Review paper

CD117 expression is correlated with poor survival of patients and progression of lung carcinoma: a meta-analysis with a panel of 2645 patients

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The aim of this research was to investigate the clinical role and prognostic value of CD117 expression assessed immunohistochemically in lung carcinoma through a comprehensive meta-analysis in which 27 publications were acquired and 2645 patients were ultimately analysed. Statistical analysis and corresponding plots were performed using STATA version 12.0. Publication bias was assessed by Begg's funnel plots and Egger's test. Pooled HR and its 95% CI (HR = 1.53, 95% CI: 1.13-2.07, p = 0.007) for overall survival of patients indicated a poor prognostic value for CD117 expression in lung carcinoma, which was accompanied by heterogeneity and publication bias. In the subgroup analysis, there was strong evidence that could support an association between CD117 expression and poor prognosis in NSCLC patients (HR = 2.03, 95% CI: 1.41-2.90, p < 0.001; heterogeneity: I2 = 41.9%, χ^2 = 15.49, p = 0.078). Multivariate analysis also revealed consistent results in high-quality studies with reported HRs (HR = 2.16, 95% CI: 1.67-2.79, p < 0.001), and Asian patients (HR = 2.12, 95% CI: 1.45-3.10, p < 0.001). The correlations between CD117 expression and age, clinical stage, TNM stage, lymph node metastasis, or histology were not statistically significant. In conclusion, CD117 expression might be a potential marker for predicting poor prognosis, faster tumour growth, and early lymph node metastasis in NSCLC.

Key words: CD117; lung carcinoma; prognosis; clinicopathological parameter; overall survival.

Introduction

Lung carcinoma is the leading cause of cancer-related death in modern times [1, 2]. Recent research suggests that the high morbidity of lung cancer results from air pollution, tobacco consumption, and hereditary factors [3, 4, 5, 6, 7]. According to morphological and immunological characteristics, lung carcinoma is divided clinicopathologically into two types: small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC). The most common histological subtypes of NSCLC include adenocarcinoma, squamous cell carcinoma, and large cell neuroendocrine carcinoma [8, 9, 10, 11, 12, 13].

Distinguishing the subtypes of lung carcinoma is crucial for determining the best choice of therapeutic strategies [14]. Although a lot of research has been done for the diagnosis and treatment of lung cancer over the last decade, the death rate of patients with lung cancer remains high. Patients with advanced stage disease are prone to higher morbidity when compared with those at early stages. Unfortunately,

most patients have already progressed to an advanced stage when their diagnosis is made, having missed the optimal treatment timing [15, 16, 17, 18, 19]. This situation emphasises the importance and value of searching for biomarkers that are conducive to predict the prognosis of lung carcinoma.

One of potential markers is CD117, a transmembrane protein that receives the message from a stem-cell factor (SCF). CD117 protein is encoded by the proto-oncogene c-kit and belongs to the tyrosine kinase receptor family [20, 21]. Recent studies have suggested that CD117 protein is aberrantly regulated in malignancies of the salivary gland [22], retinoblastoma [23], endometrium [24], papillary thyroid [25], and breast [26]. CD117 is also an authoritative protein in the diagnosis of gastrointestinal stromal tumours (GIST), where it generally shows positive expression [27]. Several studies that concentrated on CD117 protein in lung cancer showed that CD117 protein expression had no effect on progression and prognosis of lung carcinoma [20, 28], whereas other studies have suggested that CD117 protein could be used as a biomarker for lung carcinoma [29, 30, 31]. The purpose of the present comprehensive meta-analysis was to clarify the relationship between CD117 protein and lung carcinoma.

Material and methods

Search strategy

A systematic search was conducted in PubMed, Cochrane Central Register of Controlled Trials, EMBASE, Science Direct, ISI Web of Science, and Wiley Online Library databases. Literature published in Chinese was searched in CNKI, Chongqing VIP, China Biology Medicine disc, and Wanfang databases. The search string consisted of: (tumor or tumour or cancer or carcinoma or neoplasia or neoplasm or malignant*) and (lung or pulmonary or pneumocyte or alveoli or respiration or respiratory or bronchi or bronchioles) and (CD117 or c-kit or kit). The last retrieval was made on Jun 1, 2018.

Selection of studies

Studies included the reported detection of CD117 expression in lung carcinoma tissue and analysis of the relationship between CD117 expression and clinicopathological parameters or survival time of the patients. No restriction was placed on the CD117 expression testing method. Studies were excluded if they failed to offer available data or full text or if they were published as reviews or case reports. Language was restricted to English and Chinese. If repeated cohorts were found, studies with more detailed information would be selected.

Extraction of data

The data extracted from each article were as follows: name of first author, publication year, regions of patients, sample size, cancer type, testing method, cut-off value, and clinicopathological parameters (i.e. gender, age, and TNM stage). Hazard ratios (HRs) and 95% confidence intervals (CIs) were extracted directly if available in the studies; otherwise, the available numerical data or Kaplan-Meier curves were used to calculate HRs and 95% CIs according to Parmar [32] and Tierney [33].

Quality assessment

The Newcastle-Ottawa scale (NOS) (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) was used to evaluate the quality of the included studies. Selection, comparability of cohorts, and assessment of outcome were assessed in cohort studies. Selection of cases and controls, comparability of cases and controls, and ascertainment of exposure were assessed in case-control studies. The score ranged from zero to nine. This process was performed by four researchers independently (Yi-nan Guo, Mei Wu, Shuang Ren, and Lu Liang), and conflicting opinions were resolved through further discussion with other researchers (Wei-jia Mo and Gang Chen).

Statistical analysis

Odds ratios (ORs) and their 95% CIs were calculated to analyse the prognostic value and the relationship between CD117 expression and clinicopathological parameters. Heterogeneity among studies was assessed by inconsistency (I^2) and χ^2 tests [34, 35]. Heterogeneity was considered not statistically significant when $p \geq 0.05$ and $I^2 \leq 50\%$. Data were pooled using a fixed-effects model when heterogeneity was not significant; otherwise, a random-effects model was used. Sensitivity and subgroup analyses were conducted for ascertaining the possible source of heterogeneity. Publication bias was tested using Begg's funnel plots [36] and Egger's test [37]. The trim and fill method [38] was applied as a remedy measure when publication bias was found. Stata 12.0 was used to calculate the necessary data and pooled estimate values, as well as to draw forest plots. All tests were conducted as two-tailed, and a p value less than 0.05 was considered statistically significant.

Results

Description of studies

Using the keywords mentioned above, 3476 papers (3074 in English, 402 in Chinese) were retrieved (Fig. 1). After scrutinising the titles and abstracts

and then excluding duplications, we chose 46 papers (40 in English, 6 in Chinese) that preliminarily reported the expression of CD117 protein in lung cancer specimens. Five studies with unavailable full texts, 13 studies with insufficient data, and one study with a dual cohort were excluded at the full-text reviewing step. Ultimately, 27 papers were involved in the meta-analysis. The publication period of the included literature fell between 2002 and 2017. Among these papers, 22 were published in English and five in Chinese. Twelve out of 27 studies were from Europe (five from Germany, four from Italy, two from Spain, and one from Turkey), 11 studies were published in Asia (seven, three, and one were from China, Japan, and Korea, respectively), and four studies were from North America (three from the USA and one from Canada).

