical characteristics were expressed as odds ratios (ORs). By convention, a pooled HR > 1.00 indicated an unfavourable survival for the group with IGF1R positive expression, and the effect of IGF1R expression on survival was considered to be statistically significant when the 95% CI for the overall HR did not overlap 1. The heterogeneity among studies was examined by the Cochrane's Q test (Chi-squared test; Chi^2) and inconsistency (I^2) statistics, $p < 0.05$ was considered to be statistically significant [23]. When there was no significant heterogeneity among studies, the fixed effects model was employed to combine the individual HR estimates. Otherwise, the random effects model was used [24]. The distribution of score measurement according to the discrete variable was compared by non-parametric tests using SPSS 19.0. To evaluate the stability of the results, a sensitivity analysis was performed, in which one study was removed to know the influence of the individual study on the pooled HR [25]. Publication bias was investigated by Egger linear regression

Table 1. Main characteristics of studies included in the meta-analysis

Author	Year	Country	No.	Follow-up (median)	stage	Cut-off value	Detection method	IGF1R positive ratio (%)	Quality score (%)	Results
Gately K.	2013	Ireland	184	65.09	I-III	Score ≥ 200	IHC	53.80	70.78	N*
Zhang XY	2013	China	178	60	I-III	Score ≥ 20	IHC	71.35	67.65	N*
Xu C.	2013	China	200	52.6	I-IV	Score ≥ 4	IHC	78.00	55.59	P
Ludovini V.	2013	Italy	125	48.9	I-III	> 10%	IHC, FISH	36.80	61.67	N*
Yamamoto T.	2012	Japan	78	48.87	I-III	Score ≥ 200	IHC	52.56	64.37	P
Tsuta K	2012	Japan	379	58.6	I-IV	> 10%	IHC	41.42	54.26	N*
Kim YH	2012	Japan	68	30	III-IV	> 10%	IHC	54.41	63.18	N
Kim JS	2012	Houston	459	49.2	I-III	> 10%	IHC	39.22	55.74	P
Kikuchi R.	2011	Japan	238	56.5	I-IV	Score ≥ 2	IHC	55.04	60.21	N
Nakagawa M.	2011	Japan	182	68.7	I-IV	> 10%	IHC	23.62	74.64	P
Dziadziuszko R.	2010	Poland	189	63.6	I-IV	Score ≥ 2	IHC, qRT-PCR	45.56	65.71	N
Ning XH	2010	China	39	35	I-IV	Score ≥ 1	IHC	53.84	54.89	N*
Cappuzzo F.	2009	Italy	369	60	I-III	score ≥ 100	IHC	76.4	58.01	N*
Chang MH	2009	Korea	194	60	I-IV	Score ≥ 1	IHC	81.44	68.99	N*
Gong YX	2009	Manhattan	264	60	I-IV	> 10%	IHC	39.39	48.30	N*
Lee CY	2008	Korea	71	60	I-IV	Score ≥ 1	IHC	12.68	57.82	N*
Cappuzzo F.	2006	Italy	77	24	III-IV	Score ≥ 2	IHC	38.96	62.29	N

No.: Patients number; IHC: Immunohistochemistry; FISH: Fluorescence in situ hybridization; IGF1R: Insulin-like growth factor-1 receptor; qRT-PCR: Quantitative reverse transcription polymerase chain reaction. P: Studies identifying IGF1R positive expression as significant poor prognosis factor. N: Studies reporting IGF1R positive expression as good prognosis factor. N*: Studies reporting IGF1R positive expression as non-significant association with prognosis.

tests and funnel plots, $P < 0.05$ was considered to indicate statistically significant publication bias [26].

Results

Study selection and characteristics

715 studies were retrieved initially using the above search strategy. Titles and abstracts screened and the full-text articles reviewed, eventually, a total of 17 independent studies [27-43] were used in the present meta-analysis (15 in English and two in Chinese) (**Figure 1**).

The main characteristics of these studies are shown in **Table 1**. Of these studies, two were conducted in the United States, two in Europe and 13 in Asia. Overall, 3294 patients were included, with sample sizes ranging from 39 to 459 individuals. The mean follow-up period for the studies was 53.0 months (range 24 to 68.7 months). The proportion of cases with positive IGF1R expression ranged from 12.68% to 81.44%, with a median of 50.33%. Ten studies involved all disease stages, six studies included only early stage disease (I-III) and one studies included only late stage disease (III-IV). Among all the studies, four studies (23.5%) identified IGF1R positive expression as a significant poor prognosis factor, four studies (23.5%) reported that IGF1R positive expression as a good prognosis factor and nine studies (53.0%) reported that IGF1R expression as non-significant association with prognosis ($P > 0.05$).

