

## Original Article

# Neoadjuvant therapy and risk of bronchopleural fistula after lung cancer surgery: a systematic meta-analysis of 14 912 patients

Shuangjiang Li<sup>1</sup>, Jun Fan<sup>1</sup>, Jing Liu<sup>2</sup>, Jian Zhou<sup>3</sup>, Yutao Ren<sup>3</sup>, Cheng Shen<sup>1</sup>, and Guowei Che<sup>1,\*</sup>

<sup>1</sup>Department of Thoracic Surgery, West China Hospital, Sichuan University, Chengdu, <sup>2</sup>Institution of Medical Statistics, West China School of Public Health, Sichuan University, Chengdu, and <sup>3</sup>Lung Cancer Center, West China Hospital, Sichuan University, Chengdu, China

\*For reprints and all correspondence: Guowei Che, Department of Thoracic Surgery, West China Hospital, Sichuan University, Guoxuexiang No. 37, Chengdu, China. E-mail: guowei\_che@yahoo.com

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## Abstract

**Objective:** Neoadjuvant therapy has been extensively analyzed in studies addressing the risk factors of bronchopleural fistula, but their results vary hugely. Therefore, we conducted this meta-analysis to determine the association between neoadjuvant therapy and risk of bronchopleural fistula in patients undergoing lung cancer surgery.

**Methods:** We searched PubMed and EMBASE to identify the full-text literatures that met our eligibility criteria. Odds ratio with 95% confidence interval served as the summarized statistics. Heterogeneity within this meta-analysis was evaluated by *Q*-test and  $I^2$  statistic. Sensitivity analysis was performed for further assessments of robustness. Publication bias was detected by Begg's test and Egger's test.

**Results:** Thirty studies enrolling 14 912 lung cancer cases were included into this meta-analysis. The incidence of bronchopleural fistula was 2.4% (354/14 912) in the large scale. Overall, neoadjuvant therapy significantly increased the risk of bronchopleural fistula after pulmonary resections (odds ratio: 2.166; 95% confidence interval: 1.398–3.357;  $P=0.001$ ). In subgroup analysis, neoadjuvant radiotherapy (odds ratio: 3.914; 95% confidence interval: 1.401–10.935;  $P=0.009$ ) and chemo-radiation (odds ratio: 2.533; 95% confidence interval: 1.353–4.741;  $P=0.004$ ) were significantly associated with the bronchopleural fistula risk but neoadjuvant chemotherapy was not (odds ratio: 1.857; 95% confidence interval: 0.881–3.911;  $P=0.104$ ). The impact of neoadjuvant therapy on bronchopleural fistula occurrence remains statistically prominent in the other subgroups.

**Conclusions:** Neoadjuvant therapy is significantly associated with the occurrence of bronchopleural fistula after lung cancer surgery. Both neoadjuvant radiotherapy and chemo-radiation significantly increase the bronchopleural fistula risk but neoadjuvant chemotherapy does not. Some limitations still exist in this meta-analysis. The updated high-quality studies can help to further confirm and enrich our discoveries in the future.

**Key words:** neoadjuvant therapy, bronchopleural fistula, lung cancer surgery, meta-analysis

## Introduction

Currently, surgical resection is an irreplaceable curative treatment for lung cancer. Although advanced surgical techniques and managements have improved the survival rate and reduced a variety of post-operative complications, the generally poor prognosis remains a large challenge to thoracic surgeons, particularly in some high-risk patients, such as those undergoing pneumonectomy for advanced lung cancer (1–3). Since the 1990s, thoracic surgeons have increasingly paid attention to neoadjuvant therapy (NT) for improving the resectability. NT can reduce or eliminate the micro-metastasis especially in patients with advanced lung cancer (4,5). Recent systematic reviews have integrated the previously published randomized control trials (RCTs) and concluded that NT can significantly benefit the survival outcomes of operable patients (4–6). However, the impact of NT on intraoperative and postoperative complications still remains a debate (7,8).

Among the major fatal complications causing decreased survival rate, bronchopleural fistula (BPF) still troubles thoracic surgeons because of the devastating leakage from airways into pleural space (9,10). Although the incidence of BPF has been largely decreased during the last few decades, the mortality caused by its adverse effects remains high (18–50%) (9). Surgical procedures, such as operative modes and bronchial stump closure, are generally accepted as the leading causes of postoperative BPF (11,12). As an important preoperative parameter, NT has been extensively evaluated in many relevant studies addressing the risk factors of BPF. However, the clinical outcomes associated with NT vary hugely, and a consensus has not been reached on the detailed association between NT and BPF risk until now (9,13).

Recently, the statistical methods of evidence-based medicine (EBM) which are represented by meta-analyses, have been increasingly applied in clinical practice to draw relatively global conclusions by quantitatively integrating the appropriate data from homogeneous studies (4–6,14). The current evidences revealing the effects of NT on BPF risk have not yet been systematically reviewed. Therefore, we conducted this systematic meta-analysis to determine the association between NT and risk of BPF in patients undergoing lung cancer surgery.

## Patients and methods

### Statements

Patients' consent or ethical approval is not necessarily required in systematic reviews and meta-analyses. We conducted this meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (15). The additional PRISMA 2009 Checklist of our meta-analysis is given in [Supplementary Data 1](#).

### Search strategy

The literatures retrieval of our meta-analysis ranged from 24 August 2015 to 5 September, 2015. Consulting previous meta-analyses, we searched two universal electronic databases, PubMed and EMBASE (via Ovid interface), to identify the eligible literatures published between 1 January 1990 and 24 August 2015 (4). Five comprehensive search strings were combined with eight key words and two Boolean Operators ('AND' and 'OR'). The key words are listed as follows: (i) 'bronchopleural fistula' and 'bronchial fistula'; (ii) 'neoadjuvant therapy', 'induction therapy' and 'preoperative therapy'; and (iii) 'risk factor', 'incidence' and 'etiology'. The complete details of all the search strings in qualified format of each database are listed in

[Supplementary Data 2](#). Besides, we also manually searched the reference lists of original literatures to identify any possible included study with no duplication.

### Inclusion and exclusion criteria

The following inclusion and exclusion criteria were determined to confirm the included studies of our meta-analysis.

#### Inclusion criteria

(i) The target disease is primary lung cancer; (ii) a BPF develops after pulmonary resections instead of malignancy progression; (iii) the risk factors analyzed in original literatures contain the neoadjuvant chemotherapy (NC) and/or neoadjuvant radiotherapy (NR) before operations; (iv) primary demographic data or statistical results, including odds ratio (OR), relative risk (RR) and hazard ratio (HR), are reported in original literatures; and (v) only literatures in English language are considered for eligibility.

#### Exclusion criteria

(i) The following articles are directly excluded: reviews, letters, animal experiments, case reports and conference abstracts; (ii) the details of NT acceptance and BPF occurrence are uncertain; (iii) non-lung cancer malignancies and benign diseases are enrolled; and (iv) non-English languages are not accepted.

### Quality assessment

Newcastle-Ottawa Scale (NOS) was an appropriate assessment tool to evaluate the quality of original non-randomized studies (16). Three perspectives covering selection, comparability and exposure were considered for semi-quantitative estimations. The 'star system' with a maximum of nine stars was applied to grade all of the included studies. We regarded 8–9 stars as a good quality, 6–7 stars as a fair quality and lower than 6 stars as a poor quality.

### Data extraction

We designed a Microsoft Excel sheet to record the following information: (i) publication data including authors, publication years and nations; (ii) experimental data including study design, study period, NT strategies, operative modes and clinical stages; (iii) demographic data including enrolled samples, ages and the number of patients with NT and postoperative BPF; and (iv) statistical data including cohort design, statistical analysis, reported statistics with their corresponding 95% confidence interval (CI), OR extractions and authors' attitude to the significance (*P* value).