Lung cancer patients (n = 2645), ranging in number from 13 to 204 patients for each study, were included in this meta-analysis, with 969 NSCLC patients (ranging from 33 to 147) from 10 studies and 1506 SCLC patients (ranging from 13 to 204) from 17 studies; two studies researched both NSCLC and SCLC [39, 40]. In addition, 170 neuroendocrine carcinoma (NEC) patients from two studies were also included. Immunohistochemistry (IHC) was the only method used to detect the expression of CD117 protein in all the included studies, with different cut-off values. A GIST was used as a positive control in eight studies [39, 4, 41, 42, 43, 44, 45, 46]. The effect of CD117 expression on the prognosis of patients was analysed in 27 studies, and the overall survival (OS) was analysed in all 27 studies, whereas disease-free survival was also analysed in three articles. The HRs and their 95% CIs were extracted directly from seven studies [28, 30, 31, 47, 48, 49], and all data were reported with multivariate analysis. In the remaining studies without reported HRs, the available data and reported Kaplan-Meier curves were used to estimate HRs.

Seven studies showed an association between CD117 expression and poor survival of lung cancer patients [28, 30, 44, 46, 49, 50], whereas three studies [29, 42, 51] reported a relationship between CD117 expression and longer survival time of lung cancer patients. The other studies indicated no relationship between CD117 expression and the survival time of patients. The score of quality assessment ranged from six to eight points in 27 included studies, while the other three papers scored five points. The basic information of the included literature is shown in Table I.

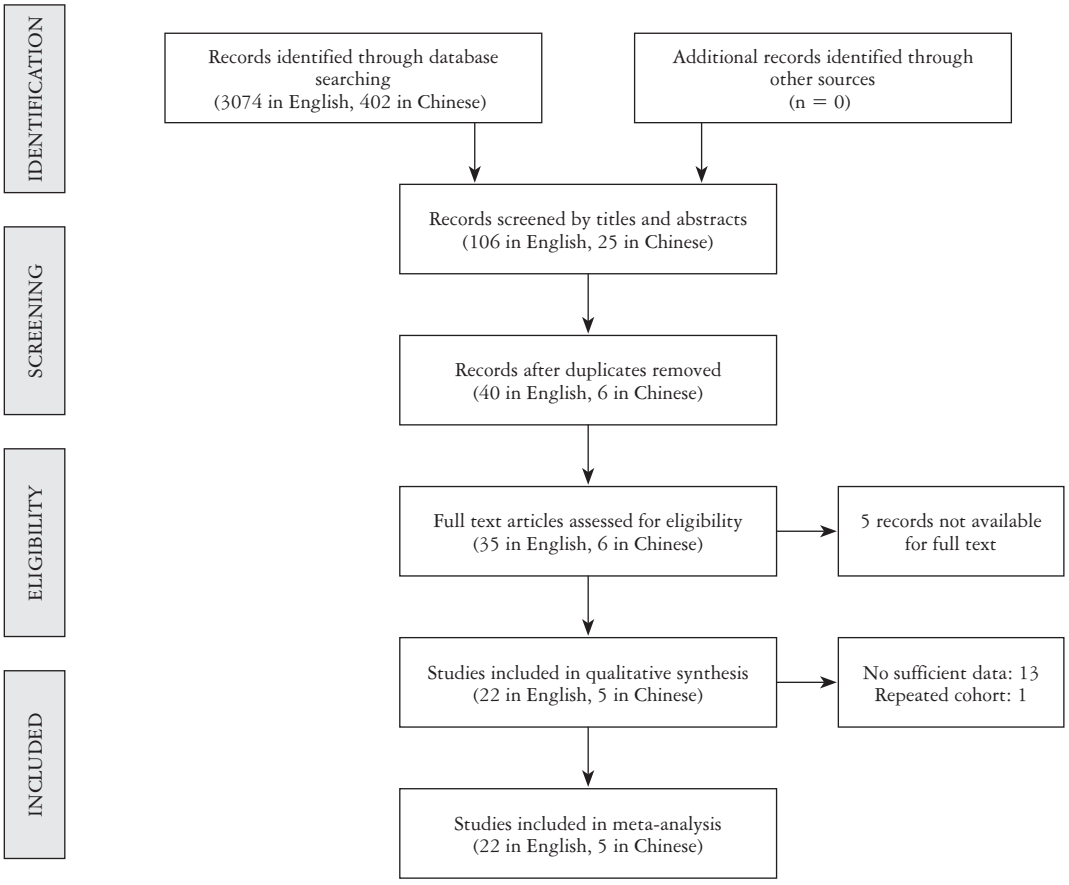

Fig. 1. Flow chart of literature search and study selection

Table I. Characteristics of the studies included in the meta-analysis

First author	Year	Country	Cancer type	Cases	Pathology stage	Adjuvant therapy ratio	Method	Cut-off value	Survival data type	Follow-up time (month)	HR estimation	HR	95% CI	Antibody	Quality score
Sakabe	2017	Japan	NSCLC	99	I-III	I-IV	IHC	0%	OS	2-104	Reported (MV)	4.672	2.264-9.638	ab32363; clone YR145, Abcam, USA	7
									DFS			3.352	1.583-7.096		
Xiao	2014	China	NSCLC	146	I-IV	I-IV	IHC	5%	OS	4-32	SC (UV)	1.49	0.88-2.50	Y703, Dako, Cytomation, Glostrup, Denmark	7
Gottschling	2013	Germany	NSCLC	100	I-II	I-IV	IHC	10%	OS	53.3 (median)	Reported (MV)	5.2	1.1-23.9	Dako	7
									DFS			1.1	0.2-6.8		
Lu	2012	China	SCLC	34&	I-IV	NR	IHC	5%	OS	22-125	SC (UV)	1.16	0.37-3.85	Dako, Glostrup, Denmark	6
Terada	2012	Japan	SCLC	54	I-IV	NR	IHC	10%	OS	3-27	SC (UV)	0.90	0.47-1.71	Dako, Glostrup, Denmark	8
Erler	2011	USA	SCLC	68	NR	NR	IHC	0%	OS	1-105	SC (UV)	1.50	0.93-2.40	Cell Marque Corporation, Rocklin, CA	5
Lopez-Martin	2007	Spain	SCLC	204	I-IV	100%	IHC	0%	OS	0.4-108	SC (UV)	0.88	0.71-1.09	Dako, Glostrup, Denmark	8
Yaren	2006	Turkey	NSCLC	69	I-IV	100%	IHC	4 points*	OS	3-103	SC (UV)	3.43	0.50-23.67	Dako, Glostrup, Denmark	5
Camps	2005	Spain	SCLC	70	I-IV	0%	IHC	0%	OS	0.3-37	SC (UV)	1.45	0.77-2.73	Dako, Cytomation, Denmark	7
Micke (1)	2004	Germany	LUAD	95	I-IV	24%	IHC	10%	OS	2-4	Reported (MV)	1.78	1.00-3.16	Dako, Hamburg, Germany	7

Table I. Characteristics of the studies included in the meta-analysis (cont.)

