Association of chronic obstructive pulmonary disease and postresection lung cancer survival: a systematic review and meta-analysis

Lan-Eng Tan, Razak A M, Chor-Shen Lim

Institute of Respiratory Medicine, Kuala Lumpur General Hospital, Kuala Lumpur, Malaysia

Correspondence to
Dr Chor-Shen Lim, Institute of Respiratory Medicine, Kuala Lumpur General Hospital, Jalan Pahang, Kuala Lumpur 50590, Malaysia; chorshen@ntu.edu.tw

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ABSTRACT

Patients with lung cancer often have chronic obstructive pulmonary disease (COPD), but the impact of COPD on postresection survival of patients with lung cancer is unclear. This study evaluated the impact of COPD on survival of patients with lung cancer following pulmonary resection. Databases searched included PubMed, Cochrane, and Embase until March 2016. Study outcomes were overall survival and pulmonary complication rate (pneumonia, bronchial fistula, and prolonged mechanical ventilation). 6 studies with a total of 3761 patients were included. The presence of COPD was associated with lower overall survival, increased frequency of pneumonia, and prolonged mechanical ventilation (p values ≤0.001). COPD had no influence on bronchial fistula development (p=0.098). In summary, COPD was associated with poorer survival and an increased frequency of certain adverse events in patients with lung cancer following resection.

Significance of this study

What is already known about this subject?

- Chronic obstructive pulmonary disease (COPD) is a common coexisting disease in patients with lung carcinoma.
- Both diseases independently increase mortality and combined disease is usually inoperable.
- Smoking is a major risk factor for these patients.

What are the new findings?

- Presence of COPD in patients with lung cancer is associated with lower overall survival, increased pneumonia frequency, and prolonged mechanical ventilation.
- COPD does not seem to affect the development of bronchial fistula in patients with lung cancer.
- This association between two diseases was apparent for all stages of lung cancer.

How might these results change the focus of research or clinical practice?

- The actual impact of COPD severity on postresection lung cancer survival remains unclear and is yet to be determined. Regional cohort studies are needed to investigate the extent of environmental and/or cultural influences on COPD and lung cancer survival.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) and lung cancer are common diseases, both of which are associated with high mortality.[1 2] Lung cancer is the leading cause of cancer death among men in the USA and worldwide. It is also the leading cause of cancer death in the USA and the second leading cause of cancer death among women worldwide.[3] COPD is the third leading cause of death in the USA and the fourth leading cause of death worldwide.[2 4] Smoking is a common risk factor for COPD and lung cancer and may be one of the reasons that patients with lung cancer and a history of smoking often have COPD.[1 3 5] In addition, there appears to be a non-confounding association of COPD and lung cancer development which may reflect the similar molecular mechanisms underlying the development of these two diseases.[6 7]

Patients with lung cancer and COPD are often considered to be inoperable, and pulmonary complications following lung cancer surgery are a major cause of death for patients who also have COPD.[1 8–10] Respiratory failure following resection can result from the reduced respiratory reserve due to COPD, and associated complications of lung resection, such as hypoventilation, hypercapnia, and hypoxia.[9] These complications can worsen overall survival (OS) and quality of life.[1 11 12] Several studies found that the prognosis of patients with lung cancer with COPD is poorer than that of patients with lung cancer without COPD.[13–15] However, the impact of COPD on perioperative and long-term prognosis and incidence of pulmonary complications after surgical resection for patients with lung cancer is unclear.

The objective of this study was to evaluate the impact of COPD on the survival of patients with lung cancer who had pulmonary resection. We evaluated OS and the incidence of certain pulmonary adverse events associated with lung resection in patients with COPD and lung cancer.

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MATERIAL AND METHODS

Search strategy

The databases of PubMed, Cochrane, and Embase were searched until March 2016 for studies that assessed the impact of COPD on the survival of patients with lung cancer who underwent lung resection. Studies were identified using the following search terms: chronic obstructive pulmonary disease, COPD, lung cancer, resection, surgical, prognosis, prognostic, predictor, and predicting. Randomized controlled trials, two-arm prospective studies, and retrospective studies were included. All included studies compared patients with lung cancer with and without COPD. Studies had to include patients who had undergone pulmonary resection and the OS and/or mortality rate assessed during a follow-up period. Non-English publications, letters, comments, editorials, case reports, proceedings, personal communication, and cohort studies were excluded from the analysis.

Data extraction

The following data were extracted: first name of the author, study design, cancer stage, method of COPD diagnosis, comparator groups, number of patients, and mean age, gender, and smoking status. Also extracted were the findings for presurgical and postsurgical resection, per cent predicted forced expiratory volume in 1 s (FEV_1), 5-year OS, rate of mortality, and the frequency of certain pulmonary adverse events (ie, pneumonia, bronchial fistula, and prolonged mechanical ventilation). Two independent reviewers extracted the data and a third reviewer was consulted to resolve any uncertainties.