Quality assessment

The global quality score for all eligible studies ranged from 48.30% to 74.64% with a median of 61.42% (**Table 1**). There was no significant difference between studies with positive, negative and non-significant results (mean of 62.59% vs. 62.84% vs. 60.26%, $P = 0.783$). Similarly, no statistical difference was appeared in global score between studies involving Asian (N = 13) or non-Asian populations (N = 4), with scores of 61.81% and 60.13%, respectively ($P = 0.681$). Moreover, there was no statistically significant correlation between patient number and the global score ($P = 0.762$). There was also no significant association between publication year and the global score ($P = 0.332$). Thus, in all the studies, no significant methodological qualitative difference was observed between different subgroups. (Supporting Information Table S1).

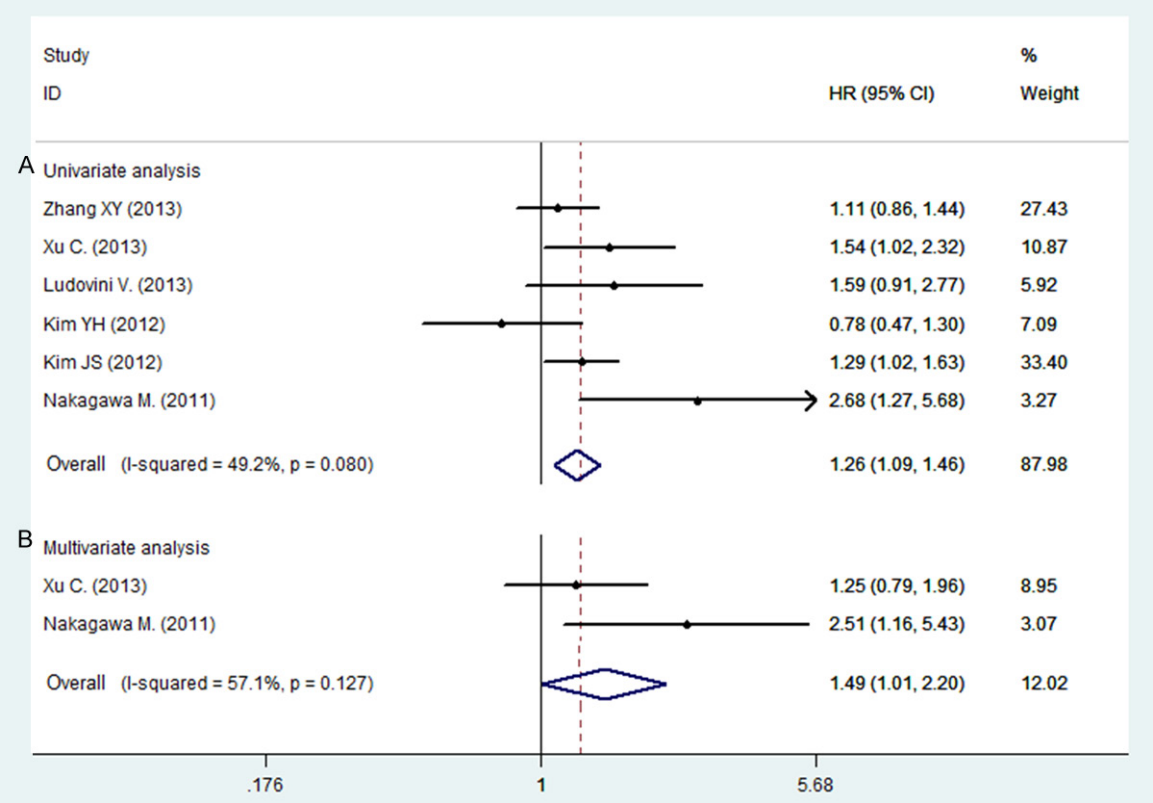

Figure 2. Forest plot showing the combined relative HR for disease free survival: A. univariate analysis; B. multivariate analysis.

