THE INFLUENCE OF POSTOPERATIVE COMPLICATIONS ON LONG-TERM SURVIVAL OF LUNG CANCER PATIENTS

Amin Andalib

Department of Epidemiology, Biostatistics and Occupational Health

McGill University, Montreal

Thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements of the degree of Master of Science

February 2012

TABLE OF CONTENTS

STATEMENT OF SUPPORT

While completing this research, I was supported by an educational training fellowship from Fonds de Recherche en Santé du Québec (FRSQ – 23484).

ACKNOWLEDGMENTS

I would like to take advantage of this opportunity to thank all those who helped in the successful completion of my Master's thesis.

Dr. Eduardo Franco, my supervisor, for his leadership and endless support throughout my Master's degree in Epidemiology, for providing countless hours of guidance, and for himself being a truly motivating role model and researcher.

Dr. Lorenzo Ferri, my co-supervisor, for being available, encouraging, and inspiring during my Master's degree training and throughout my residency in General Surgery. You are truly a role model.

Drs. Gillian Bartlett-Esquilant, Agnihotram Ramana-Kumar, and Alan Barkun, members of my thesis committee, for supporting me throughout this process and providing invaluable guidance in obtaining and manipulating the RAMQ data.

The professors and administrative staff of the Department of Epidemiology, Biostatistics and Occupational Health at McGill University, who made this journey possible.

Finally, I am extremely thankful for the support from my family and loved ones who also made the entire masters experience a smooth and enjoyable one.

ABSTRACT

Background: Surgery is essential to any curative plan for lung cancer, but is associated with a high complication rate, which in turn increases short-term mortality. However, the impact of postoperative morbidity on long-term oncologic outcomes is not understood well.

Objectives: We sought to determine the impact of complications on long-term survival after a curative surgery for lung cancer, independent of the effect on early postoperative mortality.

Methods: We studied a population-based cohort of patients with lung cancer who underwent curative-intent surgery in the province of Quebec, Canada from 2000-2005. Kaplan-Meier survival analysis was used to compare unadjusted overall survival (OS) beyond postoperative day 90 for patients with and without complications. Cox regression was used to determine the prognostic impact of 30-day postoperative complications on the OS after adjusting for confounders.

Results: The overall 30-day postoperative complication rate was 58.2% among 4,033 eligible patients. A major infectious complication (pneumonia, empyema or mediastinitis) occurred in 378 patients. The 5-year OS was lower for those with any postoperative complication (62.8%) than those without (73.8%; $P < 0.001$). Those with major infectious complications had the lowest OS (56.3%; $P < 0.001$). Postoperative complication was an independent prognostic factor after adjusting for several patient and treatment factors (HR=1.37, 95% CI:1.21–1.54). Adjusted HR for major infectious complications was 1.67 (95% CI:1.39–2.01).

Conclusions: Postoperative complications, particularly of a major infectious type, are strong negative predictors of long-term survival in lung cancer patients. The findings emphasize the importance of achieving lung resections with minimal morbidity as this translates into a beneficial impact on long-term outcomes independent of the effect on early mortality. The strong association between major infectious complications and survival may also open the door to investigational therapies targeting bacterial antigens in the perioperative period in patients undergoing lung cancer surgery.

RÉSUMÉ

Mise en Contexte: La chirurgie est essentielle à tout plan curatif pour le cancer du poumon, mais est associé à un taux élevé de complications, ce qui accroît à son tour mortalité à court terme. Toutefois, l'impact de la morbidité postopératoire sur les résultats oncologiques à long terme n'est pas bien compris.
Objectifs: Nous avons cherché à déterminer l'impact des complications sur le long terme la survie après une chirurgie à visée curative pour un cancer du poumon, indépendamment de l'effet sur la mortalité postopératoire précoce.
Méthodes: Nous avons étudié une cohorte basée sur la population des patients atteints de cancer du poumon qui a subi une chirurgie visée curative dans la province de Québec, au Canada de 2000 à 2005. Analyse de survie de Kaplan-Meier a été utilisée pour comparer de survie globale (OS) au-delà 90e jour postopératoire pour les patients avec et sans complications. La régression de Cox a été utilisé pour déterminer l'impact pronostique des complications postopératoires (jusqu'à 30 jours) sur l'OS, après ajustement pour les facteurs confondants.
Résultats: Le taux de complications postopératoires dans les premiers 30 jours était de 58,2% chez les 4033 patients éligibles. Une complication majeure infectieuse (pneumonie, empyème ou médiastinite) sont survenus chez 378 patients. L'OS de 5-ans était plus faible pour ceux avec aucune complication post-opératoire (62,8%) que ceux sans (73,8%; p <0,001). Ceux avec une complication majeure infectieuse étaient les plus faibles de l'OS (56,3%, p <0,001). Complication postopératoire était un facteur pronostique indépendant après ajustement pour plusieurs des facteurs concernant des patients et de traitement. (HR = 1,37, IC 95%:1.21-1 .54). HR ajusté pour la complication majeure infectieuse était de 1,67 (IC 95%:1.39-2 .01).
Conclusions: Les complications postopératoires, en particulier d'un type majeure infectieuse, sont forts prédicteurs négatifs de survie à long terme chez les patients du cancer du poumon. Les résultats soulignent l'importance de réaliser des résections pulmonaires avec une morbidité minime, car cela se traduit par un

impact bénéfique sur le long terme des résultats indépendants de l'effet sur la mortalité précoce. La forte association entre les complications majeures infectieuses et de la survie peut aussi ouvrir la porte à des thérapies expérimental ciblant les antigènes bactériens dans la période périopératoire chez les patients subissant une chirurgie du cancer du poumon.

