Long-term impact of developing a postoperative pulmonary complication after lung surgery

Lugg, Sebastian T; Agostini, Paula J; Tikka, Theofano; Kerr, Amy; Adams, Kerry; Bishay, Ehab; Kalkat, Maninder Singh; Steyn, Richard S; Rajesh, Pala B; Thickett, David R; Naidu, Babu

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4   Sebastian T Lugg,[2] Paula J Agostini,[1] Theofano Tikka,[1] Amy Kerr,[1] Kerry Adams,[1] Ehab

5   Bishay,[1] Maninder S Kalkat,[1] Richard S Steyn,[1] Pala B Rajesh,[1] David R Thickett,[2] Babu

6   Naidu.[1,2*]

7

8   [1] Department of Thoracic Surgery, Heart of England NHS Foundation Trust, Bordesley

9   Green East, Birmingham, B9 5SS, UK.

10   [2] Centre for Translational Inflammation Research (CITR), University of Birmingham,

11   Queen Elizabeth Hospital Birmingham, B15 2GW, UK.

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13   [*] Correspondence to: B Naidu, Centre for Translational Inflammation Research

14   (CTIR), University of Birmingham, Queen Elizabeth Hospital Birmingham, B15 2GW,

15   UK; b.naidu@bham.ac.uk

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22 **What is the key question?** Does the development of a postoperative pulmonary

23 complication (PPC) following thoracic surgery for lung resection impact on long-term

24 survival?

25 **What is the bottom line?** After excluding immediate post-operative deaths,

26 developing a PPC is a significant independent risk factor for late deaths and these

27 patients have a worse long-term survival.

28 **Why read on?** We demonstrate in our large prospective cohort that PPCs are

29 common following thoracic surgery, both the short and long-term effects of

30 developing a PPC are striking; COPD and smoking are significant independent risk

31 factors.

32

33 **ABSTRACT**

34 **Introduction** Postoperative pulmonary complications (PPC) such as atelectasis and

35 pneumonia are common following lung resection. PPCs have a significant clinical

36 impact on postoperative morbidity and mortality. We studied the long-term effects

37 of PPCs and sought to identify independent risk factors.

38 **Methods** A prospective observational study involved all patients following lung

39 resection in a regional thoracic centre over 4 years. PPCs were assessed daily in

40 hospital using the Melbourne group scale based on chest x-ray, white cell count,

41 fever, purulent sputum, microbiology, oxygen saturations, physician diagnosis and

42 intensive therapy unit (ITU)/high dependency unit readmission. Follow up included

43 hospital length of stay (LOS), 30-day readmissions, and mortality.

44   **Results** 86 of 670 patients (13%) who underwent a lung resection developed a PPC.

45   Those patients had a significantly longer hospital LOS in days (13, 95%CI 10.5-14.9 vs.

46   6.3, 95%CI 5.9-6.7; p<0.001) and higher rates of both ITU admissions (28% vs. 1.9%;

47   p<0.001) and 30-day hospital readmissions (20.7% vs. 11.9%; p<0.05). Significant

48   independent risk factors for development of PPC were COPD and smoking (p<0.05),

49   not age. Excluding early postoperative deaths, developing a PPC resulted a

50   significantly reduced overall survival in months (40 95%CI 34-44 vs. 46 95%CI 44-47;

51   p=0.006). Developing a PPC is associated with a higher non-cancer related late

52   deaths (11 vs. 5%; p=0.020). PPC is a significant independent risk factor for late

53   deaths in non-small cell lung cancer patients (HR 2.0, 95%CI 1.9-3.2; p=0.006).

54   **Conclusion** Developing a PPC after thoracic surgery is common and is associated

55   with a poorer long-term outcome.

56

57   **BACKGROUND**

58   Lung cancer is the most common cause of cancer death within the UK [1]. For those

59   patients diagnosed with non-small cell lung cancer (NSCLC) potentially curative

60   surgery is generally accepted as the most effective treatment [2]. There is some

61   evidence that patients with lung cancer in the UK present at a later stage and have a

62   higher comorbidity than patients in some other European countries [3]. Thus,

63   surgical resection rates amongst those with proven NSCLC are lower in the UK (14%)

64   compared to central Europe (24%) [4, 5]. To address this most recent European and

65   UK guidelines has widened the selection criteria for lung cancer surgery [6], which

66   has helped improve resection rates. The 5-year survival rates for lung cancer in the

67   UK is poor (9%) compared to central Europe (13%) as demonstrated in the 1999-

68   2007 EUROCARE-5 report [7]. A more recent study has shown that cancer survival in

69   England is improving, however continued investment is needed to close this

70   international gap [8]. Furthermore, whilst in hospital mortality has fallen over the

71   last 3 decades, mortality rates within the first 90 days of surgery are considerable

72   [9]. We need to understand the causes of these late complications if we are to

73   improve long-term outcomes.

