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Airflow limitation and survival after surgery for non-small cell lung cancer: Results from a systematic review and lung cancer screening trial (NLST-ACRIN sub-study)

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ABSTRACT

Objective: Lung cancer remains the single greatest cause of cancer mortality where surgery for early stage non-small cell lung cancer achieves the greatest survival. While there is growing optimism for better outcomes with screening using annual computed tomography, the impact of co-existing airflow limitation on survival remains unknown.

To compare survival in non-small cell lung cancer patients undergoing surgery stratified according to the presence or absence of pre-surgery airflow limitation.

Materials and Methods: We undertook a systematic literature search of non-screen lung cancer that encompassed studies reported between January 1946 and January 2017. Full-text articles were identified following eligibility scoring, with data extracted and analysed using a standardised analytical method (PRISMA). The results of this systematic review in non-screen lung cancers were compared to real-world results from a lung cancer screening cohort (N = 10,054), where outcomes following surgery could be compared after stratification according to pre-surgery airflow limitation.

Results: In the systematic review, 6899 subjects were included from 10 studies; 7 were retrospective, 3 were prospective. Overall survival was 950 (44%) in 2144 people with COPD and 2597 (55%) from 4755 controls (unadjusted P value < 0.001). However, the overall meta-analysed random effects odds ratio for overall survival (N = 10) and 5-year survival (N = 4) comparing those with and without COPD was 0.91 (95% CI = 0.84–1.00) and 0.99 (95% CI = 0.79–1.24) respectively. There were no signs of significant heterogeneity (I^2 = 19.1%, P = 0.27) nor publication bias as assessed by funnel plot and Egger's test (P = 0.19). In the lung cancer screening sub-study of 10,054 screening participants we found no difference in 5-year survival in those with and without airflow limitation (84% and 81% respectively, P = 0.64).

Conclusion: Survival after surgery for non-small cell lung cancer is comparable between those with and without spirometry evidence of airflow limitation. This finding was replicated in lung cancer diagnosed during screening.

1. Introduction N = 3,733

Lung cancer is one of the leading causes of cancer-related deaths in the world. In 2012, lung cancer was responsible for approximately 1.6 million deaths worldwide [1]. Lung cancer may be broadly divided into small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC), with many distinct histology subtypes in the latter [2]. In contrast to SCLC, where chemotherapy provides the mainstay of treatment with mostly palliative intent, surgery is routinely performed in early stage NSCLC with a curative intent [2,3]. Despite this, patients with lung cancer typically have a poor prognosis, reflected by an overall 5-year survival rate as low as 15% [2]. This low rate of lung cancer survival can be attributed in the main to the advanced stage at diagnosis, advanced age with associated comorbidities, and with certain lung cancer histological types, characterised by aggressive biology and rapid progression despite therapy (e.g. SCLC).

While smoking is widely recognised as the leading risk factor for the development of lung cancer, studies show between 50–70% of lung cancer patients also suffer from chronic obstructive pulmonary disease (COPD) characterised by airflow limitation [4,5]. It has been shown that the presence of COPD confers a significant and independent risk for the development of lung cancer in both non-screened [6] and screened lung cancer cases [7]. While smokers with underlying COPD are at greater risk of getting lung cancer, they may also be at greater risk of

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dying following surgery where overall 5-year survival rates have been reported to vary between 35–70% [8,9]. This may be due to death from diseases other than lung cancer such as cardiovascular disease, respiratory disease or other cancers (i.e. competing risk of death) [10]. Alternatively, it may be due to higher peri-operative risk and poorer outcomes specific to lung cancer surgery in patients with COPD [3]. The question arises: "To what degree does pre-existing COPD lead to worse survival outcomes following surgery for NSCLC?"

To answer this question for unscreened lung cancers, we have undertaken a systematic review of published studies to examine the effect of pre-existing COPD on post-surgical survival in NSCLC. We have also looked at survival following surgery for NSCLC following screening in a subset of the National Lung Screening Trial (NLST), where baseline spirometry was routinely measured in screening centres affiliated with the American College of Radiology Imaging Network (ACRIN-NLST cohort, N = 10,054 subjects) [11,12]. The findings of these analyses have relevance to the differential benefits and harms of treating "operable" lung cancer in both the unscreened and screened clinical setting.