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

ARDS	Acute Respiratory Distress Syndrome
CI	Confidence Interval
CCI	Charlson Comorbidity Index
DAG	Directed Acyclic Graph
DIS	Date of Index Surgery
HR	Hazard Ratio
ICD9-CM	International Classification of Diseases, 9^{th} revision-Clinical Modification
MED-ECHO	Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière
NSCLC	Non-Small-Cell Lung Cancer
OS	Overall Survival
POD	Postoperative Day
RAMQ	Régie de l'Assurance Maladie du Québec
SCLC	Small-Cell Lung Cancer
SD	Standard Deviation
SEER	Surveillance Epidemiology and End Results
TRALI	Transfusion Related Acute Lung Injury

1. STATEMENT OF RESEARCH PROBLEM

Worldwide, lung cancer is the most common cause of cancer-related death amongst males and the second cause in females [1]. It is a major health problem in developed countries and in North America [1]. Non-Small Cell Lung Cancer (NSCLC) accounts for approximately 85% of lung malignancies for which surgery remains the cornerstone of any potentially curative treatment plan [2]. However, lung surgery is highly invasive with a 30-day operative mortality of 1.3-3.2% and a high postoperative complication rate (25-40%), with complications being mainly pulmonary in origin [3-5].

Recent studies have shown poor long-term prognosis following postoperative complications for cancers of the colon [6], head and neck [7], liver [8], and esophagus [9]. Although early mortality is increased in patients suffering from postoperative complications, there is mounting evidence suggesting that the systemic inflammatory consequences of postoperative complications may have a secondary deleterious influence on survival by increasing risk of cancer recurrence [10,11]. Furthermore, it has recently been demonstrated that bacterial antigens, frequently encountered in postoperative infectious complications, have a direct effect on cancer cell metastatic ability [12,13].

Although the experimental data linking systemic inflammation to cancer progression is compelling, the clinical data in support of this notion are controversial and almost exclusively from retrospective, single institution surgical series or specialized cancer centers that either focus on the effect of complications on the early postoperative course or do not exclude patients who died in the immediate postoperative period when evaluating long-term survival [3-5]. This is important to note, since postoperative morbidity clearly increases operative mortality [4], and any potential impact of complications on cancer progression is likely overshadowed by the short-term increased mortality. There is even evidence that the immediate impact of postoperative morbidity exceeds the conventional 30-day period, thus supporting the use of 90 days as the limit for early postoperative events [14]. We subsequently elected to conservatively choose postoperative day 90 as the limit for early postoperative mortality.

Thus for this project the objective was to determine the impact of the postoperative complications on the long-term survival of patients undergoing a curative-intent surgery for lung cancer, independent of their impact on early postoperative mortality and beyond the postoperative day 90.

2. BACKGROUND

2.1. Lung Cancer

2.1.1. Burden of Disease

Lung cancer is currently the most common cause of cancer-related death amongst males worldwide and the second leading cause in females after breast cancer [1]. This ranking remains the same in developed countries and North America and constitutes a significant health problem [1,15]. In terms of new cases, lung cancer has the highest incidence in men worldwide and the second highest in developed countries [1]. Amongst women, lung cancer is the fourth most incident cancer worldwide and the third overall in developed countries [1].

In 2011, an estimated total of 25,400 new cases of lung cancer were diagnosed in Canada (male 13,200; female 12,200) [16]. The estimated age-standardized incidence rate of lung cancer in Canada is 65 per 100,000 in men and 51 per 100,000 in women, while the age-standardized death rate due to lung cancer is 56 per 100,000 for men and 39 per 100,000 for women [16]. The lifetime risk for a male developing lung cancer and dying from it is estimated to be 9.1% (1 in 11) and 7.7% (1 in 13) respectively [16]. For women, the lifetime risk of developing lung cancer and dying from it is estimated in 2011 to be 6.7% (1 in 15) and 5.9% (1 in 17) respectively [16]. Furthermore, both the incidence and mortality rates of lung cancer are expected to be highest for men in Quebec than in any other province in Canada [16].

2.1.2. Pathology

Smoking remains the primary cause in more than 80% of lung cancers, and second-hand smoke increases the risk of developing lung cancer by 30% [17]. This malignancy can be broadly categorized into two groups: Non-Small-Cell Lung Cancer (NSCLC) and Small-Cell Lung Cancers (SCLC). The four sub-types of NSCLC are adenocarcinoma, bronchoalveolar, squamous cell carcinoma, and large-cell carcinoma [17]. NSCLC accounts for approximately 85% of all cases of lung cancer for which surgery remains the cornerstone of any potentially curative treatment plan [2,18]. However, SCLC has a much worse clinical outcome, tends to be disseminated at the time of presentation and is therefore not amenable to cure and surgery is not offered to these patients [17,19]. Hence, SCLC is not discussed any further in this thesis.

2.1.3. Staging and Treatment Options

The main goal of pre-treatment staging of lung cancer is to determine the extent of disease, which can subsequently determine prognosis and treatment. The Tumor Node Metastasis (TNM) staging system for NSCLC is the method of choice and is validated upon a retrospective analysis of survival in diverse samples of patients representing all stages of disease [20,21]. It is periodically revised based on the survival probability for lung cancer patients, taking into consideration the evolution of advanced imaging techniques, treatments and emerging data documenting different outcomes for specific subgroups of patients. The 7th edition of the TNM staging system, which was developed by the International Association for the Study of Lung Cancer (IASLC) and approved by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC), is the most recent version [20,21].

In terms of treatment options for patients with NSCLC, surgery is the most successful option for cure [2,17,18]. Furthermore, given that the patient is able to tolerate the proposed operation, essentially only those with an early loco-regional disease (Stages I and II) are considered for a curative treatment plan [2,17,18,22]. The role of surgery in stage IIIA NSCLC is controversial; however, most institutions have adopted a multimodal treatment plan, which includes neo-adjuvant chemotherapy and potential radiotherapy followed by surgery for highly selected patients with stage IIIA disease [23].

The different types of surgeries performed for NSCLC are the following [2,17,18,24]: 1) Pneumonectomy, which is the removal of an entire lung and was previously the most common operation performed for these patients 2) Lobectomy, which is an anatomic lung-preserving surgery and is currently the procedure of choice for NSCLC due to similar long-term survivals, lower postoperative morbidity and mortality compared to pneumonectomy and better long-term outcomes without an increase in postoperative morbidity compared to lesser resections 3) Lesser resections (segmentectomy and wedge resection), which are non-anatomic procedures. In addition, lobectomy along with the lesser resections can be performed using Video-Assisted Thoracoscopic Surgery (VATS) [25,26]. There are also more extensive operations such as sleeve resections that are offered to some patients with a more locally advanced disease such as a superior sulcus/Pancoast tumor [17]. However, these operations are performed rarely and only in specialized institutions.

