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Patient-Related Risk Factors for Postoperative Pneumonia Following Lung Cancer Surgery and Impact of Pneumonia on Survival

Research Year Report

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PREFACE

This research year report is based on a study carried out during my medical research year at the Department of Clinical Epidemiology, Aarhus University Hospital, Denmark (February 2013 – October 2013) and The Department of Epidemiology, Boston University, USA (November 2013 – January 2014). During this year, I have been introduced to clinical epidemiology and the methods used in this field.

I would like to express my sincere gratitude to my main supervisor Reimar Thomsen and collaborator Mette Søgaard for always providing skillful and constructive feedback, your positive attitudes as well as being truly engaged in my work throughout the entire year. I have felt that I could come to you with anything and for that, I am truly thankful. Professor Robert Horsburgh for valuable guidance, for sharing your extensive knowledge and widening my understanding of epidemiology. Henrik Toft Sørensen for facilitating the project, providing excellent research facilities, and for generously offering me the opportunity to work on other research projects during my research year.

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LIST OF ABBREVIATIONS

COPD	Chronic Obstructive Pulmonary Disease
CCI	Charlson Comorbidity Index
CI	Confidence Interval
ICD	International Classification of Disease
DNRP	Danish National Registry of Patients
DCR	Danish Cancer Registry
HR	Hazard Ratio
LC	Lung Cancer
NSCLC	Non Small Celled Lung Cancer
OR	Odds Ratio
POP	Postoperative Pneumonia
SCLC	Small Celled Lung Cancer

CONTENTS

ABSTRACT

Objective:

To study patient-related risk factors for postoperative pneumonia (POP) following therapeutic lung cancer (LC) surgery and to investigate the impact of POP on subsequent survival.

Methods:

From January 1 1995 through December 31 2011, we identified all patients undergoing LC surgery in Denmark using nationwide Danish health registries. We examined the association between patient-related risk factors including age, sex, comorbidities, cancer stage, and previous pneumonia history, and the risk of POP within 30 days after surgery using regression analyses. Furthermore, we examined the subsequent survival comparing LC patients with and without POP.

Results:

We identified 268 episodes of POP within 30 days among 7,479 patients undergoing LC surgery (proportion: 3.6%). Strong risk factors for POP included advanced age (age ≥80 years: adjusted odds ratio [aOR]=8.31; 95% CI: 3.14-22.01 as compared to <50 years old), a medical history of previous pneumonia (aOR=2.68; 95% CI: 2.02-3.56), atrial fibrillation (aOR=2.18; 95% CI: 1.43-3.33), obesity (aOR=2.03; 95% CI: 1.16-3.56), and chronic pulmonary disease (aOR=1.90; 95% CI: 1.40-2.57). For the 7,254 patients surviving the 30-day postoperative period, the 31 day-1 year mortality was 21.6% in patients with POP vs. 16.8% in non-POP patients, and the 1-5-year mortality was 62.2% vs. 53.0%, respectively. The adjusted 31 day-1 year hazard ratio (HR) of death in patients with POP was 1.31 (95% CI: 1.00 - 1.73), and the 1-5 year HR 1.22 (95% CI 0.98 - 1.53).

Conclusion:

Major risk factors of POP in patients undergoing LC surgery are advanced age, previous pneumonia history, atrial fibrillation, obesity, and chronic pulmonary disease. In addition, development of POP is a clinical marker for decreased long-term survival of LC.

INTRODUCTION

Postoperative pneumonia (POP) is one of the most common complications in patients with lung cancer (LC) undergoing therapeutic surgical resection.(1,2) In recent studies the reported incidence of POP following LC surgery has ranged from 3.1 to 7.9%.(3-5) High age and advanced versus local malignancy have been the risk factors for POP most consistently reported.(3,4,6,7) Other suggested risk factors include male sex, chronic obstructive pulmonary disease (COPD), low FEV_1%, tobacco-smoking, obesity, diabetes mellitus, extent of surgery, induction therapy, right sided pulmonary surgery, and preoperative airway colonization by potential pathogenic microorganisms.(4,6,8,9) Robust data from large population-based studies are sparse however, and important patient-related potential risk factors including cardiovascular disease (10) and medical history of previous pneumonia (11,12) have not been studied.

Occurrence of POP may be a marker of increased mortality in patients with LC surgery, but data are sparse. A previous population-based study followed 4,033 LC patients from day 90 after surgery in the period January 1, 2000 to December 31, 2004 and found increased long-term mortality associated with occurrence of any major postoperative infectious complication (including pneumonia, mediastinitis, and pleural empyema) with an adjusted death hazard ratio (HR) of 1.67 (95% CI, 1.39–2.01).(5)

To prevent pneumonia in LC patients and understand its impact on the disease course of LC, up-to-date data on POP risk factors and prognosis are needed. We therefore did a population-based cohort study to examine patient-related risk factors for POP following therapeutic LC surgery and to assess the impact of POP on subsequent patient survival.

METHODS

The universal Danish health care system provides tax-supported health care services to all residents, guaranteeing free access to hospitals and primary medical care. The civil registration number (CPR number), a unique identifier assigned to every Danish citizen at birth or immigration, allows for accurate linkage among all medical databases used in this study.(13)

Patients with lung cancer surgery

We used the Danish Cancer Registry (DCR) and the Danish National Registry of Patients (DNRP) to identify all patients in Denmark (current population, 5.6 million) who had a diagnosis of LC and a lung resection date within 180 days following this diagnosis from January 1, 1995 through December 31, 2011 (n=7,479). The 180-day-time window was chosen in order to maximize the probability that the lung resection (i.e. LC surgery) was related to the preceding LC diagnosis and not due to some other lung disease. The DCR contains nationwide data on cancer incidence in Denmark since 1943 and is 95-98% complete and valid.(14) We excluded patients with a previous diagnosis of LC before 1995. We classified LC stage as localized (TNM-stage with N=0, and M=0), regional (TNM-stage with N>0 and M=0), metastasized (TNM-stage with M>0), or unknown (see Appendix). In order to identify the complete history of surgical procedures and a 5-year record of comorbidities at the time of LC surgery, we linked the LC patients to the DNRP. The DNRP, a nationwide registry established in 1977, contains computerized records on 99.4% of all discharges from Danish hospitals. From 1995 onwards, data on hospital specialist outpatient clinics is also included.(15)