First author	Year	Country	Cancer type	Cases	Pathology stage	Adjuvant therapy ratio	Method	Cut-off value	Survival data type	Follow-up time (month)	HR estimation	HR	95% CI	Antibody	Quality score
Pelosi (1)	2004	Italy	LCNEC	39	I-III	100%	IHC	5%	OS	2-136	SC (UV)	2.76	0.91-8.44	Dako, Cytomation, Glostrup, Denmark	8
			SCLC	27	I-III	100%	IHC		OS	8-93	SC (UV)	0.92	0.17-5.52		
Boldrini	2004	Italy	SCLC	55	I-III	0%	IHC	30%	NR	NR	NR	NR	NR	Dako, NCL-CD117 clone	8
Rohr	2004	Germany	SCLC	203	I-IV	0%	IHC	0%	OS	1-83	SC (UV)	0.48	0.37-0.64	A4502, Dako, Hamburg, Germany	7
Yoo	2004	Korea	NSCLC	147	I-III	0%	IHC	30%	OS	0.3-37	SC (UV)	1.30	0.88-1.93	Santa Cruz Biotechnology	8
Casali	2004	Italy	LCNEC	33	I-IIIA	Some#	IHC	50%	OS	2-118	Reported (MV)	5.04	0.93-27.3	clone DAK-A3; Dako, Glostrup, Denmark	6
Blackhall	2003	Canada	SCLC	41	NR	NR	IHC	35%	OS	NR	Reported (MV)	1.1	0.5-2.3	Dako Laboratories	7
Potti	2002	USA	SCLC	193	III-IV	100%	IHC	10%	OS	3-71	SC (UV)	0.66	0.48-0.90	A4502, IMPATH, CA, USA	8
Araki	2003	Japan	LCNEC	40	I-IV	29.9%	IHC	10%	OS	8-75	SC (UV)	0.62	0.11-3.63	Dako, Glostrup, Denmark	7
			SCLC	13	I-IV		IHC	10%	OS	23-71	SC (UV)	2.57	0.64-10.32		
Naeem	2002	USA	SCLC	30	I-IV	13.3%	IHC	50%	OS	1-81	SC (UV)	2.43	0.65-9.26	A4502; Dako, Carpenteria, CA	6
Micke (2)	2003	Germany	SCLC	102	I-IV	88%	IHC	10%	OS	2-4	Reported (MV)	2	1.17-3.41	Dako, Hamburg, Germany	8

Table I. Characteristics of the studies included in the meta-analysis (cont.)

First author	Year	Country	Cancer type	Cases	Pathology stage	Adjuvant therapy ratio	Method	Cut-off value	Survival data type	Follow-up time (month)	HR estimation	HR	95% CI	Antibody	Quality score
Pelosi (2)	2004	Italy	LUAD	88	I	0%	IHC	5%	OS	2-159	Reported (MV)	1.7	0.6-4.6	Dako, Glostrup, Denmark	8
			LUSC	113	I	0%	IHC		DFS			1.5	0.6-3.6		
									NR		NR	NR	NR		
Dong	2010	China	LCNEC	80	I-III	NR	IHC	5%	NR	NR	NR	NR	NR	maixin fujian, China	7
Han	2006	China	SCLC	65	NR	0%	IHC	5%	NR	NR	NR	NR	NR	Santa Cruz Biotechnology	8
Zhao	2005	China	LCNEC	90	I-IV	NR	IHC	10%	OS	1.4-176	SC (UV)	4.13	2.62-6.51	Zymed, USA	8
Sun	2006	China	SCLC	100	I-III	NR	IHC	0%	OS	0-111	SC (UV)	2.80	1.52-5.16	Gentech GA450202	8
Jiang	2004	China	SCLC	52	I-IV	NR	IHC	10%	OS	1-77	SC (UV)	2.95	1.55-5.63	Dako	6

NSCLC – non-small cell lung cancer; SCLC – small cell lung cancer; LCNEC – large cell neuroendocrine of the lung; NEC – neuroendocrine carcinoma; AD – adenocarcinomas; SCC – squamous cell carcinoma; NR – not reported; IHC – immunohistochemistry; OS – overall survival; DFS – disease-free survival; HR – hazard ratio; SC – survival curve; UV – univariate; MV – multivariate; CI – confidence interval;

[&] 23 patients were followed up and included in survival analysis.

[#] Reported by neither specific number nor percentage.

[*] Score was comprehensively evaluated by distribution of cytoplasmic stain and intensity of staining.

Prognostic role of CD117 expression in lung carcinoma

The relationship between CD117 expression and the overall survival (OS) of patients of lung cancer was analysed. In a panel of 2332 patients from 24 studies, the HRs obtained from multivariate analysis in seven studies and univariate analysis in 17 studies were included to pool the estimate value with the random effects model. A statistically significant poor effect of CD117 expression was observed on the OS (HR = 1.53, 95% CI: 1.13-2.07, p = 0.007), as shown in Fig. 2. Heterogeneity among the studies was revealed by the Cochrane Q test ($c^2 = 144.58$, p = 0.015), and the inconsistency was quantified ($I^2 = 83.4\%$). Publication bias was detected by Begg's funnel plot (Fig. 3A) and Egger's test (p = 0.003). The results were corrected by a trim and fill method [38], and Begg's funnel plot became symmetrical after correction (Fig. 3B). The adjusted HR was changed to 0.424, and the corresponding 95% CI was 0.118 to 0.730.

Subgroup analysis

Sensitivity analysis was performed to elucidate whether any single study was responsible for the observed heterogeneity. No individual study contributed predominantly to heterogeneity according to the sensitivity analysis. Considering that multiple factors might lead to heterogeneity, subgroup analysis was conducted based on lung carcinoma pathology type, the region of patients, language, variable type, and cut-off value. The results of this subgroup analysis are shown in Table II.

As shown in Fig. 4, 969 NSCLC patients from 10 studies and 1506 SCLC patients from 17 studies were analysed. In the NSCLC subgroup, CD117 expression had a negative effect on the OS of patients (HR = 2.03, 95% CI: 1.41-2.90, p < 0.001), whereas CD117 expression had no prognostic value in patients in the SCLC group (HR = 1.15, 95% CI: 0.82-1.61, p = 0.406). Heterogeneity was statistically significant in the SCLC group (heterogeneity: $I^2 = 61.1\%$, p < 0.001) but not in the NSCLC