Quality assessment

We assessed the quality of each study using an 18-item modified Delphi checklist.[16] This checklist included quality control measures such as a clearly stated hypothesis, follow-up data, eligibility standards, and length of follow-up. Quality assessment was also performed by two independent reviewers and a third reviewer was consulted for any uncertainties.

Data analysis

The primary end point was OS and was reported as HR. Adverse events were reported as OR. A χ^2-based test of homogeneity was performed and the inconsistency index (I^2) and Q statistics were determined. If the I^2 statistic was >50%, a random-effects model (DerSimonian and Laird) was used. Otherwise, fixed-effects models (inverse-variance method) were employed. For OS, an HR>1 favored the non-COPD group, whereas for adverse events an OR>1 favored the COPD group. Pooled effects were calculated and a two-sided p value <0.05 was considered to indicate statistical significance. Sensitivity analysis was carried out for the OS using the leave-one-out approach. Publication bias analysis was not performed because the number of studies was too few to detect an asymmetric funnel.[17] All analyses were performed using Comprehensive Meta-Analysis statistical software, V.2.0 (Biostat, Englewood, New Jersey, USA).

RESULTS

Literature search

Of the 268 studies that were initially identified, 249 were eliminated for not investigating the influence of COPD on survival and complications postresection in patients with lung cancer (figure 1). An additional nine studies were excluded for being single-arm studies (n=2), not being designed for evaluating the influence of COPD in patients with lung cancer who underwent resection surgery (n=4), or not reporting outcomes of interest (eg, data of survival analysis) (n=3). Eleven studies were included in the systematic review[8 15 18–26] and six[15 18–20 22 26] articles presenting data for OS were included in the meta-analysis.

Systematic review

Study characteristics

Of the 11 studies included in the systematic review, 9 were retrospective in design (table 1). The remaining two were observational non-randomized prospective studies.[8 23] Across the studies, the stage of lung cancer ranged from stage I to IV. Patients with COPD were diagnosed by a physician,[15] Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria,[19 20 22–26] the European Respiratory Society criteria,[8] the American Thoracic Society (ATS) guidelines,[21] or the criteria of Buist *et al* (1994).[18 27] Most of the studies compared the survival outcomes between patients with lung cancer with and without COPD. The sizes of the studies were variable; the number of patients with lung cancer with moderate/severe COPD ranged from 48 to 1370, and the number of patients with lung cancer in the non-COPD or mild COPD comparator arm ranged from 122 to 1558. Across the studies, the age of patients was between about 60 and 70 years, and in general there was a higher percentage of males than females in the study populations. The mean smoking index ranged from 19.6 to 66.1 pack-years.

In the one study that reported both preoperative and postoperative per cent predicted FEV_1, there was a decrease in per cent predicted FEV_1 following resection both in patients with lung cancer with and without COPD (table 2). Analysis of survival across the studies was diverse, and included progression-free survival (PFS),[15] recurrence-free survival (RFS),[24 26] disease-free survival (DFS),[22] relapse-free survival (RLFS),[23] and OS.[15 18–20 22] Generally, OS rate was lower for lung cancer patients with moderate/severe COPD (range 24–77%) compared with those without or mild COPD (range 41–92%). The highest OS rate for both groups of patients was seen in the study of Sekine *et al*[22] which included patients with early pathological stage IA (pIA) lung cancer. All other studies included patients with ≥pIA lung cancer. Four studies reported overall mortality,[8 15 18 22] which was higher in patients with COPD (range 5.3–68%) than in those without (range 1.1–51%).

Meta-analysis

Overall survival

Six of the 11 studies provided HR for OS and were included in the meta-analysis.[15 18–20 22 26] Together, the six studies included 3761 patients. The HR findings across the six studies showed heterogeneity (Q statistic=11.51, I^2=56.55%, p=0.042); therefore, a random-effects model was used. The result of the meta-analysis found that COPD

