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Research article

Incidence and risk factors of pulmonary complications after lung cancer surgery: A systematic review and meta-analysis

Ting Deng [a,b,c,1], Jiamei Song [a,b,1], Jinmei Tuo [a], Yu Wang [a], Jin Li [c], Lorna Kwai Ping Suen [d], Yan Liang [a,b], Junliang Ma [c], Shaolin Chen [a,b,*]

[a] Nursing Department, Affiliated Hospital of Zunyi Medical University, Guizhou, China
[b] School of Nursing, Zunyi Medical University, Guizhou, China
[c] Department of Thoracic Surgery, Affiliated Hospital of Zunyi Medical University, Guizhou, China
[d] School of Nursing, Tung Wah College, Hong Kong, China

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ABSTRACT

Postoperative pulmonary complications (PPCs) are associated with high mortality rates after lung cancer surgery. Although some studies have discussed the different risk factors for PPCs, the relationship between these factors and their impact on PPCs remains unclear. Hence, this study aimed to systematically summarize the incidence and determine the risk factors for PPCs.

We conducted a systematic search of five English and four Chinese databases from their inception to April 1, 2023. A total of 34 articles (8 cohort studies and 26 case-control studies) (n = 31696, 5833 with PPCs) were included in the analysis. The primary outcome was the incidence of PPC. The secondary outcome was the odds ratio (OR) of PPCs based on the identified risk factors calculated by RevMan 5.4. A narrative descriptive summary of the study results was presented when pooling the results or conducting a meta-analysis was not possible.

The pooled incidence of PPCs was 18.4 %. This meta-analysis demonstrated that TNM staging (OR 4.29, 95 % CI 2.59–7.13), chronic obstructive pulmonary disease (COPD) (OR 2.47, 95 % CI 1.80–3.40), smoking history (OR 2.37, 95 % CI 1.33–4.21), poor compliance with respiratory rehabilitation (OR 1.64, 95 % CI 1.17–2.30), male sex (OR 1.62, 95 % CI 1.28–2.04), diabetes (OR 1.56, 95 % CI 1.07–2.27), intraoperative bleeding volume (OR 1.44, 95 % CI 1.02–2.04), Eastern Cooperative Oncology Group score (ECOG) > 1 (OR 1.37, 95 % CI 1.04–1.80), history of chemotherapy and/or radiotherapy (OR 1.32, 95 % CI 1.03–1.70), older age (OR 1.18, 95 % CI 1.11–1.24), and duration of surgery (OR 1.07, 95 % CI 1.04–1.10) were significantly associated with a higher risk of PPCs. In contrast, the peak expiratory flow rate (PEF) (OR 0.99, 95 % CI 0.98–0.99) was a protective factor. Clinicians should implement targeted and effective interventions to prevent the occurrence of PPCs.

1. Introduction

Lung cancer is the most common malignant tumor and the leading cause of cancer-related deaths in the world [1]. The global incidence of new lung cancer cases in 2021 was approximately 2.207 million with the highest mortality rate of approximately 22 %

* Corresponding author.
E-mail address: 30363284@qq.com (S. Chen).
[1] Co-first author, these two authors contribute equally.

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Abbreviations

PPCs	postoperative pulmonary complications
OR	odds ratio
CI	confidence interval
COPD	chronic obstructive pulmonary disease
ECOG	Eastern Cooperative Oncology Group score
PEF	peak expiratory flow rate
NSCLC	non-small cell lung cancer
EPCO	European Perioperative Clinical Outcome
ARDS	acute respiratory distress syndrome
BMI	body mass index
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
NOS	Newcastle-Ottawa scale
MVV%	maximum ventilation volume
FEV1%	forced expiratory volume in 1 s
FVC%	forced vital capacity
DLco	diffusing capacity of the lung for carbon monoxide
AGR	albumin-to-globulin ratio
VO2/HR%-pred	preoperative oxygen pulse percentage
paO2	partial pressure of oxygen
ASA	American Society of Anesthesiologists
POD1	chest drainage on postoperative day 1
PNI	prognostic nutritional index
ILA	interstitial lung abnormality
APACHE II	acute physiology and chronic health evaluation II
AHRQ	Agency for Healthcare Research and Quality
CHD	coronary heart disease
STS	Society of Thoracic Surgeons
ESTS	European Society of Thoracic Surgeons
MGS	Melbourne Group Scale
CSRD	Chinese Society of Respiratory Diseases
ATS/ERS	American Thoracic Society Guidelines for the diagnosis of hospital-acquired pneumonia/European Respiratory Society
VATS	Video-assisted Thoracic Surgery
RATS	robotic-assisted thoracoscopic surgery
NCD	National Clinical Database
RCT	Randomized controlled trial

[2]. Surgery remains the primary therapeutic option for lung cancer, especially for early-stage non-small cell lung cancer (NSCLC) [3]. In the United States, 56 % of the patients with stage I or II NSCLC and 18 % with stage III NSCLC undergo wedge resection, sleeve resection, lobectomy, or pneumonectomy [4]. About 40 % of the patients [5,6] tend to experience postoperative pulmonary complications (PPCs) because of surgical trauma and perioperative factors, such as one-lung ventilation, ischemia-reperfusion/hypoxia-reoxygenation injury, reduced lung volumes after lung resection, reduced pulmonary function due to general anesthesia, and so on [7,8]. According to the European Perioperative Clinical Outcome (EPCO) definitions [9], PPCs include respiratory infection, respiratory failure, pleural effusion, atelectasis, pneumothorax, bronchospasm, and aspiration pneumonitis. PPCs can decrease overall survival by six months after surgery and are one of the leading causes of postoperative death [10], with a high mortality rate of approximately 84 % [11]. Therefore, identifying the predictive risk factors for PPCs is crucial in providing evidence for early assessment and optimization of perioperative interventions that can minimize the risks of PPCs and improve patients' prognosis. The related-literature search identified multiple factors that can increase the occurrence of PPCs, such as age, smoking, chronic obstructive pulmonary disease (COPD), percentage predicted forced expiratory volume in the first second (FEV1%), body mass index (BMI), surgery type, duration of operation, surgical site, type of anesthesia, and intraoperative conditions [5,6,12]. However, some studies have reported controversial results [13–16]. For example, a study showed that low FEV1% is an important risk factor for PPCs [15], which was inconsistent with another study [16]. Though, many studies have analyzed different risk factors, the relationship between these risk factors and their impact on PPCs remains unclear. Currently, there are few systematic reviews on PPCs in lung cancer. Thus, it is essential to integrate the present evidence to explore the related risk factors for PPCs in lung cancer. This study aimed to summarize the literature to determine the incidence and related risk predictors, thereby providing evidence for clinical staff to plan appropriate interventions.