74   Lung cancer resection is also associated with a considerable risk of postoperative

75   pulmonary complications (PPCs), of which pneumonia and atelectasis are the most

76   common [10]. PPCs have a significant health and economic impact on patients and

77   health care services. Indeed, as less fit patients are undergoing surgery, the

78   incidence of PPCs is likely to increase further. The longer-term effects of developing

79   a PPC in hospital following lung cancer surgery have not been defined. The

80   identification of modifiable risk factors for PPCs has a crucial role in the development

81   of innovative strategies to reduce the impact and incidence of PPCs. We hypothesise

82   that PPCs are associated with the late postoperative mortality and morbidity

83   observed following lung resection.

84   This study aims to assess both immediate and long-term impact of PPCs, and to

85   identify potentially modifiable independent risk factors.

86

87   **METHODS**

88　This prospective observational study was conducted at a single centre large regional

89　thoracic unit serving 6 million people.　Consecutive patients who underwent open

90　thoracotomy or video-assisted thoracoscopic surgery (VATS) for lung

91　resection/removal in a regional thoracic centre between April 2010 and April 2014

92　were observed. This study was conducted with the approval of the National

93　Research Ethics Service (NRES) Committee West Midlands. This study was registered

94　with the Birmingham Heartlands Hospital audit department (audit code 1672).

95　Decisions regarding patient operability and resectability were informed by the British

96　Thoracic Society guidelines for lung cancer resection [6].

97　Patients were admitted to hospital on the day of surgery. All operations were

98　performed with single lung ventilation under general anaesthesia, and patients were

99　subsequently scheduled for extubation in the operating room. Postoperatively,

100　patients were managed in a dedicated thoracic high dependency unit HDU (level 2)

101　and ward unless complications required their admission to the ITU. Postoperative

102　pain control was achieved by continuous thoracic epidural analgesia, paravertebral

103　infusion, intrathecal morphine and/or intercostal blocks or systemic opioids

104　(parenteral administration or intravenous patient-controlled administration). The

105　choice of analgesic technique was made by the anaesthetist after discussion with the

106　patient. From the first postoperative day, all patients had a daily physiotherapy

107　programme comprising deep breathing exercises, incentive spirometry, supported

108　coughing and mobilisation.

109　The Melbourne Group Scale (MGS) is a standardised scoring system validated by our

110　group to define the presence of a PPC such as pneumonia or clinically significant

111 atelectasis, which are likely to adversely affect the patient's clinical course [10-11].

112 Using this score, PPC is defined in those patients presenting with four or more of the

113 following eight dichotomous factors: chest x-ray (CXR) findings of atelectasis or

114 consolidation; raised white cell count (WCC) ($>11.2 \times 10^{9}$/l); temperature $>38^{\circ}$C; signs

115 of infection on sputum microbiology; purulent sputum differing from preoperative

116 status; oxygen saturations <90% on room air; physician diagnosis of pneumonia; and

117 prolonged HDU stay or readmission to HDU or ITU for respiratory complications. The

118 MGS was used daily by senior physiotherapists who were performing their routine

119 respiratory assessments. The discharge criteria, agreed with investigators in advance

120 included patients who were medically fit and who had been discharged from

121 physiotherapy.

122 Data collected included demographics and pre-operative record of smoking status,

123 body mass index (BMI), percentage predicted forced expiratory volume in one

124 second (FEV_1), American Society of Anesthetist (ASA) score, subjective preoperative

125 activity level and comorbidities including chronic obstructive pulmonary disease

126 (COPD) defined by clinical diagnosis of the referring clinician and staged according to

127 percentage predicted FEV_1. Postoperative data included type of analgesia used and

128 underlying pathology (including lung cancer staging if applicable). Total length of

129 stay (LOS) was defined as the LOS in hospital after the date of surgery. The HDU and

130 ITU LOS were also recorded, as well as ITU admission and 30-day readmission to

131 hospital secondary to surgical or pulmonary complications. All patients were

132 followed up for overall survival (OS) and the cause of death was obtained from both

133 the death certificate and hospital records. Deaths were classified as postoperative

134   complication for patients who died within initial hospital admission or within 30 days

135   of surgery, cancer related for those patients who died of disease

136   progression/recurrence, and non-cancer related, or cause of death uncertain where

137   records were not available or unclear.

138   **Statistical analysis**

139   Results are expressed as mean (SD or 95% CI) for continuous variables and as a

140   percentage for categorical variables. Univariate analysis of risk factors for

141   development of PPC were assessed by performing individual un-adjusted logistic

142   regression analysis, inclusion of one covariate at a time. Risk ratios with 95%CI were

143   generated for variables found to have statistically significant association with PPC on

144   univariate analysis. A backward multivariate binary logistic regression analysis was

145   performed to identify the independent predictors of PPC within this dataset.

146   The effect of PPC on hospital, HDU and ITU LOS were assessed using the Mann-

147   Whitney non-parametric test to accommodate for the presence of positive

148   skewness. Kaplan Meyer plots and the log-rank test were used to assess the impact

149   of PPC on survival. Cox regression was assessed including all risk factors in a model

150   for long-term survival. All analyses were performed using the IBM SPSS version 20

151   and SAS 9.3 statistical package version (SAS Institue, Inc, Carry NC).

