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ORIGINAL RESEARCH

KIF5B-RET fusion gene and its correlation with clinicopathological and prognostic features in lung cancer: a meta-analysis

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Background: The *KIF5B-RET* fusion gene is a novel oncogene that has been observed in a subset of lung cancers in recent years. However, the results of related epidemiological studies remain unclear. Thus, a meta-analysis was conducted to evaluate the correlation of *KIF5B-RET* expression based on RT-PCR detection with clinicopathological features and prognosis of lung cancer.

Methods: The PubMed, Google Scholar, Wiley Online, SpringerLink and Chinese National Knowledge Infrastructure databases were searched to identify the eligible studies. The association of the occurrence of *KIF5B-RET* fusion gene in lung cancer with age, gender, smoking status, histology type, differentiation and TNM stage was analyzed. HR, overall survival (OS) and progression-free survival (PFS) were used to describe the prognosis of patients with lung cancer. The OR and 95% CI were calculated to assess the correlations. Random- and fixed-effects models were used to analyze the data.

Results: A total of 13 studies, which included 8,859 lung cancer patients, were included in the study based on the inclusion criteria. A total of 121 patients with positive *KIF5B-RET* fusion gene status were detected, with a positive expression rate of 1.36%. *KIF5B-RET* fusion gene status was identified at significantly higher frequencies in female (OR=0.67, 95% CI=0.48–0.94) than male patients, and the same trend was found in young (<60 years) patients (OR=0.08, 95% CI=0.01–0.45) compared with old patients (≥60 years). No differences were found in the TNM stage, histology, differentiation and smoking. Based on the prognosis, no difference was found between the status of the positive and negative *KIF5B-RET* fusion genes in OS and PFS of patients.

Conclusion: The *KIF5B-RET* fusion gene occurred predominantly in young female patients with lung cancer. However, the relationship between the expression of the fusion gene and the prognosis of lung patients remains unclear.

Keywords: pathological parameters, KIF5B-RET, lung cancer, fusion gene

Introduction

Research has shown that lung cancer is one of the most fatal tumors among the various malignant tumors, resulting in more than one million deaths every year worldwide.[1,2] In China, lung cancer-related mortality ranks first among malignant tumors.[3] The vast majority of lung cancer patients have deteriorated at the time of initial diagnosis, making it difficult for them to undergo surgery. In recent years, chemotherapy has remained the main treatment for lung cancer. Despite continuous improvements in treatment technology, the prognosis of lung cancer remains poor, and the 5-year survival rate is only approximately 15%.[4,5]

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Smoking is a major cause of lung cancer. More than 161,000 lung cancer deaths are projected to occur in the USA in 2008. Of these, an estimated 10%–15% will be caused by factors other than active smoking.[6] The majority of lung cancer patients without a history of smoking develop cancer because of cancer-related driver genes.[7] In the past decade, with the development of tumor molecular biology, a series of driver genes related to non-small-cell lung cancer (NSCLC) has been discovered, and these genes include *EGFR, KRAS* and *EML4-ALK*, which are often referred to as lung cancer treatment targets.[8] However, in more than 40% of NSCLC patients, the driver genes are not determined.

Since 2012, approximately 4.3%–8% of patients with lung adenocarcinoma have presented with *RET* gene rearrangement, whereas the *RET* gene encodes RET receptor tyrosine kinase.[9] RET fusion genes, including kinesin family member 5B (*KIF5B*), coiled-coil domain-containing protein 6 (*CDC6*), nuclear receptor coactivator 4 (*NCOA4*) and tripartite motif containing 33 (*TRIM33*), have been discovered, and *KIF5B-RET* is one of the most important genotypes.[10] The *KIF5B-RET* fusion gene was first discovered in the liver metastases of an NSCLC patient in 2011, and has been considered to be another important tyrosine kinase inhibitor (TKI) target for NSCLC.[11] The *RET* fusion gene can induce the occurrence of thyroid cancer, which is controlled by tumor progression via the RET inhibitor, but it has been rarely observed in lung cancer.[12,13] *KIF5B-RET* is not expressed in normal lung tissue but is highly expressed in lung cancer tissues.[14] Patients with the *KIF5B-RET* genotype have unique clinical features, suggesting that the target may be a more specific molecular marker in NSCLC. The *KIF5B-RET* fusion gene is a chimeric tyrosine kinase, consisting of 638 N-terminal amino acid residues of the KIF5B protein and 402 C-terminal amino acid residues of the RET protein, including the *RET* gene coding.[15,16] A structural region is present, having tyrosine protein kinase activity, a supercoiled domain and a motor domain encoded by the *KIF5B* gene.[17] The supercoiled domain of the *KIF5B-RET* fusion protein can undergo homodimerization, activate the intracellular tyrosine kinase protein and open the oncogenic signaling pathway, and ultimately regulates cell growth and differentiation mainly through the Ras–Raf–MAPK and PI3K–Akt pathway.[17] In summary, the related targeted drugs, diagnostic methods, clinical trials and transformational studies of *KIF5B-RET/EML4-ALK* fusion genes need further study.[18]

In this study, a meta-analysis was employed to study the expression of *KIF5B-RET* in lung cancer and related pathological data of lung cancer patients, including age, sex, TNM stage, smoking status, histological classification and differentiation. The expression of *RET* in patients was also studied. The prognosis of lung cancer patients was analyzed to predict the expression of the *KIF5B-RET* fusion gene for the treatment of lung cancer.