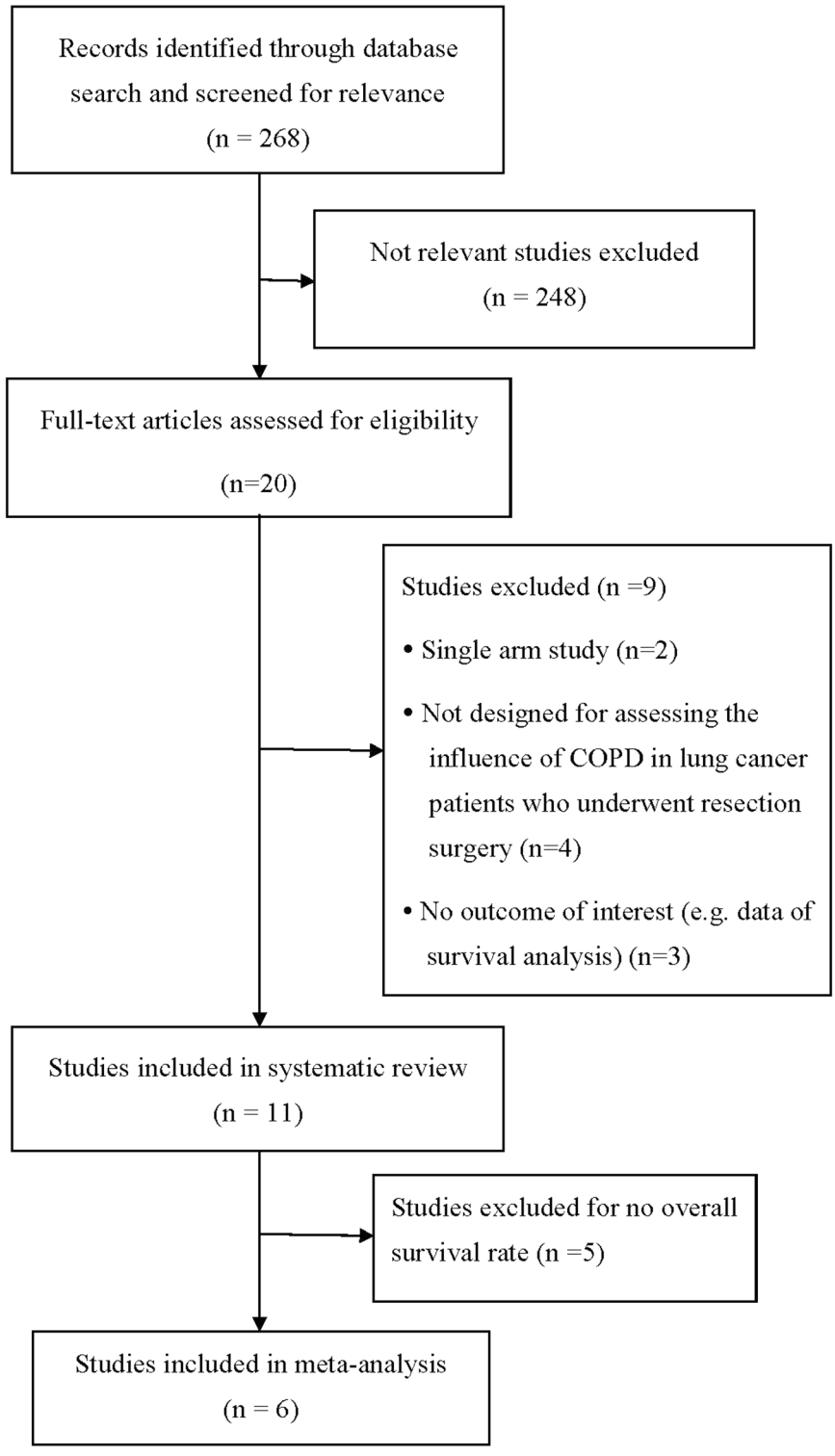

Figure 1 Flow diagram of study selection. COPD, chronic obstructive pulmonary disease.

was associated with OS ($p<0.001$, figure 2A). The pooled HR (1.63, 95% CI 1.29 to 2.06) indicated that the patients with COPD were likely to have lower survival compared with patients who did not have COPD.

Adverse events

Four studies[18 19 22 25] reported a frequency of pneumonia and prolonged mechanical ventilation; three studies reported a frequency of bronchial fistula and were included in the meta-analysis. Analysis of the studies indicated that there was no evidence of heterogeneity on the incidence for any one of these three outcomes among the three studies (Q statistic=3.528, $I^2=14.97\%$, $p=0.317$ for pneumonia; Q statistic=0.97, $I^2=0\%$, $p=0.616$ for bronchial fistula; and Q statistic=3.442, $I^2=12.83\%$, $p=0.328$ for prolonged mechanical ventilation); hence, a fixed-effect

Table 1 Summary of basic characteristics of selected studies

First author	Study design	Pathological cancer stage	Diagnostic criteria of COPD	Comparison	Number of patients	Age (years)	Male (%)	Smoking index (pack-year)
Qiang[24]	Retrospective	I-III	GOLD	Non-COPD /mild COPD	373	<65: 142 (38%) ≥65: 231 (62%)	59	NA
				Moderate/severe COPD	48	<65: 13 (27%) ≥65: 35 (73%)	81	
Yoshida[25]	Retrospective	IA	GOLD	Non-COPD	181	64.1±10.2	47	19.6
				COPD	62	70.3±7.7	89	66.1
Kuo[26]	Retrospective	I	GOLD	Non-COPD	122	63.9±11.5	66.3	NA
				COPD	59			
Zhai[15]	Retrospective	IA-IIB	Self-reported, physician-diagnosed	Non-COPD	572	67.1±10.1	49	46.1 (31.3)
				COPD	330	66.8±9.7	43	60.2 (37.1)
Sekine[19]	Retrospective	pIA-IV	GOLD	Non-COPD /mild COPD	1187	Non-COPD: 62.5 ±10.3 Mild: 69.1±7.7	62	52 (28.4)
				Moderate/severe COPD	274	Moderate: 67.6±7.1 Severe: 67.9±5.7	93	54.5 (30.0)
Kondo[20]	Retrospective	IA-IV	GOLD	Non-COPD smoker	374	65.9±9.6	91	49.1 (54.7)
				COPD smoker	157	70.6±7.1	96	63.0 (37.8)
Nakajima[21]	Retrospective	pIA-IV	ATS COPD guideline	Control	1425	63.8 (10–90)	67	0–250*
				Severe COPD	36	68.0 (55–78)	100	20–110*
Sekine[22]	Retrospective	pIA	GOLD	Non-COPD	362	61.5±10.2	49	21.0 (27.2)
				COPD	80	67.2±6.5	91	52.9 (32.0)
Licker[8]	Prospective	pIA-IV	European Respiratory Society criteria	Non-COPD /mild COPD	728	NA	NA	NA
				Moderate/severe COPD	494			
Lo′pez-Encuentra[23]	Prospective	pIA-IV	GOLD	No COPD	1558	NA	88	46
				COPD	1370		97	54.5
Sekine[18]	Retrospective	I-IV	COPD guideline†	Non-COPD	166	63.6±9.7	57	NA
				COPD	78	65.3±7.9	74	