152

153   **RESULTS**

154   There were 670 patients who underwent pulmonary resections during the study

155   period; 377 of who were male (56%). The mean±SD age of the group was 66.4±10.8

years. Mean predicted FEV_1 was 80.2±20.8%, mean BMI 26.9±8.1 kg/m^2, 328 patients (49%) had an ASA score ≥3, 176 patients (26%) had COPD, 149 patients (22%) were current smokers.

The most frequent procedure was lobectomy (n=497, 74%) followed by wedge or segmentectomy (n=111, 16%) and pneumonectomy (n=37, 5.5%). VATS lobectomy and segmentectomy were also performed (n=54, 8% and n=8, 1% respectively). Most common histological diagnosis was NSCLC (n=477, 71.2%) followed by benign disease (n=73, 11%) and metastatic disease of non-lung primary (n=69, 10.3%). Eighty-eight patients (13%) had clinical evidence of PPC using the MGS. The median day of this occurring was day 2 postoperative. The four most common positive factors to trigger a score of 4 were raised WCC (n=75, 85%), purulent sputum (n=72, 82%), CXR findings (n=69, 78%) and reduced saturations (n=68, 77%).

On univariate analysis (table 1) the significant risk factors associated with developing a PPC were percentage predicted FEV_1, ASA >3 (Risk Ratio [RR] [4 vs. 1] 4.11, 95%CI 1.53-11), self-reported preoperative activity level ≤400m (RR 1.8, 95%CI 1.20-1.68), COPD diagnosis (RR 2.13, 95%CI 2.45-15.01) and current smoking (RR [current vs. never] 6.06, 95%CI 2.57-3.40) (p<0.05). Age, BMI, type of surgery (individually or collectively), VATS approach, cancer diagnosis or staging and cardiovascular disease was not significantly associated with development of PPC.

Table 1 Baseline characteristics in PPC and non-PPC groups including univariate analysis of risk factors associated with developing PPC.

Variables	Value	Total (n=670)	PPC (n=88)	Non-PPC (n=582)	P-value
Age	Mean (±SD)	66.4 (±10.8)	67.1 (±9.6)	66.4 (±11)	0.547
FEV$_1$% predicted	Mean (±SD)	80.2 (±20.8)	75.8 (±20.7)	80.94 (±20.7)	0.034
BMI	Mean (±SD)	26.9 (±8.1)	27.2 (±5.6)	26.9 (±8.4)	0.757
Gender	Male	377 (66%)	57 (65%)	320 (55%)	0.086
	Female	293 (44%)	31 (35%)	262 (45%)	
ASA Score	1	44 (7%)	5 (6%)	39 (7%)	0.004
	2	298 (44%)	32 (36%)	266 (46%)	
	3	313 (47%)	44 (50%)	269 (46%)	
	4	15 (2%)	7 (8%)	8 (1%)	
Pre-operative activity level	≤ 400 m	185 (27%)	35 (42%)	150 (27%)	0.005
	> 400 m	465 (73%)	49 (58%)	416 (73%)	
Type of surgery	Lobectomy	497 (74%)	64 (73%)	433 (74%)	0.651
	Subsegmentectomy/wedge	111 (16%)	15 (17%)	96 (16.5%)	
	Pneumonectomy	37 (6%)	3 (3.5%)	34 (6%)	
	Exploratory/biopsy	13 (2%)	3 (3.5%)	10 (2%)	
	Sleeve	8 (1%)	2 (2%)	6 (1%)	
	Chest wall	4 (1%)	1 (1%)	3 (0.5%)	
VATS	Yes	62 (9%)	9 (10%)	53 (9%)	0.735
	No	608 (91%)	79 (90%)	529 (91%)	
Analgesia	Epidural	254 (38%)	27 (31%)	227 (39.4%)	0.443
	Intrathecal morphine	146 (22%)	23 (26%)	123 (21.4%)	