2. Methods

2.1. Search strategy and inclusion criteria for the systematic review

In order to correctly report the methods of this study, we used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [13]. A systematic literature search was performed in Ovid MEDLINE, EMBASE and the Cochrane Database of Systematic Reviews as well as Google Scholar. The search terms were

group 1: "non-small cell lung cancer/lung cancer, adenocarcinoma",

group 2: "chronic obstructive pulmonary disease/COPD/chronic bronchitis/pulmonary emphysema",

group 3: "spirometry/bronchospirometry", lung function, airflow limitation,

group 4: "pneumonectomy/lobectomy/resection/removal" and

group 5: "mortality/survival".

Our searches were limited to a publication date from 1946 until January 2017 and no language restriction was applied in these initial searches.

The abstracts of all publications found by the literature search were then read and assigned a score from 1 to 5 which represented the number of keyword groupings that each abstract contained. Publications which included keywords from at least 3 groups and which mentioned all of "*non-small cell lung cancer/lung cancer/ adenocarcinoma*", "*pneumonectomy/lobectomy /resection/removal*" and were then further analysed by reading the full-text article. Eligibility for further analysis was checked by two reviewers (RJH, JK) and a third reviewer (RPY) resolved any discrepancies. Any reasons for exclusion of studies based on their abstracts were recorded in a spread-sheet.

Any retrospective, prospective or randomised controlled study that met all of the following 6 checklist criteria were eligible for inclusion into the systematic review. The criteria were "*non-small cell lung cancer (stages I-II)*", "*spirometry criteria for COPD*", "*results stratified by COPD/ lung function*", "*preoperative lung function*", "*lung surgery*" and "*mortality/ survival (1–10 years)*". When we encountered the same patient population in separate publications, only the publication with the most recent data was included. Finally, for non-English publications, we attempted to contact the authors for an English translation. If an English translation was unattainable, this study was excluded from the final analysis. Eligibility for the systematic review was assessed by two reviewers (RJH and JK) and a third reviewer (RY) resolved any discrepancies. The reason for the final exclusion of a study not to be included was recorded in a database which comprehensively recorded the full-text articles using a summary and checklist-based approach (summarised in Fig. 1).

2.2. Data extraction for the systematic review

Data extraction was performed using a standardised record form. Two reviewers independently extracted information from each study included in the analysis (RJH, JK). Any disagreements or disparities that arose were resolved by a third reviewer (RPY). In terms of study characteristics, we extracted the author name, year of publication, country in which the study was performed, study design, follow-up period, number of patients (including the number of cases and controls), how the cases of COPD were defined, the overall survival rates for cases and controls and the proportion of patients with stage I-II NSCLC. We also included the odds ratio and 95% confidence interval for COPD and its effect on survival post-lung cancer surgery which was calculated on quantitative analysis. The key data extracted is shown in Table 1.

2.3. Statistical analysis for the systematic review

The data was analysed according to standard methods for a systematic review [13]. For published studies meeting the eligibility criteria, survival according to COPD status was summarized as odds ratios with 95% confidence interval calculated for each study and meta-analysed using a random effects DerSimonian and Laird model. The results of this analysis was plotted using a forest plot with study heterogeneity reported as the I^2 statistic and publication bias formally assessed by inspecting funnel plots for asymmetry and Egger's Test. Any p-value less than 0.05 was considered statistically significant. Meta-analysis was performed using STATA version 10.1 (Metan, Statacorp, College Station, Texas, USA). Fisher's Exact test and confidence intervals for proportions were calculated using www.openepi.com (accessed 17/6/2019).

2.4. Outcomes from a subset of the NLST-ACRIN substudy

We used data from a subset of the NLST, where subjects attending NLST screening sites affiliated to the American College of Radiology, Imaging Network (ACRIN) underwent routine pre-bronchodilator spirometric assessment [11]. In this sub-cohort of 10,054 high risk smokers randomised to CT or CXR screening, 395 lung cancers were identified after a mean follow-up of 6.4 years. Of these 328 were diagnosed within 5 years and 289 were NSCLC based on histology and 182 with NSCLC underwent surgical resection. All participants in this screening trial were followed for outcomes including death and cause of death [11].