Data presented as mean (SD) unless otherwise stated.
*Data presented as range.
†Diagnosis of COPD as described in Buist *et al* (1994)[18 27]
ATS, American Thoracic Society; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; NA, not available; pIA, pathological stage IA.

Table 2 Summary of outcomes of selected studies

First author	Comparison	Pre-FEV_1 (% predicted)	Post-FEV_1 (% predicted)	30-day mortality	Overall mortality	5-year PFS/RFS/DFS/RLFS	HR for PFS/RFS/DFS/RLFS	5-year OS	HR for OS*
Qiang[24]	Non-COPD/mild COPD	Non-COPD: 110 (16.7) Mild COPD: 82.9 (18.5)	NA	NA	NA	75% for RFS	1.72 (1.09 to 2.92) for RFS	NA	NA
	Moderate/severe COPD	69.9 (9.4)				46% for RFS			
Yoshida[25]	Without COPD With COPD	NA	NA	NA	NA	81% for RLFS For RLFS GOLD-1: 67% GOLD-2/3: 61%	For RLFS GOLD-1: 1.69 (0.79 to 3.45); GOLD-2/3: 2.20 (1.07 to 4.48)	NA	NA
Kuo[26]	Without COPD With COPD	NA	NA	NA	NA	58% for RFS 33% for RFS	1.98 (1.29 to 3.02) for RFS	NA	1.88 (1.20 to 2.94)
Zhai[15]	Without COPD With COPD	NA	NA	NA	39% 48%	61% for PFS 50% for PFS	1.67 (1.19 to 2.22) for PFS	69% 54%	1.41 (1.13 to 1.75)
Sekine[19]	Non-COPD/mild COPD Moderate/severe COPD	90 (17.1) 54.7 (8.1)	NA	0.6% 1.5%	NA	NA	NA	61% 51%	2.77 (1.78 to 4.33)
Kondo[20]	Non-COPD smoker COPD smoker	80.0 (5.9) 61.9 (7.1)	NA	NA	NA	NA	NA	58% 41%	1.23 (0.92 to 1.63)
Nakajima[21]	Control Severe COPD	2.23 (0.97–4.47)† 1.24 (0.72–1.73)†	NA	0% 8.3%	NA	NA	NA	59% 24%	NA
Sekine[22]	Non-COPD COPD	94.6 (17.8) 71.9 (15.0)	NA	0 0	13% 34%	88% for DFS 77% for DFS	2.08 (1.19 to 3.64) for DFS	92% 77%	1.96 (1.141 to 3.366)
Licker[8]	Non-COPD/mild COPD Moderate/severe COPD	88 (87 to 89)‡ 49 (48 to 50)‡	NA	15% 3%	1.1% 5.3%	NA	NA	NA	NA
Lo′pez-Encuentra[23]	No COPD COPD	70.6 (16.2)	NA	NA	NA			45% 43%	NA
Sekine[18]	Non-COPD COPD	79.6 (16.3) 48.7 (10.9)	NA	NA	51%§ 68%§			41% 36%	1.35 (0.82 to 2.21)

Data presented as mean (SD) unless otherwise stated.
*Data presented as HR (95% CI).
†Data presented as median (range).
‡Data presented as mean (95% CI).
§Five-year overall mortality.
COPD, chronic obstructive pulmonary disease; DFS, disease-free survival; FEV_1, forced expiratory volume in 1 s; GOLD, Global Initiative for Chronic Obstructive Lung Disease; NA, not available; OS, overall survival; PFS, progression-free survival; RFS, recurrence-free survival; RLFS, relapse-free survival.