Predictors of POP risk and LC prognosis

From the DNRP and Danish Civil Registration System, we assessed data on individual diseases apart from LC. We used Charlson Comorbidity Index (CCI) scores to assess overall comorbidity levels in the study cohort. (15,16) The CCI score is computed as the sum of points (between 1 and 6) assigned to each of the 19 diseases included in the index (see Appendix I). Patients were classified into three levels according to their CCI score: 0 points (‘‘low comorbidity’’); 1-2 points (‘‘moderate comorbidity’’); and ≥ 3 points (‘‘severe comorbidity’’). We excluded LC from the CCI as it represents the index disease under study. We assessed the following groups of frequent (prevalence ≥ 5%) CCI comorbidities as potentially important risk factors for POP: chronic pulmonary disease, cardiovascular disease (including myocardial infarction, congestive heart failure, peripheral vascular disease, and cerebrovascular disease), diabetes mellitus (including diabetes mellitus type I and II, and diabetes with end end-stage organ damage), and any other solitary tumor. We also analyzed the following conditions not included in the CCI: atrial fibrillation, hypertension, obesity, osteoporosis, alcoholism, a medical history of previous pneumonia within the last 5 years (previous pneumonia), sex, age, cancer stage, marital status (married vs. un-married), time from diagnosis to surgery exceeding 60 days, calendar period (1995-2000, 2001-2006, 2007-2011), and surgery type (lobectomy, sleeve- and wedge resection, laparoscopic procedures, and pneumonectomy). (See diagnosis codes in Appendix).

Information on POP

Data on POP was obtained through the DNRP. We defined an episode of POP as either a hospital discharge, a new hospital admission, a hospital outpatient clinic visit or an emergency department visit with a primary or secondary diagnosis code of pneumonia occurring within 0-30 days after

the date of surgery (index-admission with surgery included). We included both viral and bacterial pneumonias (pneumonias of any etiology) (See diagnosis codes in Appendix).

STATISTICAL ANALYSIS

We calculated proportions of POP according to the predefined risk factors. We then used logistic regression to compute crude and adjusted ORs with 95% CIs as a measure of the relative risk of POP within 30 days after LC surgery among patients with a given risk factor, compared with patients without the risk factor, adjusting for sex, age group, CCI score and cancer stage (excluding patients with unknown cancer stage). Estimates for frequent groups of frequent CCI comorbidities were adjusted for the rest CCI score excluding the given comorbidities.

Patients were followed from day 31 (end of the postoperative period) after LC surgery until death, migration, or end of follow-up, whichever came first. We estimated and plotted 31 days - 1 year-, and 1-5 years cumulated mortality and mortality rates according to presence or absence of POP for all LC surgery patients, using the Kaplan-Meier method. Subsequently, we used Cox proportional hazards regression model to compute 31 days - 1 year, and 1 - 5 years HRs with 95% CIs as a measure for the relative risk of death for LC patients with POP. HRs associated with POP were adjusted for sex, age, CCI level, cancer stage, and time from diagnosis to surgery exceeding 60 days.

All statistical analyses were performed using STATA software (version 12.0 StataCorp LP, College Station, TX).

RESULTS

Patient characteristics

We identified 7,479 patients (3,502 (46.8 %) women and 3,977 (53.2 %) men) with a first time diagnosis of LC and LC surgery between 1995 and 2011 (Table 1). Of these 268 (3.6 %) received a diagnosis of POP within a median of 10 days after surgery (IQR: 6-18 days); and 4.3% of men vs. 2.8% women developed POP. The risk of POP increased with advanced age and POP developed in 1.1% of patients <50 years compared with 4.4% in patients aged 70-79 years, and 9.7 % in patients aged ≥80 years. Table 1 shows the proportions of POP associated with different characteristics. The incidence of recorded POP increased in the later calendar periods. In total, 41.9 % of the patients had previous hospital-diagnosed comorbidity (CCI score > 0), including 13.4% with chronic pulmonary disease. Of these, 4.9% with moderate comorbidity and 4.5% with severe comorbidity developed POP compared with 2.7% in patients without recorded comorbidities. A number of 19 patients (0.3 %) died on the day of LC surgery. We identified 971 (13.0% of total) patients with a history of previous pneumonia of which 79 (8.1%) developed POP.

Risk factors for POP

After adjustment the strongest risk factors for POP included advanced age (age ≥80 years: adjusted OR=8.31; 95% CI: 3.14-22.01 as compared to <50 years old), previous pneumonia (OR=2.68; 95% CI: 2.02-3.56), atrial fibrillation (OR=2.18; 95% CI: 1.43-3.33), obesity (OR=2.03; 95% CI: 1.16-3.56), and chronic pulmonary disease (OR=1.90; 95% CI: 1.40-2.57). The groups of frequent CCI comorbidities showed moderate risk factors in the form of any diabetes (OR=1.40; 95% CI: 0.86 - 2.28), and cardiovascular disease (OR=1.37; 95 % CI: 1.01 - 1.84). Other moderate risk factors were male sex (OR=1.39 (95% CI: 1.08 - 1.80) and alcoholism with an OR of 1.30 (95% CI: 0.68 - 2.51). Interestingly, increasing cancer stage did not increase the risk of POP.

During the study period, we observed substantial changes in types of LC surgery. For this reason, we present a sub analysis of risk for POP according to surgery type for the years 2009-2011 in Table 3 (The national integrated cancer pathways, allowing fast, structured, and uniform work-up and initiation of treatment in all patients with suspected cancer was implemented in 2009). Compared to patients with lobectomy, we found the following estimates for POP in patients with pneumonectomy (OR=4.25; 95 % CI: 0.84-21.50), patients with sleeve- and wedge resection (OR=1.44; 95% CI: 0.73-2.85), and patients with laparoscopic procedures (OR=0.53; 95 % CI: 0.32-0.87).

Mortality analysis

A total of 225 patients (3.0%) died within the 30 days postoperatively. Median survival beyond this 30-day postoperative period was 4.34 years (95% CI: 4.12-4.58) in non-POP patients vs. 3.36 years (95% CI: 2.42 - 4.39) in patients with POP. The 1-year and 5-year mortalities were 16.8% vs. 21.6%, and 53.0% vs. 62.2%, in non-POP vs. POP-patients, respectively. The Kaplan-Meier survival curves from day 31 to 5 years postoperatively show consistent higher mortality in LC patients with POP compared to LC patients without POP (Figure 1). The crude 31 days-1 year HR was 1.34 (95% CI, 1.02 - 1.75), and the crude 1-year-5 years HR was 1.20 (95% CI, 0.97 - 1.50). After adjustment for differences in prognostic factors, the adjusted 31 days-1 year, 1 year- 5 years HRs in patients developing POP were 1.31 (95% CI: 1.00-1.73), and 1.22 (95% CI, 0.98-1.53), respectively (Table 4).