2. Materials and methods

2.1. Design

This study was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Appendix A) [17] and registered in PROSPERO (CRD4202240648). During the course of the actual study, we revised the inclusion and exclusion criteria and updated the literature search on April 1, 2023.

2.2. Eligibility criteria

The inclusion criteria were as follows: (1) case-control, cohort, or cross-sectional studies; (2) adult patients diagnosed with lung cancer by a pathologist and who underwent any type of lung cancer surgery; (3) study outcome was the incidence of PPCs according to the definitions by any association, and its odds ratio (OR) based on the identified factors was stated; (4) the Newcastle-Ottawa scale (NOS) score equal to or greater than 6; and (5) articles either in Chinese or English languages.

Exclusion criteria were as follows: (1) lack of clear criteria for patient diagnosis; (2) incomplete data and unclear outcome effect; and (3) duplicate or full texts not available.

2.3. Literature search and selection criteria

The following electronic databases were searched from their inception until April 1, 2023: PubMed, Cochrane Library, EMBASE, CINAHL, Web of Science, CNKI, Wanfang Database, China Science and Technology Journal Database (VIP Database), and China Biomedical Literature Database (SinoMed). The search strategy for PubMed is outlined in Supplementary Appendix Table S1 and was translated into the remaining databases. The references for the included studies were manually retrieved to identify eligible studies. The Endnote software was used to manage the literature search and screening. Two authors independently searched for articles and screened titles and abstracts to identify potentially eligible studies following the removal of duplicates. Conflicts were resolved by discussion until a consensus was reached or by consultation with a third author, if required.

2.4. Assessment of methodological quality

Cohort and case-control studies were assessed using the NOS of non-randomized studies, with an overall quality score ranging from 0 (lowest) to 9 (highest) stars [18]. Based on the number of stars in each area, these studies were categorized as high (7–9), fair (4–6), or poor (0–3) quality [19]. Studies with NOS scores equal to or greater than 6 were included in the meta-analysis.

Two researchers independently conducted the assessments simultaneously, and any disagreements were resolved through discussion or consultation with a third author.

2.5. Data extraction and management

Two researchers independently extracted the data using a standardized data extraction form. Information collected included: (1) basic information of studies: study location, sample size, study design; (2) the number of patients with PPCs and the incidence of PPCs. PPCs were defined as defined previously, included respiratory infection, respiratory failure, pleural effusion, atelectasis, pneumothorax, bronchospasm, aspiration pneumonitis, etc [9]; (3) any type of related risk factors, and its 95 % confidence interval (CI) and OR value, including general factors such as: age, sex, smoking history, BMI; co-morbidities such as COPD, congestive heart failure, emphysema, diabetes mellitus; pre-operative examination, for example, pulmonary function tests: peak expiratory flow rate (PEF), maximum ventilation volume (MVV%), forced expiratory volume in 1 s (FEV1%), forced expiratory volume in 1 s/forced vital capacity (FEV1/FVC%), forced vital capacity (FVC%), diffusing capacity of the lung for carbon monoxide (DLco); and other tests such as serum albumin, albumin-to-globulin ratio (AGR), pre-operative colonization of bacteria, peak preoperative oxygen pulse percentage (VO_2/HR%-pred, %), preoperative partial pressure of oxygen (paO_2)$\leq$60 mmHg; surgical factors such as duration of surgery, surgery approach, type of resection, intraoperative bleeding volume, tumor TNM stage, pathology type, extended resection; and other indicators such as history of chemotherapy and/or radiotherapy, poor compliance of perioperative respiratory rehabilitation (defined as: participants participated in 59 % or less of the originally planned respiratory rehabilitation actively or after reminder) [20], number of days of perioperative antibiotic use, asthenia, American Society of Anesthesiologists score $\geq$2 (ASA), Eastern Cooperative Oncology Group score (ECOG) $>$ 1, chest drainage on postoperative day 1 (POD1), and prognostic nutritional index (PNI). Conflicts were resolved by consensus or by consulting a third author, when necessary.

2.6. Statistical analyses

All statistical analyses were conducted using Review Manager (RevMan), version 5.4 (The Cochrane Collaboration, 2020) software. For dichotomous outcomes, we reported OR and 95 % CI. To further explore the data, we performed a subgroup analysis based on tumor TNM stage, age, history of chemotherapy and/or radiotherapy, intraoperative bleeding volume, and sensitivity analysis for COPD.

A forest plot was used to visually represent the data, and heterogeneity was measured using I^2 statistics. The fixed-effects model was

adopted to combine the data (I^2 <50 %); otherwise, the random-effects model was used for the meta-analysis. We also performed a sensitivity analysis to identify the sources of heterogeneity. A narrative descriptive summary of the study results was presented when pooling the results or conducting a meta-analysis was not possible. Publication bias was assessed using funnel plots.

3. Results

3.1. Search results

A total of 2599 records were retrieved, including 1272 Chinese and 1327 English articles. After removing duplicates, 1461 records were screened by title and abstract. We then read the full text of 88 articles to assess their eligibility. Finally, 34 studies met the eligibility criteria and were included in this review and meta-analysis. The PRISMA flow diagram summarizes the study selection and identification processes (Fig. 1).

3.2. Description of the included studies

The 34 studies (n = 31696, 5833 with PPCs) included 8 cohort and 26 case-control studies. There were 27 Asian and 7 Western studies. Most Asian studies (approximately 66 %) were conducted in China. A total of 46 risk factors were identified. The characteristics of the study participants are presented in Table 1.