IGF1R expression and clinical outcomes in patients with NSCLC

Among all the studies, 12 studies have analyzed the relationship between the IGF1R positive expression and overall survival (OS) in patients with NSCLC on univariate analysis, only four studies have sufficient data to estimate the HR and 95% CIs on multivariate analysis (Supporting Information Table S2). As for disease free survival (DFS) in NSCLC patients, we could have only gathered six studies to conduct the meta-analysis on univariate analysis, and two studies on multivariate analysis. As shown in **Figure 2**, IGF1R positive expression was significantly correlated with worse DFS according to univariate analysis, with a combined HR of 1.26 (95% CI: 1.09-1.46, *P* = 0.002). The fixed-effects model was used because of non-significant heterogeneity was observed among these researches (*P* = 0.080, I2 = 49.2%). Similarly, according to multivariate analysis of two studies, IGF1R positive expression was also significantly correlated with worse DFS (HR = 1.49, 95% CI: 1.01-2.20, *P* = 0.045). However, no statistically significant was observed between the positive expression of IGF1R and overall survival on univariate analysis (HR = 0.91, 95% CI: 0.82-1.01, *P* = 0.157, fixed-effect) or multivariate analysis (HR = 0.79, 95% CI: 0.45-1.41, *P* = 0.427, Random-effect) (**Figure 3**).

IGF1R expression and clinical characteristics

The associations between IGF1R positive expression and clinical characteristics were conducted among the available studies (**Table 2**). 13 studies assessed the relationship between IGF1R expression and smoking status, with a total number of 2169 patients. Four studies had sufficient data for assessing the relationship between IGF1R expression and tumor size, including 640 patients. The results suggested that the IGF1R positive expression was associated with smoking status (ever vs. none: pooled OR = 1.45, 95% CI = 1.13-1.85, *P* = 0.003) and tumor size (T1, 2 vs. T3, 4: pooled OR = 0.61, 95% CI: 0.60-0.95, *P* = 0.03). However, no significant correlations were found between IGF1R