DISCUSSION

This large 17-year nationwide study shows that strong risk factors for POP in LC patients are advanced age, a history of previous pneumonia, atrial fibrillation, obesity, and chronic pulmonary

disease. Moreover, male sex, diabetes with or without complications, any cardiovascular disease, and alcoholism increase the risk of POP moderately, i.e. by 30-40%. In addition, our study provides evidence that development of POP within the first 30 days postoperatively predicts worse long-term survival.

Many of the identified risk factors for POP following LC surgery are similar to known risk factors for community-acquired pneumonia in general populations.(10,17) One exception is atrial fibrillation, however in one previous study postoperative atrial fibrillation has been shown to be a strong risk factor for POP in 162 patients undergoing cardiac surgery.(18) A German questionnaire-based case-control study of 1,137 cases with community-acquired pneumonia and 1,044 controls has found that a history of community-acquired pneumonia increases the risk of a subsequent new pneumonia with an adjusted OR of 1.6 (95% CI: 1.3–2.1).(12) These results are further supported by the findings of a Spanish case-control study, though they reported a crude OR of 2.39 (95% CI: 1.88–3.05).(11) Our new findings concerning previous pneumonia as a risk factor of POP following LC surgery are corroborated by the above-mentioned shared risk factors for POP and community-acquired pneumonia along with previous pneumonia as a predictor of subsequent pneumonia episodes. This association is clinically important and may be a cost-effective screening tool to identify patients at high risk of POP.

We did not observe an increased POP risk with increasing cancer stage. This result is contrary to the findings of Shiono and colleagues who studied 2,105 patients undergoing LC surgery and found an adjusted OR for POP at 2.23 (95% CI: 1.27 - 3.92) for cancer stages ≥ III compared to stages I/II.(4) The explanation for this is not obvious, but could in theory be due to less lung tissue remaining for pneumonia development with increasing levels of resection/cancer stage. However, this does not agree with our finding of the highest risk of POP in patients undergoing

pneumonectomy. We speculate that patients with advanced stages of LC might be less likely to have a POP registered and coded at discharge since pneumonia might be less clinically important relative to advanced LC.

The incidence of recorded POP episodes increased over calendar time most likely due to increased registration/coding or improvement in diagnostic procedures in recent calendar periods. However, we cannot rule out that changes in LC surgery procedures over time may have contributed, though this seems unlikely.

The finding that occurrence of POP predicts poorer long-term survival in LC agrees with the results of Andalib and colleagues. Compared to their finding that any major infectious postoperative complication increased the long-term hazard of death from LC with an adjusted HR of 1.67, our observed adjusted death HRs of 1.22 to 1.31 associated with occurrence of POP tended to be somewhat lower.(5) This is to be expected since not only POP, but also mediastinitis and pleural empyema were included as major infections complications in Andalibs study. It is likely that POP is a marker of general poor condition in a LC patient and therefore explains our observation of increased long-term mortality. POP may nevertheless also causally contribute to increased mortality by mechanisms such respiratory failure, bacteremia with sepsis and shock, as well as disseminated intravascular coagulation causing multiple organ failure.(19)

Main strengths of our study include its large size and use of population-based registries with high validity as well as near complete follow-up, which in combination with data prospectively collected before LC surgery, eliminated the possibility for recall bias.(15) Still, there is a possibility of unmeasured confounding by variables not available in registries. We did not have information on tobacco smoking, which is a major risk factor for both LC and pneumonia.(10,20)

Some studies have shown that both COPD and a FEV_1/FVC ratio < 0.7 are risk factors for POP following any kind of lung resection.(4,21) Although we lacked detailed data on smoking, we did control for hospital diagnoses of COPD in the group chronic pulmonary diseases as well as other diseases related to lifestyle (e.g., cardiovascular disease).

In conclusion, this study provides evidence for several important risk factors for POP in LC patients undergoing LC surgery, at least some of which are modifiable before surgery, such as atrial fibrillation, obesity, and alcohol abuse. Development of POP predicts decreased long-term survival of operated LC, and clinicians should remain vigilant in preventing and treating pneumonia and other infections in these patients.

Conflict of interest

None to declare.

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TABLES

Table 1: Descriptive table of preoperative risk factors for postoperative pneumonia in 7,479 patients with LC undergoing LC surgery.

Risk factors	n with risk factor (% of all LC patients)	n with POP (% within risk factor category)
Sex		
Male sex	3,977 (53.2 %)	169 (4.3 %)
Female sex	3,502 (46.8 %)	99 (2.8 %)
Age groups (in years)		
< 50	457 (6.1 %)	5 (1.1 %)
50-59	1,501 (20.1 %)	39 (2.6 %)
60-69	2,822 (37.7 %)	91 (3.2 %)
70-79	2,430 (32.5 %)	107 (4.4 %)
≥ 80	269 (3.6 %)	26 (9.7 %)
Calendar period		
1995-2001	2,221 (29.7 %)	45 (2.0 %)
2002-2006	2,165 (29.0 %)	92 (4.3 %)
2007-2011	3,093 (41.4 %)	131 (4.2 %)
Comorbidity		
Individual diseases in CCI		
Myocardial infarction	248 (3.3 %)	14 (5.7 %)
Congestive heart failure	246 (3.3 %)	16 (6.5 %)
Peripheral vascular disease	527 (7.1 %)	21 (4.0 %)
Cerebrovascular disease	431 (5.8 %)	22 (5.1 %)
Dementia	16 (0.2 %)	2 (12.5 %)
Chronic pulmonary disease	1,003 (13.4 %)	61 (6.1 %)
Connective tissue disease	230 (3.1 %)	13 (5.7 %)
Ulcer disease	210 (2.8 %)	12 (5.7 %)
Mild liver disease	65 (0.9 %)	3 (4.6 %)
Diabetes I and II	213 (2.9 %)	12 (5.6 %)
Hemiplegia	10 (0.1 %)	1 (10.0 %)
Moderate to severe renal disease	91 (1.2 %)	7 (7.7 %)
Diabetes with end-stage organ damage	141 (1.9 %)	7 (5.0 %)
Other solitary tumor	560 (7.5 %)	17 (3.0 %)
Leukemia	28 (0.4 %)	0 (0.0 %)
Lymphoma	80 (1.1 %)	1 (1.3 %)
Moderate to severe liver disease	10 (0.1 %)	0 (0.0 %)
Metastatic solid tumor	248 (3.3 %)	7 (2.8 %)
AIDS	3 (0.0 %)	0 (0.0 %)
CCI Score		
CCI score: 0 (no comorbidity)	4,345 (58.1 %)	117 (2.7 %)
CCI score : 1-2 (moderate comorbidity)	2,407 (32.2 %)	118 (4.9 %)
CCI score: ≥ 3 (severe comorbidity)	727 (9.7 %)	33 (4.5 %)
Frequent CCI comorbidities		
Cardiovascular disease	1,250 (16.7 %)	66 (5.3 %)
Any diabetes	354 (4.7 %)	19 (5.4 %)
Conditions not included in CCI		
Obesity	213 (2.9 %)	14 (6.6 %)
Alcoholism	222 (3.0 %)	10 (4.5 %)