Furthermore, there is emerging evidence regarding the advantages of removing the mediastinal lymph nodes in terms of better pathologic staging, indications for adjuvant therapy and decrease in the loco-regional recurrence [17]. The complete mediastinal lymph node dissection versus a selective approach is still subject to debate. However, to further address this controversial topic, the American College of Surgeons Oncology Group (ACOSOG) is currently conducting a randomized controlled trial. The preliminary results from the trial favor the more extensive lymph node dissection, which is also not associated with a higher postoperative morbidity and mortality [3,27].

In addition to surgery, there is a role for adjuvant therapy in the curative approach to NSCLC. However, the routine use of adjuvant chemotherapy for a fully resected NSCLC became popular after randomized controlled trials revealed survival benefits and longer disease-free intervals [28-30]. However, this trend only became mainstream towards the end of 2005 and early 2006 and is still not considered an absolute indication after a complete resection of an early stage NSCLC (Stages I and II). The role of adjuvant radiotherapy for NSCLC still remains controversial [31]. Finally, neo-adjuvant chemotherapy and radiotherapy are indicated for superior sulcus/Pancoast tumors of the lung along with highly selected patients with stage IIIA disease [23,32,33].

2.1.4. Long-Term Outcomes

Lung cancer is an aggressive malignancy associated with high rates of metastasis and an overall 5-year survival of approximately 15% [1,15,16]. In fact, nearly 70% of patients with lung cancer present with a locally advanced or metastatic disease at the time of diagnosis [2]. Outcomes vary among patients with NSCLC, even within groups of patients that have the same stage at the time of diagnosis and undergo the same treatment. The likely reasons for this observed variability in the literature are likely patient heterogeneity amongst the different study populations, inconsistent staging and unpredictable tumor biology [34]. According to the data from the Surveillance Epidemiology and End Results (SEER) of the National Cancer Institute, the overall 5-year relative survival by stage at the time of diagnosis for the patients with any type of lung cancer from 2001-2007 are as follows [35]: 1) Localized disease 52.0% 2) Regional disease 24.2% 3) Distant disease 3.6%.

However, according to surgical series for patients with a loco-regional NSCLC (Stages I – IIIA) eligible for surgery, the long-term survival is much improved. Indeed, a complete surgical resection of an early-stage NSCLC (stage I and II) will improve the 5-year survival up to 55-72% and 30-51%, respectively [34,36,37]. In fact, for stages IA and IB NSCLC, the 5-year survivals after a curative surgery are increased to 77-83% and 51-73% respectively [34,36,38-40]. Moreover, the long-term survival rates differ amongst the different histological sub-types of NSCLC [38,41]. According to a ten-year report of the United States national cancer database on lung cancer comprising of 713,043 patients diagnosed with primary lung malignancies during 1985-1995, the 5-year survival post surgery for patients with stage I and II adenocarcinoma was 32-63%, for squamous cell carcinoma was 36-59% and for large cell carcinoma was 35-55% [41].

Furthermore, another important consideration regarding the long-term outcomes in cancer is the issue of disease-free survival. Even after a complete resection of tumor along with a radical dissection of mediastinal lymph nodes, the overall recurrence rate for stage I NSCLC is approximately 27% over a 5-year period [36].

Amongst these patients more than 75% had a systemic recurrence and only 11.7% developed a second primary lung cancer [36]. In addition, the rate of tumor recurrence progressively increases as does the stage of NSCLC (Stage I-IIIA) [42]. Regarding the issue of a second primary lung cancer (SPLC), approximately 12% of patients with stage I disease develop SPLC over a 5-year period following a complete surgery [36]. The Lung Cancer Study Group has also reported that the incidence of SPLC at more than five years after the surgery for the first cancer is twice that during the first five years after surgery [43]. The cumulative risk of developing a second primary lung cancer reaches 13% to 20% at 6 to 8 years [43].

2.2. Postoperative Complications and the Impact on Cancer Outcomes

2.2.1. Postoperative Complications

Surgery is the cornerstone of any potentially curative treatment plan for NSCLC, but it is highly invasive with a thirty-day operative mortality of 1.3-3.2% [3,4] and a high postoperative complication rate (25-40%), with complications being mainly pulmonary in origin [3,4,44-46] .

The frequency and types of complications vary for different types of lung resections. However, pneumonia remains a frequent infectious postoperative finding common to all lung procedures occurring at a rate of 5-25% [3,47-49]. Moreover, according to the preliminary results from the randomized controlled trial being conducted by the ACOSOG, approximately 38% of the patients with an early stage NSCLC who underwent surgery had one or more complications [3]. Infectious complications in turn result in significant systemic inflammation manifesting as fever, leukocytosis, tachycardia, and in severe cases, septic shock. In addition, non-infectious complications such as atrial fibrillation, acute respiratory distress syndrome (ARDS) or acute kidney injury are also pro-inflammatory and associated with infectious complications and subsequently contribute to the development of systemic inflammatory response syndrome [50-52]. Postoperative pulmonary complications, mainly pneumonia and respiratory failure, are the leading causes of early postoperative mortality in patients undergoing resection of lung malignancies [4,45].

2.2.2. Impact of Complications on Long-term Cancer Outcomes

There is a growing body of evidence suggesting that presence of an inflammatory state as documented by a high level of C-reactive protein (CRP) is associated with worse cancer outcomes in terms of both overall survival and disease recurrence in a variety of cancers types including NSCLC [53-55]. Furthermore, there is strong experimental data supporting the belief that the systemic inflammation mediated by bacterial infections may increase cancer recurrence. Experimental models of systemic inflammation using lipopolysaccharide (LPS), a gram negative bacterial antigen [11,56,57] or complement activation [58], have resulted in increased rates of cancer metastasis with a variety of cancer cells. Others have also demonstrated that LPS and other inflammatory mediators (e.g. cytokines) can act directly on cancers cells resulting in increased proliferation, metastatic potential, and invasiveness [10,59].