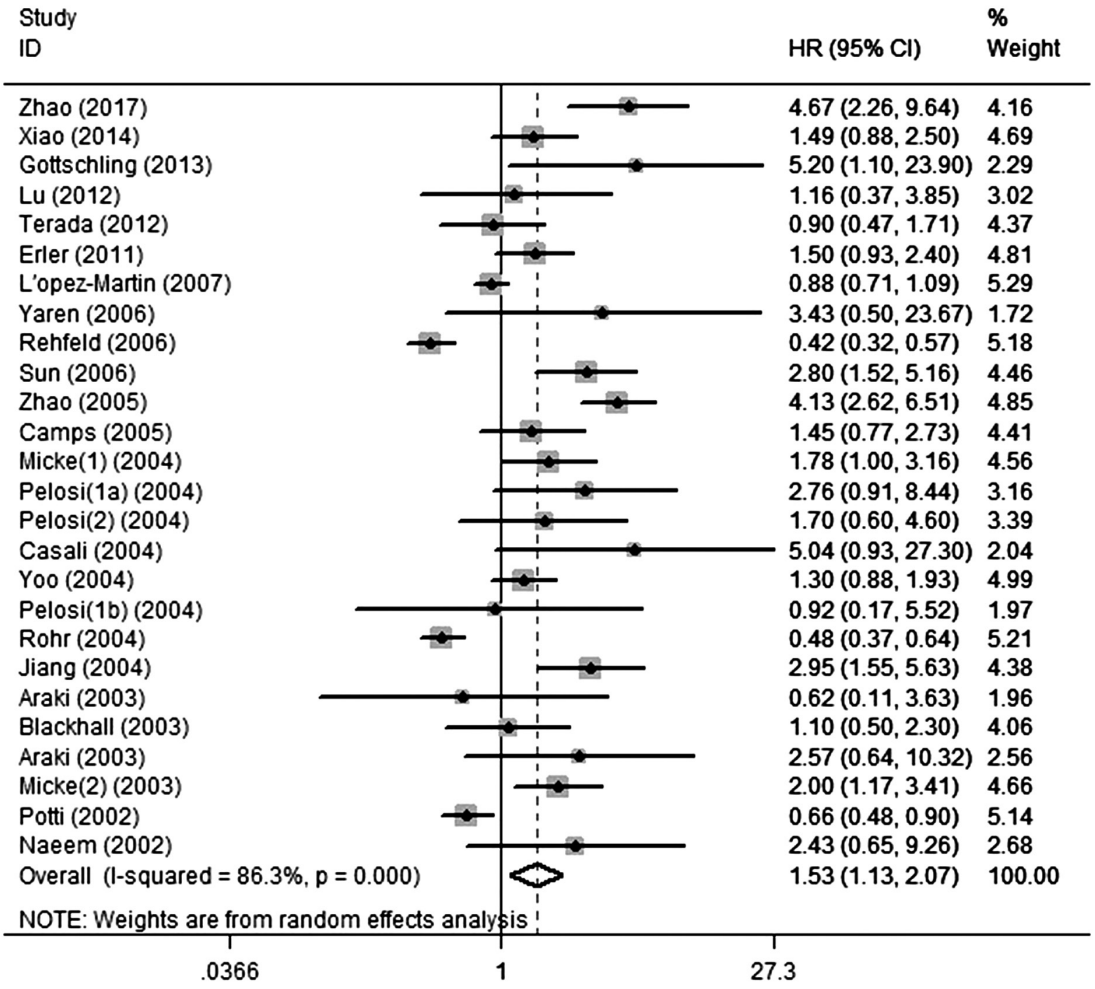

Fig. 2. Forest plot of the hazard ratio reflecting the relationship between CD117 expression and overall survival of patients with lung carcinoma. HR > 1 and corresponding 95% confidence interval was not covered; 1 implied poor prognosis in the CD117 positive group

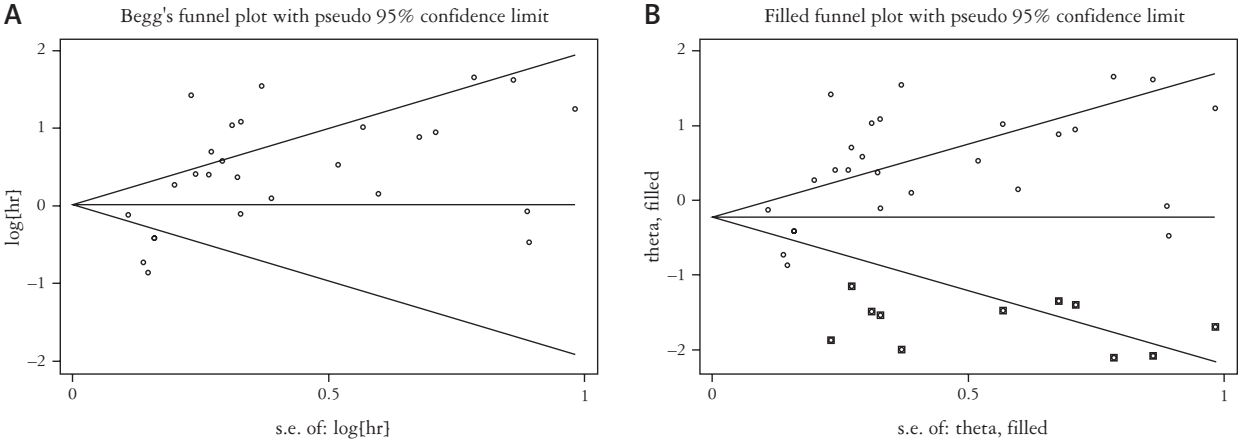

Fig. 3. Forest plot of the hazard ratio reflecting the relationship between CD117 expression and overall survival of patients with lung carcinoma. HR > 1 and corresponding 95% confidence interval was not covered; 1 implied poor prognosis in the CD117 positive group

Table II. Subgroup analyses for CD117 impact on overall survival of patients with lung cancer

XSubgroup		Number of studies	Pooled value		Model	Heterogeneity		
			HR (95%CI)	p		χ^2	I^2	p
	NSCLC	10	2.03 (1.41-2.90)	< 0.001	Fixed	15.49	41.9	0.078
Region	Europe	12	1.30 (0.87-1.93)	0.200	Random	76.62	83.0	< 0.001
	Asia	11	2.12 (1.45-3.10)	< 0.001	Random	33.52	70.2	0.001
	North America	4	1.12 (0.64-1.96)	0.702	Random	10.62	71.7	0.014
Survival analysis	Multivariate	7	2.16 (1.67-2.79)	< 0.001	Fixed	12.82	29.8	0.171
	Univariate	19	1.32 (0.93-1.86)	0.116	Random	143.92	87.5	< 0.001
Cut-off	> 5%	13	1.76 (1.15-2.68)	0.009	Random	60.69	80.2	< 0.001
	≤ 5%	11	1.40 (0.93-2.09)	0.104	Random	108.81	88.1	< 0.001
	> 10%	4	1.38 (0.99-1.92)	0.057	Fixed	3.38	11.3	0.336
	≤ 10%	24	1.53 (1.10-2.12)	0.011	Random	185.06	87.6	< 0.001

group (heterogeneity: $I^2 = 41.9\%$, $p = 0.078$). The results of the Begg's funnel plots (Fig. 5) and Egger's test ($p = 0.149$) revealed no evidence of publication bias in the NSCLC group; however, publication bias was detected in the SCLC group (Fig. 6A; Egger's: $p = 0.024$). After adjustment by the trim and fill method, Begg's funnel plot (Fig. 6B) showed a symmetric pattern, the adjusted HR was 0.827, and its 95% CI was 0.598–1.144. This result was similar to the previously determined one, which implied moderate quality of the evidence.

The subgroup analysis of the regional distribution of the population was conducted on patients from Asia, Europe, and North America. The results obtained using the random effects model showed a satisfactory effect of CD117 expression on prognosis in Asian patients (HR = 2.12, 95% CI: 1.45-3.10, $p < 0.001$; heterogeneity: $c^2 = 33.52$, $p = 0.001$, $I^2 = 70.2\%$), but no relationship was found for Europeans (HR = 1.30, 95% CI: 0.87-1.93, $p = 0.200$; heterogeneity: $c^2 = 76.62$, $p < 0.001$, $I^2 = 83.0\%$) or North Americans (HR = 1.12, 95% CI: 0.64-1.96, $p = 0.702$; heterogeneity: $c^2 = 10.62$, $p = 0.014$, $I^2 = 71.7\%$), and heterogeneity was evident in all three subgroups.

In subgroups based on analysis type (univariate or multivariate), the studies published in Chinese (HR = 3.43, 95% CI: 2.49-4.71, $p < 0.001$; heterogeneity: $c^2 = 1.27$, $p = 0.529$, $I^2 = 0.0\%$) and the HR determined by multivariate analysis (HR = 2.16, 95% CI: 1.67-2.79, $p < 0.000$; heterogeneity: $c^2 = 12.82$, $p = 0.171$, $I^2 = 29.8\%$) gave results that agreed with the general conclusion without significant heterogeneity. Literature evaluated by univariate analysis (HR = 1.32, 95% CI: 0.93-1.86, $p = 0.116$; heterogeneity: $c^2 = 143.92$, $p = 0.000$, $I^2 = 87.5\%$) showed that CD117 protein had no obvious effect on patient survival time.

