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Prognostic value of IGF-1R in lung cancer

A PRISMA-compliant meta-analysis

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Abstract

Background: Insulin-like growth factor receptor 1 (IGF-1R) is a key player in a wide array of pathological processes, while the prognostic role of IGF-1R in lung cancer remains controversial.

Methods: We conducted a meta-analysis to evaluate the prognostic value of IGF-1R in lung cancer. We searched for recent studies on the expression of IGF-1R and extracted prognostic lung cancer data from the articles.

Results: Eventually, 22 studies with 3859 patients were analyzed in our meta-analysis. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were used to quantify the ability of IGF-1R to predict survival. The results indicated that IGF-1R positive expression was associated with an unfavorable disease-free survival (DFS) in non-small cell lung cancer (NSCLC) patients on univariate analysis (HR = 1.24, 95% CI: 1.00–1.55, $P = .054$) and multivariate analysis (HR = 1.49, 95% CI: 1.01–2.21, $P = .045$), but there was no significant difference in the relationship between IGF-1R positive expression and overall survival (OS) on univariate analysis (HR = 1.04, 95% CI: 0.86–1.25, $P = .712$) and multivariate analysis (HR = 0.89, 95% CI: 0.57–1.39, $P = .602$). IGF-1R mRNA expression related to OS was obtained in 2 studies, with the pooled HR being 1.663 (95% CI: 1.071–2.583, $P = .024$). For IGF-1R expression and small cell lung cancer (SCLC), the conclusion was not statistically significant, with the pooled HR being 1.22 (95% CI: 0.66–2.27, $P = .524$).

Conclusions: Our results indicate that high expression of IGF-1R predicts poor DFS in NSCLC, yet it does not predict poor OS in NSCLC and SCLC. IGF-1R may be a useful predictor of outcomes in patients with NSCLC.

Abbreviations: AD = adenocarcinoma, CI = confidence interval, CXCR4 = CXC chemokines type 4, DFS = disease-free survival, HR = hazard ratio, IGF-1 = insulin-like growth factor 1, IGF-1R = insulin-like growth factor 1 receptor, IGFBP-3 = insulin-like growth factor binding protein-3, IHC = immunohistochemistry, NSCLC = non-small-cell lung cancer, OS = overall survival, RT-PCR = reverse transcription-polymerase chain reaction, SCLC = small-cell lung cancer, VEGF = vascular endothelial growth factor.

Keywords: IGF-1R, NSCLC, prognosis, SCLC

1. Introduction

Lung cancer is the most lethal cancer worldwide due to its high incidence and mortality.[1] To date, the 5-year overall survival rate for patients with lung cancer is less than 14%,[2] highlighting the need for novel treatment strategies. The current viewpoint regarding lung cancer is that it is not a single disease, but a collection of diseases with pathogeneses governed by distinct molecular mechanisms. Therefore, novel treatments will be available after we increase our understanding of the biology of lung cancer and discover its molecular markers.

In recent years, some cell surface markers have been found that are responsible for tumor initiation, progression, and metastasis in a small group of cancers. Many researchers have reported that high expression of these markers, such as insulin-like growth factor 1 (IGF-1), insulin-like growth factor binding protein-3 (IGFBP-3), vascular endothelial growth factor (VEGF), CXC chemokine type 4 (CXCR4), CD44, miR-21, miR-155, and lower pH indicate cancer risk, recurrence, and poor prognosis.[3–8] At the same time, many articles have been published in recent years pertaining to the prognostic value of IGF-1R in human cancers, such as esophageal cancer, breast cancer, colorectal cancer, osteosarcoma, and oral squamous cell carcinoma.[9–13]

IGF-1R is a heterotetrameric transmembrane tyrosine kinase that consists of 2 extracellular alpha-subunits and 2 transmembrane beta-subunits.[14] Alpha-subunits are entirely extracellular and are mainly responsible for ligand binding, and beta-subunits are transmembrane chains involved in the transduction of biological signals.[15] Ligand binding to the IGF-1R triggers conformational change and autophosphorylation of specific tyrosine residues, consequently initiating signal transduction.[16,17] The role of IGF-1R in malignant transformation has been well documented and reviewed by Valentinis and Baserga.[18] Moreover, many recent studies have identified new