Although the experimental data linking systemic inflammation and cancer progression is quite strong, the emerging clinical data in support of this notion is sometimes controversial [7-9,60-66]. Recent surgical series have linked the postoperative complications following a surgery for cancers of the colon and rectum [6,60,61], head and neck [7,62], liver [8], and esophagus [9,63-66] to a decrease in long-term survival. This finding is believed to be likely due to worse oncologic outcome such as tumor recurrence [6,9].

Regarding NSCLC, patients with postoperative pulmonary complications after a curative surgery were found to have a lower three-year survival [67]. However, there is no definitive evidence demonstrating the effect of such complications on the long-term survival of lung cancer patients after surgery. Furthermore, these data are exclusively from retrospective, single institution surgical series or specialized cancer centers that either focus on the effect of postoperative complications on the early postoperative course or do not exclude patients who have died in the immediate postoperative period [55,67]. This raises an important issue, since postoperative complications especially those respiratory in origin clearly increase operative mortality [4] and thus, any potential effect of complications on cancer progression may be overshadowed by the short-term increase in mortality. To date, there is only a single population-based survival analysis using SEER data, which showed a decreased long-term survival beyond the immediate thirty postoperative days for patients with stage I NSCLC who underwent a lobectomy and had complications [68]. However, even this study was limited by the use of SEER data, which captures only a non-representative 20-

30% of the population in the United States [69]. Furthermore, despite the use of the Medicare database to improve completeness of the data that limits the population to those between 65-80 years old, the study was restricted to only those patients with stage I disease, who had undergone a lobectomy, all of which decrease the generalizability of the results. In addition, recently it has been shown that the immediate impact of postoperative morbidity exceeds the conventional 30-day period for pulmonary resections, thus supporting the use of 90 days as the limit for early postoperative events [14].

2.3. Predictors of Poor Postoperative Outcomes in Lung Cancer

In order to appropriately address the issue of confounding affecting the potential relationship between the postoperative complications and long-term survival in lung cancer patients, all the patient, tumor, and treatment characteristics that may be associated with both postoperative morbidity and cancer survival in NSCLC were identified.

Age at diagnosis (above 70), sex (male) and a lower socioeconomic status are among the patients' demographic characteristics that have repeatedly been shown to lead to more frequent postoperative complications after a curative surgery for NSCLC as well as predict a worse 5-year survival [70-73]. In addition, patient comorbidities have repeatedly been shown to predict poor long-term outcomes in NSCLC especially in those with an early stage disease, who are amenable to a curative treatment [74,75]. In order to simplify the adjustment for confounding by comorbidities, there are several comorbidity indices that have been proposed and validated for their association with postoperative outcomes [76]. Amongst the many indices, the Charlson Comorbidity Index (CCI) is widely used in the literature and found to correlate with both short and long-term surgical outcomes in a variety of diseases including different malignancies such as prostate, colorectal, breast and lung cancer [77-80]. CCI is also adopted for use with the administrative databases using the International Classification of Diseases, 9th revision-Clinical Modification (ICD9-CM) codes [79]. Moreover as a cumulative index of patient's comorbidities, CCI is found to be a better predictor of both short and long-term survival in patients undergoing a curative resection for their NSCLC compared to using individual comorbidities or other cumulative comorbidity indices [80-83].

In terms of tumor characteristics, tumor size (greater than 4cm), metastasis to lymph nodes, squamous cell carcinoma on histology and a poorly differentiated histological grade are all associated with a worse 5-year survival in early-stage NSCLC patients after a curative surgery [73,84,85]. In addition, most of these tumor factors along with the pathologic stage of cancer are associated with a higher rate of postoperative morbidity in patients with NSCLC [71,86].

Regarding the treatment factors, neo/adjuvant therapy in the form of chemotherapy, radiotherapy or both has been shown to be an independent risk factor for postoperative morbidity and mortality in NSCLC patients after a curative resection [71,86,87]. Furthermore, an incomplete resection of the tumor is shown to be associated with a worse long-term outcome in patients with locally advanced NSCLC [85]. Finally, the positive impact of surgery at a high-workload center on long-term cancer outcomes is repeatedly shown for a variety of cancer types [88-90]. Access to a high-workload thoracic surgery center or a university teaching hospital is positively correlated with a better long-term survival in patients with NSCLC as well as less postoperative morbidity [91].

2.4. Studies Using Administrative Databases

2.4.1. Overview - The Quebec Provincial Database

The use of administrative data in epidemiologic studies has become routine especially when conducting research at the population level. In Canada, which is a country with a universal health care system, the provincial administrative databases are increasingly used for this purpose.

The province of Quebec maintains several centralized administrative health databases, including the hospital discharge database from the Ministry of Health's Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitaliére (MED-ECHO) and others for fee-for-service health care billing called RAMQ (Régie de l'Assurance Maladie du Québec). The provincial hospital discharge database receives abstracts of the discharge record from all acute care hospitals and most chronic care institutions. The RAMQ database provides records of all fee-for-service billings, and indicates, among other information, the type of act and place of act (at home, in chronic care institution, emergency room, outpatient clinic, and acute care institution). There are in fact three main datasets within the RAMQ master database. First is the beneficiary dataset for the patients, which provides the main demographic and socioeconomic information for each subject. Similarly, the beneficiary dataset for the physicians provides such information about the treating physicians with respect each provided service or act. Finally, the medical services claims, which in turn is divided into two subsets (prescription claims and physician claims datasets). The prescription claims dataset is used mainly for pharmacoepidemiological surveillance, and reflects the frequency and patterns of prescribing medications [92,93]. However, the physician claims dataset is more commonly used in health services research [77,94-96]. The physician making a claim to RAMQ has to provide a diagnosis such as ICD9-CM, and if applicable, a procedure code for the service provided. So either the diagnosis or the procedure codes can be used in epidemiologic studies.

Subsequently, the linkage of the hospitalization records and the different RAMQ datasets is done at the ministry level through a unique patient identifier. Once the two files are merged, the identification number is scrambled to protect confidentiality of the patients and the data are then ready for research use.