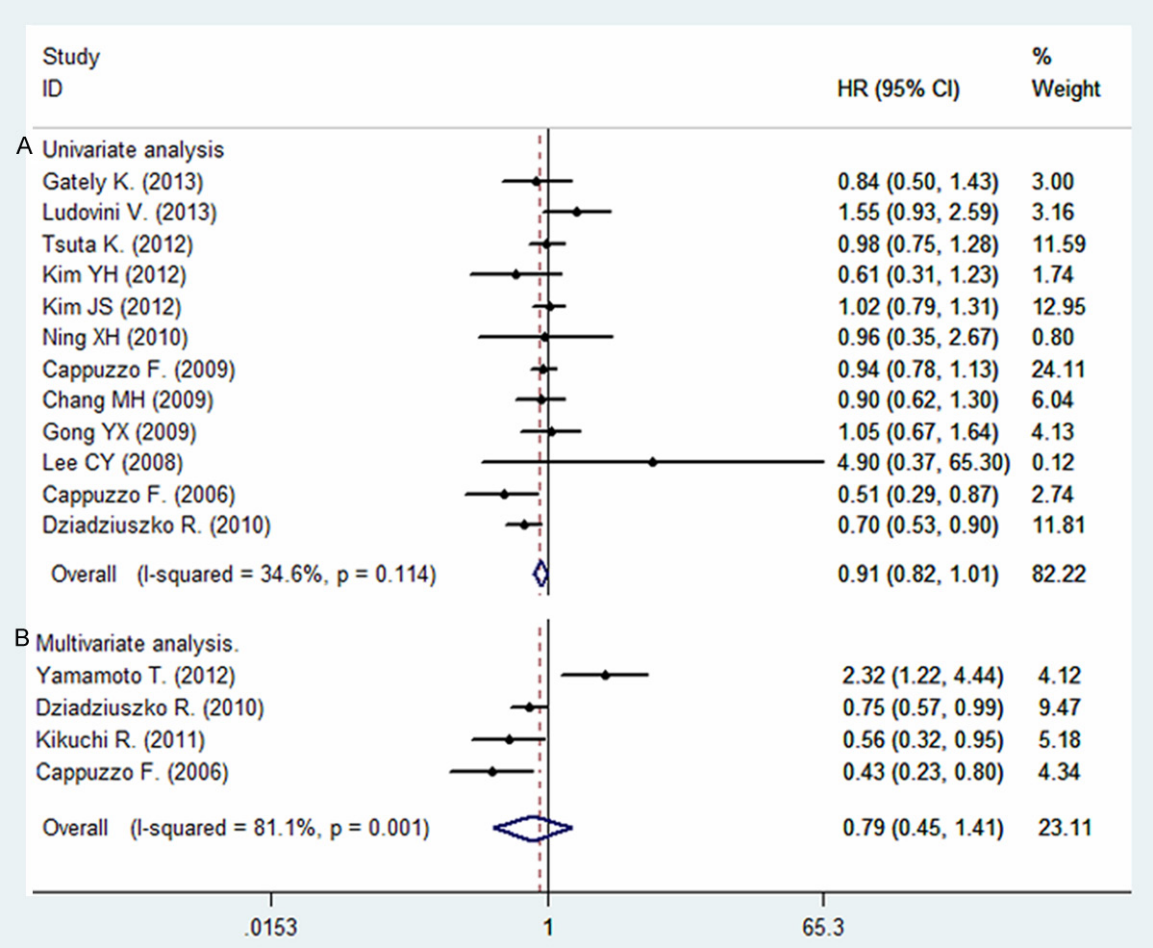

Figure 3. Forest plot showing the combined relative HR for overall survival: A. univariate analysis; B. multivariate analysis.

expression and gender (OR = 1.19, 95% CI = 0.98-1.43, *P* = p = 0.08), age (OR = 1.15, 95% CI = 0.47-2.81, *P* = 0.75), histological type (OR = 2.08, 95% CI = 0.88-4.93, *P* = 0.09), grade of tumor differentiation (OR = 1.04, 95% CI = 0.66-1.63, *P* = 0.87), TNM stage (OR = 0.93, 95% CI = 0.65-1.33, *P* = 0.71) or lymph node metastasis (OR = 1.31, 95% CI = 0.85-2.02, *P* = 0.22).

Subgroup analysis

We performed subgroup analysis in order to further explain the results of OS on univariate analysis. However, as for univariate analysis of DFS, and multivariate analysis of OS and DFS, we did not perform subgroup analysis due to their limited number of included literature. Ethnicity, patients number, follow-up period, tumor stage and quality score were included as factors in subgroup analysis (**Table 3**). After stratifying by patient number, the pooled HR in studies with smaller samples (N < 150) was 0.77 (95% CI: 0.63-0.94, *P* = 0.01), while there was no statistical significance in studies with large samples. In the subgroup analysis based on tumor stages, for late stage disease (III-IV), the association was statistically significant (HR = 0.55, 95% CI: 0.36-0.84, *P* = 0.006), but the pooled HR for all stages and early stages (I-III) was non-significant. Subgroup analysis stratified according to quality score, the pooled HRs of high quality studies (QS >60%) and low quality studies (QS < 60%) were 0.79 (95% CI: 0.67-0.94, *P* = 0.007) and 0.98 (95% CI: 0.87-1.11, *P* = 0.746), respectively. Similarly, when stratified by ethnicity and follow-up period, there was still no statistical significance.

Publication bias and sensitivity analysis

Publication bias was detected in this meta-analysis by using Egger linear regression tests. The association between IGF1R expression

Table 2. Meta-analysis assessing the association between IGF1R expression and clinical characteristics

Clinical characteristics	No. of Studies	Cases	Pooled Data			Test for Heterogeneity		
			OR	95% CI	*P*-value	Chi^2	*P*-value	I^2 (%)
Gender (male/female)	15	2554	1.19	0.98-1.43	0.08	16.49	0.28	15
Smoking (ever/none)	13	2169	1.45	1.13-1.85	0.003	22.39	0.03	46
Age (< 60/≥ 60)	3	397	1.15	0.47-2.81	0.75	5.43	0.07	63
Tumor size (T1, 2/T3, 4)	4	640	0.61	0.60-0.95	0.03	1.62	0.66	0
Histological Type (SCC/ADC)	10	1527	2.08	0.88-4.93	0.09	80.00	< 0.00001	89
Differentiation (poor/well-moderate)	9	1585	1.04	0.66-1.63	0.87	23.09	0.003	65
TNM Stage (INM Sta)	7	1596	0.93	0.65-1.33	0.71	13.17	0.04	54
Lymph Node Metastasis (NX/N0)	6	1185	1.31	0.85-2.02	0.22	12.54	0.03	60

Abbreviation: No., number; SCC, Squamous cell carcinoma; ADC, Adenocarcinoma.