Methods

Data sources and search strategy

This meta-analysis was performed according to the PRISMA recommendations. The articles were retrieved by PubMed, Google Scholar, Wiley Online, SpringerLink and China National Knowledge Infrastructure and were collected from January 2012 to August 2018. The search keywords adoption strategy included ("Lung Cancer" or "Lung Neoplasms" or "Pulmonary Neoplasm") and ("rearranged during transfection" or "*RET*") and ("kinesin family member 5B" or "*KIF5B*" or "*KIF5B-RET*") and/or "prognosis". The search was restricted to RT-PCR detection studies, which were published in English and other languages. Detailed retrieval strategies are presented in the Supplementary material.

Inclusion and exclusion criteria

The inclusion criteria for the article included the following: 1) patients with pathology confirmed as lung cancer; 2) with available patient epidemiological and clinicopathological data or patient prognosis; 3) with available data forms for analysis and 4) articles published in English or Chinese. The exclusion criteria included the following: 1) patients with pathology confirmed as benign lung tumors; 2) no relevant pathology and patient prognosis data; 3) article data could not be used for statistical analysis; 4) non-human lung cancer tissues and 5) review studies and articles published with the same patient data. In cases of repeated publication of patient data, we used the latest article version for statistical analysis.

Data extraction

The data extracted from the article were collected independently by two investigators, and disputes were resolved through negotiation. Table 1 summarizes the basic data of each article, including the author's first name, year of publication, area of patient data collection, detection method of related genes and positive expression rate of gene fusion.

Statistical analyses

Stata 12.0 (StataCorp., College Station, TX, USA) was used to analyze the data related to lung cancer patients.

Table 1 Basic information on the patients with lung cancer

Study no	First author	Year	Country	Method	Cases	Age (years)	*RET* fusion positive			OS (months)			
							KIF5B	Others	Total	Fusion-positive patients		Fusion-negative patients	
										Median	Range	Median	Range
1	Takeuchi[28] et al	2012	Japan	RT-PCR	1,529	NA	12	2	14	NA	NA	NA	NA
2	Yokota[29] et al	2012	Japan	RT-PCR	371	NA	3	0	3	51.7	0.6–60.7	36.2	0.5–146.6
3	Suehara[18] et al	2012	USA	RT-PCR	69	67.8	1	0	1	NA	NA	NA	NA
4	Wang[24] et al	2012	China	RT-PCR	936	59.7	9	4	13	NA	NA	NA	NA
5	Kohno[11] et al	2012	Japan, USA	RT-PCR	433	62.3	7	0	7	NA	NA	NA	NA
6	Cai[9] et al	2013	China	RT-PCR	392	60	6	0	6	21	12.01–30.02	52.6	42.39–62.88
7	Yoo[30] et al	2013	Korean	RT-PCR	156	63.8	2	1	3	NA	NA	NA	NA
8	Tsuta[31] et al	2014	Japan	RT-PCR	1,874	63.1	19	3	22	NA	NA	NA	NA
9	Pan[32] et al	2014	China	RT-PCR	1,139	59.4	15	0	15	NA	NA	NA	NA
10	Kim[21] et al	2015	Korea	RT-PCR	533	67.2	21	30	51	NA	NA	NA	NA
11	Tsai[33] et al	2015	Taiwan	RT-PCR	722	66	11	6	17	22.4	8.8–36.0	12	9.0–15.0
12	Song[34] et al	2016	China	RT-PCR	615	54	9	2	11	58.1	NA	52	NA
13	Yu[35] et al	2018	China	RT-PCR	90	60	6	0	6	17.5	14.0–21.1	15.8	13.6–18.0

Abbreviations: OS, overall survival; NA, not available.

Engauge Digitizer software was used to organize the survival curves of patient overall survival (OS) and progression-free survival (PFS). The summarized indicators included the patient's *KIF5B-RET* expression rate, patient-related clinicopathological parameters and patient prognosis. The OR and corresponding 95% CI were used to describe the patient's clinicopathological parameters. HRs, OS and PFS were used to analyze the prognosis of patients. The selection of the effect model of the data was based on the specific value of I^2. When $I^2 \leq 50\%$, the data have moderate or low heterogeneity, and the fixed-effects model is used for simulation. When $I^2 > 50\%$, the data have high heterogeneity, and the random-effects model is used for simulation. The publication bias for patient prognosis was simulated using a funnel plot and Egger's test.