2.4.2. Strengths

The primary objective of most administrative health databases is to identify and track persons eligible for health benefits, or to record transactions such as reimbursement for services by providers. Although the primary purpose of these databases is administrative, they are increasingly used in epidemiologic research, because of a number of important advantages [97]. In Quebec and other Canadian provinces information is available on more than 99% of the population covered by provincial health insurance plans. For instance in the province of Quebec, the

RAMQ serves as the government managed health care insurer for more than 99% of permanent residents in the province, for hospitalization and physician costs. Thus, the database virtually captures the entire population [98]. RAMQ also insures prescription drugs for adults aged 18 to 65 who do not have coverage through an employer (approximately 40% of the population in this age group), children younger than 18, and all adults older than 65. Furthermore, the information on individuals from different datasets within the administrative databases can be combined using a common identification number. These data are already compiled in electronic format, and often in a coded fashion using internationally recognized diagnosis codes such as ICD9-CM, which will facilitate analysis and improve external validity. The type of transaction such as a medical visit, act or drug dispensed, is highly accurate because this is the basis for reimbursement and is audited regularly [99]. Since any errors would constitute fraud, errors are rare.

2.4.3. Limitations and Validity

Nevertheless, there are some important limitations in using administrative data. In particular most of the information is of a translational nature such as what service was in fact provided rather than a diagnostic one. Diagnostic information is not needed for reimbursement, is not audited and so may be inaccurate. However, the physician making the claim to the RAMQ usually provides a diagnosis code (such as ICD9-CM) along with the billing code associated with the procedure or service offered to the patient. In addition, these administrative databases have been found to have reasonable to excellent accuracy for diagnosis of injuries [95], hypertension [94,100], stroke [101], diabetes [102], coronary artery disease [103,104], gastrointestinal disorders [105], asthma [106], Chronic Obstructive Pulmonary Disease (COPD) [103,107], and several other comorbidities and medical conditions [79,92,108-112]. Furthermore, the accuracy of the diagnostic codes within the medical services claims database of the RAMQ has been validated for the medical conditions included in the CCI and shown to be highly specific with low-to-medium sensitivity (10-70%) [96]. Similar validity patterns have been demonstrated for the documentation of the acute respiratory infections within the RAMQ physician billing claims [113]. Table 1 further details some of the validation studies carried out for a variety of diagnoses captured in the administrative databases.

Table 1. Accuracy of administrative databases vs. direct data gathering methods[*]

Year	Study Setting	Health Problem	Database	Sensitivity[†]	Reference
1993	Metropolitan Minneapolis	HTN	MSC PC	90% Combined	100
1993	Metropolitan Montreal	Stroke	HS	70-80%	101
1995	Province of Saskatchewan	AMI CAO	HS	97% - AMI 94% - CAO	103
1997	Province of Manitoba	HTN	MSC	85%	94
2000	Metropolitan Montreal	Injury in elderly	MSC	81%	95
2002	Province of Manitoba	Asthma	MSC	98%	106

* HTN=Hypertension; AMI=Acute Myocardial Infarction; CAO=Chronic Airway Obstruction; MSC=Medical Services Claims; PC=Prescription Claims; HS=Hospital Services.

† Sensitivity of database to correctly identify the target condition identified by direct data gathering.

Assigning the correct diagnostic code for a patient could be challenging and subject to interpretation. Multiple diagnoses of varying importance can simultaneously exist in the same patient. However, only one diagnostic code per physician claim can be submitted to RAMQ. This may partly explain the relatively low levels of agreement illustrated by the sensitivities and specificities in the above studies.

Nevertheless, for the more major diagnoses such as cancer, which would mean that the patient will likely utilize resources offered by the health care system for a relatively long period of time and for several different purposes such as diagnosis, therapy followed by surveillance services that in turn exposes the patient to multiple physicians and health institutions, undoubtedly increases the likelihood of being captured in one of the administrative datasets. Excellent sensitivities demonstrated for some chronic medical conditions such as hypertension, coronary artery disease, asthma and COPD further support this statement [100,103,106,107].

Ultimately, the sensitivity of the diagnostic codes can be significantly optimized by gathering information over a longer period of time and from various datasets provided by the RAMQ. The overlap amongst and the multiplicity of these databases will improve the accuracy by providing several sources for the desired diagnostic codes.

Moreover, as mentioned above given that the RAMQ database is set as a fee-for-service basis the information regarding the procedures is likely very accurate. However, the accuracy of identifying the right procedure performed is possibly related to the complexity and significance of the procedure. For instance for a routine and rather minor procedure such as polypectomy, which is performed in the colonoscopy suite, the accuracy of correctly identifying the performed polypectomies may be underestimated by nearly 15% [114]. However, when a major procedure such as a cancer operation that takes place under general anesthesia in the operating room and at times requires a routine postoperative admission to the intensive care unit for monitoring, which is the case for thoracotomies involving lung resections, the sensitivity of correctly identifying the performed procedure is likely much higher than for a polypectomy. In fact validation studies using the administrative discharge data from the province of Alberta and other American national datasets have demonstrated that the accuracy of information on the recorded procedures, appears to be related to the type of procedure performed in that major ones that are usually carried out in the operating room are well-coded and the minor procedures routinely performed on wards or in radiology departments are generally under-coded [115,116].

3. OBJECTIVE

The primary aim of this study was to determine the impact of the postoperative complications on the long-term survival in patients undergoing a curative-intent surgery for lung cancer, independent of their impact on early postoperative mortality and after adjusting for demographic characteristics, comorbidity factors, and type of treatment, which are known to influence outcome and could act as mediators and confounders.

4. METHODS

4.1. Study Design

The study had a population-based retrospective cohort design to determine the prognostic role of complications during the postoperative course on long-term survival in lung cancer patients after curative-intent surgery. The study was based on the linkage of administrative health care data from the province of Quebec, Canada, which has the highest incidence and mortality rates for lung cancer in the country [16].