### Statistical analysis

According to the previously published reports, the incidence of BPF was generally far lower than 20% (9). Therefore, no significant difference was observed between OR and RR, and the risk of overestimating the impact of NT on BPF development could be largely avoided (17). In this meta-analysis, we applied the OR with 95% CI as the appropriate summarized statistics. In general, OR with 95% CI could be directly extracted from the published statistical results, or extrapolated by demographic data if no statistic was reported. Moreover, if RRs or HRs were reported in original studies, they could be directly considered as ORs and incorporated into our meta-analysis (17). Remarkably, NT could be indicated as an independent risk factor of BPF if the pooled OR with 95%CI appeared >1.

$Q$ -test and  $I^2$  statistic were commonly applied to estimate the level of heterogeneity within this meta-analysis. On the one hand, low heterogeneity was defined as  $I^2 < 40\%$  and  $P > 0.1$ , determining the standard fixed-effect model (Mantel-Haenszel method) to integrate the ORs. On the other hand, if significant heterogeneity was revealed by  $I^2 \geq 40\%$  or  $P \leq 0.1$ , the random-effect model (DerSimonian and Laird method) would be used for quantitative synthesis (18). Additionally, we regarded  $I^2$  statistic as the major indicator for heterogeneity estimations because it had been proved as an effective method to quantify the inconsistency across studies (17).

Then, we conducted sensitivity analysis to evaluate the stability of this meta-analysis after identifying the possible origins of significant heterogeneity. The study contributing to the significant heterogeneity would be removed and a repeated meta-analysis of the remaining studies would be performed for adjustments. The strong stability of our meta-analysis would be confirmed if no substantial varies were

observed between the adjusted summarized outcomes and primary summarized outcomes (19).

Both Begg's test and Egger's test were used to detect the publication bias in this meta-analysis. Its presence could be suggested by the symmetry of funnel plot conducted by Begg's test, in which log ORs were plotted against their corresponding standard errors. Meanwhile, we could also confirm the significant bias if Egger's  $P$  value  $< 0.05$  (20).

Finally, all of the above statistical analyses were accomplished by STATA 12.0 (STATA Corporation, College Station, TX, USA).

## Results

### The selection of included studies

The complete procedures of literatures retrieval are displayed in Fig. 1. A total of 1617 citations were identified after the primary retrieval,

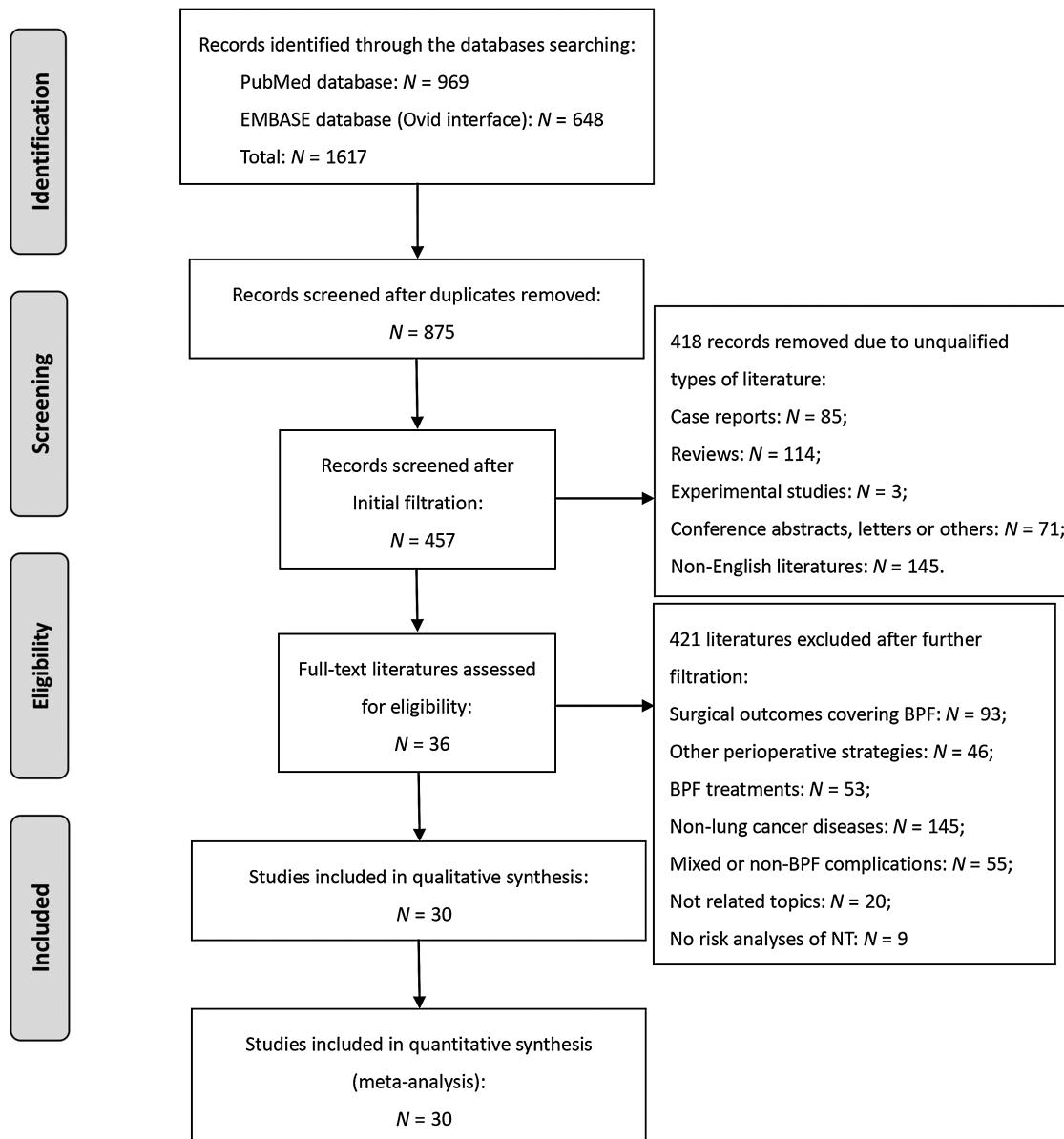


Figure 1. PRISMA flow diagram of the literatures retrieval. BPF, bronchopleural fistula; NT, neoadjuvant therapy.

including 969 citations in PubMed and 648 citations in EMBASE. After excluding 742 duplicates, 875 publications entered into the initial filtration, which was based on screening titles and abstracts. Then, 418 of them were excluded due to their unqualified article types, including 85 case reports, 114 reviews, 3 experimental studies, 71 conference abstracts and 145 literatures in other languages. The remaining 457 records were further filtrated by reading through their full contents. There were 36 among them identified for possible eligibility of the quantitative integration, and the other 421 records were excluded for different reasons (see Fig. 1). Finally, a total of 30 studies (21–50) were included into our meta-analysis after quantitative estimations. The reasons for exclusion of the six lastly filtrated studies (51–56) are briefly summarized in the [Supplementary Data 3](#).

### The quality level of included studies

The mean NOS score of all the included studies in this meta-analysis was calculated as 7.6 (ranged from 6 to 9), indicating a generally good quality. The complete details of assessments are not given but listed the final NOS score of each study in Table 1.

### The basic characteristics of included studies

We tabulated the basic characteristics of the 30 included studies as Table 1. All of these studies belong to retrospective observational studies, and were published from 1992 to 2014 (21–50).