3. Results

3.1. Literature search and study characteristics in the systematic review

Using the aforementioned search strategy (Fig. 1), we identified 288 papers including 89 duplicates that were removed from further analyses. The abstracts of these 199 papers were screened for the presence of at least 3 of the keyword groupings which excluded a further 116 papers. The full-text articles of the remaining 83 papers were acquired, scrutinised and assessed for further inclusion by applying our 6 requirement criteria outlined above. A further 73 papers were excluded on the grounds of not meeting these inclusion requirement criteria,- insufficient data for specified endpoints, duplication of data and non-English language. Ten papers published between 2001 and 2015 were included into the final systematic review [8,9,14–21] with follow-up ranging between 3 and 10 years (Table 1). This included four papers reporting 5 year survival. A flowchart summarising the process for including papers into the systematic review is shown in Fig. 1.

Of these 10 studies, 7 were retrospective, 3 were prospective and there were no randomised controlled trials. The combined study population from all 10 studies was 6899 operable non-small cell lung

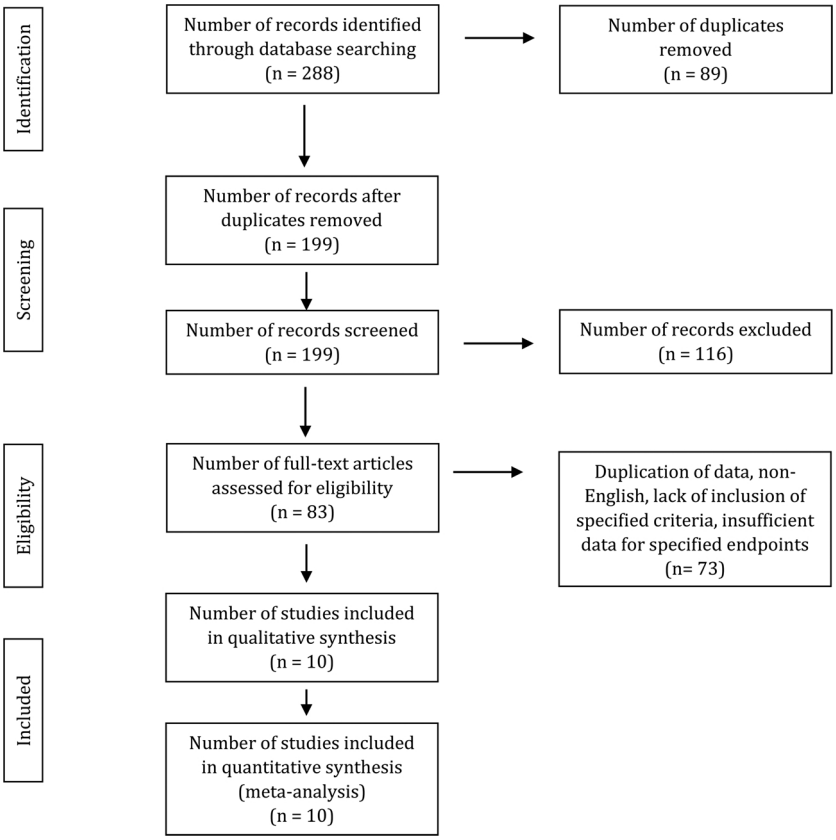

Fig. 1. Flow chart of the selection process for studies included in the systematic review.

cancer cases. Due to variation in the spirometry criteria defining COPD, a sensitivity analysis was performed where studies using comparable criteria were grouped according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD criteria, FEV1/FVC < 0.70 n = 7 and other non-GOLD criteria, n = 3) [22]. Survival in only prospective studies (N = 3) was also compared.