Osteoporosis	289 (3.9 %)	11 (3.8 %)
Previous pneumonia	970 (13.0 %)	79 (8.1 %)
Hypertension	780 (10.4 %)	28 (3.6 %)
Atrial fibrillation	359 (4.8 %)	27 (7.5 %)
Married	4,548 (60.8 %)	156 (3.4 %)
Cancer Stage		
Localized	4,825 (64.5 %)	183 (3.8 %)
Regional	1,869 (25.0 %)	60 (3.2 %)
Metastatic	567 (7.6 %)	13 (2.3 %)
Unknown	218 (2.9 %)	12 (5.5 %)
Factors related to time between diagnosis and surgery		
Neoadjuvant radio therapy	45 (0.6 %)	2 (4.4 %)
Neoadjuvant chemo therapy	128 (1.7 %)	3 (2.3 %)
Time from diagnosis to surgery > 60 days	1,192 (15.9 %)	42 (3.5 %)
Type of surgery (whole study period: 1995-2011)		
Lobectomy	4,972 (66.5 %)	190 (3.8 %)
Sleeve- and segment resection	776 (10.4 %)	31 (4.0 %)
Laparoscopic surgery	1,486 (19.9 %)	41 (2.8 %)
Pneumonectomy	245 (3.3 %)	6 (2.5 %)
Type of surgery (years 2009-2011)		
Lobectomy	863 (44.3 %)	47 (5.5 %)
Sleeve resection	144 (7.4 %)	13 (9.0 %)
Laparoscopic surgery (all types)	930 (47.7 %)	30 (3.2 %)
Pneumonectomy	12 (0.6 %)	2 (16.7 %)

CCI: Charlson Comorbidity Index, LC: Lung Cancer

Table 2: Preoperative risk factors for postoperative pneumonia in 7,479 Danish patients with lung cancer undergoing lung cancer surgery.

Variables	Crude OR (95% CI)	Adjusted OR (95% CI)
Male sex	1.53 (1.19 - 1.96)	1.39 (1.08 - 1.80)
Age groups (in years)		
< 50	1.00	1.00
50-59	2.41 (0.94 - 6.15)	2.28 (0.89 - 5.83)
60-69	3.01 (1.22 - 7.45)	2.64 (1.06 - 6.55)
70-79	4.16 (1.69 - 10.27)	3.44 (1.39 - 8.52)
≥ 80	9.67 (3.67 - 25.51)	8.31 (3.14 - 22.01)
Comorbidity		
CCI Score		
CCI score: 0 (low comorbidity)	1.00	1.00
CCI score : 1-2 (moderate comorbidity)	1.86 (1.44 - 2.42)	1.74 (1.34 - 2.27)
CCI score: ≥ 3 (severe comorbidity)	1.72 (1.16 - 2.55)	1.67 (1.12 - 2.49)
Frequent CCI comorbidities		
Cardiovascular disease	1.66 (1.25 - 2.21)	1.37 (1.01 - 1.84)
Chronic pulmonary disease	1.92 (1.43 - 2.58)	1.90 (1.40 - 2.57)
Any diabetes	1.57 (0.97 - 2.53)	1.40 (0.86 - 2.28)
Other solitary tumor	0.75 (0.46 - 1.22)	0.77 (0.47 - 1.28)
Conditions not included in the CCI		
Obesity	1.94 (1.11 - 3.39)	2.03 (1.16 - 3.56)
Alcoholism	1.28 (0.67 - 2.44)	1.30 (0.68 - 2.51)
Osteoporosis	1.07 (0.58 - 1.97)	1.14 (0.61 - 2.13)
Previous pneumonia	2.96 (2.26 - 3.89)	2.68 (2.02 - 3.56)
Hypertension	1.00 (0.67 - 1.49)	0.90 (0.60 - 1.36)
Atrial fibrillation	2.32 (1.54 - 3.51)	2.18 (1.43 – 3.33)
Time from diagnosis to surgery > 60 days	0.95 (0.68 - 1.33)	1.06 (0.75 - 1.50)
Married	0.89 (0.70 - 1.14)	0.86 (0.66 - 1.12)
Cancer stage		
localized	1.00	1.00
regional	0.84 (0.63 - 1.13)	0.85 (0.63 - 1.14)
metastatic	0.60 (0.34 - 1.05)	0.62 (0.35 - 1.10)
unknown	1.48 (0.81 - 2.69)	1.48 (0.81 - 2.70)

CCI: Charlson Comorbidity Index.

Following variables adjusted for each other: Sex, age, CCI score, cancer stage. CCI disease groups each adjusted for: sex, age, cancer stage (unknown stage excluded), and rest CCI score. Comorbidities and risk factors not in the CCI each adjusted for: sex, age, cancer stage (unknown stage excluded), and CCI score.

Table 3: Type of surgery and risk of postoperative pneumonia in 1,949 Danish patients with LC undergoing LC surgery in the years 2009-2011.

	n	POP	Crude OR (95% CI)	Adjusted OR (95% CI)
Surgery types				
Lobectomy	930	30 (3.2 %)	1.00	1.00
Sleeve- and wedge resection	144	13 (9.0 %)	1.72 (0.91 - 3.27)	1.44 (0.73 – 2.85)
Laparoscopic (all types)	863	47 (5.5 %)	0.58 (0.36 - 0.92)	0.53 (0.32 - 0.87)
Pneumonectomy	12	2 (16.7 %)	3.47 (0.74 - 16.30)	4.25 (0.84 – 21.50)

Adjusted for: age, sex, CCI score, and cancer stage (patients with unknown stage excluded [n=28]). CI: Confidence Interval, LC: lung cancer, OR: Odds Ratio.

Table 4: Postoperative pneumonia and mortality in 7,254 patients undergoing lung cancer surgery.