They enrolled a total of 14 912 patients undergoing lung cancer resections from 1979 to 2012, and non-small cell lung cancer (NSCLC) accounted for ~99.8% of all cases (14 884/14 912). Asian patients provided 77.2% of the enrolled samples (11 510/14 912) (23,30,31,34,35,40,42,45,46,49,50), including 6923 cases from China (31,35), 4347 cases from Japan (23,30,34,40,42,49,50), 177 cases from Turkey (45) and 63 cases from Korea (46). The other 3402 patients (3402/14 912, ratio = 22.8%) were from European and North American countries and reported in 19 studies (21,22,24–29,32,33,36–39,41,43,44,47,48). Postoperative BPF was diagnosed in 354 patients by endoscopic inspection and clinical manifestation. Therefore, the incidence of BPF after lung cancer surgery was 2.4% (354/14 912) in this systematic review. NC was generally applied in most of the included studies. Twelve studies independently analyzed the effects of NC (21,26,34,35,37,38,42,44–47,50), another 11 studies analyzed the effects of neoadjuvant chemo-radiation (NCR) (24,27–29,32,33,39–41,44,49), and another four studies investigated the association between NR and BPF risk (23,46,48,50). Besides, the remaining studies (22,25,30,31,36,43) enrolled both NC cases and NR cases but analyzed them together, without providing any extractable detail on each strategy. The operations performed on lung cancer patients included pneumonectomy (21,22,25,26,29–31,33,34,36–40,43–48), lobectomy (32,42) and bronchoplasty (24,27,28,41). Four large-scale studies enrolled 9570 patients (9570/14 912, ratio = 64.2%) undergoing multiple types of resections but did not report the

**Table 1.** Basic characteristics of the included studies

Authors (year)	Nation	Study design	Study period	No. of samples			Mean age (years)	NT strategies	Surgery	Stages	NOS
				Total	NT	BPF					
Alan et al. (2008) (21)	Czech	ROS	1998–2007	269	54	8	58.4	NC	Pneumonectomy	I–IV	9
Algar et al. (2001) (22)	Spain	ROS	1986–97	242	32	13	60.5	NC, NR	Pneumonectomy	I–III	7
Asamura et al. (1992) (23)	Japan	ROS	1980–90	1360	NI	26	61.2	NR	Multiple modes	I–IV	9
Burfeind et al. (2005) (24)	USA	ROS	1997–2004	73	19	1	58.0	NC, NCR	Bronchoplasty	I–IV	7
Darling et al. (2005) (25)	Canada	ROS	1990–2000	187	31	15	67.1	NC, NR	Pneumonectomy	I–IV	7
d'Amato et al. (2009) (26)	Canada	ROS	1989–2004	315	68	24	62.9	NC	Pneumonectomy	IIIa	8
Gonzalez et al. (2013) (27)	Switzerland	ROS	1999–2010	99	28	2	62.0	NC, NCR	Bronchoplasty	I–III	7
Gomez-Caro et al. (2012) (28)	Spain	ROS	2005–10	79	26	1	64.0	NCR	Bronchoplasty	I–III	7
Gudbjartsson et al. (2008) (29)	Sweden	ROS	1996–2003	130	35	8	63.4	NC, NCR	Pneumonectomy	I–IV	8
Haraguchi et al. (2006) (30)	Japan	ROS	1983–2005	114	12	12	59.8	NI	Pneumonectomy	I–IV	7
Hu et al. (2013) (31)	China	ROS	1995–2012	684	47	30	57.0	NC, NCR, NR	Pneumonectomy	II–III	8
Hampel et al. (2010) (32)	Germany	ROS	2008	36	9	2	64.1	NCR	Lobectomy	I–IV	7
Hubaut et al. (1999) (33)	France	ROS	1988–97	199	16	5	60.5	NC, NCR, NR	Pneumonectomy	I–IV	7
Ichiki et al. (2012) (34)	Japan	ROS	1992–2007	71	2	2	63.0	NC	Pneumonectomy	I–IV	6
Jichen et al. (2009) (35)	China	ROS	1995–2005	6239	652	66	55.0	NC	Multiple modes	I–IV	8
Lindner et al. (2010) (36)	Germany	ROS	2000–07	243	17	13	62.2	NI	Pneumonectomy	I–IV	7
Mansour et al. (2008) (37)	France	ROS	1999–2005	153	60	4	59.5	NC	Pneumonectomy	NI	8
Mansour et al. (2007) (38)	France	ROS	1999–2005	298	60	14	61.0	NC	Pneumonectomy	I–III	9
Margaritora et al. (2013) (39)	Italy	ROS	1995–2008	85	49	3	60.7	NCR	Pneumonectomy	I–IV	8
Matsuoka et al. (2010) (40)	Japan	ROS	1999–2004	64	33	5	64.4	NC, NCR, NR	Pneumonectomy	I–IV	8
Merritt et al. (2009) (41)	USA	ROS	1980–2007	125	16	4	54.0	NC, NCR, NR	Bronchoplasty	I–III	7
Nagahiro et al. (2011) (42)	Japan	ROS	1993–2002	767	45	12	65.3	NC	Lobectomy	NI	8
Panagopoulos et al. (2009) (43)	Greece	ROS	1999–2005	221	14	5	62.4	NC, NR	Pneumonectomy	I–IV	8
Refaï et al. (2010) (44)	Italy	RCMA	2000–07	154	77	6	63.9	NC, NCR	Pneumonectomy	I–IV	8
Samancilar et al. (2014) (45)	Turkey	ROS	2005–11	177	49	17	56.0	NC	Pneumonectomy	I–IV	7
Seok et al. (2014) (46)	Korea	ROS	1998–2011	63	13	3	59.5	NC, NR	Pneumonectomy	I–III	7
Stolz et al. (2014) (47)	Czech	ROS	1998–2012	329	61	12	55.8	NC	Pneumonectomy	NI	8
Sirbu et al. (2001) (48)	Germany	ROS	1990–99	165	19	12	57.8	NR	Pneumonectomy	I–IV	7
Sonobe et al. (2000) (49)	Japan	ROS	1989–98	547	12	10	65.3	NC, NCR, NR	Multiple modes	I–IV	8
Uramoto et al. (2011) (50)	Japan	ROS	1979–2010	1424	47	19	61.8	NC, NCR, NR	Multiple modes	I–IV	8

BPF: bronchopleural fistula, NC: neoadjuvant chemotherapy, NCR: neoadjuvant chemo-radiation, NI: no information, NOS: Newcastle-Ottawa Scale, NR: neoadjuvant radiotherapy, NT: neoadjuvant therapy, RCMA: retrospective case-matched analysis, ROS: retrospective observational study.

details of BPF occurrence in each operative mode (23,35,49,50). Other available characteristics of the included studies, including ages and clinical stages, are also listed in Table 1.

### The statistical characteristics of included studies

The cohort design of these 30 observational studies was not completely consistent. Thirteen included studies (21,24,26–29,32,37–39,41,44,45) analyzed the differences in BPF development between the patients undergoing NT followed by operations and those undergoing operations alone (NT + surgery vs. surgery alone) (Table 2). The other 17 included studies (22,23,25,30,31,33–36,40,42,43,46–50) classified 12 919 patients (12 919/14 912, ratio = 86.6%) by BPF occurrence, and evaluated the risk factors of BPF based on the patients with BPF and without BPF (BPF vs. non-BPF) (Table 2). Furthermore, more than half of these 17 studies (22,23,30,31,35,40,42,43,47) performed both univariate analysis and multivariate analysis to comprehensively identify the independent factors of BPF. However, univariate analysis was generally used for the initially identification of some clinical parameters, and the subsequent multivariate analysis was conducted to further clarify their significances on serving as independent factors. Therefore, it was possible that only the statistically significant results from multivariate analysis were finally published in relevant studies. In this meta-analysis, only four included studies reported the statistics of NT based on multivariate analysis, including OR results from three studies (23,42,47) and HR results from one study (31).

The majority of the data incorporated into this meta-analysis was originally extrapolated by published demographics (Table 2). The conducted OR with 95%CI and authors' attitude toward each study are listed in Table 2.

### Overall analysis

After quantitatively integrating the appropriate data from all the 30 included studies, the pooled OR was 2.166 (95%CI: 1.398–3.357;  $P = 0.001$ ), with a random-effect model test because of the significant heterogeneity across these studies ( $I^2 = 49.4\%$ ,  $P = 0.001$ ) (Table 3 and Fig. 2). On the whole, NT was significantly associated with the increased risk of BPF in patients undergoing lung cancer surgery.