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signaling pathways emanating from the IGF-1R that affect cancer cell proliferation, adhesion, transformation, and cell apoptosis, which are important processes in tumor development.[19,20] There have been numerous articles describing the expression of IGF-1R in human cancer types, especially in cancer development and progression. Although several conclusions of the studies reached consistency, some appeared contradictory. Yamamoto et al[21] reported in his study that high expression of IGF-1R was associated with significantly worse overall survival. Additionally, a study by Kikuchi demonstrated that a low level of IGF-1R expression was associated with poor prognosis.[22] To clarify the effect of IGF-1R as a prognostic biomarker, here we performed a meta-analysis of the published studies and aimed to elucidate the issue on the prognostic properties of IGF-1R status in lung cancer.

2. Materials and methods

2.1. Search strategy

A systematic search was carried out for original articles using the electronic search online databases such as PubMed, Medline, Embase, and Web of Science. Studies were selected using the terms: "IGF-1R," "NSCLC," "SCLC," "prognosis," and "survival" with all possible combinations. Published original and review articles were sought until June 2018, and the latter was considered a source of original works otherwise overlooked. Additionally, the relevant reviews and references reported in all the articles were examined to complete our search.

2.2. Eligibility criteria

To ensure the quality of the meta-analysis, all the studies were required to meet the following criteria: trials had to pertain to NSCLC or SCLC; IGF-1R expression was measured in human specimen; the correlation between IGF-1R expression and survival was evaluated; IGF-1R was dichotomized as high and low; sufficient samples had to be included; included studies were in English; data could be extracted. When the results obviously obtained from the same patient were involved in more than 1 publication population, only the most complete and recent research was included in this analysis.

2.3. Data extraction

Information retrieved from the studies included the first author's name and the publication year. Characteristics of the studied population included region, stage, sample size, histology type, antibody, assessment method, follow-up time, HRs of IGF-1R for overall survival (OS) and disease-free survival (DFS), along with the 95% CI values and *P* values. A comprehensive database was designed to ensure that all the data required for analysis were publicly available. Because all analyses were based on previously published studies, no ethical approval or patient consent was necessary.

2.4. Statistical analysis

In the included studies, immunohistochemical (IHC) and reverse transcription-polymerase chain reaction (RT-PCR) were used to determine the levels of IGF-1R in the samples. The easiest and most accurate method was to extract the HRs and CIs from articles. If these data were not explicitly reported, the HRs and CIs were calculated according to Tierney's methods.[23] Heterogeneity tests for pooled HRs were carried out by using I^2 statistic and Q statistic. A *P* value of less than .05 was considered to be significant. A random effect model was applied if obvious heterogeneity was observed ($P < .05$ or $I^2 > 50\%$); otherwise, the fixed effect model was used. The results were statistically significant only when the 95% confidence intervals did not overlap with 1. Publication bias was evaluated by a funnel plot with Begg test. All calculations for our meta-analysis were performed with Stata Statistical Software Version 11.0 and Excel software.

3. Results

3.1. Studies selection and characteristics of included studies

A total of 768 studies for IGF-1R and lung cancer prognosis were identified from a primary literature search in PubMed, Medline, Embase, and Web of Science. Of which, 676 studies were excluded based on manual screening of the title or abstract, and the full text was evaluated for the remaining studies. Of the 92 candidate studies, 28 articles were related to animals, 41 articles were concerned with cell lines, and 1 study was involved with the same patients as another study. Therefore, ultimately 22 articles with a total number of 3859 patients associated with survival were considered eligible for inclusion in this review (Fig. 1).[21,22,24–43] All the included studies were in English.