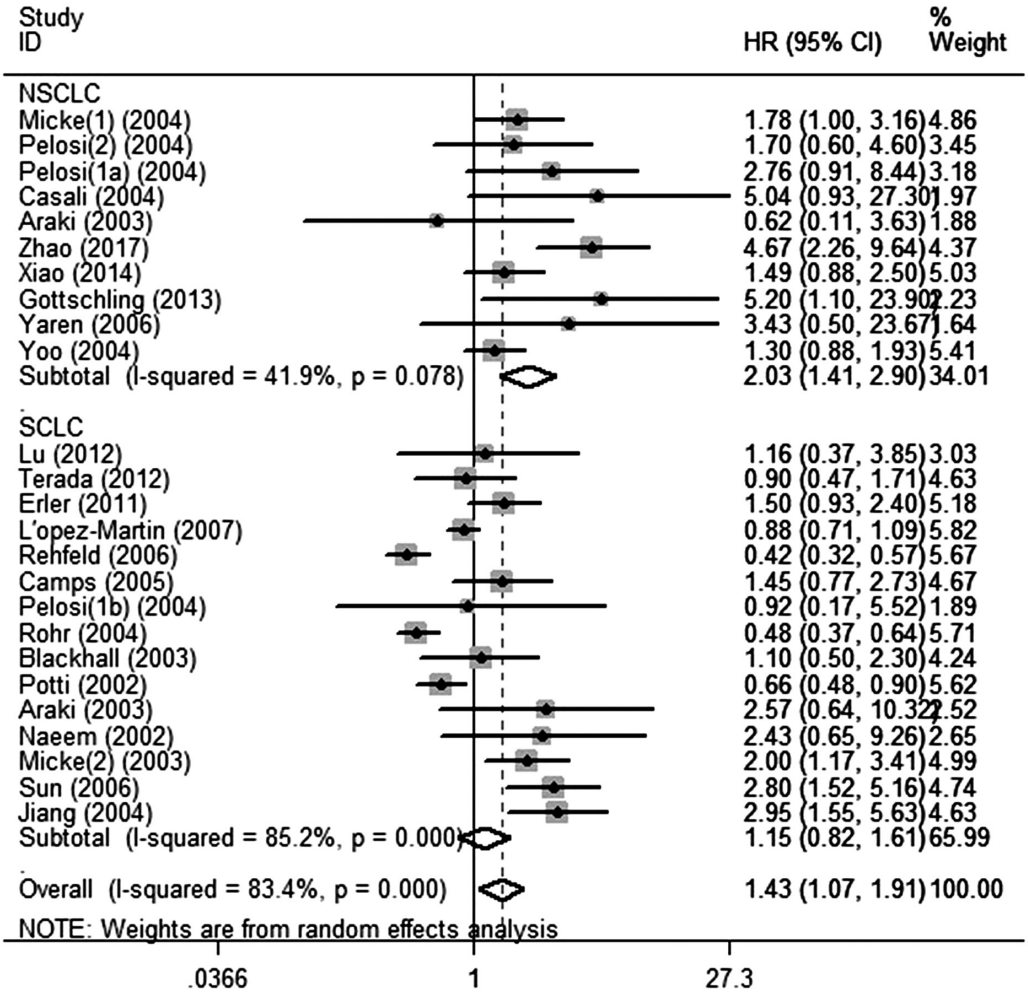

Fig. 4. Forest plot of the hazard ratio reflecting the relationship between CD117 expression and overall survival of patients with non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). HR > 1 and the corresponding 95% confidence interval were not covered; 1 implied poor prognosis in the CD117 positive group

For the subgroup analysis based on different cut-off values, the studies were grouped twice with a cut-off of 5% or 10%. The group with a cut-off point > 5% (HR = 1.76, 95% CI: 1.15-2.68) predicted similar results to the general population, whereas other groups with other cut-off values showed negative results. Nevertheless, heterogeneity still existed except for the group with a cut-off value > 10%.

The clinical value of CD117 expression in lung carcinoma was also investigated in the current meta-analysis. As shown in Table III, CD117 expression was associated with a larger size of tumour (OR = 2.01, 95% CI: 1.07-3.79, p = 0.030), gender (OR = 0.76, 95% CI: 0.59-0.98, p = 0.037), and lymph node metastasis (OR = 0.55, 95% CI: 0.31-0.96, p = 0.037). The association between CD117 expression and other features was found to be insignificant, such as: age (OR = 0.88, 95% CI: 0.67-1.16, p = 0.371), clinical stage (OR = 0.93, 95% CI: 0.68-1.27, p = 0.638), T stage (OR = 1.04, 95% CI: 0.52-2.10, p = 0.902), N stage (OR = 0.76, 95% CI: 0.49-1.19, p = 0.229), M stage (OR = 1.05, 95% CI: 0.66-1.68, p = 0.836), and histology (OR = 1.05, 95% CI: 0.67-1.66, p = 0.819; Figs. 7, 8).

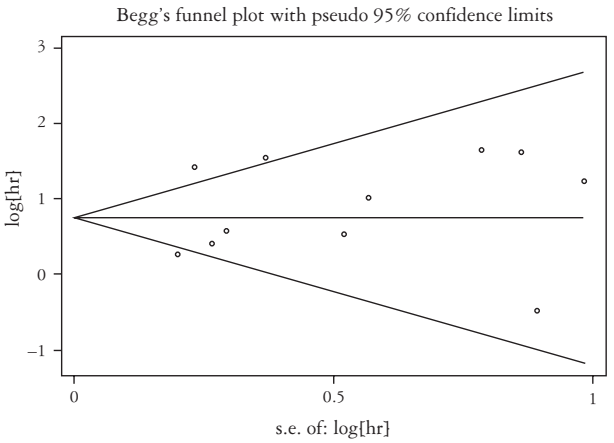

Fig. 5. Begg's funnel plot for visual detection of potential publication bias of studies included in the NSCLC group

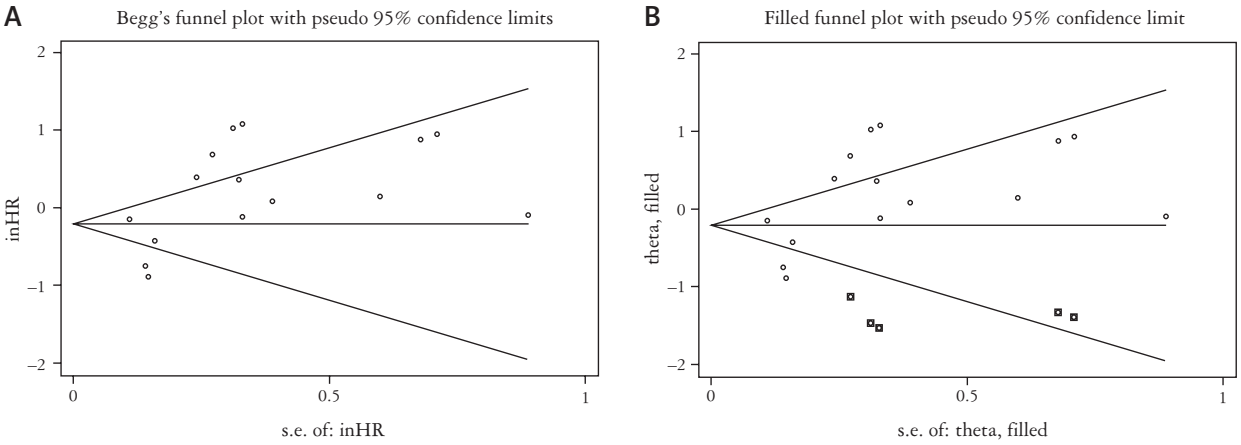

Fig. 6. Begg's funnel plot for visual detection of potential publication bias of studies included in the small cell lung cancer (SCLC) group. A) Before trim and fill method used. B) After correction by a trim and fill method