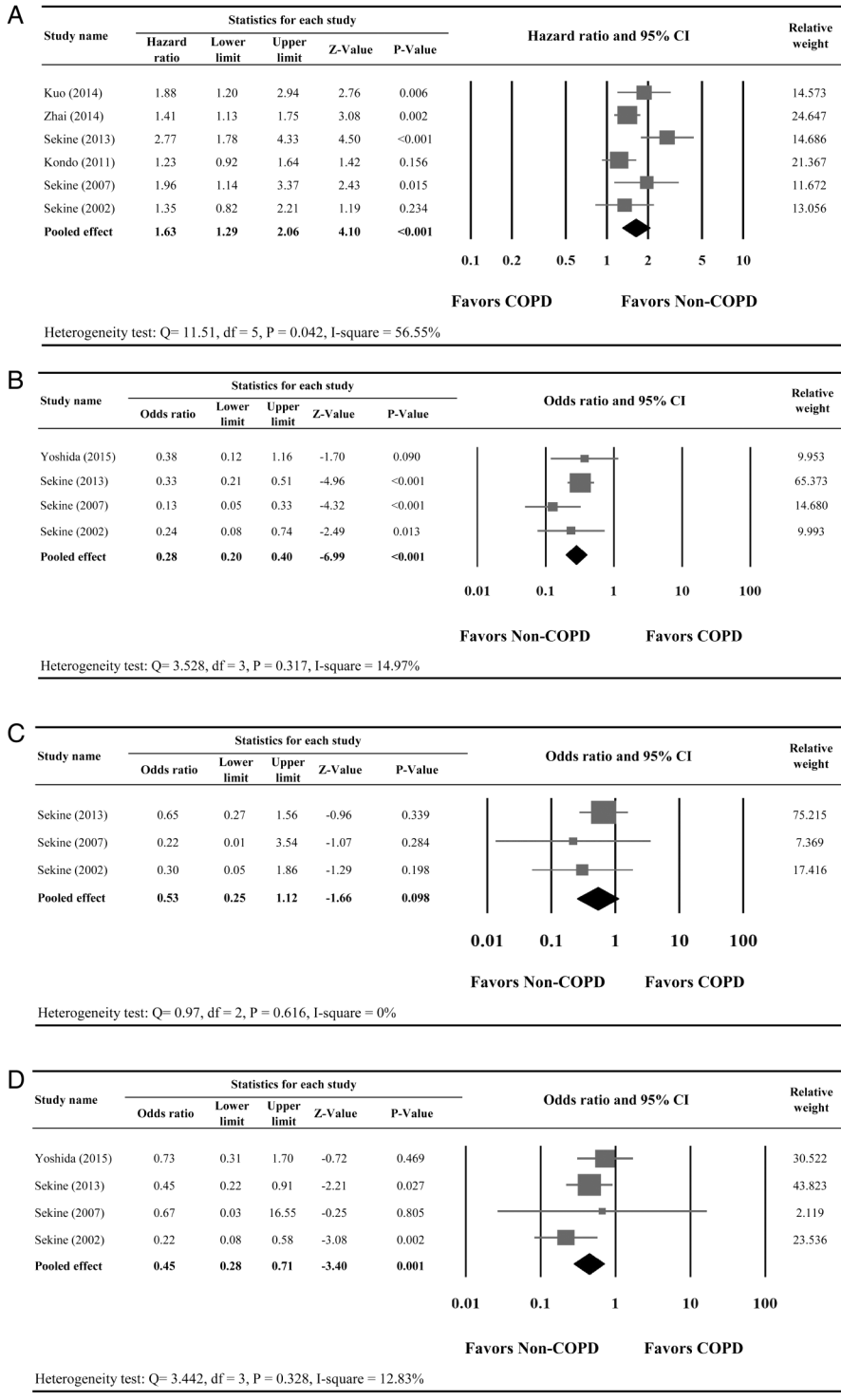

Figure 2 Forest plots showing results for the meta-analysis. Forest plots for (A) overall survival, and the frequency of (B) pneumonia, (C) bronchial fistula, and (D) prolonged mechanical ventilation are shown. COPD, chronic obstructive pulmonary disease.

model was used for each meta-analysis. For pneumonia, the overall OR was 0.28 (95% CI 0.20 to 0.40, p<0.001, figure 2B), indicating that the incidence of pneumonia in patients with lung cancer with COPD was significantly higher than in patients with lung cancer who did not have COPD. The overall OR for bronchial fistula was 0.53 (95% CI 0.25 to 1.12, p=0.098; figure 2C), suggesting that there was no significant difference in the incidence of bronchial fistula between lung cancer with or without COPD. The pooled OR for prolonged mechanical ventilation revealed that the incidence of the use of mechanical ventilation was lower in patients with lung cancer without COPD compared with those with COPD (0.45, 95% CI 0.28 to 0.71; p=0.001; figure 2D).