The characteristics of these studies are listed in Table 1, where 10 studies included patients from Asia, 10 from Europe, and 2 from the USA, respectively. Almost all the studies used IHC analysis to examine the expression of IGF-1R in lung cancer tissues except 2 studies, which used indirect RT-PCR analysis. Statistical calculations for OS in NSCLC were performed in 14 studies, for a total of 2704 patients. The median patient number of the studies was 167 (range 33–459). The studies considered stage I (n = 1), stages I–III (n = 4), stages I–IV (n = 7), and stages III–IV (n = 2). Seven studies including 1393 patients were involved in the DFS calculation for NSCLC. The patient numbers ranged from 68 to 459. Two studies included information for stages I–III, 4 for stages I–IV, and 1 for stages III–IV. IGF-1R

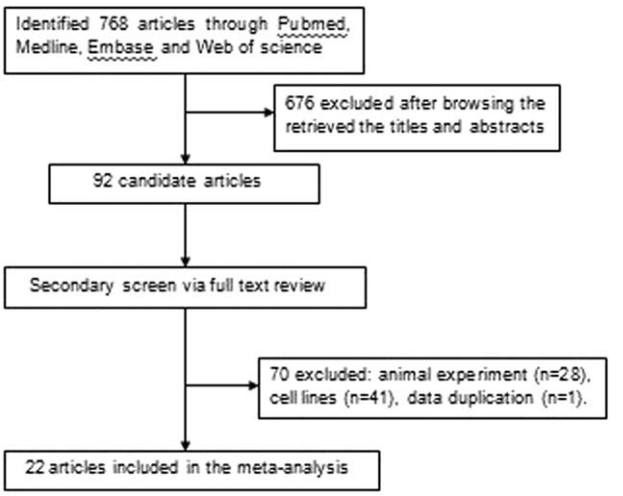

Figure 1. Flow diagram of the meta-analysis.

Table 1

Main characteristics of eligible studies.

First author	Y	Region	Age	Follow-up	n	Histology	Stage	Antibody	Method	Cut-off	Survival	Univariate HR	Multivariate HR
Gately K	2013	Ireland	41–88,66.1	65.09m	184	NSCLC	I-III	Ventana G11	IHC	200	OS	0.823 (0.498,1.284)	
V. Ludovini	2013	Italy	40–84,66	48.9	125	NSCLC	I-III	Lab Vision Neomarkers	IHC	10%	OS	1.55 (0.93,2.59)	
Yamamoto T	2012	Japan	19–82,65	48.84	78	NSCLC	I-III	Signalway Antibody	IHC	200	OS		2.32 (1.22,4.44)
Tsuta K	2012	Japan	37–88,65.1	58.6m	379	NSCLC	I-IV	Ventana	IHC	10%	OS	1.03 (0.78,1.35)	
Kim YH	2012	Japan	29–86,68	30	68	NSCLC	III-IV	Ventana	IHC	10%	OS	0.63 (0.32,1.24)	
Kim JS	2012	American	32–89,66	49.2m	459	NSCLC	I-IV	CST	IHC	1	OS	1.201 (0.877,1.544)	
Kikuchi K	2011	Japan	23–88,65	56.5	238	ADC	I-IV	CST	IHC	2	OS		0.56 (0.32,0.95)
Dziadziuszko R	2010	Poland	nm	63.6	189	NSCLC	I-IV	Ventana	IHC	2	OS	0.7 (0.53, 0.90)	0.75 (0.57, 0.99)
Cappuzzo F	2009	Italy	37.4–85.1,66.7	60	369	NSCLC	I-III	Novus Biologicals	IHC	100	OS	0.89 (0.73, 1.01)	
Gong YX	2009	American	nm	60	264	NSCLC	I-IV	Ventana	IHC	10%	OS	1.09 (0.73,1.69)	
Lee CY	2008	Korea	nm	60	71	NSCLC	I	BioSource International	IHC	1	OS	5.67 (0.57, 41.39)	
Vilmar A	2014	Denmark	51–75.4,63.3	72	33	NSCLC	I-IV	Ventana	IHC	1+	OS	1.32 (0.86–2.02)	
Fu S	2016	China	nm	60	80	NSCLC	I-IV	Invitrogen	IHC	5	OS	3.392 (1.614,6.897)	
Humar M	2017	Slovenia	40–82,63	72	167	NSCLC	III-IV	Ventana	IHC	1+	OS	0.766 (0.523, 1.121)	0.776 (0.518, 1.162)
Vilmar A	2014	Denmark	51–75.4,63.3	72	33	NSCLC	I-IV	Life Tech	RT-PCR	nm	OS		2.19 (0.96–4.99)
Agullo-Ortuno MT	2014	Spain	37–85,65.9	37m	115	NSCLC	I-IV	nm	RT-PCR	2.866	OS		1.49 (0.90–2.55)
Zhang XY	2013	China	nm	60	178	ADC	I-III	BioSource International	IHC	20	DFS	1.11 (0.86, 1.44)	
Xu C	2013	China	nm	52.6	200	ADC	I-IV	Abcam	IHC	4	DFS	1.54 (1.02, 2.32)	1.25 (0.79, 1.96)
V. Ludovini	2013	Italy	40–84,66	48.9	125	NSCLC	I-III	Lab Vision Neomarkers	IHC	10%	DFS	1.59 (0.91,2.77)	
Kim YH	2012	Japan	29–86,68	30	68	NSCLC	III-IV	Ventana	IHC	10%	DFS	0.85 (0.48,1.45)	
Kim JS	2012	American	32–89,66	49.2m	459	NSCLC	I-IV	CST	IHC	1	DFS	1.34 (1.05,1.66)	
Nakagawa M	2011	Japan	nm	68.7	182	ADC	I-IV	Abcam	IHC	10%	DFS	2.681 (1.269,5.682)	2.506 (1.157,5.435)
Reinmuth N	2014	Germany	nm,61.3	3.6y	181	NSCLC	I-IV	Ventana	IHC	1+	DFS	0.8 (0.52,1.23)	
Chang MH	2009	Korea	63 (38,85)	60	194	SCLC	I-IV	CST	IHC	1	OS	0.82 (0.56,1.22)	
Gately K	2011	Ireland	48–77,64	2.5y	21	SCLC	I-IV	Ventana	IHC	3+	OS	3.11 (1.397,6.534)	
Badzio A	2010	Poland	37–82, 57	211	84	SCLC	I-III	Ventana	IHC	88	OS	0.946 (0.626, 1.430)	