Table 3. A summary of HRs for the overall and subgroup analyses of IGF1R and overall survival of non-small cell lung cancer patients

		No. of studies	HR	95% CI	Heterogeneity	
					I^2	*P*-value
Overall		12	0.91	0.82-1.01	34.6%	0.114
Ethnicity	Asian	8	0.93	0.82-1.06	39.8%	0.113
	Non-Asian	4	0.87	0.74-1.03	37.5%	0.187
Patient numbers	> 150	6	0.96	0.86-1.08	0.0%	0.976
	< 150	*6*	*0.77*	*0.63-0.94*	*34.6%*	*0.03*
Follow-up period	> 60 month	6	0.88	0.77-1.00	12.1%	0.338
	< 60 month	6	0.96	0.82-1.01	51.7%	0.066
Tumor stage	I-III	4	0.99	0.86-1.14	18.3%	0.299
	I-IV	6	0.87	0.75-1.02	14%	0.325
	III-IV	*2*	*0.55*	*0.36-0.84*	*0.0%*	*0.690*
Quality score	*> 60 QS*	*6*	*0.79*	*0.67-0.94*	*54.4%*	*0.052*
	< 60 QS	6	0.98	0.87-1.11	0.0%	0.867

No.: Number; HR: Hazard ratio; CI: Confidence interval; IGF1R: Insulin-like growth factor-1 receptor.

and the OS in NSCLC patients had no significant publication bias existed on univariate analysis ($P = 0.268$) and the funnel plot seemed symmetrical (**Figure 4**). However, on univariate analysis of DFS and multivariate analysis of OS and DFS, the number of studies included was no more than ten, so these tests have no power to detect publication bias. Thus, we did not detect the publication bias of them. In addition, the assessment of publication bias also showed that the Egger tests were not significant ($P > 0.05$) for studies included in analysis of clinicopathological characteristics and the funnel plots seemed symmetrical (figures were not shown). Sensitivity analysis showed that the pooled HRs were similar when one study was removed. Therefore, our results were statistically reliable.

Discussion

Our meta-analysis is based on published data and was performed using univariate analysis followed by further multivariate analysis. To the best of our knowledge, this study is the first meta-analysis focusing on IGF1R expression in resected NSCLC. Our results suggest that IGF-1R positive expression is associated with an unfavourable DFS on both univariate and multivariate analysis, and IGF1R expression is also associated with smoking status and tumor size. However, IGF1R expression is not significantly associated with OS, but after subgroup analysis, IGF1R positive expression became associated with a favourable OS in studies with smaller samples, late stage disease (III-IV) and high quality.

IGF-1R is frequently disordered in human cancer and activation of IGF1R can activate the PI3K/AKT/mTOR and the Ras/Raf/MAPK pathways, which can promote proliferation, apoptosis, metastasis and resistance in cancer [44, 45]. Moreover, IGF1R has become a target of anti-cancer therapy in solid tumors, including NSCLC. In a recent randomized phase II trial, 156 patients were randomized to paclitaxel-carboplatin with or without figitumumab, their results indicated a higher response rate and longer progression-free survival (PFS) in figitumumab-treated patients, especially in patients

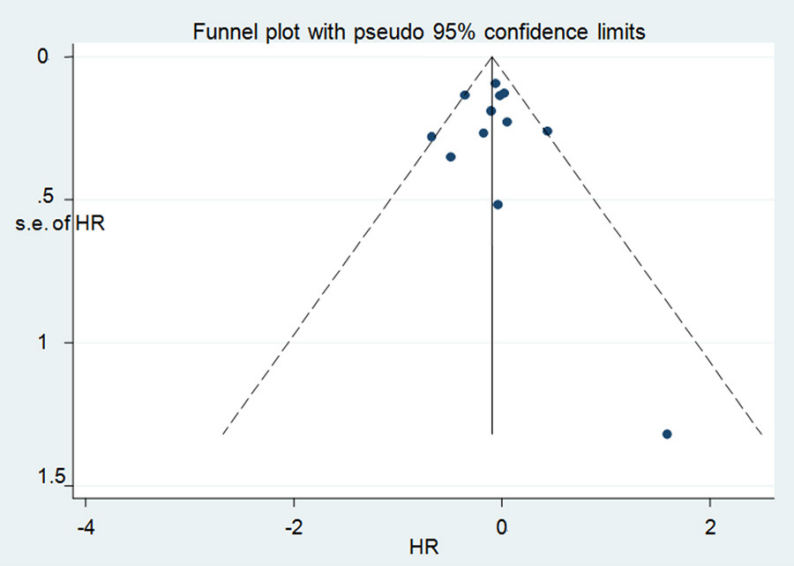

Figure 4. Funnel plot designed to visualize a potential publication bias on univariate analysis of overall survival.