Results

Study selection and characteristics of included studies

A total of 1,028 articles were retrieved from relevant databases. Through the preliminary reading and analysis of the title and abstract, 887 articles were excluded because of a lack of significant relevance to the paper. The full text of the remaining 141 articles was downloaded and viewed, excluding the abstract, and the *KIF5B-RET*-related factors in animal lung cancer models and cell experiments were detected. Further analysis of the articles excluded 16 articles that could not be extracted and published using the same patient data. Finally, 13 related articles were included. The search results are presented in Figure 1.

A total of 8,859 patients were included in the 13 articles, including 169 patients with *RET*-positive disease, with a positive expression rate of 1.91%. A total of 121 patients had the *KIF5B-RET* fusion gene, with a positive expression rate of 1.36%.

Clinicopathological parameters

The *KIF5B-RET* fusion gene was identified at significantly lower frequencies in male (OR=0.67, 95% CI=0.48–0.94; Z=2.30, p=0.022) than in female patients, and the same trend was present in older (≥60 years) patients (OR=0.08, 95% CI=0.01–0.45; Z=2.87, p=0.004) compared with younger patients (<60 years) (all $p<0.05$) (Figures 2 and 3).

No differences were found in the TNM stage (I+II vs III+IV; Z=1.63, p=0.104; I^2=0.0%, p=0.998), histology (adenocarcinoma of the lung vs non-adenocarcinoma; Z=1.41, p=0.158; I^2=57.7%, p=0.021), differentiation

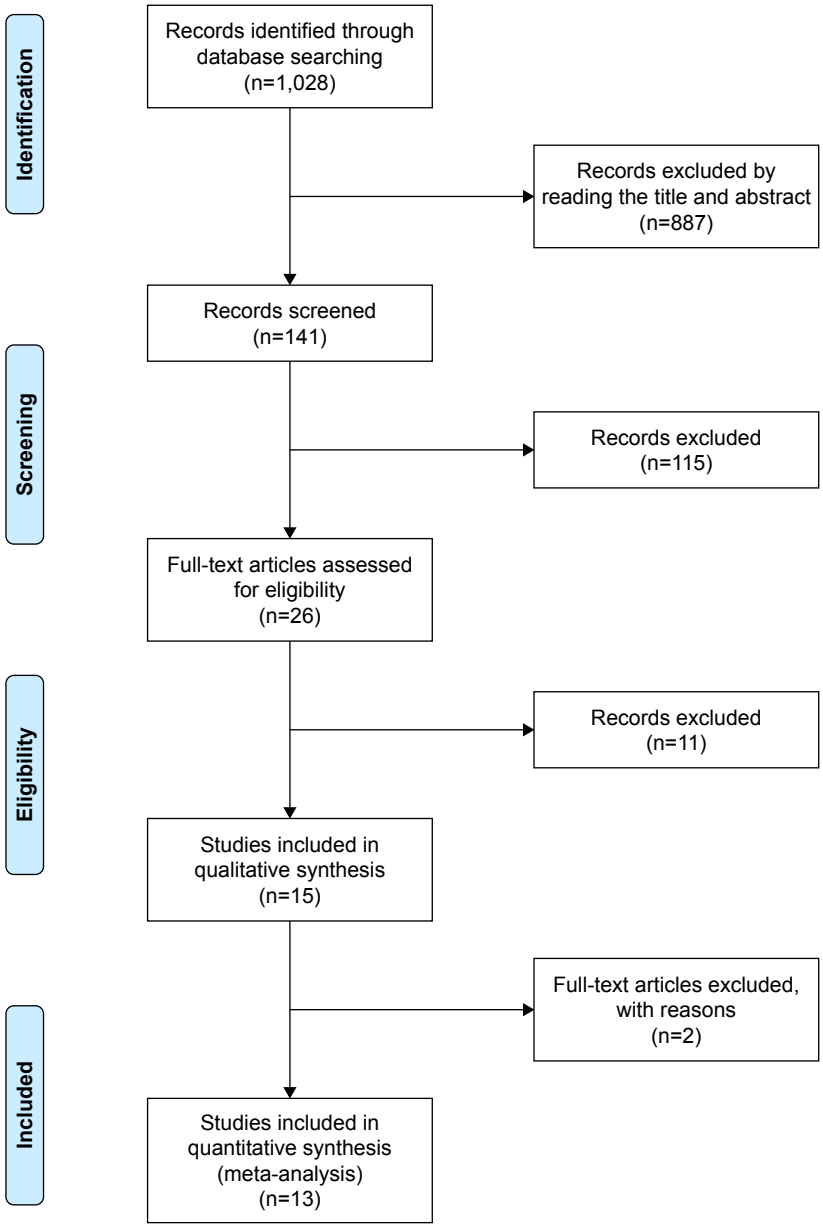

Figure 1 Flow diagram of the study selection procedure and specific reasons for exclusion in the meta-analysis.