AD = adenocarcinoma, CI = confidence interval, DFS = disease-free survival, HR = hazard ratio, IHC = immunohistochemistry, n = number of patients, nm = not mentioned, NSCLC = non-small-cell lung cancer, OS = overall survival, SCLC = small-cell lung cancer.

mRNA expression for OS was performed in 2 studies including a total of 148 patients. Statistical calculations for OS in SCLC were performed in 3 studies including a total of 299 patients. The patient numbers ranged from 21 to 194. The IGF-1R expression was dichotomized into high and low levels, and different appraisal procedures were chosen in each study, as is shown in Table 1.

3.2. Outcomes from eligible studies

We performed a meta-analysis to identify whether IGF-1R could be a robust prognostic biomarker. For the studies evaluating DFS for IGF-1R (Fig. 2), we found that higher expression levels of IGF-1R were associated with an unfavorable DFS in NSCLC patients on univariate analysis (HR = 1.24, 95% CI: 1.00–1.55, $P = .054$) and multivariate analysis (HR = 1.49, 95% CI: 1.01–2.21, $P = .045$), but the relationship between IGF-1R positive expression and OS had no significant difference on univariate analysis (HR = 1.04, 95% CI: 0.86–1.25, $P = .712$) and multivariate analysis (HR = 0.89, 95% CI: 0.57–1.39, $P = .602$) (Fig. 2). IGF-1R mRNA expression related to OS was obtained in 2 studies, with the pooled HR being 1.663 (95% CI: 1.071–2.583, $P = .024$) (Fig. 2). The conclusion was not statistically significant for IGF-1R expression and SCLC, with the pooled HR being 1.22 (95% CI: 0.66–2.27, $P = .524$) (Fig. 2).

3.3. Publication bias

Finally, the publication bias of the included studies for all clinical outcomes was evaluated by funnel plots and Begg tests (Fig. 3). With the limited number of included articles, we only detected the publication bias of univariate analysis for OS and DFS in NSCLC patients. The funnel plots for all clinical outcomes were symmetric, and the *P* value of Begg regression intercepts of OS and DFS showed that there was no evidence for significant publication bias in the meta-analysis.