### Subgroup analysis

To further investigate the impact of NT on BPF risk in detail, we stratified the enrolled patients into several subgroups according to operative modes, NT strategies, cohort design, OR extractions and the origins of patients, and analyzed them separately. The complete results conducted from subgroup analysis are listed in Table 3.

When analyzing the subgroups stratified by operative modes, we removed four studies (23,35,49,50) due to the scarcity of extractable data on each operative mode. The summarized outcomes pooled 20 studies for pneumonectomy (OR: 1.694; 95%CI: 1.022–2.806;  $P = 0.041$ ) (21,22,25,26,29–31,33,34,36–40,43–48), 2 studies for

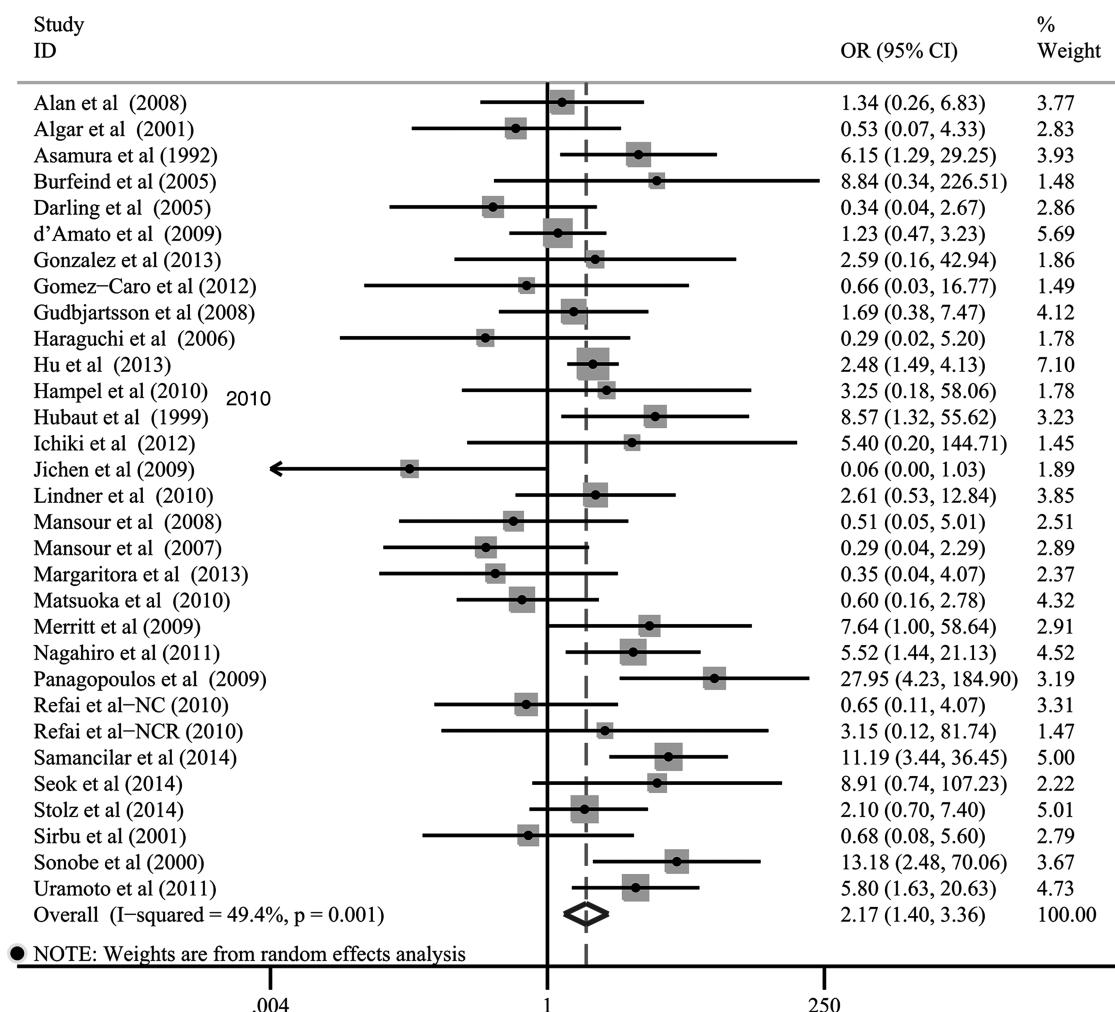
**Table 2.** Statistical characteristics of the included studies

Authors (year)	Cohort design	OR with 95% CI	P value	OR extractions	Analysis	Attitude
Alan et al. (2008) (21)	NT + surgery vs. surgery	1.340 (0.263–6.830)	0.663	DDE	Univariate	Not significant
Algar et al. (2001) (22)	BPF vs. non-BPF	0.532 (0.067–4.238)	0.545	DDE	Univariate	Not significant
Asamura et al. (1992) (23)	BPF vs. non-BPF	6.145 (1.291–29.252)	0.023	Reported	Multivariate	Significant
Burfeind et al. (2005) (24)	NT + Surgery vs. Surgery	8.838 (0.345–226.514)	0.260	DDE	Univariate	Not significant
Darling et al. (2005) (25)	BPF vs. non-BPF	0.338 (0.043–2.67)	0.472	DDE	Univariate	Not significant
d'Amato et al. (2009) (26)	NT + surgery vs. surgery	1.231 (0.469–3.234)	0.615	DDE	Univariate	Not significant
Gonzalez et al. (2013) (27)	NT + surgery vs. surgery	2.593 (0.157–42.94)	0.488	DDE	Univariate	Not significant
Gomez-Caro et al. (2012) (28)	NT + surgery vs. surgery	0.66 (0.026–16.769)	1.0	DDE	Univariate	Not significant
Gudbjartsson et al. (2008) (29)	NT + surgery vs. surgery	1.688 (0.381–7.466)	0.486	DDE	Univariate	Not significant
Haraguchi et al. (2006) (30)	BPF vs. non-BPF	0.290 (0.016–5.200)	0.189	DDE	Univariate	Not significant
Hu et al. (2013) (31)	BPF vs. non-BPF	2.479 (1.487–4.133)	<0.001	Reported	Multivariate	Significant
Hampel et al. (2010) (32)	NT + surgery vs. surgery	3.25 (0.182–59.062)	0.443	DDE	Univariate	Not significant
Hubaut et al. (1999) (33)	BPF vs. non-BPF	8.571 (1.321–55.615)	0.046	DDE	Univariate	Significant
Ichiki et al. (2012) (34)	BPF vs. non-BPF	5.400 (0.202–144.707)	1.0	DDE	Univariate	Not significant
Jichen et al. (2009) (35)	BPF vs. non-BPF	0.064 (0.004–1.029)	1.0	DDE	Univariate	Not significant
Lindner et al. (2010) (36)	BPF vs. non-BPF	2.606 (0.529–12.843)	0.228	DDE	Univariate	Not significant
Mansour et al. (2008) (37)	NT + surgery vs. surgery	0.508 (0.052–5.005)	0.656	DDE	Univariate	Not significant
Mansour et al. (2007) (38)	NT + surgery vs. surgery	0.293 (0.038–2.288)	0.188	DDE	Univariate	Not significant
Margaritora et al. (2013) (39)	NT + surgery vs. surgery	0.354 (0.035–4.065)	0.571	DDE	Univariate	Not significant
Matsuoka et al. (2010) (40)	BPF vs. non-BPF	0.602 (0.164–2.781)	0.590	DDE	Univariate	Not significant
Merritt et al. (2009) (41)	NT + surgery vs. surgery	7.643 (0.996–58.636)	0.023	DDE	Univariate	Significant
Nagahiro et al. (2011) (42)	BPF vs. non-BPF	5.52 (1.44–21.13)	0.011	Reported	Multivariate	Significant
Panagopoulos et al. (2009) (43)	BPF vs. non-BPF	27.955 (4.226–184.898)	0.002	DDE	Univariate	Significant
Refaï et al.-NC (2010) (44)	NT + surgery vs. surgery	0.654 (0.105–4.074)	0.647	DDE	Univariate	Not significant
Refaï et al.-NCR (2010) (44)	NT + surgery vs. surgery	3.146 (0.121–81.739)	1.0	DDE	Univariate	Not significant
Samancilar et al. (2014) (45)	NT + surgery vs. surgery	11.194 (3.438–36.449)	0.029	DDE	Univariate	Significant
Seok et al.-NC (2014) (46)	BPF vs. non-BPF	10.000 (0.825–121.172)	0.090	DDE	Univariate	Not significant
Seok et al.-NR (2014) (46)	BPF vs. non-BPF	5.667 (0.193–165.982)	1.0	DDE	Univariate	Not significant
Stolz et al. (2014) (47)	BPF vs. non-BPF	2.100 (0.700–7.400)	0.420	Reported	Multivariate	Not significant
Sirbu et al. (2001) (48)	BPF vs. non-BPF	0.682 (0.083–5.598)	0.720	DDE	Univariate	Not significant
Sonobe et al. (2000) (49)	BPF vs. non-BPF	13.175 (2.478–70.060)	0.020	DDE	Univariate	Significant
Uramoto et al. (2011) (50)	BPF vs. non-BPF	5.8 (1.63–20.634)	0.002	DDE	Univariate	Significant