	Morphine Infusion	63 (9.5%)	9 (10%)	54 (9.3%)	
	PCA	50 (7.5%)	4 (5%)	46 (8%)	
	Paraveterbral	146 (22%)	24 (27%)	122 (21.2%)	
	Other	5 (1%)	1 (1%)	4 (0.7%)	
Pathology	NSCLC	477 (71.2%)	64 (73%)	413 (71%)	0.598
	Small cell LC	10 (1.5%)	3 (3%)	7 (1%)	
	Carcinoid	27 (4%)	4 (4.5%)	23 (2%)	
	Metastatic disease	69 (10.3%)	6 (7%)	63 (11%)	
	Benign	73 (11%)	11 (12.5%)	62 (11%)	
	Other	14 (2%)	0	14 (4%)	
NSCLC Staging	0	5 (1%)	0	5 (1%)	0.762
	IA	120 (26%)	13 (22%)	107 (26%)	
	IB	112 (24%)	10 (17%)	102 (25%)	
	IIA	94 (20%)	14 (23.3%)	80 (20%)	
	IIB	53 (11%)	9 (15%)	44 (11%)	
	IIIA	77 (16%)	13 (22%)	64 (16%)	
	IIIB	5 (1%)	0	5 (1.3%)	
	IV	4 (1%)	1 (1.7%)	3 (0.7%)	
COPD	Yes	176 (26%)	38 (43%)	138 (24%)	<0.001
	No	494 (74%)	50 (57%)	444 (76%)	
COPD Severity (FEV_1% predicted)	Mild (<80)	51 (29%)	12 (32%)	39 (29%)	0.904
	Moderate (50-80)	95 (54%)	19 (61%)	76 (56%)	
	Severe (30-50)	27 (16%)	6 (16%)	21 (15%)	

IHD	Yes	85 (13%)	15 (17%)	70 (12%)	0.665
	No	585 (87%)	73 (83%)	512 (88%)	
HTN	Yes	279 (42%)	37 (42%)	242 (42%)	0.934
	No	391 (58%)	51 (58%)	340 (58%)	
Diabetes	Yes	80 (12%)	14 (16%)	66 (11%)	0.220
	No	590 (88%)	74 (84%)	516 (89%)	
Smoking status	Current	149 (22%)	35 (40%)	114 (20%)	<0.001
	Ex	391 (68.5%)	48 (54%)	343 (59%)	
	Never	129 (22.5%)	5 (6%)	124 (21%)	

178   PPC, postoperative pulmonary complication; FEV_1, forced vital capacity in 1 second;

179   BMI, body mass index; ASA, American College of Anaesthetists; VATS, Video-assisted

180   thoracoscopic surgery; PCA, patient controlled analgesia; COPD, chronic obstructive

181   pulmonary disease; HTN, hypertension; IHD, ischaemic heart disease, NSLC, non-

182   small cell lung cancer.

183

184   Using backward logistic regression to identify perioperative variables independently

185   associated with PPCs our multivariate analysis included all variables. No significant

186   interactions across any of the variables were found. Only COPD diagnosis and

187   smoking status were associated with the development of a PPC (table 2). Patients

188   who had COPD were 1.81 times more likely to develop PPC compared to non-COPD

189   patients (95%CI 1.11–2.95; p=0.017). Current smokers were 5.42 times more likely to

190   develop PPC that never smokers (95%CI 1.99-14.76; p<0.001), and ex-smokers were

191   2.8 times more likely to develop PPC than never smokers (95%CI 1.08-7.28; p=0.035).

192   The goodness-of-fit test of this model remained non-significant during these steps

193   with a p value very close to 1 showing a very good model fit (Hosmer and Lemeshow

194   p=0.975). The overall predictive power of the model was 66.3% indicated by the area

195   under the curve (ROC). The resulting logistic model had a sensitivity of 60.2% and

196   specificity of 65.9% with the cut-off probability point set at 0.12. So in our model, a

197   probability more than 0.12 means that a patients has 60.2% possibility to have a

198   PPC. When the yielded probability is less than 0.12, patients have 65.9% chance to

199   not develop PPC. The sensitivity of the model is the percentage of the group

200   accurately identified by the model as having a PPC and the specificity is the

201   percentage correctly identified as not having one.

202

203   **Table 2** Preoperative risk factors associated with PPC on multivariate analysis.

Variables	Estimate	SE	P-value	OR	95% CI
Constant	-3.18	0.45	<0.001	-	-
COPD	0.59	0.25	0.017	1.81	1.11 - 2.95
Current smoker (vs. never)	1.69	0.51	<0.001	5.42	1.99 - 14.76
Ex smoker (vs. never)	1.03	0.49	0.035	2.80	1.08 - 7.28

204   COPD, chronic obstructive pulmonary disease.

205

206   Patients in the PPC group had a significantly longer (days) hospital LOS (12.7, 95%CI

207   10.5-14.9 vs. 6.3, 95%CI 5.9-6.7; p<0.001), longer HDU LOS (4.2, 95%CI 3.4-4.9 vs. 1.9

208   95%CI 1.8-2.1, p<0.001) and longer ITU LOS (2.1, 95%CI 1.0-3.3 vs. 0.2, 95%CI 0.1-0.4,

209　p<0.001). In the PPC group there were higher rates of ITU admissions (28% vs. 1.9%;

210　p<0.001) (figure 1, table 3). The 30-day hospital readmission was higher in the PPC

211　group (21% vs. 12%; p=0.023). Patients who developed a PPC in hospital had higher

212　rate of readmission secondary to pneumonia and lower respiratory tract infections

213　(9.1% vs. 3.8%; p=0.046).