Table III. The relationship between CD117 expression and clinicopathological parameters

Clinicopathological features	Number of studies	Number of cases	Pooled value		Model	Heterogeneity		
			OR (95%CI)	p		χ^2	I^2	p
Gender	16	1525	0.76 (0.59-0.98)	0.037	Fixed	16.80	0.0%	0.537
Age	11	1031	0.88 (0.67-1.16)	0.371	Fixed	7.03	0.0%	0.723
Stage	9	836	0.99 (0.71-1.38)	0.942	Fixed	13.91	28.1%	0.177
T stage	8	750	1.04 (0.50-2.16)	0.902	Random	24.36	71.3%	0.001
N stage	6	651	0.76 (0.49-1.19)	0.229	Fixed	2.18	0.0%	0.904
M stage	3	296	1.05 (0.66-1.68)	0.836	Fixed	1.25	0%	0.535
Lymphatic Metastasis	4	318	0.55 (0.31-0.96)	0.037	Fixed	6.45	38.0%	0.168
Tumour size	6	532	2.01 (1.07-3.79)	0.030	Random	13.81	63.8%	0.017
Histology	4	461	1.05 (0.67-1.66)	0.819	Fixed	1.36	0.0%	0.714

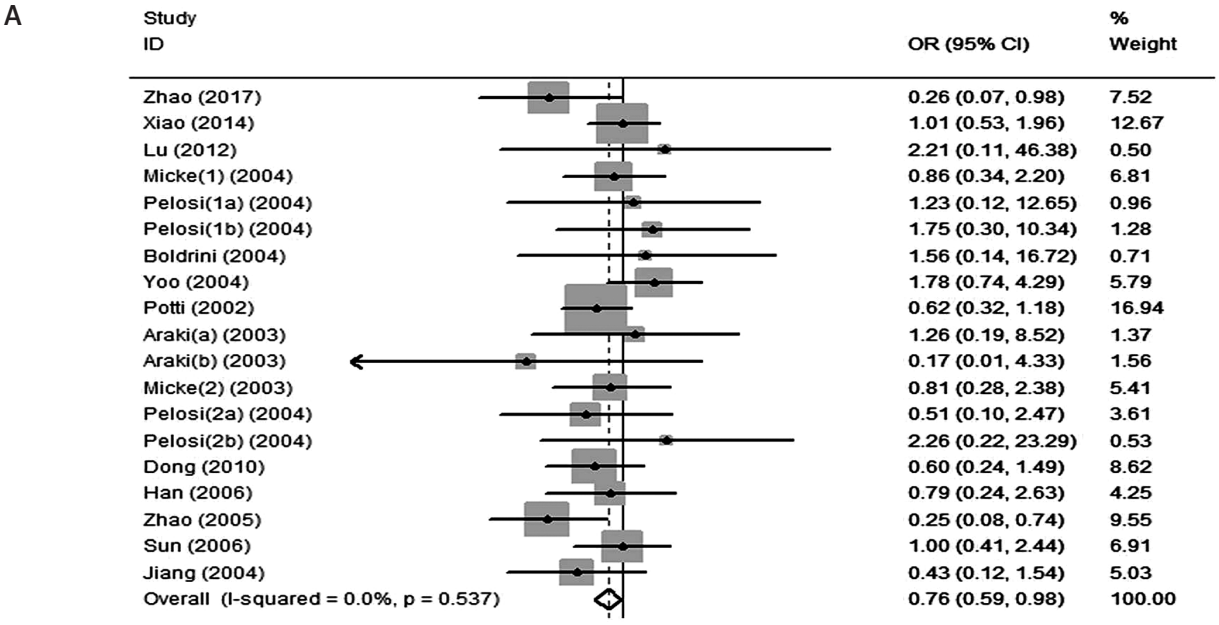

Fig. 7. Forest plot of the odds ratio reflecting the relationship between CD117 expression and the clinicopathological parameters of patients. A) Gender; B) Age; C) Stage; D) T stage

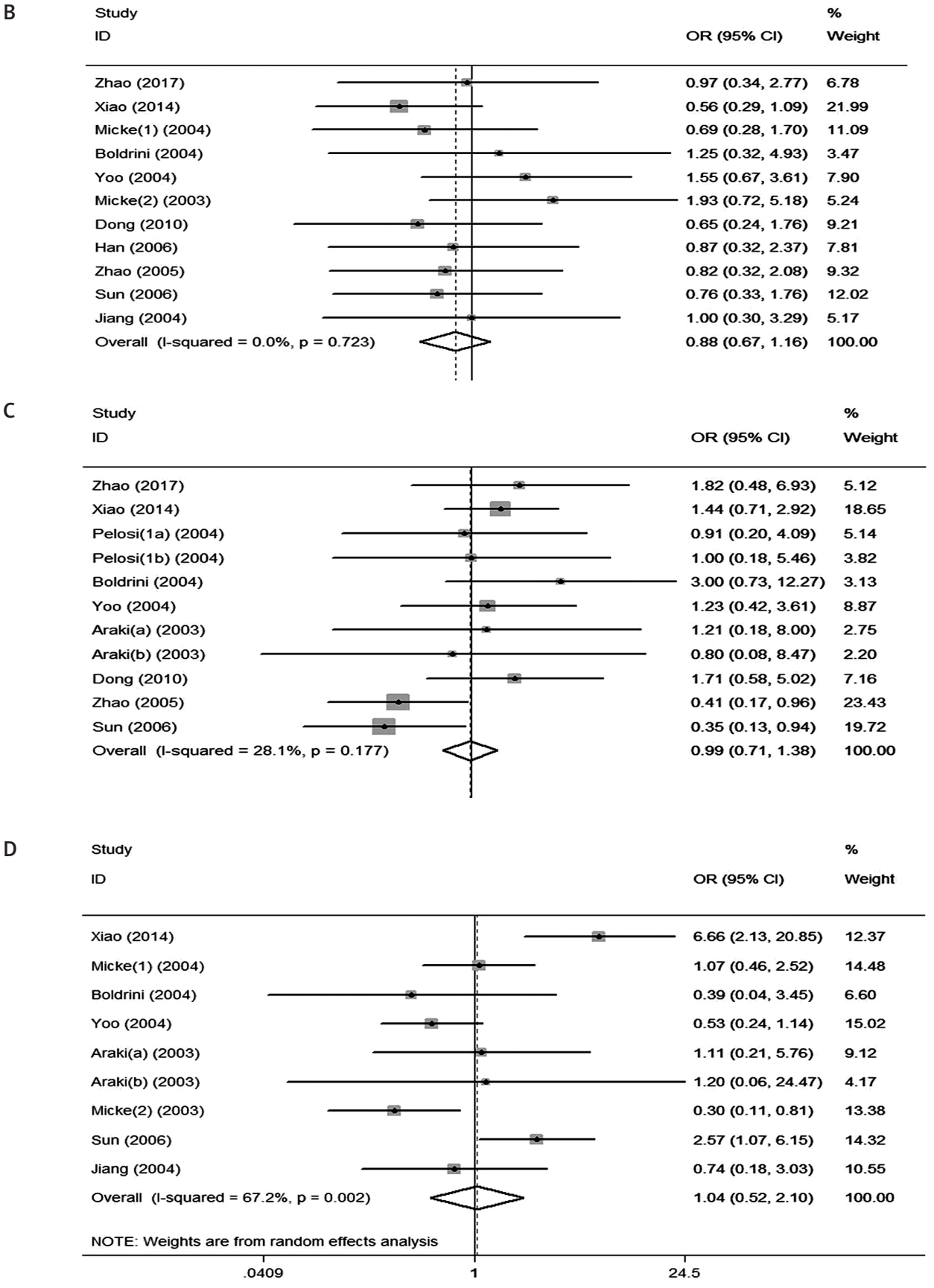

Fig. 7. Forest plot of the odds ratio reflecting the relationship between CD117 expression and the clinicopathological parameters of patients. A) Gender; B) Age; C) Stage; D) T stage (cont.)