CI, confidence interval; DDE, demographic data extrapolated; NC, neoadjuvant chemotherapy; OR, odds ratio.

**Table 3.** Meta-analysis of the association between NT and risk of BPF after lung cancer surgery

Outcomes	N	Enrolled samples	Heterogeneity ( $I^2$ , P)	Model	OR (95% CI)	P value	Publication bias		Conclusion
							Begg (P)	Egger (P)	
Overall	30	14 912	$I^2 = 49.4\%, P = 0.001$	Random	2.166 (1.398–3.357)	0.001	0.262	0.389	Significant
Operative modes	26 <sup>a</sup>								
Pneumonectomy	20	4163	$I^2 = 49.9\%, P = 0.005$	Random	1.694 (1.022–2.806)	0.041	0.526	0.292	Significant
Lobectomy	2	803	$I^2 = 0.0\%, P = 0.744$	Fixed	5.022 (1.487–16.967)	0.009	1.0	NI	Significant
Bronchoplasty	4	376	$I^2 = 0.0\%, P = 0.593$	Fixed	4.029 (1.057–15.357)	0.041	0.734	0.430	Significant
NT strategies	24 <sup>b</sup>								
NC	12	10 217	$I^2 = 58.5\%, P = 0.005$	Random	1.857 (0.881–3.911)	0.104	0.304	0.332	Not significant
NR	4	3012	$I^2 = 15.4\%, P = 0.315$	Fixed	3.914 (1.401–10.935)	0.009	1.0	0.88	Significant
NCR	11	1479	$I^2 = 31.8\%, P = 0.145$	Fixed	2.533 (1.353–4.741)	0.004	1.0	0.766	Significant
Cohort design	30								
NT + surgery vs. surgery	13	1993	$I^2 = 37.1\%, P = 0.080$	Fixed	1.830 (1.130–2.965)	0.014	0.743	0.625	Significant
BPF vs. non-BPF	17	12 919	$I^2 = 56.9\%, P = 0.002$	Random	2.539 (1.401–4.603)	0.002	0.434	0.693	Significant
OR extractions	30								
DDE	26	11 772	$I^2 = 53.4\%, P = 0.001$	Random	1.889 (1.087–3.284)	0.024	0.532	0.361	Significant
Reported	4	3140	$I^2 = 0.0\%, P = 0.493$	Fixed	2.813 (1.838–4.307)	<0.001	0.308	0.290	Significant
Origins of patients	30								
Asian	11	11 510	$I^2 = 62.4\%, P = 0.003$	Random	3.281 (1.567–6.869)	0.002	0.213	0.950	Significant
Non-Asian	19	3402	$I^2 = 29.3\%, P = 0.107$	Fixed	1.611 (1.069–2.427)	0.023	0.974	0.966	Significant

<sup>a</sup>The details of each operative mode in Refs (23,35,49,50) are not given.<sup>b</sup>The details of NT strategies in Refs (22,25,30,31,36,43) are not given.**Figure 2.** Overall analysis for the association between NT and risk of BPF after lung cancer surgery. CI, confidence interval; NC, neoadjuvant chemotherapy; NCR, neoadjuvant chemo-radiation; OR, odds ratio.

standard lobectomy (OR: 5.022; 95%CI: 1.487–16.967;  $P = 0.009$ ) (32,42) and 4 studies for bronchoplasty modes (OR: 4.029; 95%CI: 1.057–15.357;  $P = 0.041$ ) (24,27,28,41). All of them indicated that NT was an independent factor predisposing to postoperative BPF (Table 3 and Fig. 3A).

Considering the NT strategies, there were six studies (22,25,30,31,36,43) excluded because no relevant detail of NT was reported in these studies. Pooled analyses suggested that NR (OR: 3.914; 95%CI: 1.401–10.935;  $P = 0.009$ ) (23,46,48,50) and NCR (OR: 2.533; 95%CI: 1.353–4.741;  $P = 0.004$ ) (24,27–29,32,33,39–41,44,49) were both significantly associated with the increased risk of BPF, with low heterogeneity (Table 3 and Fig. 3B). The summarized outcomes integrating 12 available studies (21,26,34,35,37,38,42,44–47,50) revealed the higher frequency of BPF occurred in patients treated with NC compared with those without NC (OR: 1.857; 95%CI: 0.881–3.911). However, the current evidences did not show the significant impact of NC on BPF occurrence after lung cancer surgery ( $P = 0.104$ ).

The other subgroups covered all of the 30 included studies. The association between NT and BPF risk was commonly prominent in these subgroups, including cohort design (NT + surgery vs. surgery alone, OR: 1.830; 95%CI: 1.130–2.965;  $P = 0.014$ ; BPF vs. non-BPF, OR: 2.539; 95%CI: 1.401–4.603;  $P = 0.002$ ), OR extractions (demographic data extrapolated, OR: 1.889; 95%CI: 1.087–3.284;  $P = 0.024$ ; Reported statistics, OR: 2.813; 95%CI: 1.838–4.307;  $P < 0.001$ ), Asian populations (OR: 3.281; 95%CI: 1.567–6.869;  $P = 0.002$ ) and non-Asian populations (OR: 1.611; 95%CI: 1.069–2.427;  $P = 0.023$ ) (Table 3 and Fig. 3C–E).

### Sensitivity analysis

The forest plot derived from sensitivity analysis was shown as Fig. 4. We found that none of the independent results from 30 included studies was out of the estimated ranges under visual inspection. That means no substantial vary was observed between the adjusted summarized outcomes and primary summarized outcomes. The leave-one-out method and repeated meta-analysis for adjustments were no more necessary. Given such estimations, the strong robustness of our meta-analysis was clarified.

### Publication bias

The funnel plots conducted by Begg's test and Egger's test for publication bias assessments in overall analysis were shown as Fig. 5A and B. We did not display the plots of subgroup analysis but list their results in Table 3. Finally, there was no evidence indicating any publication bias within the overall analysis (Begg's  $P$  value = 0.262; Egger's  $P$  value = 0.389) and subgroup analysis (Table 3 and Fig. 5).