214　Of all patients there were 176 (26%) deaths with a median follow up of 12 months

215　(95%CI 9.4-14.6). Causes of death included early postoperative complications (8.5%),

216　cancer related deaths (65%), non-cancer related deaths (21%) and cause of death

217　uncertain (5%). Patients with a PPC had a significantly higher 30-day (9% vs. 0.7%;

218　p<0.001) and 90-day mortality (17% vs. 2.9%; p<0.001).

219

220　**Table 3** Morbidity and mortality following the development of a PPC.

Variables		PPC (n=88)	Non-PPC (n=582)	P-value
Number of ITU admissions		25 (28%)	11 (1.9%)	<0.001
Mean LOS (95% CI) (days)	Hospital	12.7 (10.5-14.9)	6.3 (5.9-6.7)	<0.001
	HDU	4.2 (3.4-4.9)	1.9 (1.8-2.1)	<0.001
	ITU	2.1 (1.0-3.3)	0.2 (0.1-0.4)	<0.001
Number of 30-day hospital readmissions	Total	18 (21%)	67 (12%)	0.023
	Pneumonia/LRTI	8 (9%)	22 (4%)	0.046
	Postoperative complication	10 (11%)	43 (7%)	0.198
	Uncertain	0	2 (0.3%)	0.754

Number of deaths	Total	37 (42%)	139 (24%)	<0.001
	30 day-mortality	8 (9%)	4 (0.7%)	<0.001
	90 day-mortality	15 (17%)	16 (3%)	<0.001
Cause of death	Postoperative complication	9 (10%)	6 (1%)	<0.001
	Excluding postoperative complication	28 (32%)	133 (22%)	0.017
	Cancer related	18 (20%)	97 (17%)	0.380
	Non-cancer related	Total	10 (11%)	27 (5%)	0.020
		Respiratory	6 (6.8%)	13 (2.2%)	0.028
		Cardiovascular	3 (3.4%)	10 (1.7%)	0.395
		Other	1 (1.1%)	4 (0.7%)	0.507
	Uncertain	0	9 (1.5%)	0.615

221   PPC, postoperative pulmonary complication; ITU, intensive treatment unit; LOS,

222   length of stay; HDU, high dependency unit; LRTI, lower respiratory tract infection.

223

224   Excluding patients who died of a postoperative complication (15/670, 2%), those

225   who develop a PPC have a reduced OS with a mean follow up of 40 months (95%CI

226   34.1-43.8 vs. 45.8, 95%CI 44.3-47.3; p=0.006) (figure 2). There were a significantly

227   increased number of non-cancer related deaths in those who develop PPC (11 vs.

228   5%; p=0.020), of which, non-cancer respiratory cause of death are more frequent in

229   patients with a PPC. Significant independent risk factors for late deaths in patients

230   with NSCLC were PPC (Cox regression: HR 2.00, 95%CI 1.19-3.20; p=0.005), cancer

231   stage, age and 30-day readmission to hospital (table 4).

232

233   **Table 4** Significant Independent risk factors for late deaths in patients with non-small

234   cell lung cancer.

Variables	Estimate	SE	P-value	HR	95% CI
PPC	0.69	0.25	0.006	2.00	1.19 – 3.20
Staging IIA/B	1.07	0.22	<0.001	2.92	1.89 – 4.56
Staging IIIA	1.28	0.25	<0.001	3.60	2.20 – 5.85
Staging IIIB	1.91	0.61	0.002	6.72	1.61 –18.90
Age	0.03	0.01	0.003	1.04	1.01 - 1.06
Readmission (30-days)	0.62	0.23	0.008	1.86	1.15- 2.89

235   PPC, Postoperative pulmonary complication.

236

237   **DISCUSSION**

238   Our study has confirmed that PPCs are common in thoracic surgery. The short-term

239   morbidity of developing a PPC following thoracic surgery is striking, with significantly

240   longer hospital, ITU and HDU LOS, higher frequency of ITU admissions and higher

241   frequency of hospital readmissions secondary to pulmonary infections. Furthermore,

242   patients who develop a PPC have a significantly increased mortality, both in the early

243   and late stages following surgery. After excluding immediate post-operative deaths,

244   developing a PPC is a significant independent risk factor for late deaths and these

245   patients have a worse long-term survival. Furthermore we observed a high rate of

246   non-cancer related deaths in this cohort.

247   The frequency of PPCs observed at this regional thoracic surgery unit (13%) is

248 concurrent with other studies [10-15]. The incidence of PPC following thoracic

249 surgery ranges between studies predominantly because there is no standard; it is

250 dependent on the type of complications included, the definition of pulmonary

251 complications, and the type of surgery. Use of the objective MGS to define PPC does

252 not include rare but serious postoperative complications such as broncho-pleural

253 fistulas, which required re-operation in 0.4% of our patients, and also pulmonary

254 embolism, which has been described in 2% of patients after thoracic surgery [16].

255 However, the fact that those more frequent, and probably less severe PPCs detected

256 by the MGS were still associated with a higher short and long-term mortality rate is

257 an important message.