(High vs Poor + Mod; Z=1.00, p=0.316; I^2=89.7%, p=0.002) and smoking (Yes vs No; Z=1.88, p=0.061; I^2=72.1%, p=0.000). The details are shown in Figures 2 and 3.

Prognosis

We analyzed six articles reporting OS and two articles reporting PFS for the *KIF5B-RET* fusion gene. The results showed no difference in OS and PFS between the positive and negative *RET* fusion genes (OS: Z=1.6, p=0.109; I^2=67.3%, p=0.009; PFS: Z=1.75, p=0.080; I^2=0.0%, p=0.723) (Figure 4).

Publication bias

Egger's test showed that no publication bias was observed in the comparison between the positive and negative *RET* fusion gene. Funnel plots are presented in Figures 5 and 6. A graph of risk of bias (Figure 7) and a summary of risk of bias (Figure 8) were generated to describe the risk of bias of each study.

Discussion

In recent years, genetic testing has been used to divide the same pathological type of lung cancer into various "molecular

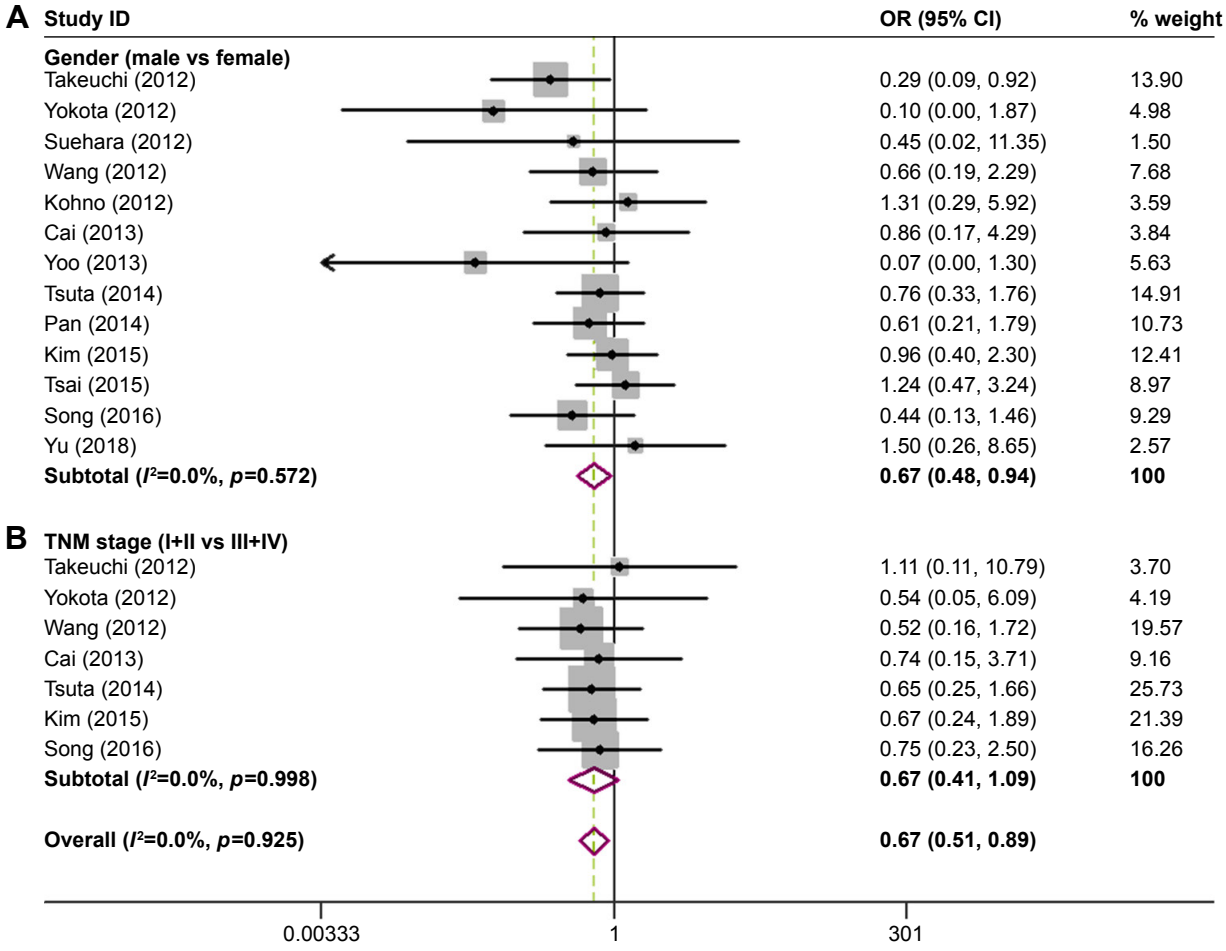

Figure 2 Meta-analysis of the association between *RET* fusion genes and clinicopathological features. (**A**) Gender: female vs male patients (Z=2.30, p=0.022); (**B**) TNM stage: I+II vs III+IV (Z=1.63, p=0.106).