Follow-up interval	Cumulated mortality POP (%)	Cumulated mortality non-POP	Crude HR (95 % CI)	Adjusted HR (95% CI)
31 days - 1 year	21.6 %	16.8 %	1.34 (1.02 - 1.75)	1.31 (1.00 - 1.73)
1 year – 5 years	62.2 %	53.0 %	1.20 (0.97 - 1.50)	1.22 (0.98 - 1.53)

*225 patients died within 30 first days. Estimates adjusted for sex, age, CCI score, cancer stage, and time between diagnosis and surgery > 60 days. CI: Confidence Interval, HR: Hazard Ratio

FIGURES

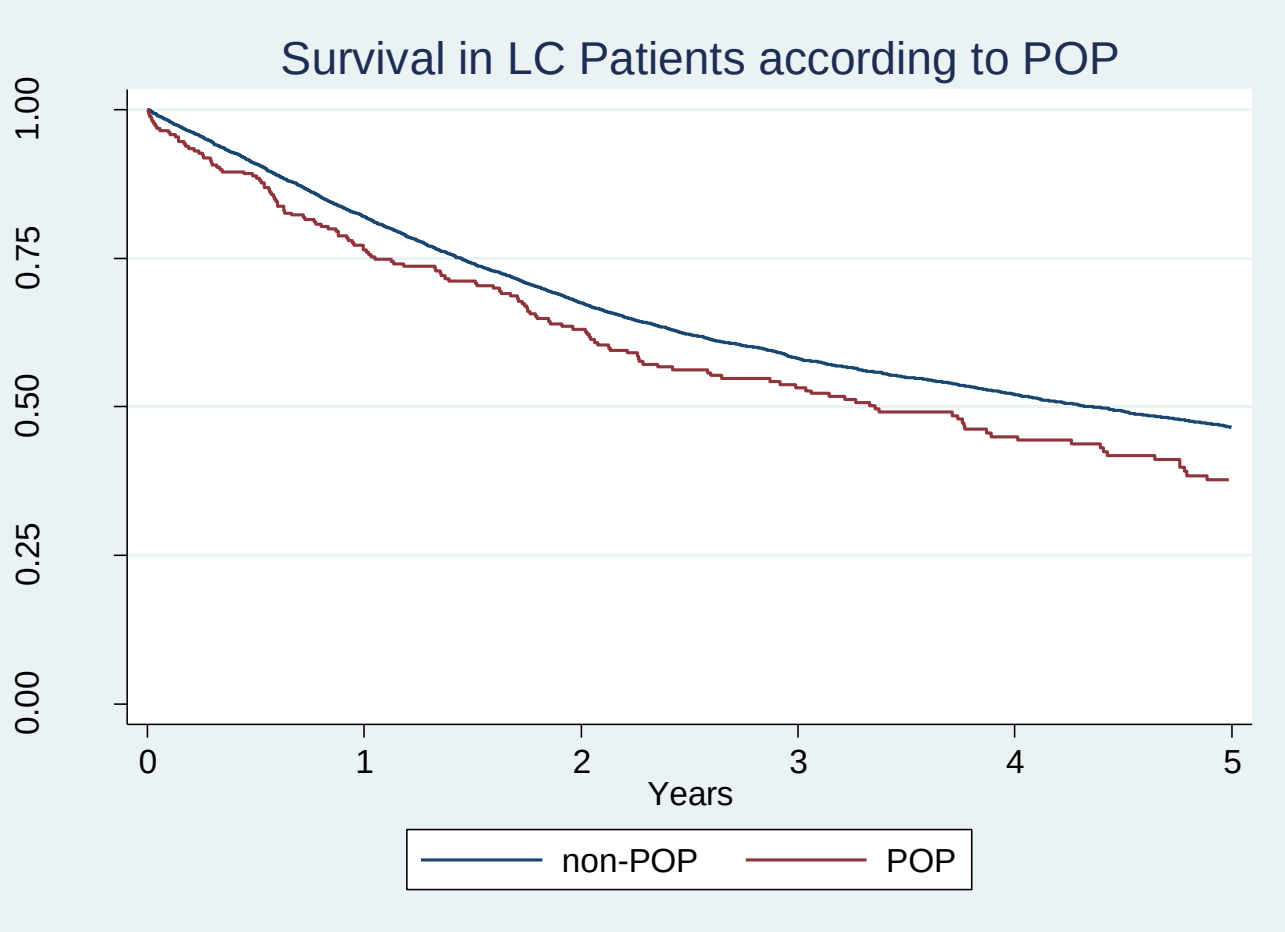


Fig. 1: Kaplan-Meier survival curve of survival in patients undergoing LC surgery according to the presence of POP. LC patients followed from postoperative day 31.
LC: Lung Cancer, POP: Postoperative Pneumonia

APPENDIX

Table 5: International Classification of Disease (ICD)-8 and ICD-10 Diagnosis Codes Used in: "PATIENT-RELATED RISK FACTORS FOR POSTOPERATIVE PNEUMONIA FOLLOWING LUNG CANCER SURGERY AND IMPACT ON SURVIVAL"

Disease Category	ICD-8	ICD-10
Lung cancer	NA	C33-34
Lobectomy	35240-35370	KGDC00, KGDC10, KGDC13, KGDC20, KGDC23, KGDC26, KGDC96
Sleeve- and segment resection	35200	KGDB10, KGDB20
Laparoscopic surgery	NA	KGDD01, KGDD11, KGDD97, KGDC01, KGDC11, KGDC97, KGDB11, KGDB21
Pneumonectomy:	35380-35400	KGDD00, KGDD10, KGDD20, KGDD23, KGDD26, KGDD96
Risk factors:		
Diseases included in the Charlson comorbidity index (CCI): myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, type 1 or 2 diabetes, hemiplegia, moderate to severe renal disease, type 1 or 2 diabetes with end organ damage, any tumor, leukemia, lymphoma, moderate to severe liver disease, metastatic solid tumor, AIDS	410, 427.09, 427.10, 427.11, 427.19, 428.99, 782.49, 440, 441, 442, 443, 444, 445, 430-438, 290.09-290.19, 293.09, 490-493, 515-518, 712, 716, 734, 446, 135.99, 530.91, 530.98, 531-534, 571, 573.01, 573.04, 249.00, 249.06, 249.07, 249.09, 250.00, 250.06, 250.07, 250.09, 344, 403, 404, 580-583, 584, 590.09, 593.19, 753.10-753.19, 792, 249.01-249.05, 249.08, 250.01-250.05, 250.08, 140-194, 204-207, 200-203, 275.59, 070.00, 070.02, 070.04, 070.06, 070.08, 573.00, 456.00-456.09, 195-198, 199, 079.83	I21, I22, I23, I50, I11.0, I13.0, I13.2, I70, I71, I72, I73, I74, I77, I60-I69, G45, G46, F00-F03, F05.1, G30, J40-J47, J60-J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3, M05, M06, M08, M09, M30, M31, M32, M33, M34, M35, M36, D86, K22.1, K25-K28, B18, K70.0-K70.3, K70.9, K71, K73, K74, K76.0, E10.0, E10.1, E10.9,E11.0, E11.1, E11.9, G81, G82, I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61,E10.2-E10.8, E11.2-E11.8, C00-C75, C91-C95, C81-C85, C88, C90, C96,B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85, C76-C80, B20-B24
Main outcome:		