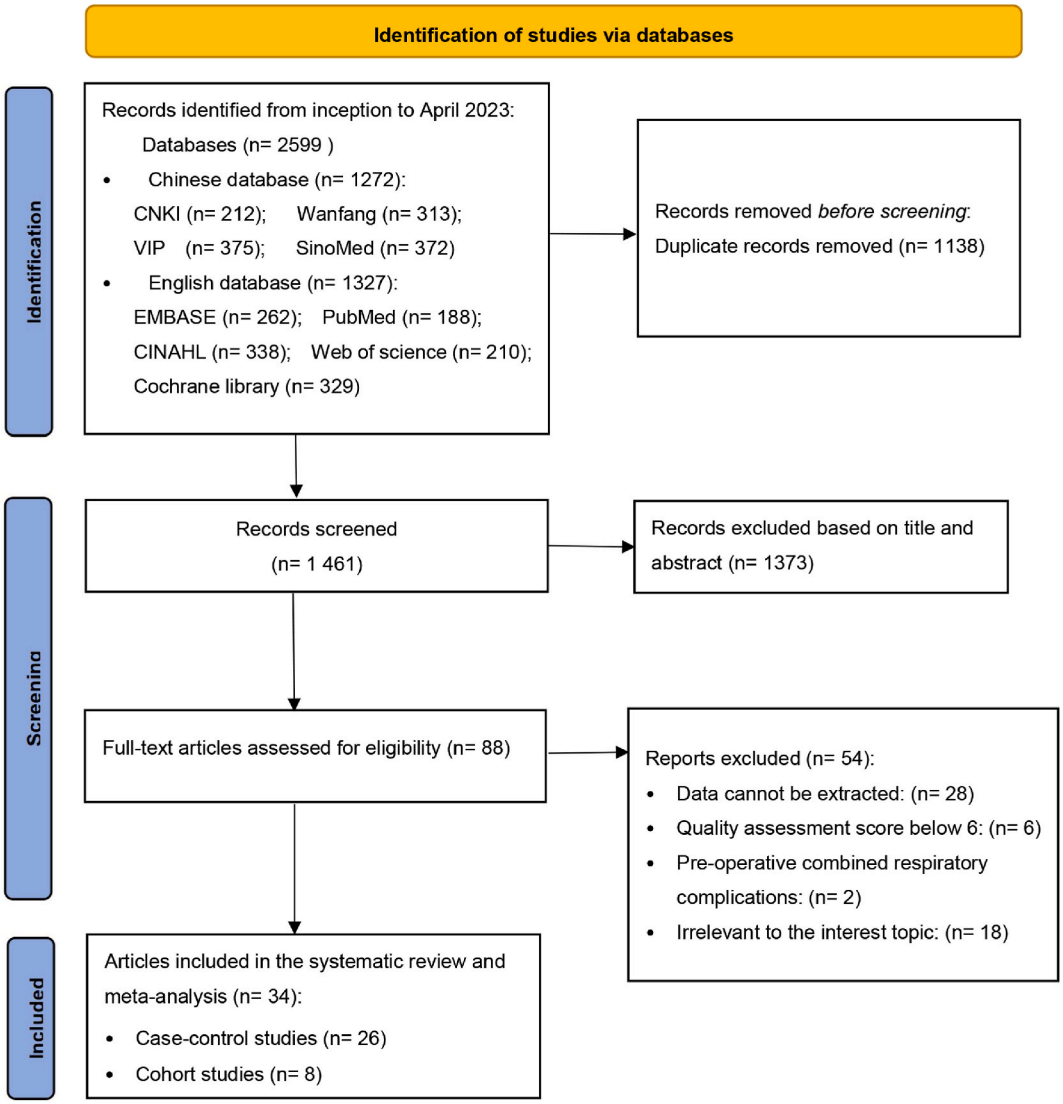

Fig. 1. PRISMA flow diagram for identification of inclusion studies.

3.3. Quality assessment

Although most studies did not mention controls for confounding factors, all 34 studies included in this review were of high quality (Supplementary Table S2).

3.4. Incidence of PPCs

The average incidence of PPCs was 18.4 % in all included studies.

3.5. Demographics factors

3.5.1. Age

Eighteen studies [22–25,29,30,32,35–38,40–43,46–48] investigated age as a risk factor for PPCs after lung cancer surgery. Random-effects model showed that older patients were more likely to develop PPCs ($I^2 = 97$ %, $p < 0.00001$, OR = 1.18, 95 % CI = 1.11 to 1.24, $p < 0.00001$) (Fig. 2). Nonetheless, variations across age groups were present among the different studies. We merged the data into two age subgroups for further subgroup analysis, individuals aged 60–69 years and those over 70 years, and it showed that age over 70 years had a significantly greater impact on PPCs (OR = 2.08, 95 % CI = 1.20 to 3.61, $p = 0.009$) (Supplementary Fig. S1A).

3.5.2. Sex

Ten studies revealed that male sex was a risk factor for PPCs after lung cancer surgery [11,22,27,31,34,37,39,42,45,48] ($I^2 = 61$ %, p=0.007, OR = 1.62, 95 % CI = 1.28 to 2.04, $p < 0.0001$) (Fig. 3, Supplementary Fig. S1B).

3.5.3. Smoking history

Sixteen studies [10,21,22,26,29,30,32,35–39,41,42,45,46] focused on this predictor. The pooled summary estimated concerning the history of smokers exhibited a significant association with the development of PPCs by random-effects model analysis ($I^2 = 98$ %, $p < 0.00001$, OR = 2.37, 95 % CI = 1.33 to 4.21, p=0.003) (Fig. 4). Two studies [10,41] that focused on current smoking indicated significant differences ($I^2 = 36$ %, $p < 0.21$, OR = 4.42, 95 % CI = 2.27 to 8.63, $p < 0.0001$) (Supplementary Fig. S1C).

3.6. Comorbidity

3.6.1. COPD

Twelve studies [11,23,25,28–30,32,35,37,41,42,47] measured the risk odds of COPD. Random-effect analysis was performed, and it showed that the incidence of PPCs was significantly higher in patients with COPD than those without COPD ($I^2 = 83$ %, $p < 0.00001$, OR = 2.47, 95 % CI = 1.80 to 3.40, $p < 0.00001$) (Fig. 5). To explore the origin of any heterogeneity, a sensitivity analysis was undertaken by exclusion of individual studies one by one. Notably, after excluding three studies [23,29,42], I^2 was reduced to 25 %. It still demonstrated statistical significance (OR = 2.21, 95 % CI = 1.89 to 2.59, $p < 0.00001$), indicating the robustness of the final results. However, they were not excluded ultimately as the reason of heterogeneity could not be identified (Supplementary Fig. S2A).

3.6.2. Diabetes

The findings from summarizing seven studies [23,25,39,42,47–49] indicated that diabetes was a risk factor for PPCs after surgery ($I^2 = 82$ %, $p < 0.0001$, OR = 1.56, 95 % CI = 1.07 to 2.27, $p = 0.02$) (Supplementary Fig. S2B).

3.7. Pulmonary function test indicators

Four studies [5,28,37,47] investigated the relationship between PEF and PPCs ($I^2 = 66$ %, $p = 0.03$). A meta-analysis using a random-effects model demonstrated that higher PEF was a protective factor against PPCs (OR 0.99, 95 % CI 0.98 to 0.99, $p = 0.0004$) (Supplementary Fig. S3A).

3.8. History of chemotherapy and/or radiotherapy

Five studies discussed this predictor [26,29,42,48,49]. It was a significant risk factor according to the random-effects model meta-analysis ($I^2 = 70$ %, $p = 0.010$, OR = 1.32, 95 % CI = 1.03 to 1.70, $p = 0.03$) (Supplementary Fig. S6A). A subgroup analysis was performed, and the results indicated that a history of preoperative radiotherapy and chemotherapy was a significant risk factor for PPCs ($I^2 = 0$ %, $p = 0.72$, OR = 1.45, 95 % CI = 1.26 to 1.67, $p < 0.00001$) (Fig. 6). The findings of the fixed-effects model used for sensitivity analysis showed consistency, indicating the reliability of the results (Supplementary Fig. S6A).

Table 1
Characteristics of included studies.