3.2. Analysis of overall survival in the systematic review

Overall survival (N = 10 studies) was 950 (44%) in 2144 people with COPD and 2597 (55%) from 4755 controls (unadjusted P value < 0.001). The overall random effects odds ratio for overall survival following lung cancer surgery, comparing those with and without COPD was 0.91 (95% CI [0.84, 1.00]; heterogeneity testing p = 0.27; I^2 = 19.1%). Survival in those studies reporting 5 year data (N = 4 studies) was 80 (50%) in 159 people with COPD and 189 (56%) from 338 controls (unadjusted P = 0.25). The odds ratio for 5 year survival based on these 4 studies [8,9,18,20] was 0.99 (95% CI [0.79,1.24], P = .87). Survival in the prospective studies (N = 3) was comparable (43% or 637/1471 with COPD and 45% or 736/1645 with no COPD, P = 0.43). This suggests that the presence of COPD had a negligible impact on medium-term survival after lung cancer surgery (Fig. 2). Although under-powered, a similar finding was made in the sensitivity analyses where no significant difference in overall mortality could be found. There was no evidence of publication bias (Eggers tests p = 0.19).

3.3. Survival in the NLST-ACRIN sub-study

The outcomes from the NLST-ACRIN sub-study censored to 5 years are summarised in Table 2. Of the 328 lung cancer cases identified during the screening study, 289 were NSCLC with 153 (53%) being stages 1 and 2. The overall 5 year post-surgery survival in those with and without COPD was not significantly different (84 and 81% respectively, P = 0.65). These results were not affected by screening arm nor was there a difference when the analysis was limited to stage 1–2 NSCLC cases (Table 2). The prevalence of COPD in early stage cancers that did not undergo surgery was 92–100%, regardless of detection pathway, and was significantly higher than the expected 40–50% who underwent surgery (Fig. 3). The overall mortality for those not diagnosed with lung cancer was linearly related to COPD severity, where mortality rates were 3–4 times higher in those with GOLD 3–4 grade COPD compared to those with normal lung function (Fig. 4). These findings were also independent of screening arm.

4. Discussion

From our systematic review of the literature, we found no statistically significant decrease in overall and 5-year survival in early stage lung cancer cases following surgery for patients with COPD compared to those without COPD. This is reflected by a random effects odds ratios for COPD post-lung cancer surgery of 0.91 (N = 10, 95% CI [0.84, 1.00] for overall survival and 0.99 (N = 4, 95% CI [0.79, 1.24]) for 5-year survival. Therefore, COPD has a negligible impact on medium-term survival post-lung cancer surgery for early stage disease. There was little heterogeneity in our results (N = 10), with an I^2 result of only 19.1%, and minimal publication bias (Egger's test was negative, P = 0.19). These findings were confirmed in our analyses of all-cause mortality in early stage NSCLC in the NLST-ACRIN sub-study, where the mortality rates censored to 5 years were comparable in those with and without baseline COPD. These findings suggest that for smokers with predominantly mild-to-moderate COPD, outcomes following lung cancer surgery are comparable to those for non-COPD.

Of the 10 studies included in this review, 8 studies showed little difference in mortality while 2 studies (Nakajima and Yoshida) observed that COPD was associated with a 30%–40% greater mortality

Table 1
Data Extraction for each eligible study comparing cases (COPD) with controls.