4. Discussion

IGF-1R is a key player in a wide array of pathological processes, which may partly explain the prognostic associations in cancer.[16,44,45] Some evidence showed that IGF-1R is a key driver of oncogenic transformation in a defined subset of cancer. The prognosis of other cancer types such as prostate cancer, colorectal cancer, and breast cancer was reported to be associated with high levels of IGF-1R expression, while the prognostic role of IGF-1R in lung cancer remains controversial.

The correlation between IGF-1R expression and lung cancer has been explored by many studies; however, the patients they included were too few to draw a firm conclusion. Moreover, the studies had different cut-off values for positive IGF-1R expression, which resulted in inconsistent conclusions. The present study conducted a comprehensive search for related studies, and finally included 22 studies (including 3859 patients) to investigate whether IGF-1R could be a prognostic factor in lung cancer.

The results of the meta-analysis showed that high expression of IGF-1R was associated with poor DFS in NSCLC, yet poor OS in NSCLC and SCLC was not predicted, which suggested that IGF-1R participates in the development of NSCLC and could be a prognostic factor in NSCLC. However, the conclusion was not persuasive enough, and needs to be refined for several reasons. If the number of cohorts included for meta-analysis was sufficient,

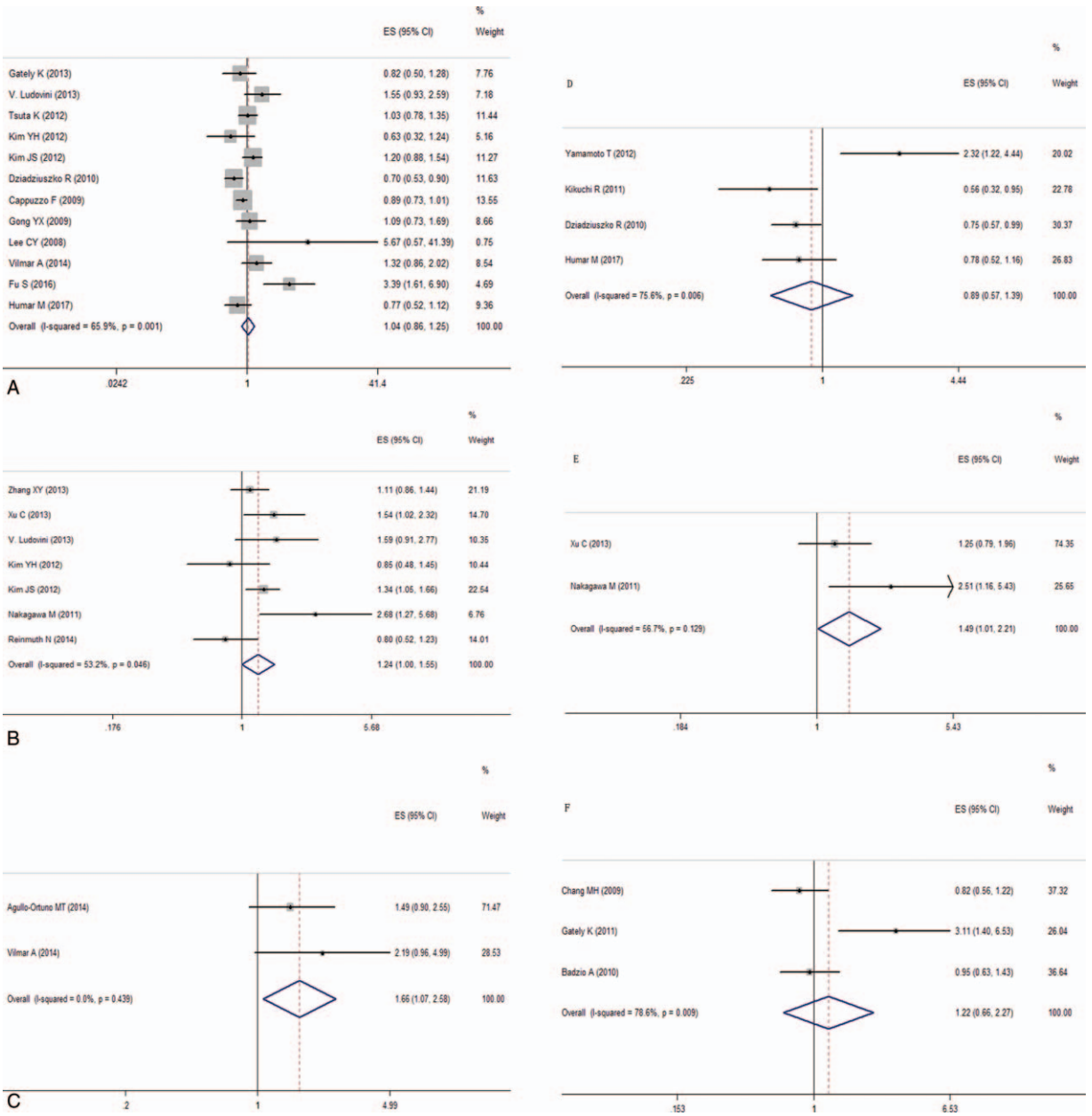

Figure 2. Forest plot showing the combined relative HR of NSCLC for overall survival. A, Univariate analysis; D. multivariate analysis. Forest plot showing the combined relative HR of NSCLC for disease-free survival: B. univariate analysis; E. multivariate analysis. Forrest plots of studies evaluating mRNA expression of NSCLC related to OS: C. multivariate analysis. Forest plot showing the combined relative HR of SCLC for overall survival: D. multivariate analysis.

the experimental design would be more practical and more rigorous, and the results would be more reliable.

And yet, several questions remain poorly defined and limit the transfer of IGF-1R from bench to bedside as a prognostic biomarker: the methodology utilized to estimate IGF-1R status affected the prognostic property. The HR was directly extracted from the data included in the article or calculated from the survival curves. Actually, the method for extrapolating HR from survival curves seemed to be less reliable because this strategy did not completely eliminate inaccuracy in the extracted survival rates. Another important factor for prognosis is clinical treatment, which includes surgery, postoperative radiotherapy or chemotherapy, and palliative treatment after relapse or disease progression. Because of the variation in treatments and lack of assessed studies, it is difficult to say whether the prognostic effect of IGF-1R is associated with clinical treatment or not based on the available studies. Therefore, future standardized protocols are expected to improve the quality of this review.

Even though our research was somewhat imperfect, the remarkable potential of IGF-1R as a prognostic biomarker cannot be overlooked. The present study showed a significant correlation between aberrant IGF-1R expression and unfavorable disease-free survival in NSCLC. Based on our findings, we hypothesized that targeting of IGF-1R may have broader coverage. Confirming this critical role, in preclinical settings, a large amount of experimental data clearly demonstrates that