Author (year)	Country	Study design	Type of study	Sample size	Populations	Surgery type	Diagnostic criteria for PPCs	Incidence of PPCs	Risk factors
Kim HE et al., 2021 [21]	Korea	Case-control study	Retrospective	Case = 27 Control = 95	Patients with stage IIIA NSCLC	VATS and thoracotomy	Clavien-Dindo	22.10 %	③④⑯
Jeong WG et al., 2021 [22]	Korea	Case-control study	Retrospective	Case = 51 Control = 211	Patients with stage I and stage II NSCLC	VATS and thoracotomy	EPCO	19.50 %	①②③⑦⑪⑯⑲㉗㉘㊷
Wang X et al., 2021 [23]	China	Case-control study	Retrospective	Case = 54 Control = 298	Patients with NSCLC	Total thoracoscopic surgery	Unclear	15.30 %	①⑤⑥㉝
Zhang YY et al., 2021 [24]	China	Case-control study	Retrospective	Case = 30 Control = 65	Patients with NSCLC	VATS	STS/ESTS	31.60 %	①④㉒㉝
Chen DD et al., 2021 [25]	China	Case-control study	Prospective	Case = 68 Control = 230	NSCLC in the elderly	VATS	literature review	22.80 %	①⑤⑥⑬⑲㊴
Mao X et al., 2021 [5]	China	Case-control study	Retrospective	Case = 34 Control = 90	Patients with NSCLC	Unclear	literature review	27.00 %	⑬⑰⑱
Yao L et al., 2021 [26]	China	Case-control study	Retrospective	Case = 112 Control = 614	lung cancer patients	VATS	literature review	15.43 %	③⑯⑳㉗㉝㊵㊸
Cao C et al., 2020 [27]	America	Case-control study	Retrospective	Case = 141 Control = 947	Primary lung cancer	RATS	Clavien-Dindo	13.00 %	②⑯⑱㉘㊹
Chen CY et al., 2020 [28]	China	Case-control study	Retrospective	Case = 29 Control = 121	lung cancer patients	Thoracoscopic surgery and thoracotomy	STS/ESTS	19.30 %	⑥⑰⑱
Che Q et al., 2020 [29]	China	Case-control study	Retrospective	Case = 55 Control = 60	Patients with NSCLC	Thoracoscopic lobectomy	literature review	47.83 %	①③⑥⑰㉕㉝㊵㊶
Liu Y et al., 2019 [30]	China	Case-control study	Prospective	Case = 49 Control = 249	lung cancer patients	Unclear	Unclear	16.44 %	①③⑥㉙㉚㊶
Zhang YX et al., 2019 [31]	China	Case-control study	Retrospective	Case = 65 Control = 76	Patients with post-operative NSCLC co-infection of the lungs	Thoracoscopic surgery and minimally invasive surgery	CSRD/ATS/ERS	46.10 %	②㉞㊲
Ma J et al., 2019 [32]	China	Case-control study	Retrospective	Case = 51 Control = 203	Patients with NSCLC	VATS	Self-defined	21.65 %	①③⑥㉕㊺
Yang R et al., 2019 [33]	China	Case-control study	Retrospective	Case = 181 Control = 548	lung cancer patients	VATS or RATS	literature review	24.80 %	④㉗㉝㉟

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Table 1 (*continued*)

Author (year)	Country	Study design	Type of study	Sample size	Populations	Surgery type	Diagnostic criteria for PPCs	Incidence of PPCs	Risk factors
Kaufmann KB, 2019 [15]	Germany	Case-control study	Retrospective	Case = 114 Control = 262	Patients with lung cancer undergoing VATS for bilobectomy, lobectomy, or segmentectomy.	VATS	EPCO	30 %	⑱㉓㉕㉜
Im Y, 2019 [6]	Korea	Case-control study	Retrospective	Case = 52 Control = 436	Patients aged >70 years with normal spirometry who underwent curative lung resection for stage I and II NSCLC	VATS	Expert consensus	10.7 %	④⑪㉗㊷
Haruaki H et al., 2018 [34]	Japan	Case-control study	Retrospective	Case = 119 Control = 218	Patients aged 80 and above with lung cancer	VATS	NCD	35.3 %	②⑬㉕㉘
Agostini PJ et al., 2018 [10]	America	Case-control study	Prospective	Case = 21 Control = 264	patients who underwent single lobectomy for pulmonary malignancies	VATS	MGS	7.4 %	①③
Li H et al., 2018 [35]	China	Case-control study	Prospective	Case = 55 Control = 261	lung cancer patients	Thoracoscopic surgery and thoracotomy	Clavien-Dindo	17.40 %	①③⑥㉙㉚㊶
Li J et al., 2018 [36]	China	Case-control study	Retrospective	Case = 43 Control = 298	lung cancer patients	Thoracotomy	literature review	13.40 %	①③⑮⑯⑱㉗
Zhou K et al., 2017 [37]	China	Case-control study	Retrospective	Case = 75 Control = 358	Primary NSCLC	Thoracoscopic surgery and thoracotomy	EPCO	17.32 %	①②③⑥⑰㉕㉖
Huang J et al., 2017 [38]	China	Case-control study	Retrospective	Case = 79 Control = 121	Patients with stage 1 and 2 lung cancer	Thoracoscopic surgery and thoracotomy	Unclear	39.50 %	①③⑦⑱㉕㉖㉗
Takahashi Y et al., 2016 [39]	Japan	Case-control study	Retrospective	Case = 82 Control = 265	Patients with malignant tumors of the lung	A small thoracotomy	literature review	23.60 %	②③⑤⑯⑱㉔㊱㊹
Lee JY et al., 2011 [40]	Korea	Case-control study	Retrospective	Case = 26 Control = 391	Lung cancer surgery patients	VATS	literature review	6.2 %	①④⑬㉛
Agostini P, 2010 [41]	Britain	Case-control study	Prospective	Case = 34 Control = 200	lung cancer surgery patients	VATS	MGS	14.5 %	③④⑥㊷
Ferguson MK, 2009 [42]	America	Case-control study	Retrospective	Case = 1028 Control = 6863	Patients with primary lung cancer who have undergone lung resection	Unclear	Self-defined	13 %	①②③⑤⑥⑧⑨⑩⑭⑯⑱㉗㊵㊷㊹
Dai Q et al., 2022 [43]	China	Cohort study	Retrospective	Case = 16 Control = 58	Primary lung cancer patients	VATS	Self-defined	21.60 %	①㉑
Okada S et al., 2022 [44]	Japan	Cohort study	Retrospective	Case = 29 Control = 159	Elderly patients undergoing surgery for NSCLC	Thoracoscopic surgery and thoracotomy	Clavien-Dindo	15.4 %	㉕㊻
Shinya T et al., 2021 [45]	Japan	Cohort study	Retrospective	Case = 61 Control = 410	Primary lung cancer patients	VATS	Clavien-Dindo	12.9 %	②③⑬