Author	Year	Country	Study Design	Follow-Up (Years)	Number of Patients (Cases/ Controls)	Definition of Cases	5-year Overall Survival for Cases/ Controls	Proportion of Patients with Stage I-II NSCLC	Odds Ratio (95% CI)	Comment
Iwasaki et al. [8]	2005	Japan	Retrospective	5	50 (12/38)	COPD defined by GOLD criteria*	70.0%/72.4%	72.0%	0.83 (0.30, 2.29)	No significant difference in 5-year survival for patients with and without COPD
Lopez-Encuentra et al. [14]	2005	Spain	Prospective	10	2994 (1370/1624)	COPD defined by GOLD criteria*	43.0%/45.0%	63.7%	0.98 (0.90, 1.06)	No significant difference in 10-year survival for patients with and without COPD
Sekine et al. [9]	2002	Japan	Retrospective	5	244 (78/166)	COPD defined by GOLD criteria*	36.2%/41.2%	68.9%	0.95 (0.73, 1.24)	No significant difference in 5-year survival for patients with and without COPD
Sekine et al. [15]	2013	Japan	Retrospective	10	1461 (363/1098)	COPD defined by GOLD criteria*	51.0%/61.5%	62.1%	0.85 (0.73, 0.98)	COPD patients have significantly poorer long-term survival
Lee et al. [16]	2014	Korea	Retrospective	7	221 (111/110)	COPD defined by GOLD criteria*	29.7%/32.7%	33.0%	0.97 (0.76, 1.24)	No significant difference in 7-year survival for patients with and without COPD
Santambrogio et al. [17]	2001	Italy	Prospective	3	88 (43/45)	COPD defined by FEV_1 %predicted between 40-79%	67%/67%	100%	0.99 (0.67, 1.47)	No significant difference in 3-year survival for patients with and without COPD
Ueda et al. [18]	2006	Japan	Prospective	5	100 (43/57)	COPD defined by FEV_1 %predicted $< 70\%$	58.4%/48.3%	$> 72.0\%$	1.17 (0.73, 1.89)	No significant difference in 5-year survival for patients with and without poor lung function ($FEV_1 < 70\%$)
Nakajima et al. [19]	2009	Japan	Retrospective	6	1461 (36/1425)	Severe COPD defined by FEV_1 %predicted 30–50% and controls defined by normal lung function or FEV_1 %predicted $> 50\%$	24.4%/58.6%	63.0%	0.68 (0.51,0.92)	COPD patients have poorer prognosis but are still candidates for surgical resection.
Sawabata et al. [20]	2007	Japan	Retrospective	5	103 (11/92)	Cases defined by FEV_1 %predicted 30-50% and controls defined by normal lung function or FEV_1 %predicted $> 50\%$	79.0%/79.0%	100%	1.11 (0.29, 4.24)	No significant difference in 5-year survival for patients with and without COPD
Yoshida et al. [21]	2015	Japan	Retrospective	8	243 (62/181)	COPD defined using GOLD criteria*	66.9%/80.7%	88.9%	0.64 (0.40, 1.03)	COPD patients have significantly poorer long-term survival

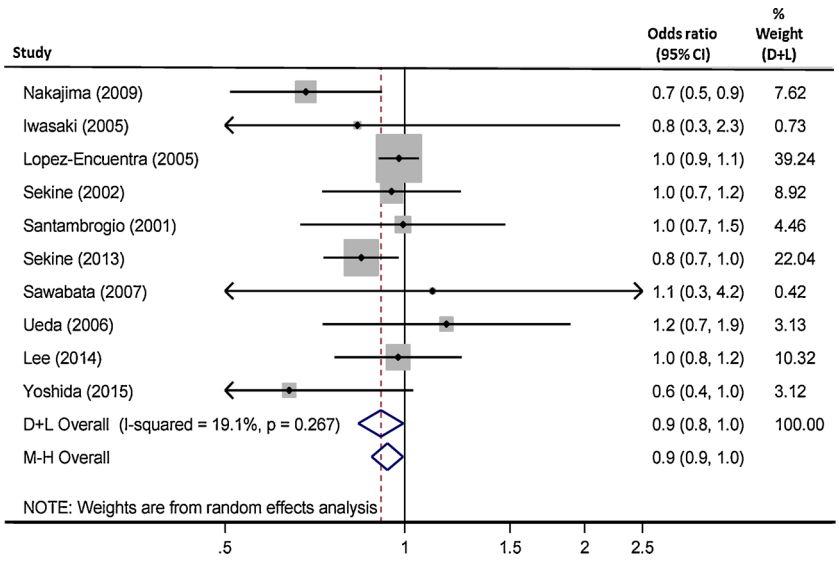

Fig. 2. Forest Plot of odds ratio of all cause death within 3–10 years of lung cancer surgery for unscreened NSCLC for those with and without spirometric-based COPD. Legend: Random (D + L = DerSimonian-Laird) and fixed (M-H = Mantel-Haenszel) effect models are shown. Box size is proportional to the random effects weight and results below 1 favour reduced odds of all cause death in those without sprirometric-based COPD.

Table 2
Summary of outcomes (5-year survival) for operable lung cancer in the NLST-ACRIN sub-study sub-grouped by COPD status and clinical stage.