### Discussion

To the best of our knowledge, this is the first meta-analysis to systematically evaluate the association between NT and risk of BPF in patients undergoing lung cancer surgery. In our meta-analysis, we quantitatively integrated the clinical data from the studies published since the 1990s when NT was already widely applied in a proper way (29). We enrolled 14 912 surgical patients from 30 included studies, and NSCLC accounted for almost all of the enrolled cases (14 884/14 912, ratio = 99.8%). The other cases were small cell lung cancer (SCLC) cases (28/14 912, ratio = 0.2%) but the details of BPF development in these cases were not available. Therefore, this meta-analysis could be approximately regarded as the evaluation of the association

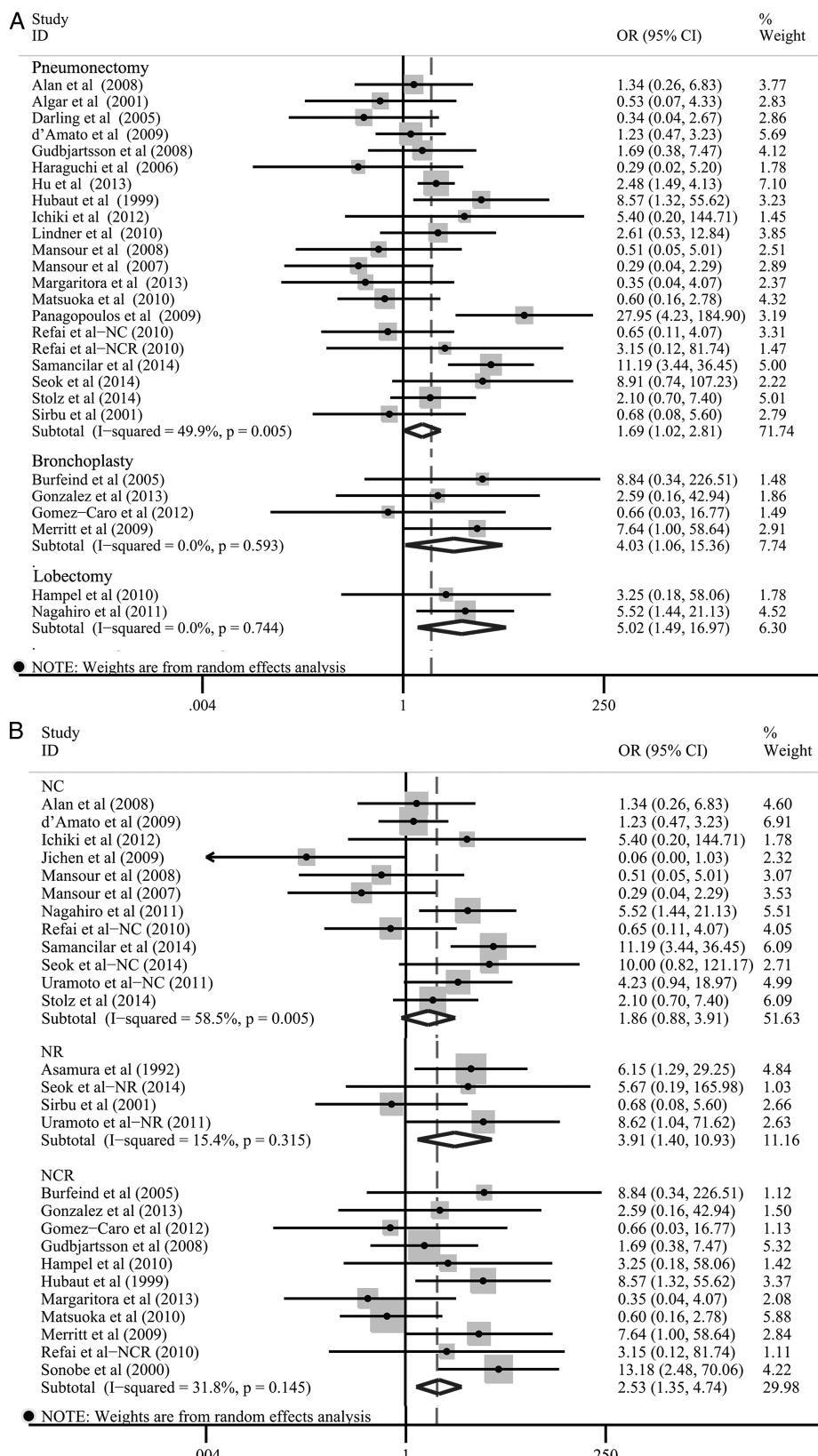
between NT and risk of BPF after NSCLC resections. We also discovered that no high-quality RCT or prospective study reported the effects of NT on BPF risk, which may be because of some inherent limitations in this addressed issue.

The discussion on safe applications of NT has never been stopped. According to the latest systematic reviews, NT is generally considered as an essential strategy in multidisciplinary treatments for lung cancer patients to improve the resectability and survival rate (4–6). However, some clinical reports have also mentioned the potential adverse effects of NT on bronchial stump healing after lung cancer surgery (57). Given such concern, we propose that applying EBM methods to a larger number of pooled evidences may better clarify the impact of NT on BPF development. The main issue to be addressed is whether the association between NT and BPF risk is statistically reliable. Therefore, we quantitatively integrated the currently available evidences, which led to the conclusion that NT was an independent risk factor of BPF occurrence after lung cancer surgery. However, we discovered the remarkable high inconsistency among the included studies ( $I^2 = 49.4\%$ ,  $P = 0.001$ ), suggesting the significant heterogeneity of pooled outcomes.

The earliest relevant multivariate analysis enrolling >1000 patients was reported by Asamura et al. (23) in 1992. It revealed that NR was a significant risk factor of BPF. This conclusion was supported by Uramoto et al. (50) after analyzing 1424 surgical patients. Both NR and NC were identified to be significantly associated with BPF formation after lung cancer surgery in this study. On the basis of NT, Hu et al. (31) even designed an effective clinical risk model to evaluate the development of BPF. However, the significant relationship between NT and risk of BPF was not shown in most of the included studies (21,24–30,32,34–40,44,46–48), including the currently largest study which enrolled 6239 surgical patients from China (35). Refai et al. (44) proposed that adequately balanced comparison should be a prerequisite to demonstrate the impact of NT on surgical outcomes. They performed a case-matched analysis in 77 pairs of propensity score-matched patients and indicated that either NC or NCR was not significantly associated with the increased risk of BPF. However, too small sample size under balanced comparison might cause large negative effects on conducting statistically significant outcomes.

Therefore, we performed detailed subgroup analyses to further dissect the heterogeneity. When stratifying the sources of ORs, the significant heterogeneity was revealed among the pooled OR results extrapolated by demographic data based on univariate analysis ( $I^2 = 53.4\%$ ,  $P = 0.001$ ) but not among the reported statistics from multivariate analysis ( $I^2 = 0.0\%$ ,  $P = 0.493$ ). One possible reason might be related to the bias risks from confounding factors. Multivariate analysis using logistic regression or Cox proportional hazards model is generally applied to eliminate the bias from other confounding factors in observational studies. In this meta-analysis, the majority of included studies just reported the demographic results instead of any statistic from multivariate analysis. Most confounding factors were not adequately adjusted and might increase the heterogeneity across the included studies. Besides, the validity of pooled outcomes in our meta-analysis might be attenuated by the negative effects of various confounders.

The major confounding factors in this meta-analysis, including operative modes, advanced stages and bronchial stump closure, should be seriously considered. It has been widely accepted that pneumonectomy can increase the risk of BPF compared with lesser pulmonary resections, particularly in right side (9,13). The subgroup analysis based on operative modes indicated the significant impact of NT on BPF risk in patients undergoing pneumonectomy, lobectomy and bronchoplasty, respectively. However, we could not further eliminate the



**Figure 3.** Subgroup analysis for the association between NT and risk of BPF in subgroups stratified by (A) operative modes, (B) NT strategies, (C) cohort design, (D) OR extractions and (E) the origins of patients. DDE, demographic data extrapolated; NR, neoadjuvant radiotherapy.