Any postoperative pneumonia (POP)	480–486; 073; 471;	J12-J18, A481, A709
Alcoholism related disorders: alcohol-psychosis, alcoholic liver disease, acute alcoholic pancreatitis, chronic alcoholic pancreatitis, alcohol-induced pseudo-Cushings syndrome, alcohol addiction and psychiatric consequences, alcoholic polyneuropathia, alcoholic myopathia, degenerative changes in the nervous system caused by alcohol, alcoholic cardiomyopathia, alcoholic gastritis, problems with alcohol-abuse, alcoholic liver disease, disulfiram-alcohol reaction, alcoholic pellagra, contact about rehabilitation after alcohol abuse, advice and control of alcohol abuse	291, 303, 979.59, 571.0, 577.10	K70, K852, K860, F101-F109, G621, G721, G312x, I426, K292, Z721, K70, T500A, E244, E529A, Z502, Z714
Atrial Fibrillation	427.4, 427.93, 427.94	DI48, BFCB02, BFCB52, BFFB03, BFFB04, DI513A, BFFA04
Osteoporosis	723.0	BLHM7, BUBS3, DM80, DM81, DM82
Hypertension	401, 402, 403, 404, 410.0, 400, 411.0, 412.0, 412.1, 413.0, 414.0	DI10, DI15, DI11, DI12, DI13, DI674, DH350H, FB4200
Obesity	277	BBHC, BUBS0, DE65, DE66, BZFA21, DZ718B2, DZ488D, DT983B
Neoadjuvant chemotherapy		BWHA
Neoadjuvant radiation therapy		BWG

Table 6: Distribution of pneumonia diagnoses in 268 patients with POP after LC surgery.	
Pneumonia diagnosis	n (% of total pneumonias)
(DJ139) Pneumonia w. S. Pneumoniae	2 (0.8 %)
(DJ149) Pneumonia w. H. Influenzae	2 (0.8 %)
(DJ150) Pneumonia w. K. Pneumoniae	2 (0.8 %)
(DJ152) Staphylococcal pneumonia	2 (0.8 %)
(DJ154) Streptococcal pneumonia	1 (0.4 %)
(DJ155) Pneumonia w. E. Coli	1 (0.4 %)
(DJ158) Other bacterial pneumonia	5 (1.9 %)
(DJ159) Bacterial pneumonia NOS	37 (13.8 %)
(DJ180) Bronchopneumonia	9 (3.4 %)
(DJ181) Lobar pneumonia	7 (2.6 %)
(DJ189) Pneumonia NOS	200 (74.6 %)

LC: Lung Cancer; POP: Postoperative Pneumonia

DANSK RESUMÉ

Formål: Formålet med dette kohortestudie var at undersøge sammenhængen mellem patientrelaterede risikofaktorer for postoperativ pneumoni (POP) efter kurativt intenderet operation for lungecancer samt at undersøge overlevelsen efter POP.

Metode: Ved hjælp af nationale danske sundhedsregistre fandt vi frem til alle danske patienter opereret for lungecancer i perioden 1. januar 1995 til 31. december 2011. Vi undersøgte med logistisk regressionsanalyse associationen mellem patientrelaterede risikofaktorer herunder alder, køn, komorbiditet, cancerstadium, tidligere pneumonihistorik, og risikoen for POP inden for de første 30 dage postoperativt. Efterfølgende brugte vi Cox regression til at undersøge overlevelsen for lungecancerpatienter hhv. med og uden POP.

Resultater: Ud af 7.479 patienter opereret for lungecancer fandt vi 268 tilfælde af POP (proportion: 3,6 %). Betydende risikofaktorer for POP var fremskreden alder (alder ≥80 år: justeret odds ratio [aOR]= 8.31; 95% CI: 3.14-22.01 sammenlignet med patienter under 50 år), tidligere pneumoni (aOR=2.68; 95% CI: 2.02-3.56), atrieflimren (aOR=2.18; 95% CI: 1.43-3.33), fedme (aOR=2.03; 95% CI: 1.16-3.56), og kronisk lungesygdom (aOR=1.90; 95% CI: 1.40-2.57). For de 7.254 patienter, der overlevede de første 30 dage postoperativt var 31-365-dages mortaliteten 21,6 % for patienter, der udviklede POP og 16,8 % for de, der ikke gjorde. 1-5-års-mortaliteten var hhv. 62.2% og 53.0% for de to grupper. Den justerede 31-365 dages hazard ratio (HR) for død hos patienter med POP var 1.31 (95% CI: 1.00 - 1.73), og 1-5 års HR var 1.22 (95% CI 0.98 - 1.53).

Konklusion: Vigtige risikofaktorer for POP hos patienter, der opereres for lungecancer er fremskreden alder, tidligere pneumoni, atrieflimren, fedme, og kronisk lungesygdom. Derudover er POP en klinisk markør for dårligere langtidsoverlevelse efter operation for lungecancer.

Supplementary Information

Background: LC patients as the population under study

With an annual 3.900 new cases in Denmark and 1.8 million new cases (12.9% of the total) globally in 2012 LC is the most common type of cancer in Denmark as well as in the world.(22) LC patients constitute a heterogeneous population but from a treatment perspective, they can be divided into patients with small-celled lung cancer (SCLC), which constitute approximately 10-15% of all LC, and patients with non-small celled lung cancers (NSCLC). SCLC is an aggressive form of LC and hence rarely operable at the time of diagnosis. Nonetheless, SCLC is relatively sensitive to chemotherapy and for this reason; the treatment of SCLC is primarily chemo- and/or radiation therapy.(23) The mainstay of curative treatment of NSCLC is surgical resection, which is possible in about 25% of the cases.(24) It is therefore important to keep in mind that this study only deals with a fraction of the total population of patients with LC.

LC Staging

An LC patient's eligibility for surgical resection is determined through the staging process and the staging of LC is based on the TNM-classification system. The TNM system serves to place LC growth at a particular stage, and includes the overall features of the tumor (T), lymph nodes (N), and metastatic status (M). Apart from hidden, yet to be identified tumors (occult: TxN0M0) and confined carcinomas in situ (stage 0; tis), there are four basic stages (I-IV) of LC within the TNM classification system (Table 5). In Table 5, the operability of the different LC stages can also be seen.

Table 5: Staging of LC within the TNM classification system

Stage	**TNM-stages**	**Treatment**
Ia	T1, N0, M0	Operable
Ib	T2, N0, M0	Operable
IIa	T1, N1, M0	Operable
IIb	T2, N1, M0 or T3, N0, M0	Operable
IIIa	T1-2, N2, M0 or T3, N1-2, M0	Possibly operable
IIIb	T(any), N3, M0 or T4, N(any), M0	Inoperable
IV	T(any), N(any), M1	Inoperable

LC: Lung Cancer

Research Objectives

This study comprised two main objectives:

Study 1: The primary objective was to examine the associations between multiple patient-related risk factors (Study 1 exposures) and POP (Study 1 outcome) in patients undergoing LC surgery (study population).