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Table 1 (*continued*)

Author (year)	Country	Study design	Type of study	Sample size	Populations	Surgery type	Diagnostic criteria for PPCs	Incidence of PPCs	Risk factors
Yang GQ et al., 2021 [46]	China	Cohort study	Retrospective	Case = 70 Control = 94	Patients with post-operative NSCLC co-infection of the lungs	Unclear	Self-defined	42.68 %	①③⑬㉔㊳
Lai Y et al., 2018 [47]	China	Cohort study	Prospective	Case = 144 Control = 581	Patients with NSCLC	Thoracoscopic surgery and thoracotomy	STS/ESTS	19.86 %	①⑤⑥⑧⑰⑱㉕㉝
Kim ES et al., 2016 [11]	Korea	Cohort study	Prospective	Case = 113 Control = 230	Patients with COPD in combination with lung cancer	Open approach or a thoracoscopic approach	literature review	16.60 %	②④⑥⑫⑯㉕
Ceppa DP, 2012 [48]	America	Cohort study	Retrospective	Case = 8439 Control = 4531	patients having undergone an anatomic pulmonary resection by either thoracotomy or VATS	Thoracoscopy surgery and thoracotomy	STS database	20.34 %	①②⑤⑧⑨⑭⑯⑱㉖㊵
Berry MF, 2010 [49]	America	Cohort study	Retrospective	Case = 164 Control = 176	lung cancer surgery patients	Thoracoscopy surgery and thoracotomy	STS database	48 %	⑤⑭⑯⑱㉖㊵

Notes: Type of risk factors: 1. General factors: ①Age; ②Sex; ③Smoking history; ④Body Mass Index(BMI); **2. Comorbidity:** ⑤Diabetes; ⑥Chronic Obstructive Pulmonary Disease (COPD); ⑦Pulmonary emphysema; ⑧Coronary heart disease (CHD); ⑨Congestive heart failure; ⑩Renal insufficiency; ⑪Interstitial lung abnormality (ILA); ⑫Phthisis; **3. Pre-operative examination: (1) Pulmonary function tests:** ⑬Forced Expiratory Volume in the first Second/Forced Vital Capacity (FEV1/FVC%); ⑭Forced Vital Capacity (FVC%); ⑮Maximal voluntary ventilation (MVV%); ⑯Diffusing Capacity of the Lung for Carbon Monoxide (DLCO); ⑰Peak Expiratory Flow (PEF); ⑱Forced Expiratory Volume in One Second (FEV1); **(2) Other examinations:** ⑲Serum albumin; ⑳Albumin-to-globulin ratio (AGR); ㉑Pre-operative colonization of bacteria; ㉒Peak preoperative oxygen pulse percentage (VO_2/HR%-pred, %); ㉓Preoperative partial pressure of oxygen (paO_2)≤60 mmHg; ㉔CDl4/HLA-DR; **4. Surgical factors:** ㉕Surgery duration; ㉖Surgery approach; ㉗Type of resection; ㉘Pathology type; ㉙Tumor pN Staging; ㉚Tumor pT staging; ㉛Intraoperative red blood cell transfusion; ㉜Intraoperative crystalloid infusion rate; ㉝Intraoperative bleeding volume; ㉞Intraoperative lymph node dissection; ㉟Length of anesthesia; ㊱Extended resection; **5. Other predictors:** ㊲Number of days for using perioperative antibiotics; ㊳Urban living; ㊴Asthenia; ㊵History of chemotherapy and/or radiotherapy; ㊶Poor adherence to respiratory rehabilitation; ㊷American Society of Anesthesiologists score ≥2 (ASA); ㊸Acute Physiology and Chronic Health Evaluation II ≥ 10 (APACHE II); ㊹Eastern Cooperative Oncology Group score standard >1 (ECOG); ㊺Chest drainage on postoperative day 1 (POD1); ㊻ Prognostic nutritional index (PNI).

Abbreviations: Video-assisted Thoracic Surgery (VATS); robotic-assisted thoracoscopic surgery (RATS); Non-Small Cell Lung Cancer (NSCLC); European Perioperative Clinical Outcome definitions (EPCO); the European Society of Thoracic Surgeons/The Society of Thoracic Surgeons (ESTS/STS); Chinese Society of Respiratory Diseases (CSRD); Melbourne Group Scale (MGS); American Thoracic Society Guidelines for the diagnosis of hospital-acquired pneumonia/European Respiratory Society (ATS/ERS); The National Clinical Database (NCD).

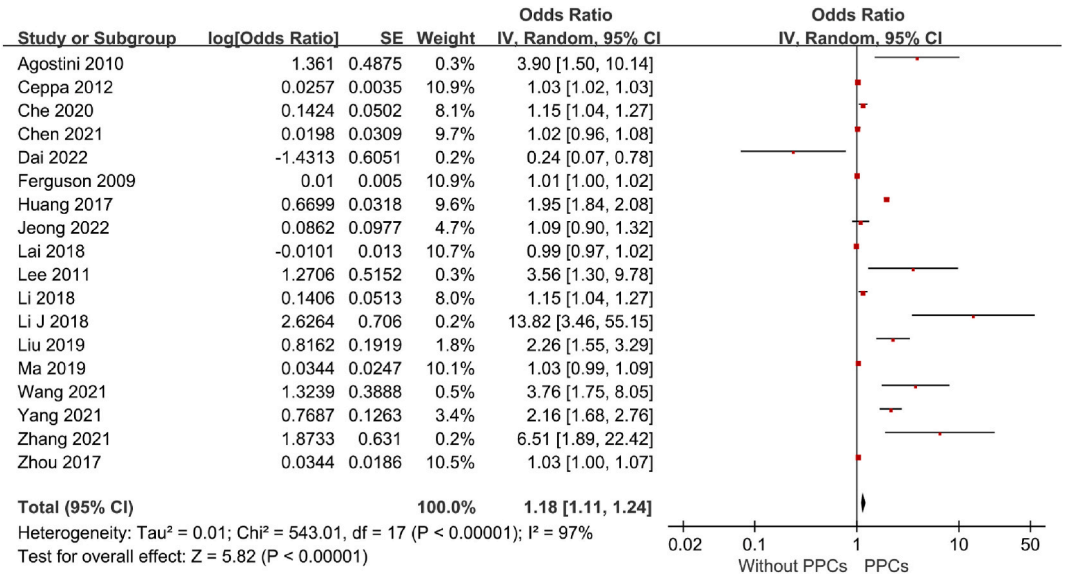

Fig. 2. Forest plot of age as a risk factor for postoperative pulmonary complications (PPCs) after lung cancer surgery.