subtypes", and individualized treatments can be achieved by selecting molecularly targeted drugs.[19] The *KIF5B-RET* fusion gene is an independent and key molecular target for the development and progression of lung cancer, mainly in patients with *EGFR*, *KRAS* wild-type, non-smoker and young male lung adenocarcinoma.[20–22] Several multi-target molecular targeted drugs are available internationally that may provide individualized treatment for patients with *RET* fusion genes.[23] The emergence of the molecular subtype of *KIF5B-RET* fusion genotype lung cancer has further improved the pattern of NSCLC molecular typing diagnosis and treatment.

A total of 13 articles meeting the inclusion criteria were included in this meta-analysis, including 8,859 patients with lung cancer. Among them, 169 patients were RET positive, with a positive expression rate of 1.91%, whereas 121 patients had the *KIF5B-RET* fusion gene, with a positive expression rate of 1.36%. Analysis of clinicopathological parameters showed that the *KIF5B-RET* fusion gene was differentially expressed according to age and sex ($p<0.05$). In the TNM stage, histology, differentiation and smoking, *RET* was expressed between the higher frequencies and lower frequencies groups, and no difference was observed in the expression (all p-values >0.05). In particular, smoking was significantly associated with lung cancer. The *KIF5B-RET* fusion gene was originally found in the liver metastases of a lung cancer patient who did not have a history of smoking. Increasing evidence has indicated that the *KIF5B-RET* fusion gene is present in lung cancer patients who do not smoke or only smoke lightly. Kohno et al found that the proportion of non-smokers in patients with *KIF5B-RET* fusion gene-positive lung adenocarcinoma was 85.7% (6/7).[11] Wang et al examined the status of the *RET* fusion gene in 936 patients with NSCLC who underwent lung resection in China.[24] The proportion of non-smokers in lung adenocarcinoma patients with positive *RET* fusion gene was 81.8% (9/11). In KIF5B, the proportion