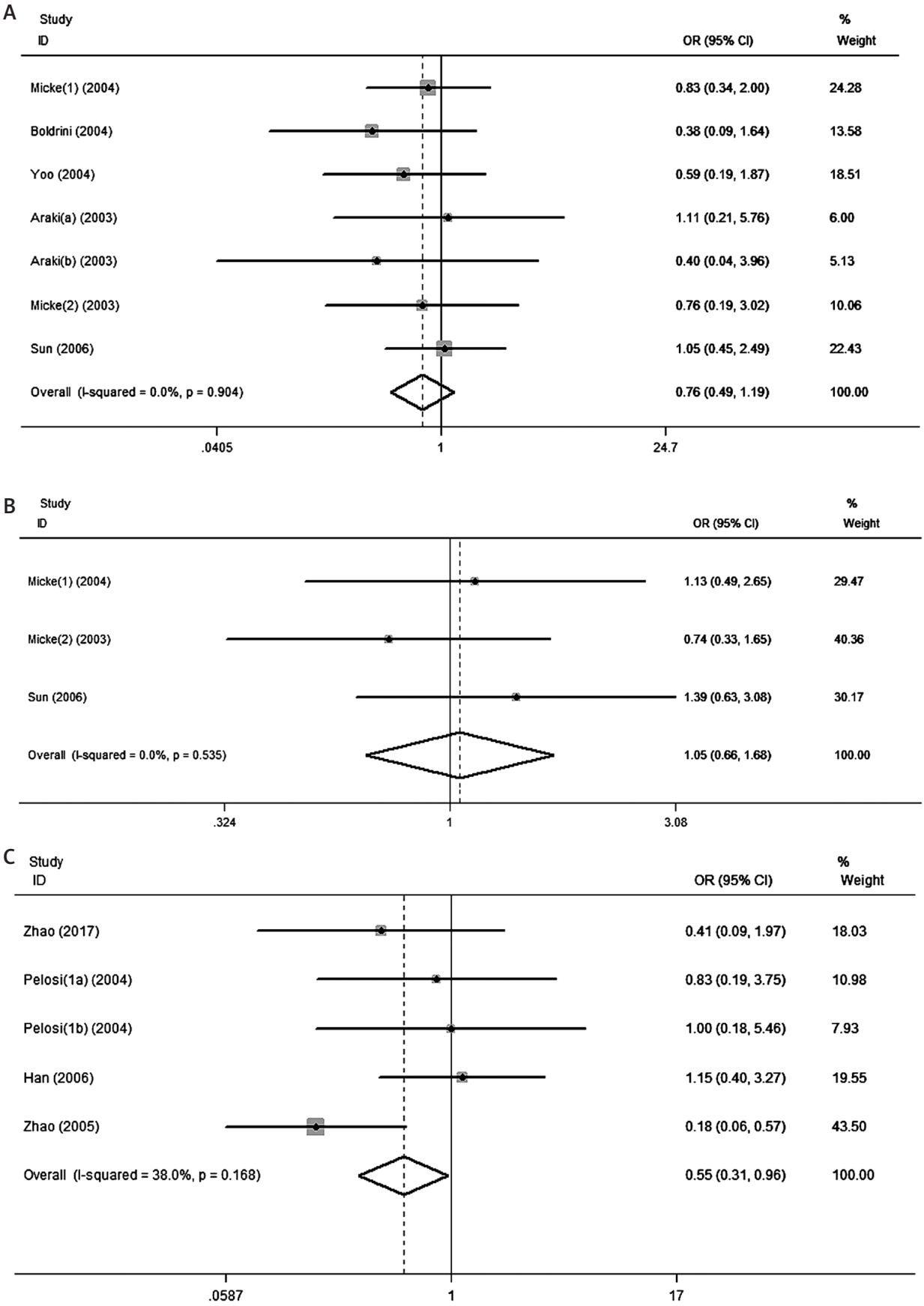

Fig. 8. Forest plot of the odds ratio reflecting the relationship between CD117 expression and the clinicopathological parameters of patients. A) N stage; B) M stage; C) Lymph node metastasis; D) Tumour size; E) Histology