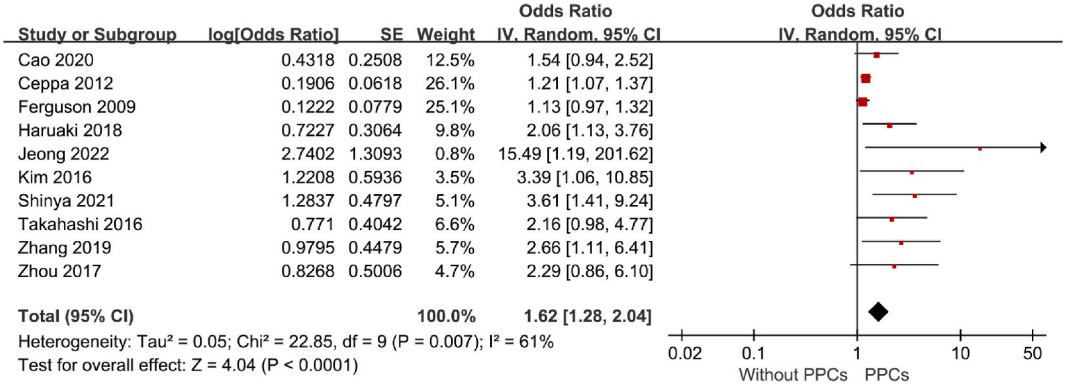

Fig. 3. Forest plot of estimated risk factors of postoperative pulmonary complications (PPCs) after lung cancer surgery associated with sex.

3.9. Poor adherence to respiratory rehabilitation

Three studies [29,30,35] investigated this indicator. Our results demonstrated that low compliance with respiratory rehabilitation was a significant risk factor for PPCs after surgery ($I^2 = 56$ %, $p = 0.10$, OR = 1.64, 95 % CI = 1.17 to 2.30, $p = 0.004$) (Supplementary Fig. S6B).

3.10. ECOG>1

The summarized results of three studies [27,39,42] indicated that ECOG >1 was a significant risk factor for PPCs after surgery ($I^2 = 0$, $p = 0.50$, OR = 1.37, 95 % CI 1.04 to 1.80, $p = 0.02$) (Supplementary Fig. S6C).

3.11. Operative factors

3.11.1. Type of lung resection and surgery approach

Although seven studies [6,22,23,26,33,36,38,42] evaluated the impact of the type of lung resection on PPCs, the data could not be combined due to the various surgical resection methods used in different studies. These studies reported that pneumonectomy [6,26,36,38,42], lobectomy [22,33,36,38], bilobectomy [6,33,42], sleeve resection [26,42], segmentectomy [26,33], and wedge resection [26] might be the cause of PPCs. Four studies [37,38,48,49] explored the impact of different surgical approaches on PPCs. Unfortunately, the data could not be combined due to the different categories used in these studies. Two studies [48,49] demonstrated a reduction of PPCs risk through Video-assisted Thoracoscopic Surgery (VATS) in comparison to open thoracotomy.

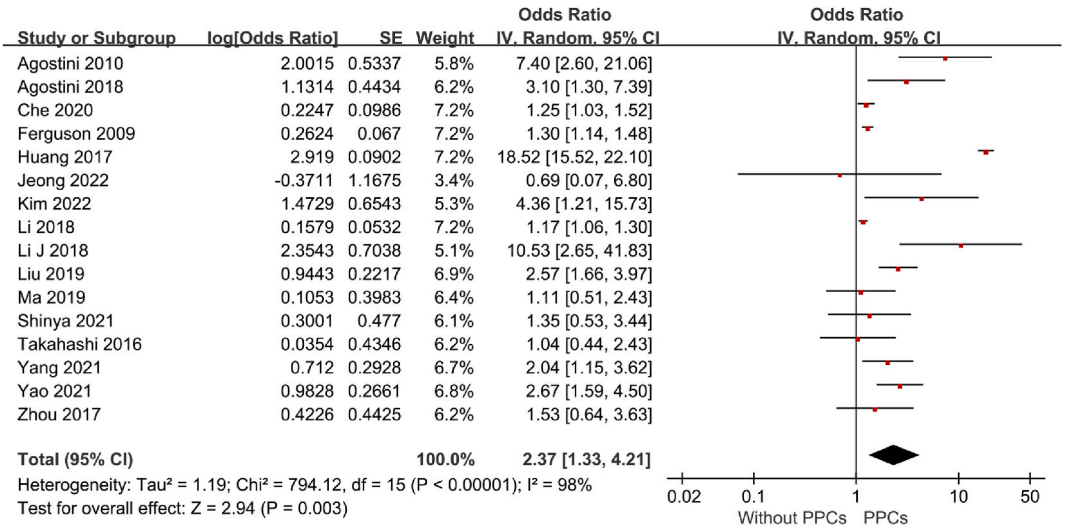

Fig. 4. Forest plot of the estimated risk factor of postoperative pulmonary complications (PPCs) after lung cancer surgery associated with a smoking history.

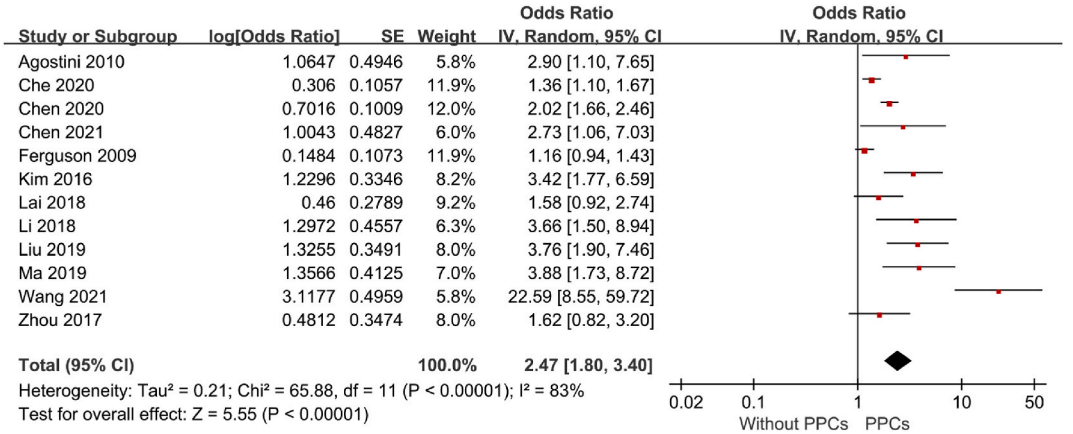

Fig. 5. Forest plot of the estimated risk factor of postoperative pulmonary complications (PPCs) after lung cancer surgery associated with chronic obstructive pulmonary disease (COPD).

3.11.2. Duration of surgery

Nine studies [11,15,29,32,34,37,38,44,47] indicated that longer duration of surgery was associated with a significantly higher probability of PPCs ($I^2 = 97$ %, $p < 0.00001$, OR = 1.07, 95 % CI = 1.04 to 1.10, $p < 0.00001$) (Supplementary Fig. S5C).