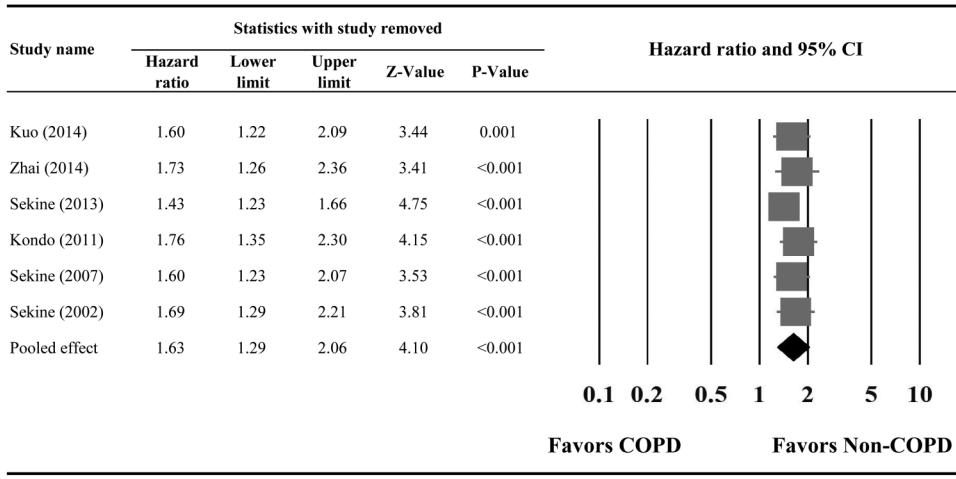

Figure 3 Sensitivity analysis for the meta-analysis of the overall survival. COPD, chronic obstructive pulmonary disease.

Sensitivity analysis

Sensitivity analysis was performed using the leave-one-out approach in which the meta-analysis of the OS was performed with each study removed in turn (figure 3). The direction and magnitude of combined estimates did not vary markedly with the removal of each study, indicating that the data were not overly influenced by any one of the studies and that the results are reliable (table 3).

Quality assessment

Using the Delphi checklist, the studies were found to be of good quality (table 4).

However, only 2 of the 11 studies were multicentre and reported competing interest and source of funding.[8 23] In addition, none of the studies clearly described the intervention or reported what other interventions were used. None of the studies reported the outcome measured both before and after the intervention.

The quality assessment was similar when evaluating only the six studies included in the meta-analysis. None of the included studies were multicentre; the intervention and any co-interventions were not clearly described, and no outcomes were measured prior to intervention. Only the study of Zhai *et al*[15] reported the number of patients lost to follow-up and disclosed author conflict of interest and funding source. The study of Sekine *et al*[19] did not clearly define the outcome measures. Three of the five studies reported adverse events.[19]

DISCUSSION

This meta-analysis investigated the influence of COPD on the survival and risk of complication in patients with lung cancer following tumor resection. The pooled population consisted of patients with stage I–IV cancer, and was not limited to patients with non-small cell lung cancer (NSCLC). We found that the presence of COPD was associated with lower OS and an increased frequency of pneumonia and prolonged mechanical ventilation (p values ≤0.001). The presence of COPD did not influence the rate of bronchial fistula development in these patients with lung cancer (p=0.098). Sensitivity and quality analysis indicated that the findings are reliable.

The poorer survival of patients with lung cancer with COPD following resection likely reflects the deterioration of pulmonary function due to the lung resection and the presence of COPD. It may also reflect the increased risk of death due to acute COPD exacerbation.[1] In addition, patients with lung cancer with COPD following resection have an increased rate of postoperative complications including pneumonia and the need for a tracheostomy.[22] They also have an increased risk of cancer recurrence.[22]

Several factors, such as severity of COPD and the stage and histology of the lung cancer of patients, may influence the survival rate.[1] The six studies included in the meta-analysis differed with respect to cancer stage, tumor histology, and severity of COPD. Lung cancer stage might affect the outcome of survival analysis. Zhai *et al*,[15] in a retrospective study, evaluated the impact of COPD on overall and PFS in patients with early-stage NSCLC. They found that the 5-year OS in patients with COPD was significantly lower than in patients without COPD. The 5-year PFS was also lower for patients with COPD. Sekine *et al*,[18] in a retrospective chart review, included patients with NSCLC stages I–IV. They found no difference in the overall 5-year survival rate between patients with NSCLC with or without COPD (36.2% vs 41.2%, respectively; p=0.1023). They also found that there was no difference in survival among patients with different stages of lung cancer. Two other retrospective studies from the same group, that is, Sekine *et al*[22] and Sekine *et al*,[19] evaluated the influence of COPD on long-term survival in patients with lung cancer following surgical resection. One study evaluated patients with stage IA lung cancer[22] and the other included stages pIA-IV.[19] Regardless of the lung cancer stage, both studies found that patients with COPD had poorer overall long-term survival following resection surgery than patients without COPD. Therefore, for the patients with COPD, the effect of lung cancer stage on survival after surgery requires further study. The poorer long-term survival for patients with lung cancer with COPD resulted from a higher rate of tumor recurrence and metastasis,[22] possibly suggesting that COPD itself is impacting cancer progression.