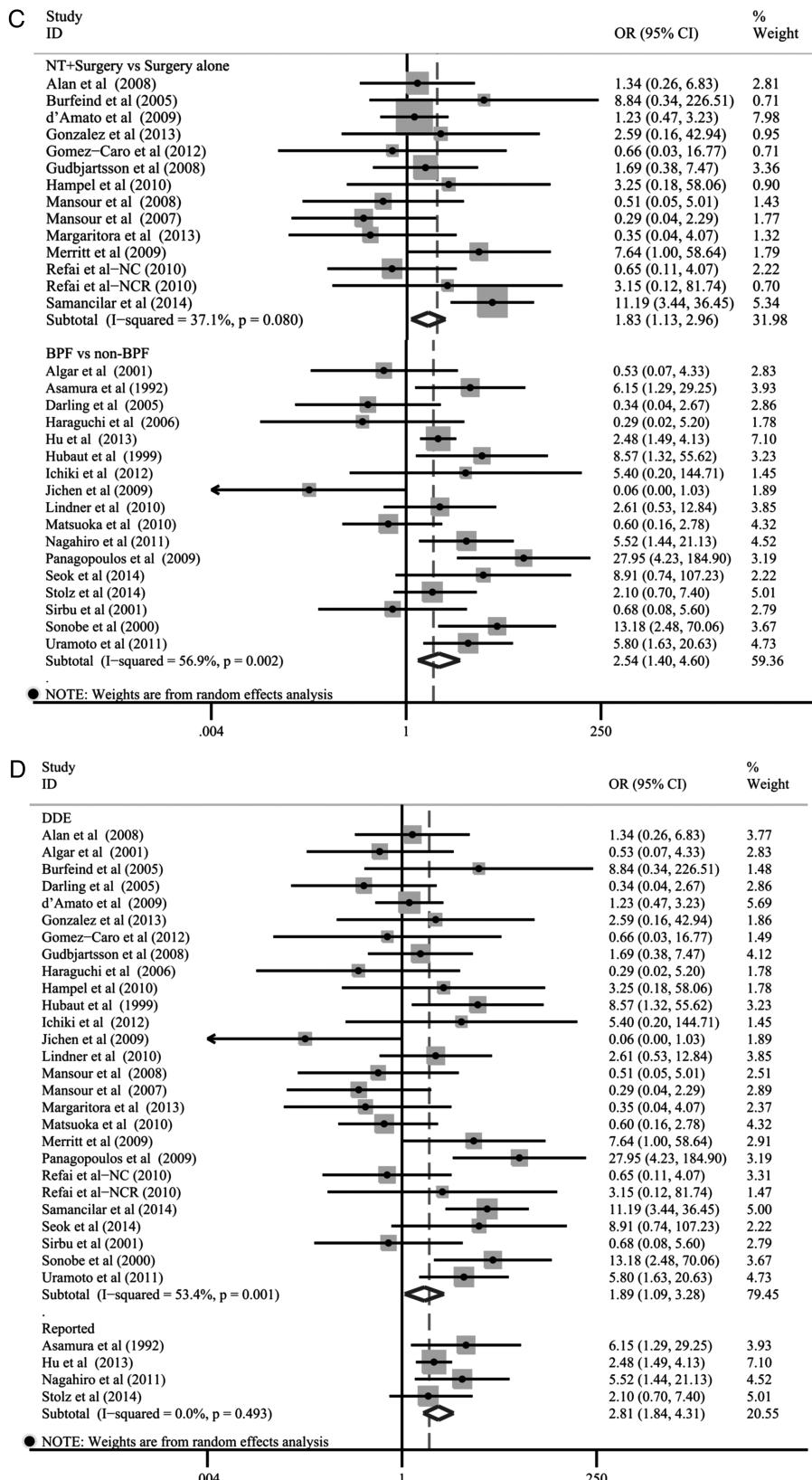


Figure 3. Continued

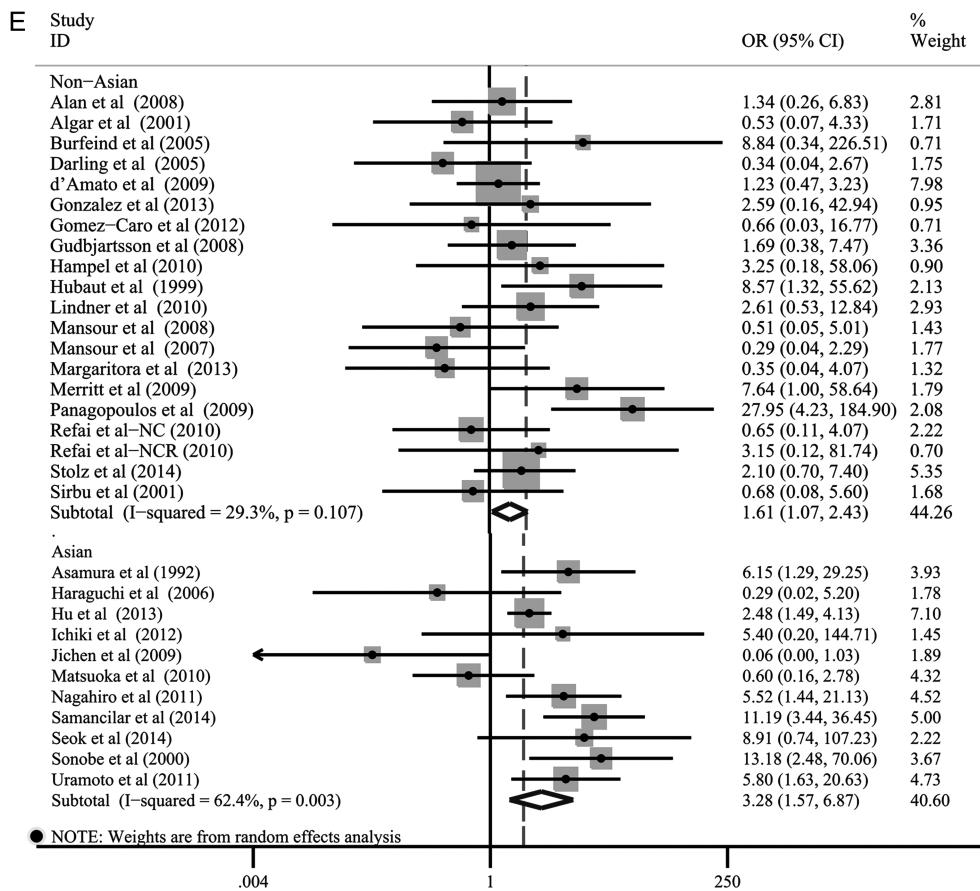


Figure 3. Continued

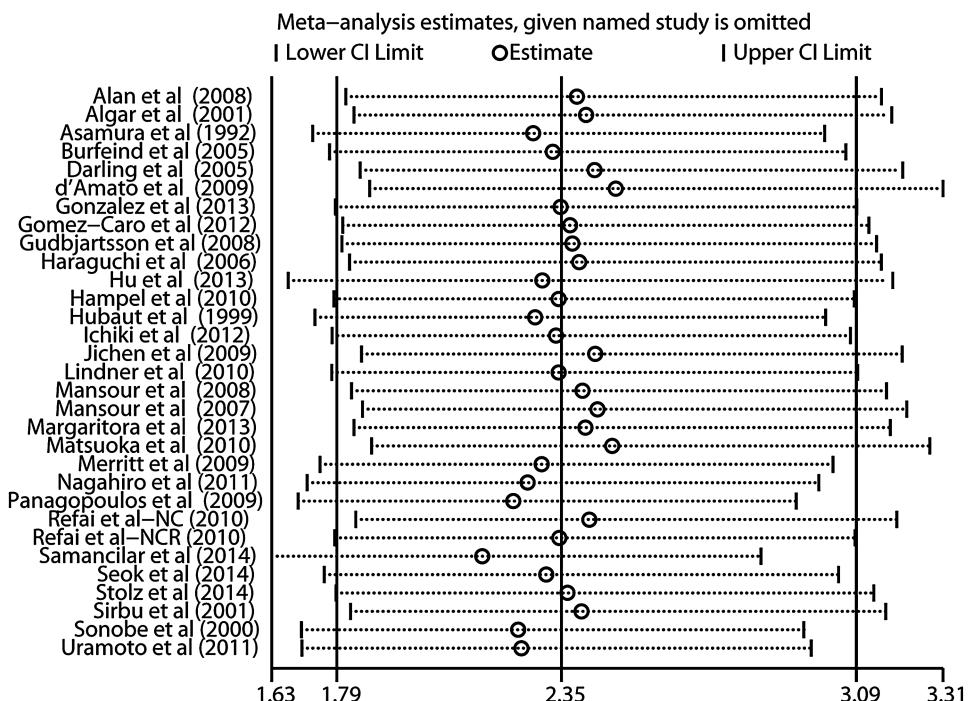
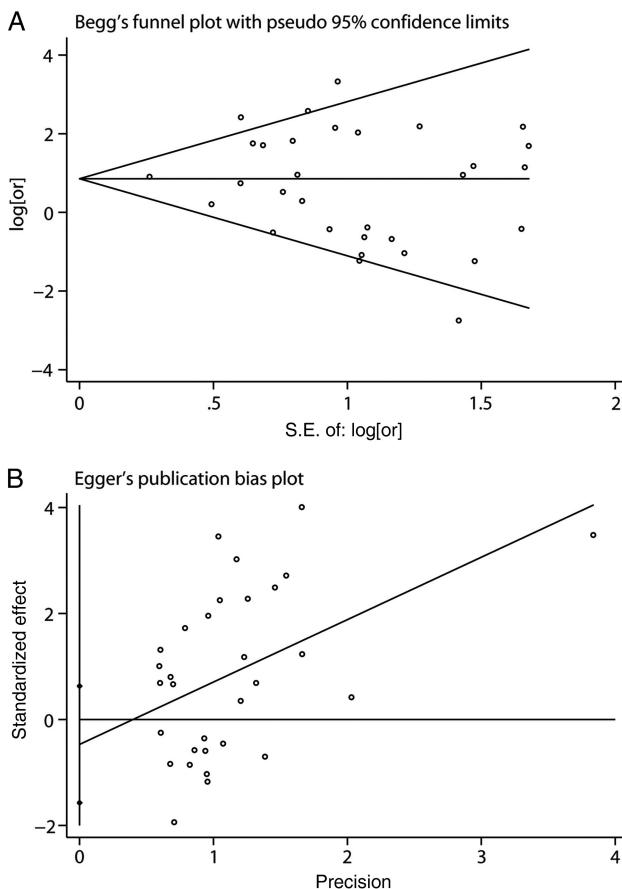


Figure 4. Sensitivity analysis of the association between NT and risk of BPF after lung cancer surgery.



**Figure 5.** Publication bias of the association between NT and risk of BPF detected by (A) Begg's test and (B) Egger's test.

bias caused by right pneumonectomy due to the scarcity of extractable details. Although NT has remarkable efficacies on treating advanced lung cancer, incomplete resection is still an important factor that cannot be ignored for the prognosis and risk of BPF in lung cancer patients (58). In this meta-analysis, all the included studies enrolled the patients with different stages but analyzed them together. We found a significant difference in the clinical stages between patients with NT and without NT in many included studies, which might result in some bias risks on the pooled outcomes. Unfortunately, we finally gave up the further analysis because no data of BPF occurrence in each lung cancer stage was reported in these studies.

For thoracic surgeons, the choices of bronchial closure and reinforcement can be mandated by some widely accepted factors of BPF, including the applications of NT. Recent EBM investigations have quantified the impact of bronchial stump coverage and closure on BPF development, but some controversial results still exist until now (11,12). One important reason is that thoracic surgeons usually make more efforts on buttressing the bronchial stumps in patients considered at high risk of BPF (including those treated with NT), resulting in an unbalanced comparison with patients at low risk of BPF. The varying degrees of baseline risks between groups of patients classified by NT application might bring large interference on pooling accurate outcomes (12).

Similarly, in our study, we were unable to effectively evaluate the bias caused by bronchial closure and reinforcement on BPF incidence between patients with NT and without NT because of the following

three reasons. First, researchers performed various bronchial closure methods across the different studies, and that could not be quantitatively analyzed. Second, additional buttress at the bronchial stump was generally performed in patients treated with NT rather than those without NT, which interfered the equal comparison. Third, few included studies provided the extractable details of bronchial closure and reinforcement in patients undergoing NT. Therefore, according to what Di Maio et al. (12) described, we speculated that the special bronchial stump reinforcement might slightly attenuate the impact of NT on BPF risk.

In the subgroup analysis stratified by NT strategies, one issue drawing our interest was that both NCR and NR significantly increased the risk of BPF but NC did not. It suggested that the development of BPF was mainly driven by NCR and NR rather than NC itself, which was consistent with the discoveries from most of the included studies. As some reports indicated, the incidence of BPF even slightly decreased in patients treated with NC (35,37,38,44). However, the pooled OR for NC group appeared an obvious trend towards the increased risk of BPF (OR: 1.857; 95%CI: 0.881–3.911;  $P = 0.104$ ). Two studies with nearly 1000 surgical patients also demonstrated the significant relationship between NC and occurrence of BPF (42,45). Therefore, the actual effects of NC on risk of BPF need further affirmations and modifications in the future studies based on a larger sample size.