Lung Cancer Characteristics	CT arm	CXR arm	Total	P value
Total Lung cancer cases	180	148	328	
- SCLC	19 (11%)	20 (14%)	39 (12%)	
- NSCLC	161 (89%)	128 (86%)	289 (88%)	0.42
NSCLC undergoing surgery	116 (64%)	66 (45%)	182 (55%)	
Survival in NSCLC by COPD status				
- COPD	51	34	85	
- COPD Survival to 5 years	44 (86%)	27 (79%)	71 (84%)	0.81
- Non-COPD	62	32	94	
- Non-COPD Survival to 5 years	55 (89%)	21 (66%)	76 (81%)[#]	0.38
- Unknown status	3	0	3	
Stage 1-2 NSCLC undergoing surgery	101 (56%)	52 (35%)	153 (47%)	
Survival in stage 1-2 NSCLC by COPD status				
- COPD	46	31	77	
- COPD Survival to 5 years	44 (96%)	27 (87%)	71 (92%)	0.78
- Non-COPD	62	32	94	
- Non-COPD Survival to 5 years	55 (89%)	21 (63%)	76 (81%)	0.38
- Unknown status	3	0	3	

[#] The overall 5 year post-surgery survival in those with and without COPD was not significantly different (84 and 81% respectively, P = 0.65).

(see Fig. 2). For the sake of thoroughness of our review, we decided to further analyse these studies to determine if there were any differences in the methodology or patient group in these studies that may have led to these contradictory results. Nakajima et al. have an odds ratio of 0.68 (95% CI [0.51, 0.92]), however they split their patients into a severe COPD group and a control group containing people with normal lung function, mild COPD and moderate COPD [19]. This is not comparable to the other studies in this review which have split patients simply into those with COPD and those without COPD. In 2013, Sekine et al. reported an odds ratio of 0.84 (95% CI [0.73, 0.97]), however this study was primarily concerned with the severity of COPD [15]. In our analysis, we calculated an approximate overall survival rate for COPD of 51.0% in the Sekine study [15] by calculating actual survival numbers combining patients with mild, moderate and severe COPD. In the multivariate analysis of long-term overall mortality carried out by Sekine et al., only severe COPD was associated with poorer long-term outcome post-lung cancer surgery [15]. This finding accords with other

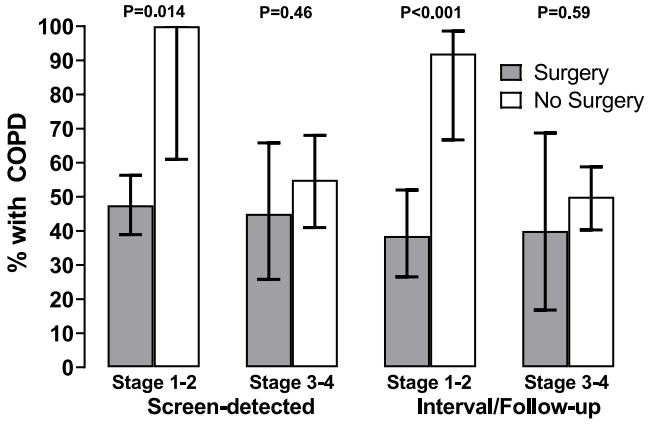

Fig. 3. Prevalence of COPD (%) in early and late stage lung cancer detected during screening or during Interval/Follow-up, stratified by surgery in the NLST-ACRIN sub-study. Legend: Bars represent % spirometry-defined COPD (± 95% Confidence Interval). Fisher's Exact P values are shown for pairwise comparisons.

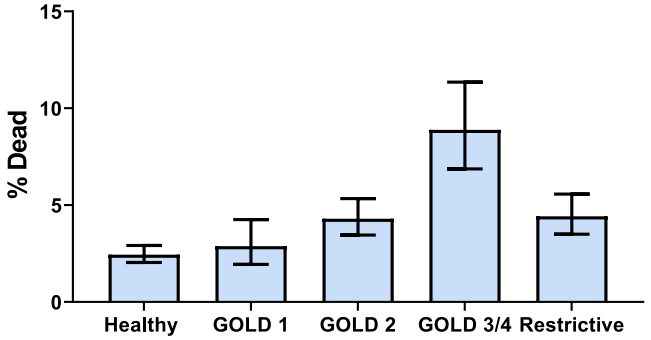

Fig. 4. Overall % mortality for non-lung cancer-related deaths according to severity of airflow limitation in the NLST-ACRIN screening sub-cohort censored at 5 years follow-up. Legend: Bars represent % dead after 5 years (± 95% Confidence Interval).