Table 3 Summary of adverse events of selected studies for meta-analysis

First author	Comparison	Pneumonia		Bronchial fistula		Prolonged mechanical ventilation		Empyema		Tracheotomy	
		N (%)	OR (95% CI)	N (%)	OR (95% CI)	N (%)	OR (95% CI)	N (%)	OR (95% CI)	N (%)	OR (95% CI)
Yoshida[25]	Non-COPD	7 (3.9)	0.38 (0.12 to 1.16)	NA	NA	20 (11.1)	0.73 (0.31 to 1.70)	2 (1.1)	0.22 (0.04 to 1.35)	4 (2.2)	0.06 (0.01 to 0.27)
	COPD	6 (9.7)	Reference	NA	NA	9 (14.5)	Reference	3 (4.8)	Reference	10 (16.1)	Reference
Sekine[19]	Non-COPD/mild COPD	56 (4.7)	0.33 (0.21 to 0.51)	20 (1.7)	0.65 (0.27 to 1.56)	24 (2.0)	0.45 (0.22 to 0.91)	21 (1.8)	0.97 (0.36 to 2.59)	79 (6.7)	0.52 (0.34 to 0.80)
	Moderate/severe COPD	36 (13.1)	Reference	7 (2.6)	Reference	12 (4.4)	Reference	5 (1.8)	Reference	33 (12.0)	Reference
Sekine[22]	Non-COPD	8 (2.3)	0.13 (0.05 to 0.33)	1 (0.3)	0.22 (0.11 to 3.54)	1 (0.3)	0.67 (0.03 to 16.55)	1 (0.3)	0.67 (0.03 to 16.55)	11 (3.0)	0.25 (0.10 to 0.62)
	COPD	12 (15.4)	Reference	1 (1.3)	Reference	0 (0)	Reference	0 (0)	Reference	9 (11.3)	Reference
Sekine[18]	Non-COPD	5 (3)	0.24 (0.08 to 0.74)	2 (1.2)	0.30 (0.05 to 1.86)	7 (4.2)	0.22 (0.08 to 0.58)	NA	NA	NA	NA
	COPD	9 (11.5)	Reference	3 (3.8)	Reference	13 (16.7)	Reference	NA	NA	NA	NA

COPD, chronic obstructive pulmonary disease; NA, not available.

Severity of COPD might be another factor that affects the outcome of survival analysis. Sekine *et al*[19] found that the 5-year survival was influenced by COPD severity, such that patients with severe COPD had the lowest survival rate. The study stratified patients into (1) non-COPD: forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) $\geq 70\%$, (2) mild COPD: $FEV_1/FVC < 70\%$ and $FEV_1 \geq 80\%$ predicted, (3) moderate COPD: $FEV_1/FVC < 70$ and $50\% \leq FEV_1 < 80\%$ predicted, and (4) severe COPD: $FEV_1/FVC < 70$ and $30\% \leq FEV_1 < 50\%$ predicted. The 5-year survival for the non-COPD, mild, moderate, and severe COPD were 61.5%, 50.2%, 55.3%, and 25.1%, respectively ($p<0.001$). The study of Licker *et al*[8] also stratified COPD patients' severity as: (1) normal/mild: $FEV_1 \geq 70\%$, (2) moderate: FEV_1 from 50% to < 70%, and (3) severe: $FEV_1 < 50\%$. The overall mortality seen in the Licker *et al* study was lower for non-COPD /mild COPD (1.1%) compared to moderate/severe COPD (5.3%). They found that patients with severe COPD had the highest risk for 30-day mortality (OR=1.9, 95% CI 1.2 to 3.9).

The severity of COPD may influence postoperative 30-day mortality compared with those without COPD. In the study of Sekine *et al*,[19] patients with severe COPD had higher 30-day mortality (8.3%) compared with those with no (0.5%), mild (1.1%), or moderate (0.4%) COPD.[16] Another study found that the 30-day mortality was 8.3% for patients with severe COPD compared with 0% for those without COPD.[21] In contrast, the study of Sekine *et al*[22] found no difference in the 30-day postoperative mortality between patients with or without COPD (0% each). It is unclear if perioperative mortality fully accounts for the differences in 5-year survival observed between patients with and without COPD. We were unable to perform a meta-analysis to evaluate the influence of COPD severity on 30-day mortality, since in the two studies that reported 30-day mortality postsurgery there were no patient deaths within that time frame (ie, a zero 30-day mortality rate).

COPD may also impact postoperative complications. The studies of Sekine *et al*[19 22] found that the rate of pneumonia and tracheostomy were higher in patients with COPD. In addition, the study of Sekine *et al*[19] found that a higher grade (more severe) COPD was associated with higher rates of postoperative complications ($p \leq 0.05$). The findings of the above studies are consistent with our results that the rate of pneumonia and prolonged mechanical ventilation for patients with lung cancer were higher in those with COPD than those without COPD.