4.2. Study Population

We identified all patients aged 18 and older who underwent lung cancer surgery in the province of Quebec, Canada from January 01, 2000 to December 31, 2004. The complete list of the different lung surgeries and their respective procedure codes used in RAMQ and the MED-ECHO registrant databases can be viewed in Appendix 1. We used three main exclusion criteria to define the study cohort. First, we excluded subjects with any metastatic disease (including that in lymph nodes) prior to or on the date of index surgery based on the ICD9-CM diagnosis codes. We also excluded patients with a previous oncologic resection for lung cancer or reoperation beyond 30 days after the index surgery. Using these two criteria we identified all patients that underwent a curative-intent lung cancer surgery. Finally, patients who died prior to postoperative day 90 were excluded. After enforcing the inclusion and the exclusion criteria, the study cohort comprised of 4,033 subjects. The ascertainment of the study cohort is provided in detail in Table 2.

Table 2. Ascertainment of the study cohort*

	Excluded	**Study Cohort**
Patient and treatment criteria		
Lung surgery in Quebec during 01/2000 – 12/2004		9,169
Age at surgery ≥ 18		9,169
Lung surgery performed for lung cancer	1,109	8,060
Metastatic disease criteria		
ICD9-CM codes for metastatic solid tumors†	3,656	4,404
Reoperation criteria		
Previous lung surgery > 30d prior to index surgery	50	4,354
Repeat lung surgery after POD30 of index surgery	65	4,289
Survival criteria		
Died before POD90 of the index surgery	256	4,033
Study cohort		4,033

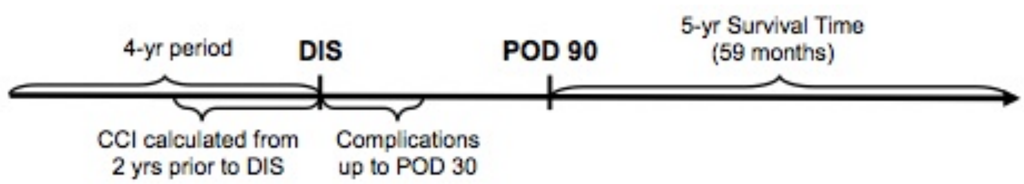
* ICD9-CM=International classification of diseases, 9th revision-clinical modification; POD=Postoperative day.
† Patients with metastasis to lymph nodes are also among those excluded.

4.3. Data Source and Linkage

4.3.1. Data Source

Information on survival and prognostic factors was gathered from the two main provincial health care databases: RAMQ and the Ministry of Health's MED-ECHO. We collected medical acts and diagnoses from four years prior to up to one year after the index date of lung surgery. Information on all-cause mortality was obtained up to five years post index surgery date. The RAMQ database has three components: 1) patient beneficiary dataset 2) physician beneficiary dataset and 3) medical services claims. The MED-ECHO database contains hospitalization records with data on all hospital admissions. RAMQ serves as the government-managed health care insurer for all hospitalization and physician costs for more than 99% of permanent residents in the province of Quebec [98]. Figure 1 shows how the data on the study cohort was gathered.

Figure 1. Schematic diagram representing the data collection*



* Covariates were identified either form the 4-year period prior to or on the DIS. The comorbidities were obtained from the 2-year period prior to DIS. The frequency and types of the complications were determined up to POD 30. The starting time for the survival analysis was set at POD 90. DIS=Date of index surgery; POD=Postoperative day; CCI=Charlson Comrbidity Index.

4.3.2. Identification of Subjects

The RAMQ and MED-ECHO databases provided records on all patients who had undergone a lung surgery during the study period (the list of different lung surgeries is provided in Appendix 1). The ICD9-CM diagnosis codes for lung cancer (162.3-5; 162.8-9) were used to identify subjects that had the index surgery for lung cancer from both the RAMQ and the MED-ECHO datasets. After merging the duplicate entries were eliminated.

4.3.3. Identification of Variables

Information on patient's age, sex, socioeconomic status (income, education and area of residence), treating surgeon's years of experience, and dates of index lung surgery and death was obtained from the beneficiary datasets for both patients and physicians. Data regarding comorbidities, administration of neo/adjuvant therapy and 30-day reoperation status were gathered from both medical services claims and MED-ECHO datasets.

Furthermore, both medical services claims and MED-ECHO datasets were explored using the respective ICD9-CM diagnosis codes to gather data on the occurrence of the postoperative complications. Subsequently, the duplicate entries from the two sources were eliminated.

4.3.4. Linkage Procedure

Data from both RAMQ and MED-ECHO databases were linked using a denominalized and encrypted 10-digit number as a unique identifier for each subject in the study cohort.

4.4. Outcome

The primary outcome was the 5-year overall survival (OS) defined as the all-cause mortality beyond postoperative day 90 from the date of the index lung surgery. Information regarding death for each subject was obtained from the beneficiary dataset of RAMQ for patients. The cut-off of postoperative day 90 was chosen arbitrarily since early postoperative mortality may result from operative complications attributable to perioperative events, and their effects may conceivably even surpass postoperative day 30 [14]. Thus, this cut-off was chosen conservatively to study the impact of postoperative morbidity on long-term outcome and thus to provide insights into the potential deleterious oncologic sequelae of surgical complications.

4.5. Main Exposures

Three key prognostic variables thought to predict the long-term survival in the study cohort were investigated. These complication-related prognostic variables were the following: 1) any postoperative complication (binary variable) 2) pulmonary vs. non-pulmonary postoperative complications each containing both infectious and non-infectious morbidities (3-category variable) and 3) major infectious vs. minor infectious vs. non-infectious postoperative complications (4-category variable). Pneumonia, empyema, and mediastinitis were considered to be major infections and other types were classified as minor infections (e.g., wound and urinary tract infection). The occurrence of postoperative complications was considered until postoperative day 30. These postoperative complications were identified via ICD9-CM diagnosis codes from both administrative datasets. The diagnostic codes are summarized in Appendix 2.

4.6. Other Covariates

All considered covariates were selected *a priori* and were linked to both postoperative complications and long-term survival in lung cancer patients [70-76,78-91]. The independent prognostic value and the potential confounding effect of the covariates detailed below were investigated. The variables were categorized in three levels to permit assessment of a dose-prognosis relationship.