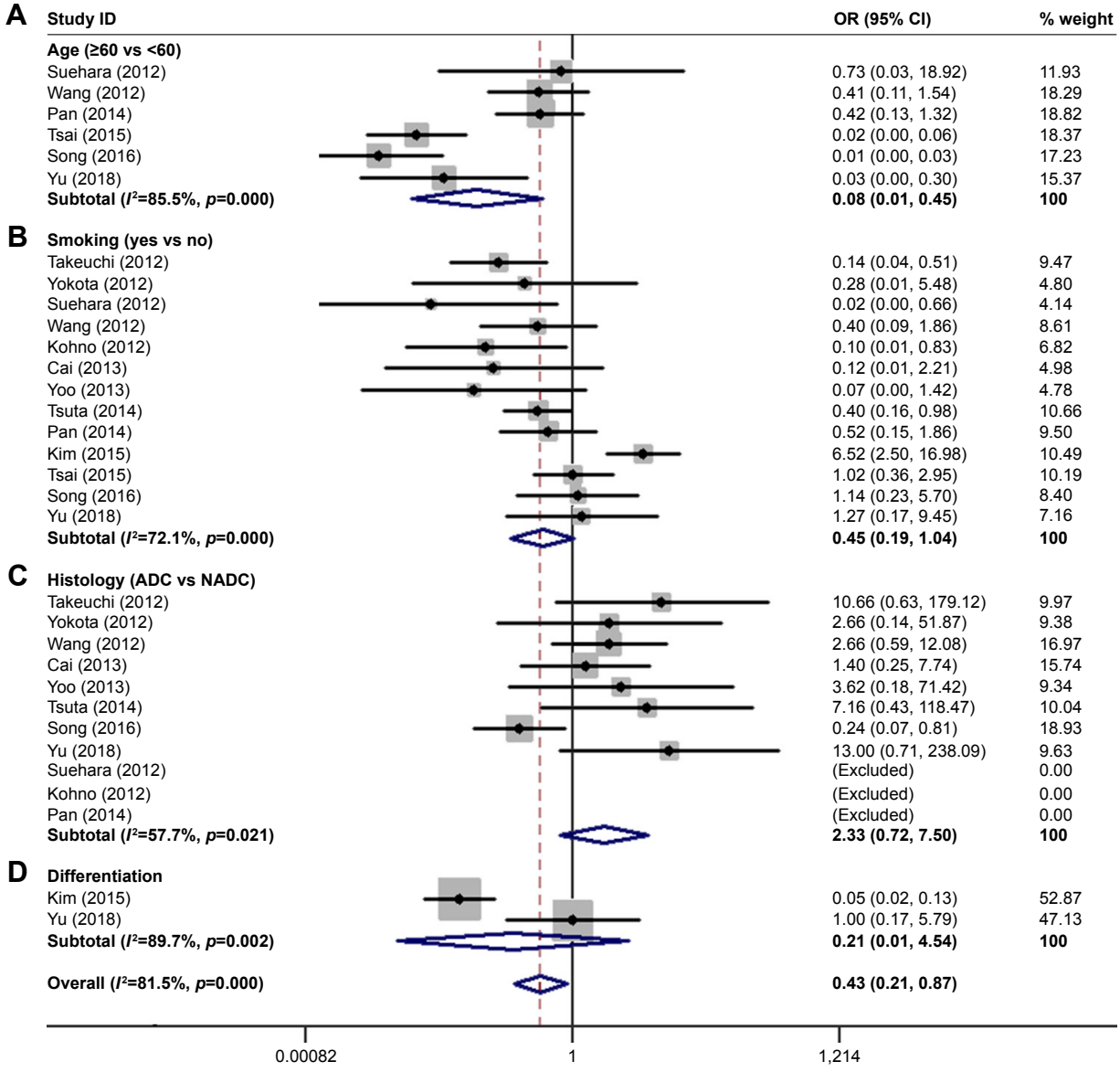

Figure 3 Meta-analysis of the association between *RET* fusion genes and clinicopathological features. (**A**) Age: ≥60 vs <60 years (Z=2.87, p=0.004); (**B**) smoking: yes vs no (Z=1.88, p=0.061); (**C**) histology: adenocarcinoma of the lung (ADC) vs non-adenocarcinoma (NADC) (Z=1.41, p=0.158); (**D**) differentiation: high vs poor + moderate (Z=1.00, p=0.316).

Note: Weights are from random-effects analysis.

of non-smokers in patients with positive *RET* fusion gene lung adenocarcinoma was 63.6% (7/11). These findings suggest that the *KIF5B-RET* fusion gene is more common in patients who do not smoke or only smoke lightly. Furthermore, the above data objectively support the research results of this paper.

Specific targeted drugs against the *KIF5B-RET* fusion gene have not been developed, but some TKIs that inhibit the activity of RET proteins have been widely clinically tested in thyroid cancer, and the US Food and Drug Administration has approved vandetanib for the treatment of hereditary thyroid gland medullary carcinoma. Kohno et al[11] showed that vandetanib can inhibit the growth of NIH3T3 lung cancer cells containing the *KIF5B-RET* fusion gene. Lipson et al found that Ba/F3 cells transfected with the *KIF5B-RET* fusion gene showed high expression and phosphorylation activation of RET, whereas in vitro studies found that multi-targeted drugs, sunitinib, sorafenib and vandetanib, are effective in inhibiting the proliferation of this cell, whereas gefitinib did not have this effect.[25]

Lung cancer driver genes have been a hotspot in NSCLC-targeted therapy research. TKI treatment targeting the *EGFR* mutation and *EML4-ALK* fusion gene has introduced new