A number of factors that might have confounded our results include cardiovascular comorbidity, smoking status preresection and postresection, and the criteria for excluding patients from resection. Among those factors, smoking status is an important variable when assessing COPD. The three main causes of smoking-related deaths are cardiovascular disease, lung cancer, and COPD.[27] In smokers with COPD, the rate of development of lung cancer is about fourfold higher than that of the control group of smokers without COPD, and the 5-year survival rate in COPD smokers is poorer than that in non-COPD smokers in terms of both overall and cancer-related mortality.[20] We attempted to perform a meta-regression analysis to assess and to adjust the effects of potential covariates (smoking

Table 4 Quality assessment of included studies

First Author (year)	Qiang (2015)	Yoshida (2015)	Kuo (2014)	Zhai (2014)	Sekine (2013)	Kondo (2011)	Nakajima (2009)	Sekine (2007)	Licker (2006)	Lo′pez-Encuentra (2005)	Sekine (2002)
Is the hypothesis/aim/objective of the study clearly stated in the abstract, introduction, or methods section?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Are the characteristics of the participants included in the study described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were the cases collected in more than one centre?	N	N	N	N	N	N	N	N	Y	Y	N
Are the eligibility criteria (inclusion and exclusion criteria) to enter the study explicit and appropriate?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were participants recruited consecutively?	Y	Y	N	Y	Y	Y	Y	N	Y	Y	Y
Did participants enter the study at a similar point in the disease?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the intervention clearly described in the study?	N	N	N	N	N	N	N	N	N	N	N
Were additional interventions (co-interventions) clearly reported in the study?	N	N	N	N	N	N	N	N	N	N	N
Are the outcome measures clearly defined in the introduction or methods section?	Y	Y	Y	Y	N	Y	N	Y	Y	Y	Y
Were relevant outcomes appropriately measured with objective and/or subjective methods?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were outcomes measured before and after intervention?	N	N	N	N	N	N	N	N	N	N	N
Were the statistical tests used to assess the relevant outcomes appropriate?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the length of follow-up reported?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the loss to follow-up reported?	N	N	N	Y	N	N	Y	N	N	N	N
Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Are adverse events reported?	N	Y	N	N	Y	N	N	Y	N	N	Y
Are the conclusions of the study supported by results?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Are both competing interest and source of support for the study reported?	Y	Y	N	Y	N	N	N	N	Y	Y	N

N, no; Y, yes.

index) on the meta-analysis estimates. However, this was not possible because Sterne *et al* (2011)[17] indicate that the power of meta-regression is limited when <10 studies are included. Only six of the included articles in our study reported an 'average smoking index (pack-year)', and one article reported a range of smoking index. In addition, smoking status was examined based on questionnaires completed by patients, which might reduce the validity of the outcome. Although we did not include an average smoking index (pack year) in our meta-analysis, smoking cessation in smokers on being diagnosed with lung cancer should be encouraged. A previous meta-analysis demonstrated that comparing to those who stopped smoking following a diagnosis of early stage lung cancer, those who continue to smoke was associated with a higher chance of recurrence, second primary tumor development, and an increased all-cause mortality.[28]

There are several limitations to this study that should be considered when interpreting the results. All six studies included in the meta-analysis were retrospective in design; none was the report of randomized controlled trials or prospective study, and three of the six were performed by the same group of investigators. One of these three latter studies investigated patients in the USA,[18] and two were designed studying a Japanese population.[19 22] Consequently, it is not clear how the findings from these two studies relate to other geographic regions and races. In addition, it is possible that some of the same patients were included in both Japanese studies. The patient populations differed across the six studies with respect to COPD severity and lung cancer stage and type. Our analysis did not evaluate how different COPD severity or stage of lung cancer might impact on the 5-year survival of patients with resectable lung cancer. Only two of the included studies[8 19] presented survival analysis stratified by COPD severity and the individual data were not sufficient to perform a meta-analysis. Lead time bias could influence survival in our studies. In other words, the screen-detected lung cancer and COPD may have an earlier date of diagnosis compared with non-screen-detected cases, and consequently a longer apparent survival.[29] In addition, non-screen-detected cases with no lead time might have more advanced lung cancer stage and COPD severity. Data for lead time are not available in our included articles. Several of the studies describe aspects of the clinical management of the patients. Difference in the management of patients and healthcare systems may also have impacted our results. Heterogeneity in the management of patients with COPD was found in our included studies. The studies reported by Sekine *et al* described the procedure of clinical management in detail; all participants with COPD were involved in a pulmonary rehabilitation programme perioperatively according to the severity of COPD. Incentive spirometry and nebulizing by distilled water with or without a bronchodilator were routinely encouraged for enhancing lung expansion and airway clearance for 1–2 weeks before and after surgery.[18 19 22] In the study of Licker *et al*,[8] prophylactic antibiotics were administered (cefuroxime 1.5 g per 8 hours for 24 hours), and Qiang *et al*[24] excluded patients who had received neoadjuvant therapy (chemotherapy and/or radiation therapy).

In conclusion, the meta-analysis found that COPD was associated with worse survival outcomes and higher incidences of pneumonia and prolonged mechanical ventilation in patients with lung cancer. Since COPD is linked with poorer survival and an increased frequency of certain adverse events in patients with lung cancer following resection, the prevention and management of COPD is a major issue when treating patients with lung cancer. More prospective multicentre studies from diverse geographic regions are necessary to further explore the connection between COPD and survival in patients with lung cancer.

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