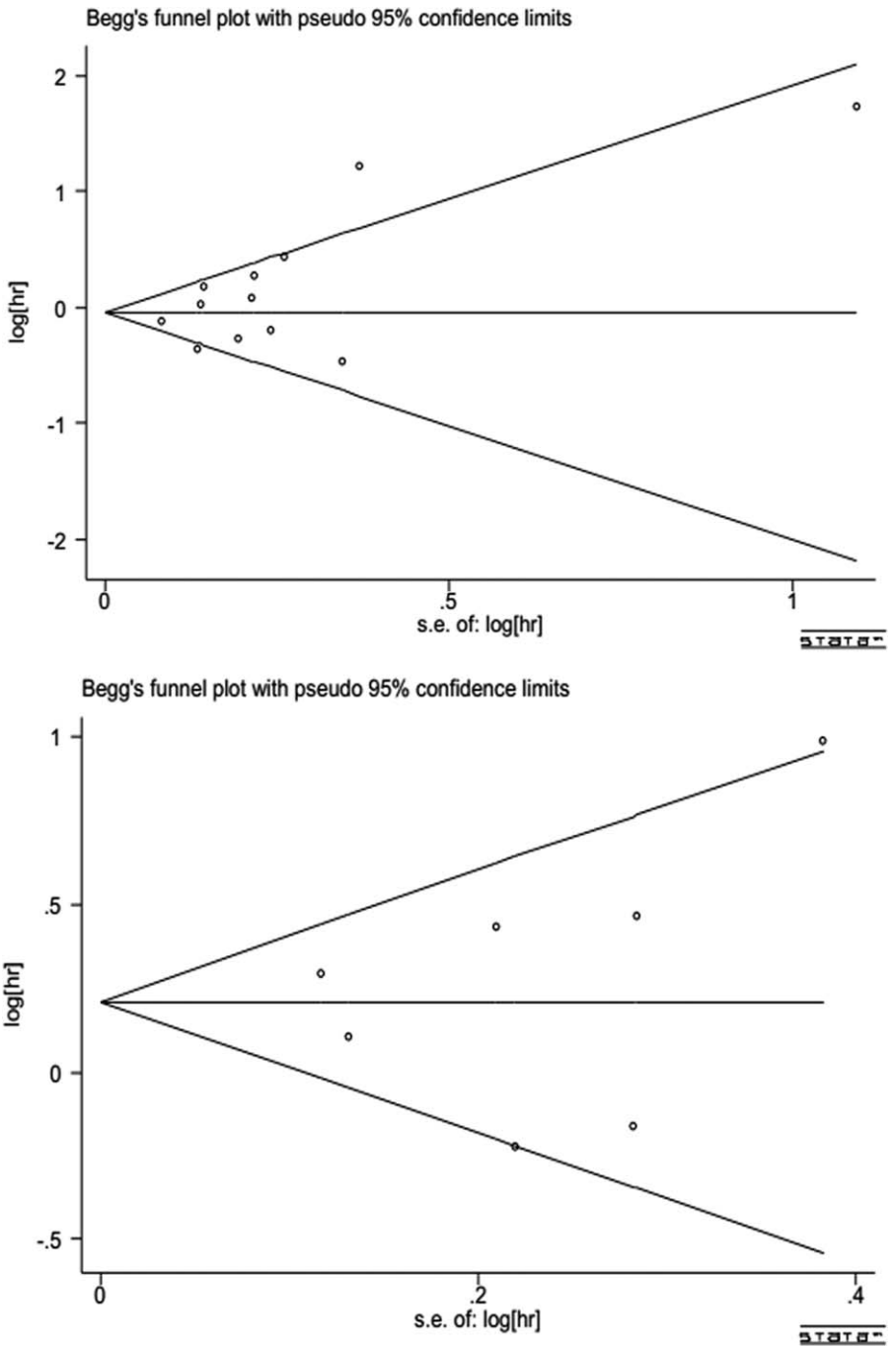

Figure 3. Begg funnel plots of publication bias test. A, Begg funnel plots of publication bias test for the overall merged analysis of OS. B, Begg funnel plots of the publication bias test for the overall merged analysis of DFS. DFS = disease-free survival, OS = overall survival.

inhibition of IGF-1R would be beneficial for cancer treatment.[46–48] In vivo and in vitro studies using IGF-1R antibodies and small molecule inhibitors have shown that IGF-1R is functionally essential for tumor cell growth and proliferation in most if not all forms of cancer.[49–52] We infer that in the case of cancer, IGF-1R inhibitors could improve survival and prognosis. Our results give us an indication of how to select suitable patients with lung cancer for anti-IGF-1R therapy, which should be more successful and cost-effective. Last but not the least, we should try to block the IGF-1R pathway so as to prolong the survival of lung cancer patients.

Further studies are required to investigate whether alteration of IGF-1R could occur in the process of lung cancer targeted therapy and whether this change could result in a new perspective for the treatment of lung cancer. Additionally, studies are required to evaluate the application of IGF-1R as a biomarker for lung cancer prognosis and targeted therapy. Furthermore, adverse effects of anti-IGF-1R inhibitors that could occur during biological processes require careful assessment. More large-scale investigations and better understanding of the mechanism of IGF-1R are needed to explore the prognostic and treatment value of IGF-1R.

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Author contributions

Conceptualization: Fenglong Bie.
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Software: Tao Yan.
Writing – original draft: Jun Xu.
Writing – review & editing: Jiajun Du.

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