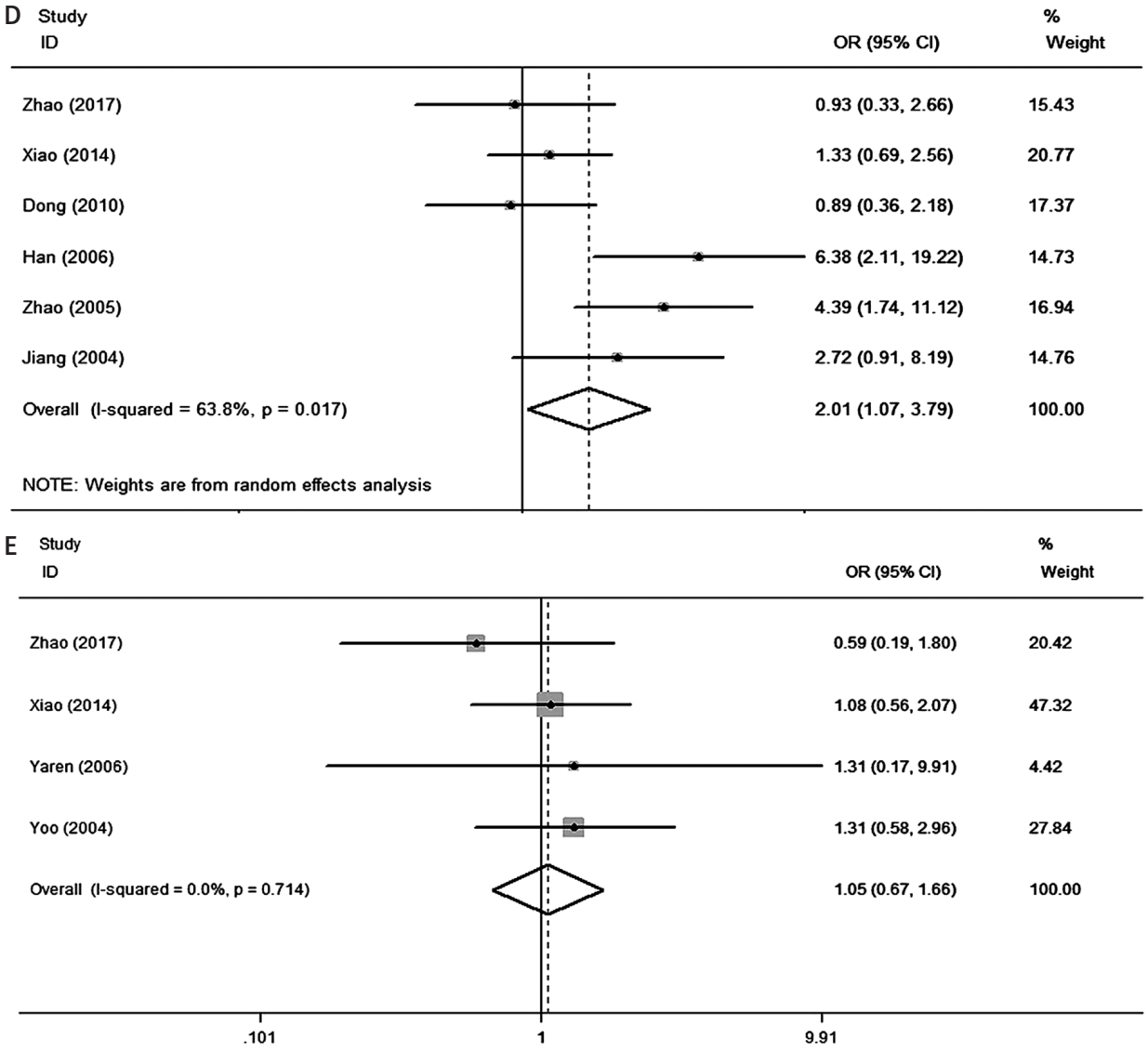

Fig. 8. Forest plot of the odds ratio reflecting the relationship between CD117 expression and the clinicopathological parameters of patients. A) N stage; B) M stage; C) Lymph node metastasis; D) Tumour size; E) Histology (cont.)

Discussion

The value of CD117 expression in lung carcinoma is a matter of debate because some studies have identified CD117 expression as a prognostic marker for undesirable outcome while others have suggested that CD117 expression is a prognostic marker for good patient outcome. Therefore, a pooled analysis of data from these studies was of great importance.

A previous meta-analysis of CD117 expression in lung carcinoma was published as a part of the analysis conducted by Zhao *et al*. [52]. When compared to their eight included studies on lung carcinoma, our meta-analysis had a larger sample size. In addition, the relationship between CD117 expression and clinicopathological features was also analysed in the current meta-analysis. The results from Zhao *et al.* implied that CD117 expression had no relationship with the OS or disease-free survival (DFS) of patients with lung carcinoma. However, the subgroup analysis based on cancer type showed a significant correlation between CD117 expression and the OS of NSCLC patients [52]. The same conclusion was made in a multivariate analysis of eight Asian groups in a paper published in Chinese. Our meta-analysis also showed that a larger tumour size was accompanied by a high CD117-expression, and this finding was supported by the meta-analysis by Yan *et al*. [53], who found that mutation of CD117 protein was more frequently-seen in larger tumours than in smaller ones in GISTs. They suggested that CD117 might be a promoter of tumour growth in lung carcinoma and GISTs.

The finding that CD117/c-kit, a member of the type III tyrosine kinase receptor family [54], is aber-

rantly expressed in various malignancies [20, 55, 56], aroused tremendous interest in investigating its effect on the progression and prognosis of cancer. GISTs are the most authoritative cancer with known CD117 upregulation, and studies have suggested that the upregulation or mutation of c-kit is correlated with the prognosis and progression of GISTs [57, 58, 59, 60, 61]. For example, Ma *et al*. [57] reported that CD117 played an oncogenic role in GISTs, based on the finding that CD117 protein was co-expressed with Ki-67 and negatively correlated with apoptotic protease-activating-1 (APAF-1) in GIST tissues. Based on results from an *in vitro* study, Nakahara *et al.* [62] suggested that c-kit mutation could promote self-activation and proliferation of GIST cells because c-kit was a membrane receptor that regulated the proliferation and survival of cells. It has been reported in the literature that more than 70% of cases of SCLC and LCNEC express the c-Kit receptor [20, 31, 63], while it is rare in NSCLC [28]. Simultaneously, CD117 overexpression in high-grade tumours was observed in SCLC and LCNEC [40]. In other words, CD117 expression is common in more aggressive and fast-growing tumours. However, the Information about histological grade of lung carcinoma included is too small, so we cannot perform statistical analysis. More research on CD117 expression in lung carcinoma is needed.

Some studies have suggested that c-kit mutation in GISTs could stimulate the resistance to chemotherapy [64, 65, 66, 67]. Lu *et al*. found that no mutation in c-kit exons 9 and 11 was detected in the 36 included cases [68]. In Boldrini's study, 60 SCLC samples were tested, about 40% of which expressed c-kit, two patients had mutations in exon 9, and three patients had mutations in exon 11. The low mutation rate of c-kit gene may be one of the reasons that the expression of CD117 protein is not strongly correlated with the activation mutation in SCLC [69]. CD117 promoted the development of prostate cancer through the JAK2/STAT1 signal pathway [70] and the ERK pathway, and induced the proliferation and metastatic activity of colorectal cancer cells [71]. In a study of lung maintenance and repair, Liu *et al.* [72] found that CD117-positive cells participated in vascular endothelial repair rather than acting on lung epithelial cells.

Several studies have focused on the mechanism of CD117 expression in lung carcinoma. However, CD117 expression had a negative effect on the OS of lung carcinoma patients, possibly due to its contribution to chemo-resistance [73, 74]. In the subgroup analysis of lymph node metastasis, only one case of NSCLC and LCNEC, and three cases of SCLC were included. Moreover, the correlation between lymph node metastasis and CD117 expression is mainly reflected in SCLC [39, 75], which may be biologically relevant to the clinical behaviour of SCLC. The small sample size may be an important reason for publication bias. In the subgroup analysis of gender, we found that the positive rate of CD117 expression in male patients was higher than in female patients. Xiao *et al.* [20] proposed in their study that the expression of CD117 is related to smoking, and the global smoking rate in men is higher than in women, which may be one of the reasons why there are more men in CD117 protein-expressed patients. Unfortunately, due to too few data on smoking to be statistically analysed, more literature needs to be included in the future.

The pooled HR in the present meta-analysis, based on the data from all the included studies, was accompanied by conspicuous heterogeneity. The sensitivity analysis results indicate that the heterogeneity did not arise predominantly from any individual study. Stratified analysis shows that studies with a focus on NSCLC revealed consistent conclusions whereby a high level of CD117 expression was associated with a shorter patient survival time. Studies that used multivariate analysis also confirmed these results. Thus, the heterogeneity mainly came from the different types of lung carcinoma from all the included studies.

This meta-analysis had some limitations. Because of the language capabilities of the authors, only papers published in Chinese and English were included. The scale of included studies in our meta-analysis was not sufficiently large to illustrate the role of CD117 protein in lung carcinoma. Some of the included studies also had a small sample size, which could have led to bias. The use of estimated HRs and their 95% CIs from studies that provided available data or Kaplan-Meier survival curves reduced the reliability of the results. These limitations, together with other factors, like the standard of TNM stage, diagnosis guidelines from different periods, and positive result bias, caused publication bias in this analysis.

Conclusions

The current analysis shows that CD117 expression is significantly associated with poor prognosis in lung carcinoma and especially in NSCLC. In particular, evidence from studies that performed multivariate analysis confirmed the value of CD117 expression as a marker for the prognosis of lung carcinoma. The analysis of the relationship between CD117 expression and clinicopathological features revealed an association between CD117 expression and tumour growth, patient gender, and lymph node metastasis. Considering the limitations of the present meta-analysis, larger scale and high-quality studies of the influence of CD117 expression on lung carcinoma are needed to provide further confirmation of the role of CD117 expression in lung carci

The authors declare no conflicts of interest.

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