Study 2: The secondary objective was to assess the mortality (Study 2 outcome) in LC patients with POP (Study 2 exposure) compared to LC patients without POP.

To encompass both these objectives we designed a prospective cohort study of patients undergoing LC surgery using nation-wide Danish health registries. The design enabled us to make both an analysis of preoperative risk factors for POP and follow the cohort exposed to POP for a long period of time comparing these LC patients' risk of death with the unexposed cohort. With exposures recorded prior to the outcomes the study classifies to the term *prospective* even though it was based on analysis of historical data.(25) The design enabled us to collect 5 years of previous medical history for each LC patient and follow each LC patient from different times of entry until death, censoring due to emigration, or end of follow-up.

Methodological considerations

In the following different methodological issues will be defined and addressed where they might appear in the study at hand. Rather than discussing strengths and limitations of the study in a separate section, this discussion will take place according to the theoretical constructs of sources of error.

The estimates in the study represent the product of all elements of study design, study conduct, and data analysis. The overall methodological goal of the study was to obtain *reliable* and *valid* estimates of the associations between exposures and outcomes with *generalizability* to a target population.(26) *Reliable* estimates are characterized by little random error or high precision (i.e. estimates with narrow confidence intervals) – a property of large study populations and large number of outcomes. The main advantage of epidemiological studies such as ours is thus precision and this will not be discussed in further detail. *Valid* estimates on the other hand are results of accuracy and refers to the absence of systematic errors or biases in the estimates of causal associations. By *generalizability*, we understand the legitimacy of inference to the target population, and in nationwide population-based studies such as this, *generalizability* is high if *internal validity* is high.

We can classify violations of *internal validity* into *selection-*, *information-*, and *confounding biases*. Only *confounding biases* can be dealt with in statistical analyses and will therefore be discussed in the statistical methods section. *Selection-*, and *information* bias should for this reason be eliminated or reduced through the design of the study.(26)

Selection bias

Selection bias is a result of a systematic error that influences study participation or the procedures used to select subjects for the study. The bias arises when the association of exposure and outcome is different between study-participants and non-participants.(26) *Selection bias* due to identification is of relevance to this study since we analyzed historical data in registries and therefore had to identify them through certain criteria. We restricted to LC patients with a maximum of 180 days between date of diagnosis and date of surgery. Since surgical procedure codes of lung resection registered in the DNRP are not exclusive to LC surgery this restriction was

made in order to maximize the probability that a lung resection was related to the preceding LC diagnosis (i.e. LC surgery) and not some other lung disease. Examples of other conditions that require surgical lung resection are volume reduction and bulla pulmonis (emphysema surgery). Procedure codes exclusive to emphysema surgery do exist, but so far, no validation studies have examined the coding in DNRP of lung resection due to these conditions. Because of the lack of exclusiveness to LC surgery codes it can be argued that some emphysema surgery might be coded similar to regular lung resection and hence LC, which argues for the 180-day time restriction. We cannot know whether the LC patients undergoing LC surgery beyond this 180-day time window differed from the LC patients studied according to the risk of POP. From our analyses we know that compared to patients undergoing LC surgery within 60 days from date of diagnosis the LC patients exceeding this time window did not have an increased risk of POP (aOR=1.03 (95% CI: 0.73 - 1.46). This argues against *selection bias* as a substantial error in the data. The 180-day restriction is thus a practical compromise that increases the *internal validity* of the study at the cost of some *precision*. However, it is possible that LC patients with increased time between diagnoses and surgery dates are more likely to undergo neoadjuvant chemo- and/or radiotherapy. Especially radiotherapy is known to cause pneumonitis, which is likely to increase the risk of POP and our study is limited from inferring on these patients.(27) It can be argued that, the risk found for LC patients included in the study probably also apply to those who exceeded the 180-day time restriction. In sum, it can be argued that in this study *selection bias* caused by the 180-day time restriction is not a violation of *internal validity* and thus *generalizability* especially when inferring on populations of LC patients undergoing surgery within 180 days after diagnosis.

Information bias

Information bias occurs when there is a systematic error in the collection of information on exposure and/or outcome.(26) When information on exposure or outcome is incorrect we call it *misclassification*. *Misclassification* can be either *differential* (i.e. systematic) which for dichotomous variables biases the association in an unpredictable manner or *non-differential*, which generally biases the association towards the null.

Information bias of the exposures could have arisen from incorrect coding of the comorbidities and conditions examined as risk factors for POP in Study 1. Previous validation studies of the comorbidities in the CCI have shown a high positive predictive value of 98.0% in the DNRP, whereas completeness or sensitivity is likely to be less high.(28) A low sensitivity can result in erroneously low CCI scores with a tendency of shift from higher categories towards lower. In this specific case, the *non-differential misclassification* of the polytomous exposure will then result in a weakening of the estimated association between CCI and POP. Because of the bias towards null, an association between a dichotomous exposure and an outcome found in spite of the presence of *non-differential misclassification* is generally strong proof of a true association. Data on most of the risk factors found for POP are dichotomous and extracted from the DNRP including cardiovascular disease, chronic pulmonary disease, diabetes, obesity, alcoholism, previous pneumonia, and atrial fibrillation.

It can be argued that the presence of substantial *differential misclassification* is more devastating to any study than *non-differential misclassification*, especially if the direction of the resulting bias is unpredictable. The surprising finding of decreasing risk of POP (Study 1 outcome and Study 2 exposure) with increasing cancer stage might be the result of *differential misclassification* if LC patients with high stages of cancer less frequently are diagnosed/coded with POP in its presence.

Even if this is the case, our conclusions on risk factors for POP other than cancer stage do not change.

STATISTICAL METHODS

Study 1

We examined the associations between the different patient-related risk factors and POP using logistic regression analyses. Whereas an outcome is continuous in linear regression, in logistic regression the outcome variable is binary such as POP vs. non-POP in our Study 1. Logistic regression requires linearity of the log odds but it does not require any assumptions about the distribution of the explanatory variables and these can be continuous, binary or categorical.(29) A requirement is independence between the individual observations and it can be argued that this assumption is fulfilled for all the exposure variables used in this study. This is especially true for variables where clustering do not occur. For instance, it is impossible to think that a DNRP diagnosis of atrial fibrillation for one LC patient can affect another LC patient's DNRP diagnosis of atrial fibrillation. When dealing with infectious diseases however, because of outbreaks clustering can occur.(30) In theory, it is therefore possible that an LC patient with POP has infected another LC patient in our study. Nevertheless, it is highly unlikely that this is a common phenomenon in our data requiring special attention. The same can be said about a history of previous pneumonia and we argue that the assumption of independency is fulfilled.