4.6.1. Age

Patients' age was obtained from the beneficiary dataset of RAMQ for patients and estimated by subtracting the birth year and month from the date of the index surgery. Age was then categorized into tertiles rounded to the nearest deciles (3-category variable; < 60 year-old, 60-69 year-old, ≥ 70 year-old).

4.6.2. Sex

Sex of the patients was determined using the beneficiary dataset for the patients (binary variable; female, male).

4.6.3. Socioeconomic Status

4.6.3.1. Education

A community-level variable based on the proportion of people without a high school diploma as a proxy for educational attainment was imputed to each patient using the Statistics Canada's 2001 censuses data provided by the RAMQ and based on the 6-digit postal code area of residence of each patient. The educational levels were then divided into tertiles (3-category variable; high, middle, low). High level of education was considered to be less than 27% without a high school certificate in the respective postal code and greater than 39% would place the patient in the low level. The tertiles and the respective cut-offs were defined given the data obtained on the study cohort.

4.6.3.2. Income

The average household income in the various census enumeration areas was estimated from Statistics Canada's 2001 census data. The 6-digit postal codes were used by the RAMQ to link each patient to their respective census enumeration area. The imputed aggregate-level incomes were then divided into tertiles (3-category variable; high, middle, low). Low category was defined by an income less than $38,180 and the cut-off for the high-income category was revenue greater than $50,830. The tertiles and the respective cut-offs were defined given the data obtained on the study cohort. The patients with zero income were assigned a value equal to the minimum Canada and Quebec Pension Plan in 2001 (120 patients).

4.6.3.3. Geographic Area of Residence (Urbanicity)

A 3-category variable was generated for each patient's geographic area of residence based on the administrative region in which the patients' postal codes were contained using the beneficiary dataset for the patients. This variable was labeled urbanicity and used as a proxy to study the effect of proximity to major medical institutions and living in a major city vs. more remote locations. The categories were as follows: urban *(Montreal, Québec, Laval, Montérégie),* sub-urban *(Lanaudière, Estrie, Saguenay-Lac-St-Jean, Laurentides, Mauricie, Outaouais),* or rural/remote *(Chaudières-Appalaches, Abitibi-Témiscamingue, Gaspésie, Bas-St-Laurent, Côte-Nord, Nord-du-Québec, Nunavik, Terres-Cries-de-la-Baie-James)*.

4.6.4. Comorbidities

Patients' comorbidities were identified via their respective ICD9-CM diagnosis codes using both MED-ECHO and the medical services claims datasets from the 2-year period preceding the date of index surgery. Comorbidities were then compiled together to calculate the CCI score for each patient. CCI was used as a cumulative marker of each patient's comorbid conditions [78-80]. Finally, a 4-category variable was generated based on the CCI scores in an increasing order of severity (0, 1, 2, ≥3). A detailed list of all the medical conditions included in the CCI along with their respective scoring weights, are provided in Appendix 3.

4.6.5. Neo/Adjuvant Therapy

The use of adjuvant therapy in the treatment of NSCLC with a curative intent is not standard, especially with reference to stages I and II. The routine use of adjuvant chemotherapy for fully resected NCSLC only became popular towards the end of 2005 [28-31]. However, the time period for this study precedes this trend in the multi-modal therapeutic approach. Furthermore, the neo-adjuvant chemotherapy and radiotherapy are only indicated in the case of the Pancoast tumor of the lung [32,33].

Nevertheless, to evaluate the prognostic impact and control for potential confounding, the information on whether a patient received chemotherapy and/or radiotherapy as an adjuvant (postoperative) or neo-adjuvant (preoperative) treatment was gathered from the medical services claims dataset from RAMQ using their procedure codes (Chemotherapy – 0734 and Radiotherapy – 8553) and respective service dates. Subsequently, a 3-category variable was created based on the time of the administration of the combination therapy (none, therapy within 3 months pre/post lung surgery, therapy beyond 3 months pre/post lung surgery).

4.6.6. 30-day Reoperations

Some patients from the study cohort underwent repeat lung surgeries. If the reoperation(s) was performed within 30 days of the index lung surgery, this was deemed to be a proxy for postoperative complication and the information was used to generate a binary variable (none vs. reoperation by postoperative day 30).

4.6.7. Experience of the Treating Surgeon

The decade in which the treating surgeon obtained his/her medical degree was obtained from the beneficiary dataset for the physicians from RAMQ. A 4-category variable was made based on the years of experience of the surgeon by subtracting the year of the index surgery from the year corresponding to the mid decade of graduation (>20 years, 16-20 years, 10-15 years, < 10 years). Experience of the treating surgeon, as measured by years since training, was used as a proxy for the volume of lung surgeries performed by the surgeon.

4.7. Statistical Analysis

4.7.1. Descriptive

Distributions of categorical baseline characteristics for the patients were determined. The frequencies for the different types of the postoperative complications were also described. In addition, chi-square test was used to compare the baseline characteristics between the cohort of the patients pre and post elimination of the subjects with metastatic disease by the date of index lung surgery.

4.7.2. Kaplan-Meier Cumulative Survival

Kaplan-Meier curve was used to depict the 5-year cumulative survival for the entire study cohort from the date of index lung surgery. The cumulative risk of postoperative mortality using different cut-offs (postoperative day 30, 90, 180, and 365) were also tabulated for the full cohort from the date of index surgery and log-rank tests were used to compare them stratified based on the occurrence of the complications.

In addition, Kaplan-Meier survival analyses were used to illustrate the OS for the study cohort from the postoperative day 90 as starting point. Cumulative survival distributions based on the occurrence and type of postoperative complications, were compared by log-rank tests.

4.7.3. Multivariate Analysis (Predictors of survival)

The prognostic impact of postoperative complications was also examined using the Cox proportional hazards model [117]. Follow-up time was considered from postoperative day 90 for time-to-event analysis. To determine the outcome status we considered patients who continued to be RAMQ beneficiaries throughout the 60-month period of observation. Each exposure variable was analyzed independently. Since the missing data comprised a small proportion of the dataset for certain variables and given the large sample size of the study cohort, subjects with missing data were excluded from the regression analysis. The hazard ratio (HR) (and associated 95% confidence intervals [CI]) was used as a measure of the strength of association based on a baseline (i.e., a single reference category) and adjacent contrasts (i.e., using the previous category as referent).