with squamous cell carcinoma [46]. Nevertheless, the phase III trials of figitumumab were terminated in 2010, because the HR was 1.1 towards the control arm. Furthermore, a randomized, phase II study comparing erlotinib plus R1507 (a monoclonal antibody against IGF1R) versus erlotinib plus placebo suggested that R1507 failed to show an improvement in PFS in unselected patients [47]. Thus, the reported clinical trials have given us serious concerns about the ability of IGF1R inhibition to serve as effective cancer treatments.

The prognostic significance of IGF1R expression has been examined in many cancers, including NSCLC. According to our study, IGF1R positive expression is associated with smoking status and tumor size, as well as an unfavourable DFS. Peled N. et al. considered that high IGF1R expression acted as an indicator for resistance to gefitinib in NSCLC cell lines and NSCLC patients, but did not seem to play a role in the intrinsic resistance to this drug [48]. Nevertheless, another study in 83 patients showed IGF1R expression measured by immunohistochemistry does not appear to be related to gefitinib resistance [49]. Gualberto A et al. found IGFIR was differentially expressed in histological subtypes (P = 0.04), with highest levels observed in squamous cell tumors [50]. However, our result suggested that IGF1R expression was irrelevant to histological subtypes. So far, the inconsistency of results for reported IGF-1R expression and outcomes may depend on the investigators and antibodies used for analysis, patient samples, disease stages, or the presence of other poorly understood pathways and regulators related to IGF-1R. Therefore, the results of our study provide useful information for clinicians assessing the prognosis of NSCLC patients and making personalized therapy decisions.

To be sure, there were some potential limitations in this study. Firstly, most included studies were retrospective studies, and no RCTs had been found. Owing to limitations in the original studies, we could not perform further subgroup analysis on univariate analysis of DFS, and on multivariate analysis of OS and DFS. Furthermore, we included studies with detection method by IHC, but the types or the dilutions of primary antibody were not the same in all the studies (Supporting Information Table S3). So, variability in protein expression assessment must be considered a potential source of bias. We also noticed that the cut-off values were arbitrarily selected and varied greatly between studies, which might produce the high heterogeneity. Nevertheless, due to the limited information of the original studies, we could not conduct further subgroup analysis by cut off values and histological type. Additionally, the HR was reconstructed from the survival curves when it was not reported directly in a study, this approach did not completely eliminate inaccuracy during extracting the survival rates despite being undertaken independently by two reviewers. The estimated HR might thus be less reliable than when obtained directly from published statistics. In our analysis, we don't know whether previous adjuvant therapy has an impact on the prognostic significance of IGF1R. These issues had to be investigated by well designed prospective studies. Because none of the tests for funnel plot have power to detect publication bias when the number of studies included was no more than ten. Thus, we did not detect the publication bias on univariate

analysis of DFS and multivariate analysis of OS and DFS, so publication bias might exist on them. Meanwhile, another potential source of bias cannot be ignored, we did not include unpublished papers, comment and abstracts, which may also lead to publication bias, since studies with positive results tend to be accepted by journals, whereas negative results often are rejected or even not be submitted.

In summary, positive expression of IGF1R was associated with unfavourable disease free survival in patients with NSCLC on univariate and multivariate analysis, but not associated with overall survival on univariate and multivariate analysis. With respect to clinical characteristics, IGF1R positive expression was related to smoking status and tumor size. However, since the limitations mentioned above, these findings need to be explained with cautions when applied to clinical practice. More prospective cohort studies with large samples are needed to further demonstrate the correlations between IGF1R expression and the survival in NSCLC patients.

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Disclosure of conflict of interest

None.