studies suggesting that COPD (especially GOLD 3–4) is associated with more aggressive forms of lung cancer [12,23], shorter volume doubling time [24,25] and greater mortality from non-lung cancer related deaths [26]. This latter finding was strongly born-out by our findings in the NLST-ACRIN sub-study showing that while increasing severity of COPD

is associated with an increased risk of lung cancer [7], the effect on other causes of deaths is even greater [26]. This means that while the presence of airflow limitation increases a smoker's risk of lung cancer in a simple linear relationship [7], it also increases the likelihood that smokers will die prematurely of other smoking related complications (Fig. 4) [26]. In the context of CT screening for lung cancer, this raises an important consideration with regards to the benefits of screening in this very high risk co-morbid group [27,28]. It also suggests that spirometry should be routinely performed in high risk smokers undergoing screening so that the relative benefits versus harms of lung cancer screening can be correctly assessed [29].

We believe there are several strengths to this study. Firstly, we have followed the recognised methodology for undertaking a systematic review in accordance with the PRISMA statement [13]. In our screening process, we used a strict 5 group keyword search of recognised databases such as Ovid MEDLINE, EMBASE and Cochrane Database of Systematic Reviews. We adopted extensive and repeated searches to attain all possible abstracts relevant to our topic. For those not available in English language, we contacted the authors for an English translation of the papers. We then applied a stringent set of 6 checklist "requirement" criteria to include only those studies with appropriate parameters and correct follow-up data that could be compared. Secondly, our systematic review was both multi-centre and multi-national; including studies from several countries in both Europe, USA and Asia. Yet, in spite of this diverse study pool, our systematic review had minimal heterogeneity. Third, an important strength of our study was the requirement to define COPD on spirometry terms [22]. This is relevant because "self-reported" COPD is a very unreliable way to assign COPD status, particularly in a study of lung cancer cases where between 50–70% of cases have pre-existing COPD yet less than one half of these individuals will have been "diagnosed" [30]. In our NLST-ACRIN study we show that "self-reported" COPD was strongly linked to increasing severity of airflow limitation, best reflecting severe or very severe COPD (GOLD 3–4). In the study by Zhai et al. [31] which relied on self-reported COPD, the authors concluded the overall mortality after surgery for early stage lung cancer was much higher in those with COPD but no spirometry was performed to confirm the diagnosis. We suggest that this increased mortality is primarily based on severe COPD. Lastly, although for completeness our search dates back to 1946, the 10 studies in our analysis date from 2001 to 2015, and thus represent recent approaches to the surgical management of lung cancer in the non-screening setting.

While inclusion into our systematic review was regulated by our set of 6 rigid checklist "requirement" criteria, we identified several studies that highlight important points regarding the effect of COPD on outcomes other than death [31–40]. An alternative outcome of interest is how lung cancer surgery affects the lung function of patients with and without COPD. Several studies have shown that COPD patients actually have a significantly smaller loss in FEV_1 post-surgery than patients without COPD and, in some cases, COPD patients may actually have improved lung function post-surgery [31,32]. This is important because quality of life after surgery is also a crucial factor to take into consideration. In addition, the potential for postoperative complications should influence the decision for lung cancer surgery as these complications negatively impact the patient's quality of life [34–38]. While some studies have shown that patients with COPD have a comparable postoperative complication rate to patients without COPD, other studies show the presence of COPD confers a significant risk for pulmonary complications such as prolonged air leak, pneumothorax, pneumonia and atelectasis [34–36]. Perioperative mortality is another outcome of interest that has been widely reported throughout the literature, however the results vary. Many studies report that perioperative mortality is not significantly different between patients with and without COPD with some reporting no perioperative mortality at all [8,15,17,31,37]. Other studies, report that perioperative mortality is significantly increased in patients with COPD compared to those without COPD, making COPD an independent risk factor for perioperative mortality [16,17,39,40]. These disparities in results indicate that a systematic review of the evidence, examining the effect of COPD on postoperative mortality in early stage lung cancer is indeed required.