258 Patients who develop a PPC are more than twice as likely to be readmitted within

259 30-days of surgery, and nearly 3 times more likely to re-present with respiratory

260 tract infections. Hospital readmission is not only a serious morbidity; we

261 demonstrate it also to be an independent risk factor for the late deaths observed in

262 our study. Patients who are readmitted within 30-days of lung cancer surgery have

263 been shown to have a 6-fold increase in 90-day postoperative mortality [17]. In our

264 study the 90-day mortality was 2.6 times that of 30-day mortality, compatible with

265 other study findings [9, 18]. Thus, this increased mortality following thoracic surgery

266 is not explained by immediate postoperative deaths alone; we hypothesised that

267 PPCs have a role in these later deaths observed.

268 Our study has shown that PPCs are significantly associated with reduced OS

269 following thoracic surgery for lung resection. There is a paucity of data on the

270 impact of PPCs on long-term outcome in thoracic surgery. A retrospective study

271 which included patients aged 66-80 who have undergone a lobectomy for stage 1

272 NSCLC found that development of a PPC was associated with reduced 5-year OS

273 (52.7 vs. 65.9%, p<0.001) and was an independent risk factor for mortality (HR 1.46,

274 95% CI, 1.24-1.73) [19]. We have also shown that developing a PPC is a independent

275 risk factor for late deaths, but in comparison our study is not limited by any inclusion

276 criteria other than national guidelines [6]. Therefore we have included those patients

277 who are older and have more advanced staging of cancer, which we and other

278 authors have found to be additional independent risk factors for late deaths [20, 21].

279 We demonstrate for the first time that after excluding immediate postoperative

280 deaths, patients with a PPC are more likely to die of late non-cancer related deaths.

281 This compares to the outcome of patients who are admitted to hospital secondary to

282 community acquired pneumonia (CAP), these patients have an increased risk of

283 subsequent pneumonia and mortality after discharge, and a substantial proportion

284 of these deaths are due to non-malignant respiratory disease [22]. Some of the late

285 deaths in patients who developed a PPC were secondary to cardiovascular disease,

286 indeed there is increasing evidence that pneumonia is associated with increased risk

287 of cardiovascular complications, which may be due to residual inflammation having a

288 role in triggering procoagulant pathways in these individuals [23].

289 COPD and current smoking were found to be independent risk factors in the

290 development of PPCs in ours and other studies [10, 21]. Our multivariate model for

291 assessing of risk factors has a c-index of 0.66 therefore it cannot be used as a

292 diagnostic/highly predictive tool as we would like a predictive power ideally more

293 than 80-90%. Nevertheless, our analysis identified factors having significant

294   association with PPC. Those patients diagnosed with COPD have increased risk of

295   both pneumonia and atelectasis after surgery [24, 25]. We found on univariate

296   analysis that a lower preoperative FEV_1 percentage predicted was associated with

297   the development of a PPC, though on multivariate analysis, FEV_1 is not an

298   independent risk factor, as previously shown [10]. In our study carbon monoxide

299   lung diffusion capacity (DLCO) was performed only in patients with limited exercise

300   tolerance or lung volumes so data are limited. However, studies have shown DLCO

301   not to be an independent risk factor for long-term survival following thoracic surgery

302   for lung cancer [26, 27]. Risk modification for patients with COPD would be through

303   a pulmonary rehabilitation programme [28], which in thoracic surgery has shown

304   encouraging results in reducing PPCs [29], but more robust studies are needed in this

305   field.

306   Smoking is the biggest independent risk factor for developing PPCs; indeed our study

307   has shown PPCs to be up to five times more common in current smokers when

308   compared to never smokers, similar to other study findings [30]. Key mechanisms

309   are likely to involve the effect smoking has on impairing the mucociliary escalator

310   [31], and also both the antimicrobial and pro-inflammatory functions of alveolar

311   macrophages, which decreases further during anaesthesia and surgery [32]. Risk

312   modification would be in the form of smoking cessation; however the duration

313   needed in order to reduce postoperative risk remains a debated topic and is a much-

314   needed area of future research.

315   Independent risk factors for developing PPCs have previously been identified as

316   smoking, advanced age (≥75 year old), reduced mobility, ASA ≥3, cardiovascular

317 comorbidity, COPD and BMI >/ 30kg/m^2 [10-14]. Interestingly BMI, age and ASA were

318 not significant risk factors for the development of PPCs in our study. Other

319 investigators have found that obesity does not confer greater morbidity and

320 mortality after lung resection [33]. We have shown that age is not a predictive factor

321 for development of PPC which we believe is an important finding for the clinical

322 community and is supported by other studies showing no significant difference in

323 postoperative complications in patients over the age of 75 [21, 34].