The universally acknowledged mechanisms underlying BPF formation induced by NCR or NR contain the following two perspectives. On the one hand, anti-cancer agents can cause some injuries on vascular walls, resulting in the insufficiency of bronchial stump or anastomosis. Yamamoto et al. (59) firstly investigated the detailed association between NT and bronchial mucosal blood flow (BMBF), and discovered that NCR significantly reduced the BMBF but NC did not. Thus, NCR may be significantly associated with the increased risk of bronchial complications including BPF. On the other hand, vary degrees of fibrosis progression are commonly developed at the bronchial stump after NT intervention, especially in patients receiving NCR or NR (32). An experiment conducted by Inui et al. (60) clarified this mechanism during the early period after giving NR in mongrel dogs. In subsequent clinical reports, the fibrosis induced by a series of inflammatory reactions at the bronchial stumps was also identified in patients with NCR or NR, resulting in the unimpeded BMBF (57,61). Therefore, the lack of regional BMBF directly predisposes to the insufficient bronchial stump or anastomosis (59,60).

Furthermore, higher dose of NR may also be an independent risk factor of BPF (51). However, we failed to further investigate the dose responses of NR because continuous variables were not considered in this meta-analysis. In addition, the scarcity of available data about NR doses in the current studies also hugely reduced the feasibility of quantitative integrations. Therefore, a critical dose of NR accurately predicting the occurrence of BPF was not identified, resulting in slightly negative effects on the integrality of our meta-analysis.

## Limitations

Finally, several major limitations of this meta-analysis should be acknowledged. First, integrating the data mainly originated from univariate analysis might cause some adverse effects on the validity of our meta-analysis, because the bias risks from some confounding factors were insufficiently eliminated. Second, no RCTs or prospective studies were available for our meta-analysis. Perhaps it might be related to some inherent limitations of the addressed issue itself. Third, we were unable to further identify the association between

dose responses of NR and risk of BPF in this meta-analysis due to the scarcity of available data. Four, the current evidences came from many countries. Thus, inevitable variability in clinical settings of different countries should be judiciously considered. Last, only the literatures published in English language were considered for eligibility of this meta-analysis. We would identify more additional literatures if removing the language limitation.

## Conclusions

In conclusion, this meta-analysis indicates that NT is significantly associated with the BPF risk after lung cancer surgery. The further analysis clarifies both NCR and NR are independent risk factors of BPF in patients undergoing lung cancer surgery. NC does not significantly increase the risk of postoperative BPF but shows a tendency of higher BPF incidence. Some confounding factors may weaken the accuracy of pooled outcomes. The association between NR doses and BPF development remains a debate. Therefore, the updated high-quality studies can help to further confirm and enrich our discoveries in the future.

## Supplementary data

Supplementary data are available at <http://www.jjco.oxfordjournals.org>.

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## Conflict of interest statement

None declared.

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