Logistic regression can be used to estimate ORs as a measure of risk. In short, risks as probabilities may take any value between 0 and 1, and odds are the probability of outcome divided by the probability that it does not happen. ORs are then the odds in the exposed group divided by the odds in the unexposed group.

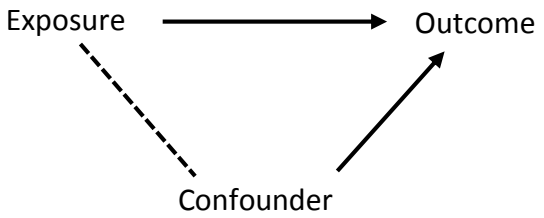
$$\text{Odds} = \frac{\text{Probability (A happens)}}{\text{Probability (A does not happen)}}$$

$$\text{Exposure odds ratio} = \frac{\text{(Odds in exposed group)}}{\text{(Odds in unexposed group)}}$$

ORs are more difficult to understand than relative risks. However, if the outcome of measure is a rare event (probability < 0.1), ORs approach the relative risk and interpretation is similar.(31) Because POP is a rare event in this study, we can interpret the ORs as if they were relative risks.

Confounding

When dealing with different covariates, some of them may become confounders by obscuring the association under study (e.g. between a single risk factor and POP). Confounding is a systematic error, leading us to mix or confuse the effect of an exposure with the effect of another variable; the confounder. The following characteristics apply to confounders: A confounder is associated with both the exposure (risk factor) and the outcome under study (POP). Furthermore, a confounder cannot be an intermediate step in the causal path between exposure and outcome. The relationship between exposure, outcome, and the confounder is illustrated below:



Age is an example of a confounder in the association between cardiovascular disease and POP. Age is associated with cardiovascular disease as well as POP without being in the causal path (i.e. cardiovascular disease does not cause age increase). Studying this association without at least adjusting for age would bias the estimate towards an increased association possibly resulting in a

type I error (i.e. the incorrect rejection of a true null hypothesis). In this study, we used multiple logistic regression analyses to examine the associations between different individual risk factors and POP adjusting for age, sex, CCI score, and cancer stage. By treating these variables as potential confounders, we minimized or eliminated the bias that they could have exerted on the associations under study. Controlling for these variables is not a guarantee of a "true" estimate of association, and there is still the possibility of unknown-, unmeasured as well as residual confounding. Residual confounding might arise when a variable is divided into categories that are too broad. The disadvantage of narrowing the categories, however, is the possibility of too few events in each category resulting in a loss of precision. Residual confounding may also arise if adjustment for confounding variables is limited due to non-differential misclassification in these and the adjusted estimate of association falls between the confounded and the true value.(26) Unmeasured confounding is caused by a variable that there is no information about but at the same time is known to be a confounder of the association under study. An example in Study 1 is cigarette smoking and for this reason, missing information on cigarette smoking is a limitation to our study. Unknown confounding is the result of a variable that there is no knowledge about. Furthermore, it can be argued that only variables that bias the estimate in any given association under study need adjustment.(32) In general, confounding can be addressed by means of study design through restricting, matching or randomizing, or by statistical analysis through stratification, standardization or regression analysis.(33)

Effect-measure modification

Effect-measure modification is also known as heterogeneity of effect or statistical interaction (not to be confused with biological interaction). Effect-measure modification, as the name implies, is a difference of effect across strata and its presence, size and direction can be a result of choice of

measure.(34) In fact, because of the ambiguity of the construct Rothman, Greenland and Lash suggest using the terms risk-difference modification and risk-ratio modification, as appropriate. Importantly, effect-measure modification should be handled very differently from confounding in statistical analysis. In general, the effect of confounding should be eliminated or at least minimized while effect-measure modification is something to point out and keep in the results.(35) In this study, we found odds-ratio modification of the types of surgery in different calendar periods. This was due to an increased sensitivity of POP in recent years along with substantial changes in surgical procedures during the study period. Interpretation of data stratified on calendar periods was nearly impossible due to a combination of a trend of increase in sensitivity of POP and changes in the surgical methods used at a given time (i.e. introducing new procedures while phasing out others). As a compromise, we decided to present an analysis of only the most recent data since it represents the current situation (Table 3).

Study 2

In the mortality analysis follow-up started for each LC patient on postoperative day 31 (see section on immortal person-time bias for explanation) and ended on date of death, emigration or end of follow-up (31 December 2011).

Methods for survival analysis that allow for death rates not to be constant focus on hazards (the instantaneous rate at time *t*), and survivor function, which is illustrated by the survival curve. A method frequently used to estimate the survival curve is the Kaplan-Meier function, which we used to compute hazard ratios for death in different follow-up intervals (day 31-1 year, 1 year – 5years) with the method of Cox proportional hazard regression.(36)

Immortal person-time bias

Our definition of POP In the mortality analysis (study 2), our exposed cohort had to meet the following entry criteria: a diagnosis of POP within the 30 first postoperative days as well as survival for at least these 30 days. The unexposed cohort had to survive the first 30 postoperative days as well. This period of time is referred to as *immortal person-time* because the LC patients meeting the entry criteria would be "immortal" for the duration of this time if it were included in a mortality analysis. The LC patients were of course not immortal during this time and in fact 225 LC patients died within 30 days. Including immortal person-time in the denominators of the mortality rates in the mortality analysis would have downwardly biased these. For this reason, the correct way of handling immortal person-time in a study is to exclude follow-up time allocated to a specific exposure category.(37) As a consequence of this we cannot see how POP affects short-term (i.e. 30 day) survival. In other words, we can only comment on the mortality of patients LC patients who survive the first 30 days postoperatively, and this is a limitation to the study design. From a clinical perspective, it can be argued that a negative effect of POP on long-term survival is highly important and an indication for intensifying preventive strategies.

Clinical Perspectives

This study provides information on risk factors for POP in LC patients. This knowledge can be used to implement preventive strategies such as reduction of modifiable risk factors and intensifying preoperative antibiotic treatment for LC patients at high risk for POP. Normally intensive antibiotic treatment is reserved for LC patients undergoing pneumonectomy but our findings might argue that this treatment may also be offered to other patients at high risk for POP.(38) Implementation of such changes require further studies, preferably ones with the possibility of controlling for smoking status.

Conclusion

We argue that the methods used for the study are appropriate for the research objectives and that the overall methodological goal is met.

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