324 **Study strengths and limitations**

325 This is a real-life study involving consecutive patients undergoing thoracic surgery in

326 a tertiary centre; our patient demographics and staging of cancer is comparable to

327 national data [9]. The main limitation of our study is the low number of VATS cases

328 recorded. VATS lobectomy has since increased to 1/3 of all lobectomies carried out

329 in the UK due to the perceived minimally invasive nature of the procedure with

330 reduced complications. Indeed we have previously described that the PPC incidence

331 in VATS cases seems to be lower [35]. The data of this study precedes the growth of

332 VATS lobectomies, therefore the majority of our lung resections over the time frame

333 were done via thoracotomy, within in the latter half of the study 2 of the 5 surgeons

334 had started to perform an increasing number of VATS lobectomies (35%), compared

335 to the first half of the study period (3.4%). The finding of VATS approach not to show

336 a significant reduction in incidence of PPC is most likely because of under powering.

337 Further studies into the effects of transition of thoracotomy to VATS on PPC

338 frequency and long-term outcome will need to be conducted. There is limitation

339 with regards to the patient follow up data; as information on mortality and cause of

340   death were obtained from hospital records and death certificates in a retrospective

341   manner, in a few patients cause of death could not be ascertained (5%). Additionally,

342   we did not follow up for cancer recurrence and therefore could not assess the effect

343   of PPC on disease free survival in patients with lung cancer, which would be an

344   interesting area for further investigation.

345

346   **CONCLUSION**

347   In summary, developing a PPC after thoracic surgery is associated with a poorer

348   long-term outcome. We have found COPD and smoking are independent risk factors

349   for developing PPCs, whilst age was not a predictive factor. Further research is

350   required into the effect of risk modification on the development of PPCs and

351   subsequent long-term outcome following thoracic surgery.

352

353   **Contributors**

354   STL carried out data collection and drafted the final manuscript. PJA, AK, KA carried

355   out data collection. TT performed the statistical analysis. EB, MSK, PBR, RSS and BN

356   were involved in patient selection for surgery. BN and DRT have critically reviewed

357   the manuscript and given final approval of the version to be published. All authors

358   read and approved the final manuscript.

359   **Competing interests**

360   There are no conflicts of interests to declare.

361 **Ethics approval**

362 The study received ethics approval by the National Research Ethics Service (NRES)

363 Committee West Midlands, Edgbaston.

364

365 **REFERENCES**

366 1. Office for National Statistics: Deaths Registered in England and Wales (Series
367 DR), 2013.
368 2. Pearson FG. Current status of surgical resection for lung cancer. *Chest* 1994;
369 106: 337S-339S.
370 3. Imperatori A, Harrison RN, Leitch DN, et al. Lung cancer in Teeside (UK) and
371 Varese (Italy): a comparison of management and survival. *Thorax* 2006; 61:
372 232-239.
373 4. Damhuis RA, Schutte PR. Resection rates and postoperative mortality in 7,
374 899 patients with lung cancer. *Eur Respir J* 1996; 9: 7–10.
375 5. Rich AL, Tata LJ, Stanley RA, et al. Lung cancer in England: information from
376 the National Lung Cancer Audit (LUCADA). *Lung Cancer* 2011; 72: 16-22.
377 6. Lim E, Baldwin D, Beckles M, et al. Guidelines on the radical management of
378 patients with lung cancer. *Thorax* 2010; 65: 1–27.
379 7. De Angelis R, Sant M, Coleman MP, et al. Cancer survival in Europe 1999-
380 2007 by country and age: results of EUROCARE--5-a population-based study.
381 *Lancet Oncol* 2014; 15: 23-34.
382 8. Walters S, Benitez-Majano S, Muller P, et al. Is England closing the
383 international gap in cancer survival? *Br J Cancer* 2015;113:848-60.
384 9. Powel H, Tata L, Baldwin D, et al. Early mortality after surgical resection for
385 long cancer: an analysis of the English National Lung cancer audit. *Thorax*
386 2013; 68: 826-834.
387 10. Agostini P, Cieslik H, Rathinam S, et al. Postoperative pulmonary
388 complications following thoracic surgery: are there any modifiable risk
389 factors? *Thorax* 2010; 65: 815-818.
390 11. Agostini P, Naidu B, Cieslik H, et al. Comparison of recognition tools for
391 postoperative pulmonary complications following thoracotomy.
392 *Physiotherapy* 2011; 97: 278–283.
393 12. Stéphan F, Boucheseiche S, Hollande J, et al. Pulmonary complications
394 following lung resection: a comprehensive analysis of incidence and possible
395 risk factors. *Chest* 2000; 118: 1263-1270.
396 13. Brunelli A, Al Refai M, Monteverde M, et al. Stair climbing test predicts
397 cardiopulmonary complications after lung resection. *Chest* 2002; 121: 1106-
398 1110.