Given the recent interest in CT screening for lung cancer [27,28], there is a growing interest in the outcomes of lung cancer surgery especially with regards to "competing cause of death". In his recent review on CT screening, Mazzone expands the current concept of "overdiagnosis" to encompass the screening of high risk smokers who die of other complications of smoking [28]. This "overtreatment" is highly relevant to those with co-existing COPD as airflow limitation is associated with premature death from cardiovascular disease, respiratory disease and other cancers [41–43]. Mortality from competing risk of death therefore undermines the value of CT screening in those at risk of death from other diseases. For this reason we re-examined the "COPD effect" on outcome after surgery in the NLST-ACRIN study where spirometry had been routinely performed at baseline. We found that although outcomes for those with COPD were comparable to those with no COPD, severity of airflow limitation was directly related to death from other causes. This finding means those at greatest risk of lung cancer (GOLD 3–4) also have a greater risk of dying from non-lung cancer smoking complications [44].

This systematic review has several limitations. First, all of the studies included in the systematic review were observational studies as we found no randomised controlled studies. We accept that by analysing observational studies, the strength of the evidence is much weaker than if data from randomised controlled studies were analysed. However the question we pose cannot be ethically answered by a randomised controlled trial. Second, the classification of COPD varied among the studies considered in this systematic review. There currently exists a widely-accepted Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification system for COPD established in 2001 [22]. Although GOLD classification is the current gold standard for diagnosing COPD and grading its severity, prior to 2004 it was not consistently used. Third, most of our studies were hospital-based case series studies which have very small study sizes; in fact all but 3 have a study population of less than 1000. We understand that smaller study populations lead to a reduction in statistical power which therefore decreases the chance of detecting a true effect. While the studies themselves had limited power, in doing a systematic review we aimed to increase this power by pooling the collective populations to create a sufficiently large study size. Fourth, the type of surgical treatment was not standardised across the studies included, where treatment ranged from pneumonectomies to lobectomies. The type of procedure that a patient underwent was usually chosen at the operating surgeon's discretion therefore there was poor consistency across study populations and even within cohorts. This, along with the small size of individual studies prevented us from looking independently at the association between the procedure type and long-term survival. Fifth, there are several instances of intrinsic bias within our study. The studies included in our systematic review look at a non-screening population, from many centres where the role of surgery in the treatment of "early stage" lung cancer is varied. This reduces the generalisability of our findings and leads to poor external validation. Furthermore, our main aim was to analyse patients with stage I–II NSCLC, however most of the studies analysed included a wide range of patients suffering from stages I–IV NSCLC (Table 1). For this reason we examined the "COPD effect" on a subgroup of the NLST where post-surgical outcomes were limited to early stage lung cancer and this verified the findings of our systematic review. Importantly, we show in the NLST study, that the prevalence of COPD in un-operated early stage lung cancer was 100% and 92% in screen and non-screen detected lung cancer respectively, compared to the expected 40–50% prevalence seen across all lung cancers (Fig. 3). While the basis of this observation remains unclear, this finding provides further understanding as to why those with COPD had only half the benefit from screening as those with no COPD [45].

Our finding that COPD patients have similar medium-term survival post-lung cancer surgery to those without COPD has several future implications. First, this evidence supports the premise that the presence of COPD should not be a factor in any exclusion criteria for lung cancer surgery or screening [46]. However, while the presence of COPD alone is not enough to create a significant survival disparity, the presence of severe COPD is another question entirely. Both Nakajima et al. and Sekine et al. have shown that GOLD III COPD ($FEV_1/FVC < 0.7$ and FEV_1 %predicted 30–50%) is associated with significantly reduced medium-term survival compared with non-COPD patients, post-lung cancer surgery [15,19]. This would support the use of routine pre-operative lung function testing in order to minimise the number of GOLD III/IV COPD patients undergoing lung cancer surgery. In conclusion, the results of our systematic review show that there is no significant difference in medium-term survival between NSCLC patients with and without mild-to-moderate COPD undergoing surgery for early stage disease.

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Author contributions

RJH, concept and design of the study, acquisition, analysis and interpretation of data; drafting, critically revising and final approval of version for submission

JK, acquisition, analysis and interpretation of data; final approval of version for submission

GDG, analysis and interpretation of data; drafting, and final approval of version for submission

RPY concept and design of the study, acquisition, analysis and interpretation of data; drafting, critically revising and final approval of version for submission

Declaration of Competing Interest

None to declare in relation to this manuscript.

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