3.11.3. Tumor stage

Two studies [30,35] discussed the relationship between tumor staging and PPCs in patients who underwent lung cancer surgery ($I^2 = 65$ %, $p = 0.006$, OR = 4.29, 95 % CI = 2.59 to 7.13, $p < 0.00001$) (Supplementary Fig. S5A). A higher incidence of PPCs was observed in patients with advanced pTN stages, pT4 ($I^2 = 0$, $p = 0.94$, OR = 2.38, 95 % CI = 1.25 to 4.52, $p = 0.008$), and pN3 ($I^2 = 0$, $p = 0.58$, OR = 11.81, 95 % CI = 5.52 to 25.27, $p < 0.00001$) (Supplementary Fig. S5A). Specifically, subgroup analyses revealed a higher incidence of PPCs in patients with advanced pT stages including pT2-pT4 ($I^2 = 0$, $p = 1.0$, OR = 2.25, 95 % CI = 1.52 to 3.34, $p < 0.0001$), as well as in advanced pN stages including pN1-pN3 ($I^2 = 0$, $p = 0.86$, OR = 8.09, 95 % CI = 5.19 to 12.59, $p < 0.00001$) (Supplementary Fig. S5A).

3.11.4. Intraoperative bleeding volume

Six studies [23,24,26,29,33,47] summarized the relationship between intraoperative bleeding and PPCs. Sensitivity analyses suggested that intraoperative bleeding over 100 ml was a significant risk factor for PPCs ($I^2 = 53$ %, p=0.09, OR = 2.13, 95 % CI = 1.16 to 3.88, $p = 0.01$) (Supplementary Fig. S5B).

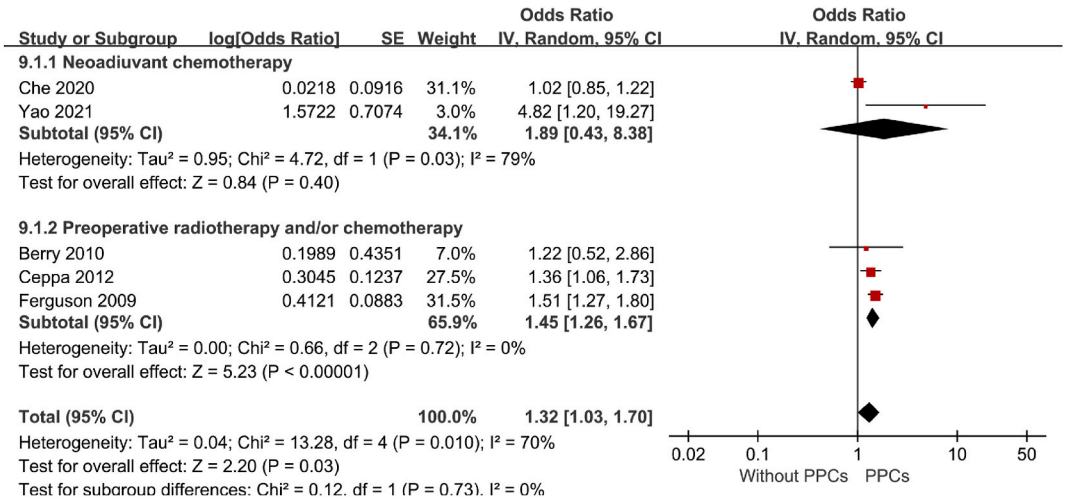

Fig. 6. Forest plot of the history of chemotherapy and/or radiotherapy and the risk of postoperative pulmonary complications (PPCs) after lung cancer surgery subgroup analysis.

3.12. Other predictors

Sixteen studies [6,11,15,22,24–26,31,32,36,39,40,42–44,46] reported other risk factors which could not be summarized in the meta-analysis. Except for the type of pathology, the following risk factors were found to be statistically significant: comorbidities such as renal insufficiency, interstitial lung abnormality (ILA), maximal voluntary ventilation (MVV%), intraoperative lymph node dissection, CDl4/HLA-DR, urban living, chest drainage on POD_1, number of days using perioperative antibiotics, extended resection, surgical approach, phthisis, AGR, acute physiology and chronic health evaluation II score (APACHE II)$\geq$10, asthenia, peak VO_2/HR %-pred (%), preoperative $paO_2 \leq 60$ mmHg, preoperative colonization of bacteria, intraoperative red blood cell transfusion, intraoperative crystalloid infusion rate, and PNI. There were no significant differences among related factors, such as ASA$\geq$3, congestive heart failure, coronary heart disease (CHD), emphysema, FEV1, FEV1/FVC%, FVC%, DLco, BMI, albumin ($p > 0.05$) (Supplementary Table S3).

3.13. Publication bias

The funnel plot showed a significant publication bias for smoking history, but not for other risk factors (Supplementary Fig. S7).

4. Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis conducted to assess the pooled prevalence and risk factors for PPCs after lung cancer surgery. All the 34 included studies were of high quality rendering the current findings relatively reliable. We summarized 46 risk factors for the development of PPCs after lung cancer surgery. However, only 22 risk factors were used to calculate effect sizes. Our updated and extended results showed that PPCs were significantly associated with age, sex, smoking history, COPD, diabetes mellitus, PEF, operative time, intraoperative bleeding volume, tumor TNM staging, history of chemotherapy and/or radiotherapy, poor compliance with respiratory rehabilitation, and ECOG>1.

In our study, age was identified as a significant risk factor for PPCs. Age $\geq$70 years was a significant risk factor for PPCs, consistent with the guidelines [50]. This could be because elderly patients suffer from impaired immune function, malnutrition, frailty, or the development of comorbidities, which could negatively impact their post-operative prognosis [44]. However, the included studies rarely stratified the age groups, and it was difficult to analyze the impact of different age groups on PPCs. Therefore, future studies should categorize the patients based on their age into separate groups to determine the impact of age on PPCs after lung cancer surgery.

Smoking is an independent risk factor for PPCs [51]. Interestingly, the incidence of PPCs was higher in men (OR 1.32, $p = 0.008$) (Supplementary Fig. S1B) in the meta-analysis, probably due to the higher number of male smokers [52]. Regrettably, a subgroup analysis targeting smoking status (smoker vs non-smoker) in males and females was unavailable due to the absence of extracted data in the included studies. Consequently, future research should explore the potential correlation between smoking and the risk of PPCs, specifically among males. Smoking severely impairs the antimicrobial function of alveolar macrophages and their ability to decrease inflammation, as well as the ability of cilia to clear foreign bodies/pathogens from the airway [53,54]. Another study showed that smoking cessation six weeks before surgery appeared to reduce the incidence of PPCs compared to current smokers [55]. Therefore, the guidelines [50] recommend quitting smoking at least four weeks before surgery. However, the possible effects of smoking duration and dose on PPCs remain unclear, which needs to be further investigated.