399   14. Bernard A, Deschamps C, Allen MS, et al. Pneumonectomy for malignant
400   disease: factors affecting early morbidity and mortality. *J Thorac Cardiovasc*
401   *Surg* 2001; 121: 1076-1082.
402   15. Licker MJ, Widikker I, Robert J, et al. Operative mortality and respiratory
403   complications after lung resection for cancer: impact of chronic obstructive
404   pulmonary disease and time trends. *Ann Thorac Surg* 2006; 81: 1830-1837.
405   16. Christensen TD, Vad H, Pedersen S, et al. Venous thromboembolism in
406   patients undergoing operations for lung cancer: a systematic review. *Ann*
407   *Thorac Surg* 2014; 97: 394-400.
408   17. Hu Y, McMurry TL, Isbell JM, et al. Readmission after lung cancer surgery is
409   associated with a 6-fold increase in 90-day postoperative mortality. *J Thorac*
410   *Cardiovasc Surg* 2014; 148: 2261-2267.
411   18. Pezzi CM, Mallin K, Medez AS, et al. Ninety-day mortality after resection for
412   lung cancer in nearly double 30-day mortality. *J Thorac Cardiovasc Surg* 2014;
413   148: 2269-2277.
414   19. Rueth NM, Parsons HM, Habermann EB, et al. The long-term impact of
415   surgical complications after resection of stage 1 nonsmall cell lung cancer: a
416   population-based survival analysis. *Ann Surg* 2011; 254: 368-374.
417   20. Camogeorgakis T, Anagnostopoulos CE, Connery CP, et al. Independent
418   predictors for early and midterm mortality after thoracic surgery. *Thorac*
419   *Cardiovasc Surg* 2007; 55: 380-384.
420   21. Sekine Y, Suzuki H, Yamada Y, et al. Severity of chronic obstructive pulmonary
421   disease and its relationship to lung cancer prognosis after surgical resection.
422   *Thorac Cardiovasc Surg* 2013; 61: 124-130.
423   22. Hedlund JU, Ortqvist AB, Kalin ME, et al. Factors of importance for the long
424   term prognosis after hospital treated pneumonia. *Thorax.*1993;48(8):785-9.
425   23. Prina E, Ranzani OT, Torres A. Community-acquired pneumonia. *Lancet* 2015;
426   386: 1097-1108.
427   24. Schussler O, Alifano M, Dermine H, et al. Postoperative pneumonia after
428   major lung resection. *Am J Respir Crit Care Med* 2006; 173: 1161-1169.
429   25. Stolz, AJ, Schutzner J, Lischke R, et al. Predictors of atelectasis after
430   pulmonary lobectomy. *Surg Today* 2008; 38: 987-992.
431   26. Guo X, Cao H, Xu J, et al. Forced vital capacity predicts long-term survival for
432   curative-resected NSCLC. *Med Oncol* 2014; 31 :146.
433   27. Wang J, Olak J, Ferguson MK. Diffusing capacity predicts operative mortality
434   but not long-term survival after resection for lung cancer. *J Thorac Cardiovasc*
435   *Surg* 1999; 117: 581-6.
436   28. British Thoracic Society Standards of Care Subcommittee on Pulmonary
437   Rehabilitation. Pulmonary rehabilitation. *Thorax* 2001; 56: 8270–334.
438   29. Bradley A, Marshall A, Stonehewer L, et al. Pulmonary rehabilitation
439   programme for patients undergoing curative lung cancer surgery. *Eur J*
440   *Cardiothorac Surg* 2013; 44: 266-271.
441   30. Bluman LG, Mosca L, Newman N, et al. Preoperative smoking habits and
442   postoperative pulmonary complications. *Chest* 1998; 113: 883–889.
443   31. Ramos EM, De Toledo AC, Xavier RF, et al. Reversibility of impaired nasal
444   mucociliary clearance in smokers following a smoking cessation programme.
445   *Respirology* 2011; 16: 849-855.

446 32. Kotani N, Hashimoto H, Sessler DI, et al. Smoking decreases alveolar
447   macrophage function during anesthesia and surgery. *Anesthesiology* 2000;
448   92: 1268–1277.
449 33. Mungo B, Zogg CK, Hooker CM. Does obesity affect the outcome of
450   pulmonary resections for lung cancer? A National Surgical Quality
451   Improvement Program analysis. *Surgery* 2015;157: 792-800.
452 34. Cerfolio RJ, Bryant AS. Survival and outcomes of pulmonary resection for
453   non-small cell lung cancer in the elderly: a nested case-control study. *Ann*
454   *Thorac Surg* 2006; 82: 424-429.
455 35. Agostini P, Adams K, Kalkat M, et al. Is physiotherapy routinely required
456   following video-assisted thoracoscopic surgery? *Interact CardioVasc Thorac*
457   *Surg* 2013; 17 (suppl 2): S155-S162.

458

459 **FIGURE LEGENDS**

460

461 **Figure 1** Effect of PPC on hospital length of stay (days). PPC, postoperative

462 pulmonary complication; LOS, Length of stay; ITU, Intensive treatment unit; HDU

463 High dependency unit, TOTAL; Total length of hospital stay.

464

465 **Figure 2** Overall survival of patients with and without a PPC excluding early

466 postoperative deaths. PPC, Postoperative pulmonary complication; Black line: no

467 PPC, Grey line: PPC.