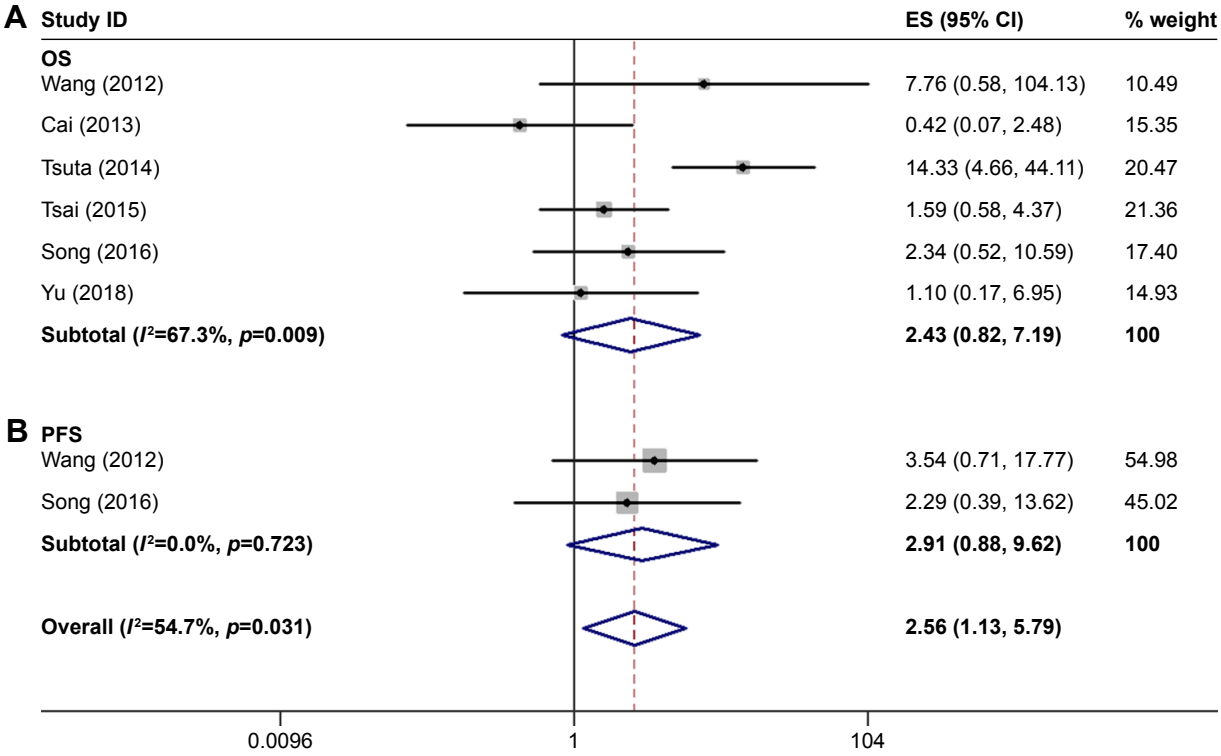

Figure 4 Meta-analysis of the association between *RET* fusion genes and prognosis. (**A**) OS (*Z*=1.6, *p*=0.109); (**B**) PFS (*Z*=1.75, *p*=0.080).
Note: Weights are from random-effects analysis.
Abbreviations: ES, effect size; OS, overall survival; PFS, progression-free survival.

ideas for NSCLC treatment.[26] However, more than 40% of NSCLC-driven genes remain unclear.[27] The discovery of the *KIF5B-RET* fusion gene has injected new vitality into the field of lung cancer research. However, to establish a diagnosis and treatment model that is truly similar to the current *EGFR* mutation, the *ALK* fusion gene requires a large amount of preclinical research and a high level of clinical evidence.

The results of this study showed that the expression of the *KIF5B-RET* fusion gene does not affect the patient's OS and PFS. This finding may be partly due to the low expression rate of the *KIF5B-RET* fusion gene in lung cancer. Hence, more research data are needed to supplement this result. In the near future, we predict that researchers worldwide will

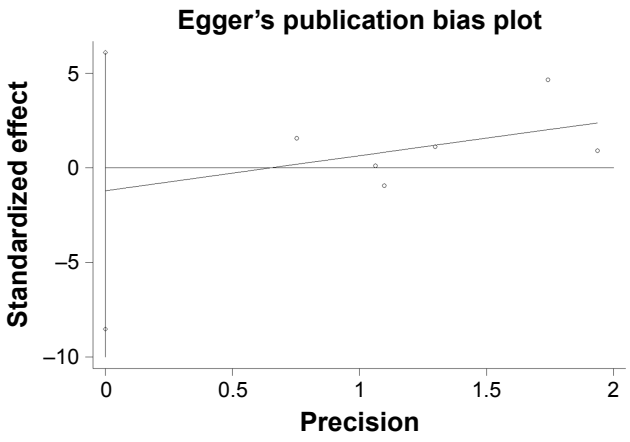

Figure 5 Egger's publication bias plot of overall survival.

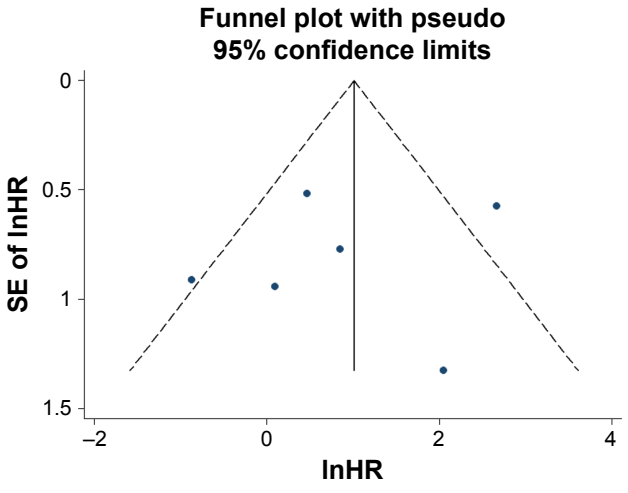

Figure 6 Funnel plot of overall survival.
Abbreviation: lnHR, natural log of the hazard ratio.