Our study also identified COPD and pulmonary hypofunction as risk factors [7,56] for PPCs. This might be due to the impaired gas

exchange and the reduced ability of cilia to remove bacteria from the airways in these patients [11]. Therefore, respiratory rehabilitation is of particular importance. Preoperative respiratory muscle training can restore and improve lung function [57] and has been shown to significantly improve respiratory function in the early postoperative period and reduce the risk of PPCs [58]. However, some patients hardly comply with pulmonary rehabilitation because of postoperative incision pain and a lack of awareness about respiratory function exercises [30]. Furthermore, our study showed that poor compliance with perioperative respiratory rehabilitation was strongly associated with the development of PPCs. A study showed that poor adherence to perioperative respiratory exercises increased the risk of PPCs by 92.3 % [29]. In contrast, PEF is a sensitive indicator of the degree of airway patency and the strength of the respiratory muscles and was found to be a protective factor in our study [28]. It has been shown that the risk of PPCs reduced by 40.7 % when preoperative PEF increased by 1 L/min [29]. Therefore, more attention should be paid to increasing the clinical adherence to perioperative pulmonary rehabilitation of the patients in future.

Diabetes is a systemic disorder of glucose metabolism that leads to the development of PPCs in several ways [23]. Chronic hyperglycemia impairs leukocyte function and reduces monocyte chemotaxis and adhesion, which in turn reduces the ability of the body's immune system to engulf and kill pathogenic microorganisms [38]. Therefore, patients with diabetes are prone to infections [59]. However, these studies are controversial [60,61]. For example, a study showed that patients in the diabetic group had a higher rate of PPCs than those in the control group (28.1 % vs. 20.7 %) [60], whereas another study reported no significant negative effect [61]. Although the effect of diabetes on PPCs in lung cancer remains unclear, glycemic control is essential in patients with diabetes.

Our meta-analysis also showed that tumor TNM staging, operative time, and intraoperative bleeding volume were important risk factors for PPCs. The pN stage of lung cancer tumors reflects the extent of lymph node metastasis and is a strong predictor of poor prognosis [62]. It has been reported that the more advanced the pN stage of lung cancer, the higher the risk of PPCs [30,35]. The guidelines clearly pointed out that the TNM stage determines the surgical method; the higher the stage of TNM, the more complex the treatment [63], the wider the lymph node dissection, the greater the intraoperative trauma and bleeding, and the longer the operative time. Our study also demonstrated that intraoperative bleeding over 100 ml was a significant risk factor for PPCs. It is known that the greater the removal of lung tissue, greater the trauma and higher the lung volume reduction [64]. However, we could not conduct a meta-analysis due to the heterogeneity among these studies. Pneumonectomy and lobectomy were both identified as important risk factors in five [6,26,36,38,42] and four studies [22,33,36,38], respectively. To our understanding, the utilization of minimally invasive procedures such as VATS could potentially reduce the occurrence of PPCs [48,49]; only four studies [37,38,48,49] concentrated on this predictive factor, with two of them [48,49] demonstrating that VATS contributes to a reduction in the risk of PPCs. Significantly, none of these studies evaluated the potential risk of PPCs associated with robotic-assisted thoracoscopic surgery (RATS). Moreover, few included studies focused on the impact of diverse analgesic methods on PPCs. Hence, it is necessary to determine which surgical resection method, surgical approach, and analgesic method has the lowest risk for PPCs in the future.

Moreover, some patients require pre-operative radiotherapy and chemotherapy to increase the likelihood of surgical resection [65] and their impact cannot be ignored.

The ECOG score is a dimension of health status that reflects a patient's mobility and ability to perform regular activities [66] and has a prognostic and predictive effect on lung cancer [67]. Higher ECOG scores correlate with deteriorating health and quality of life [68]. However, it is difficult to distinguish whether a high score is caused by comorbidities or the cancer itself [69]. In our study, only three studies that discussed the ECOG performance status were included, and their association was unclear because of the limited number of participants.

Currently, there is no consensus regarding the definition of pulmonary complications. Seventeen studies used different scales to define PPCs after surgery in this systematic review, including the Society of Thoracic Surgeons (STS), European Society of Thoracic Surgeons (ESTS/STS), Melbourne Group Scale (MGS), Chinese Society of Respiratory Diseases (CSRD), American Thoracic Society Guidelines for the diagnosis of hospital-acquired pneumonia/European Respiratory Society (ATS/ERS), Clavien-Dindo, and European Perioperative Clinical Outcome (EPCO). Differences between these criteria may have limited the internal validity of our study. Thus, a dedicated criterion for PPCs should be established through multidisciplinary collaborations.

There are some limitations of this meta-analysis. First, we formulated strict inclusion and exclusion criteria; only cohort studies and case-control studies were included. None of the included studies had a randomized controlled trial (RCT) study design; this design may not be suitable and feasible for investigating etiology or natural history of disease due to ethical concerns related to disease development and progression. Most of the included studies were retrospective, which might have introduced some bias in the results of this meta-analysis especially since certain parameters were not available. Second, heterogeneity still remained among the studies. Although we attempted to explore several sources of heterogeneity, other confounding factors still existed. Third, most of the included studies were conducted in Asia, and only seven studies were conducted in Western countries, which could potentially cause bias. Finally, we did not include studies in languages other than English and Chinese, nor did we analyze them.

Future research should focus on conducting large-scale observational and multicenter studies on diverse populations to comprehensively identify the potential risk factors and establish prediction models for PPCs after lung cancer surgery that could aid in the timely screening of high-risk groups without increasing costs. Finally, effective prevention and treatment strategies for PPCs should be developed to prevent the over-treatment of the patients leading to wastage of medical resources.

5. Conclusion

In conclusion, we found that the TNM stage, COPD, smoking history, poor compliance with respiratory rehabilitation, sex, diabetes, intraoperative bleeding volume, ECOG >1, history of chemotherapy and/or radiotherapy, age, and duration of surgery were significantly associated with a higher risk of PPCs after lung cancer surgery. In contrast, higher PEF was a protective factor. These findings

suggest that early screening and identification of individuals at high risk for PPCs before lung cancer surgery would contribute to effective prevention.

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Data statement

Raw data from the studies in the paper can be obtained by contacting the authors via email.

CRediT authorship contribution statement

Ting Deng: Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation. **Jiamei Song:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation. **Jinmei Tuo:** Writing – review & editing, Methodology. **Yu Wang:** Writing – review & editing, Methodology. **Jin Li:** Writing – review & editing, Methodology. **Lorna Kwai Ping Suen:** Writing – review & editing, Methodology. **Yan Liang:** Writing – original draft, Methodology, Investigation, Data curation. **Junliang Ma:** Writing – review & editing, Methodology. **Shaolin Chen:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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