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Table S1. Result of the methological assessment by the European lung cancer working party score

Subgroups	No. of studies (%)	Global score % (Mean [95% CI])	*P*-values
Publication year			
Before 2010	7 (41.2%)	59.43 (53.02-65.84)	0.332
After 2010	10 (58.8%)	62.81 (57.96-67.65)	
Results			
Positive	4 (23.5%)	62.59 (48.23-76.94)	0.783
Negative	4 (23.5%)	62.84 (59.22-66.47)	
N*	8 (53.0%)	60.26 (54.42-66.11)	
Patient number			
< 150	6 (35.3%)	60.70 (56.91-64.49)	0.762
≥ 150	11 (64.7%)	61.80 (56.28-67.34)	
Ethnicity			
Asian	13 (76.5%)	61.81 (58.17-65.45)	0.681
non-Asian	4 (23.5%)	60.13 (44.12-76.14)	

Positive: Studies identitying IGF1R positivity as a significant poor prognosis factor. Negative: Studies reporting IGF1R positivity as a good prognosis factor. N*: Studies reporting IGF1R positivity as non-significant association with poor prognosis.

Table S2. IGF1R expression and clinical outcomes in patients with NSCLC

Author & year	Overall survival						Disease-free survival					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR estimation	HR	95% CI	HR estimation	HR	95% CI	HR estimation	HR	95% CI	HR estimation	HR	95% CI
Gately K. 2013	K-M	0.84	0.50-1.43									
Zhang XY. 2013							HR	1.11	0.86-1.44			
Xu C. 2013							K-M	1.54	1.02-2.32	HR	1.25	0.79-1.96
Ludovini V. 2013	HR	1.55	0.93-2.59				HR	1.59	0.91-2.77			
Yamamoto T. 2012				HR	2.32	1.22-4.44						
Tsuta K. 2012	K-M	0.98	0.75-1.28									
Kim YH. 2012	K-M	0.61	0.31-1.23				K-M	0.78	0.47-1.3			
Kim JS. 2012	K-M	1.02	0.79-1.31				K-M	1.29	1.02-1.63			
Kikuchi R. 2011				HR	0.56	0.32-0.95						
Nakagawa M. 2011							HR	2.68	1.27-5.68	HR	2.51	1.18-5.44
Dziadziuszko R. 2010	HR	0.70	0.53-0.90	HR	0.75	0.57-0.99						
Ning XH. 2010	K-M	0.96	0.35-2.67									
Cappuzzo F. 2009	K-M	0.94	0.78-1.13									
Chang MH. 2009	K-M	0.90	0.62-1.30									
Gong YX. 2009	K-M	1.05	0.67-1.64									
Lee CY. 2008	K-M	4.90	0.37-65.30									
Cappuzzo F. 2006	K-M	0.51	0.29-0.87	HR	0.43	0.23-0.80						

IGF1R: Insulin-like growth factor-1 receptor; K-M: Kaplan-Meier curve; HR: Hazard ratio.

Table S3. Information of antibody sources

Author	Year	Species	Suppliers	Dilution
Gately K.	2013	Rabbit monoclonal	Ventana Medical Systems, Tucson, AZ	1:100
Zhang XY	2013	Mouse	BioSource International, Camarillo, USA	1:50
Xu C.	2013	Rabbit	Abcam, Cambridge, UK	1:100
Ludovini V.	2013	Mouse	Lab Vision Neomarkers, USA	1:50
Yamamoto T.	2012	Rabbit polyclonal	Signalway Antibody, Pearland, USA	1:100
Tsuta K.	2012	Rabbit monoclonal	Ventana Medical Systems, Tucson, AZ	NA
Kim YH	2012	Rabbit monoclonal	Ventana Medical Systems, Tucson, AZ	1:1
Kim JS	2012	NA	Cell Signaling Technology, Danvers, MA	NA
Kikuchi R.	2011	Rabbit polyclonal	Cell Signaling Technology, Danvers, MA	1:100
Nakagawa M.	2011	Mouse monoclonal	Abcam, Cambridge, USA	1:500
Dziadziuszko R.	2010	NA	Ventana Medical Systems, Tucson, AZ	NA
Ning XH	2010	Rabbit	Boster, Wuhan, CHN	1:50
Cappuzzo F.	2009	NA	Novus Biologicals, Littleton, CO	NA
Chang MH	2009	Mouse monoclonal	Abcam, Cambridge, UK	1:1000
Gong YX	2009	Rabbit monoclonal	Ventana-Roche, Tuscon, AZ	NA
Lee CY	2008	Mouse monoclonal	BioSource International, Camarillo, USA	1:50
Cappuzzo F.	2006	Mouse	Novus Biologicals, Littleton, CO	1:50

NA: Not available.