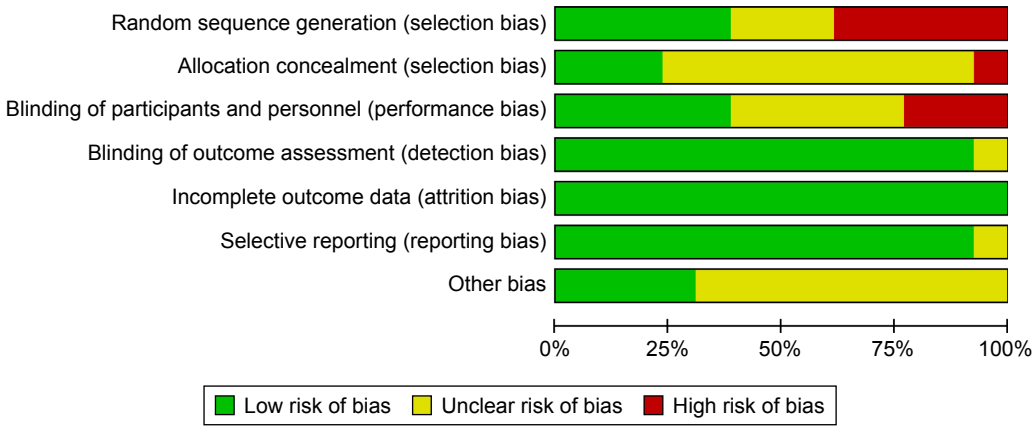

Figure 7 Graph of risk of bias.

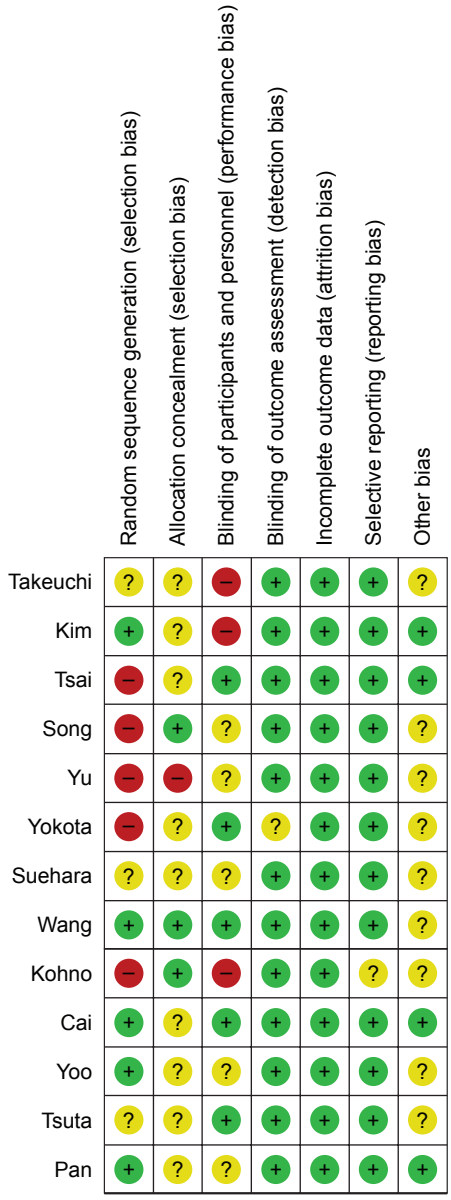

Figure 8 Summary of risk of bias.

continue to actively explore the diagnostic techniques and undertake clinical trials on *KIF5B-RET* fusion genes.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

Electronic search strategy

PICOS

P (patient or population): Lung Cancer

[MESH] (((((Lung Cancer) OR Pulmonary Neoplasm) OR Neoplasms, Lung) OR Neoplasms, Pulmonary) OR Cancer, Lung) OR Pulmonary Neoplasm.

I (intervention/exposure): RT-PCR detection the KIF5B-RET fusion gene expression

[MESH] ((((kinesin family member 5B) OR KIF5B protein, human) OR kinesin family member 5B, human) OR KIF5B-RET) OR KIF5B-RET fusion protein, human.

RET [MESH] (((((((Proto Oncogene Proteins) OR Proto-Oncogene Products, Cellular) OR Cellular Proto-Oncogene Products) OR RET) OR Proto Oncogene Products, Cellular) OR c-onc Proteins) OR Cellular Proto-Oncogene Proteins) OR Proto-Oncogene Proteins, Cellular.

C (comparison/control): Negative expression of KIF5B-RET fusion gene.

O (outcome): Clinicopathological (age, sex, TNM stage, smoking status, histological classification and differentiation); Prognosis (PFS, OS).

Prognosis [MESH] ((((Prognoses) OR Prognostic Factors) OR Factor, Prognostic) OR Prognostic Factor) OR Factors, Prognostic.

S (study design): Diagnostic study.