4.7.4. Model Selection and Goodness-of-Fit

Control of confounding considered variables known *a priori* to be linked to both postoperative complications and long-term survival in lung cancer patients, such as age, sex, socioeconomic status (education, income, urbanicity), comorbidities (CCI), neo/adjuvant therapy, 30-day reoperations and surgeon's experience. This full model was labeled Model I.

A second model (Model II) was derived that included only empirical confounders of the relation between complications and survival. Empirical confounders were chosen on the basis of a stepwise 2% change-in-estimate rule in either direction for the target HR [118]. All the components of the CCI (Appendix 3) were individually included in evaluating the empirical confounding. Using this technique age, gender, CCI, neo/adjuvant therapy, and the surgeon's years of experience as categorical variables along with congestive heart failure, peripheral vascular disease, diabetes and renal disease as individual components of CCI were included in the empirical model (Model II) and were subsequently analyzed.

Both models were applied separately using each of the three main exposure variables. The adjusted HR corresponding to the postoperative complications and their sub-types along with the adjusted effect measures for the various covariates were reported. In addition, the goodness-of-fit and any deviation from the proportionality of hazards for the full model (Model I) were graphically depicted using the Cox-Snell residuals.

The statistical analysis was carried out using the STATA software (Stata Corp, Texas, USA), version 11. Inference was based on a two-sided 5% level for all the statistical analyses. 95% CI were reported for all estimates.

4.8. Ethical Considerations

The study proposal was reviewed and approved by the Institutional Review Board of McGill University (A06-E37-10B). Use of de-identified population health data from the RAMQ and the MED-ECHO databases was approved by the *Comission d'Accès à l'Information du Québec*, a provincial agency that oversees access to public administrative databases (10 17 28) [119].

5. RESULTS

5.1. Descriptive

A cohort of 9,169 patients was identified encompassing all patients aged 18 and older who underwent a lung surgery in the province of Quebec, Canada from 2000 to 2005 (Table 2). Of these, 8,060 patients underwent lung cancer surgery.

We excluded from this subcohort 3,656 patients with ICD9-CM codes corresponding to any metastatic disease (including that in lymph nodes) prior to or by the index surgery date.

The distributions of baseline characteristics between the cohort of patients pre and post elimination of those with metastatic disease are detailed in Table 3. The 3,656 patients who were omitted were overall less educated, living in sub-urban or rural areas, operated on by less experienced surgeons, and had received more neo/adjuvant therapy.

Table 3. Comparison of the study cohort and the subcohort of patients with metastatic disease

Patient Characteristics	**Full Cohort** N=8,060	**Metastatic Cohort**[†] N=3,656	**Non-Metastatic Cohort**[‡] N=4,404	***P***[¶]
Age – N (%)				0.37
< 60	2,903 (36.0)	1,287 (35.2)	1,616 (36.7)	
60 – 69	2,733 (33.9)	1,260 (34.5)	1,473 (33.4)	
≥ 70	2,424 (30.1)	1,109 (30.3)	1,315 (29.9)	
Sex – N (%)				0.07
Male	4,604 (57.1)	2,129 (58.2)	2,475 (56.2)	
Income[§] *– N (%)*				0.45
High	2,704 (33.6)	1,208 (33.0)	1,496 (34.0)	
Middle	2,679 (33.2)	1,241 (34.0)	1,438 (32.6)	
Low	2,677 (33.2)	1,207 (33.0)	1,470 (33.4)	
Education[#] *– N (%)*				< 0.05
High	2,572 (31.9)	1,092 (29.9)	1,480 (33.6)	
Middle	2,878 (35.7)	1,337 (36.6)	1,541 (35.0)	

Low	2,610 (32.4)	1,227 (33.5)	1,383 (31.4)	
Urbanicity – N (%)				< 0.05
Urban	4,326 (53.7)	1,792 (49.0)	2,534 (57.5)	
Sub-urban	2,404 (29.8)	1,237 (33.8)	1,167 (26.5)	
Rural/Remote	1,317 (16.3)	621 (17.0)	696 (15.8)	
Missing	13 (0.2)	6 (0.2)	7 (0.2)	
Neo/adjuvant Therapy – N (%)				< 0.05
None	6,421 (79.7)	2,518 (68.9)	3,903 (88.6)	
≤ 3m pre/post surgery	784 (9.7)	550 (15.0)	234 (5.3)	
> 3m pre/post surgery	855 (10.6)	588 (16.1)	267 (6.1)	
Surgeon's Experience – N (%)				< 0.05
≥ 20 years	4,577 (56.8)	2,074 (56.7)	2,503 (56.8)	
16 – 20 years	1,673 (20.8)	717 (19.6)	956 (21.7)	
10 – 15 years	452 (5.6)	194 (5.3)	258 (5.9)	
< 10 years	1,012 (12.5)	517 (14.2)	495 (11.2)	
Missing	346 (4.3)	154 (4.2)	192 (4.4)	

† Metastatic cohort refers to the group of patients that were removed as part of the first exclusion criterion from the full cohort.
‡ Non-Metastatic cohort refers to the remaining patients in the master cohort from which the study cohort was constructed.
¶ *P* values are two-sided estimates from the χ^2 test.
§ High-income group cut-off was > $50,830 and for low-income group was set < $38,180 (Canada's 2001 census data – based on the postal code).
# High-education group consisted of < 27% without high school diploma; low-education group was set at > 39% (Canada's 2001 census data – based on the postal code).

Subsequently, from the 8,060 subcohort we excluded 50 patients with a previous lung surgery more than thirty days prior to the index surgery, 65 patients with a repeat resection beyond 30 days past the index operation, and 256 subjects that did not survive beyond postoperative day 90. The final study cohort consisted of

4,033 eligible patients who underwent a potentially curative lung resection for their lung cancer and survived at least until postoperative day 90 (Table 2).

Most patients were male (N=2,225; 55.2%), older than 60 years of age (N=2,511; 62.3%), and resided in a major city or urban area (N=2,304; 57.1%). Other sociodemographic characteristics are shown in Table 4. Most patients underwent a lobectomy (N=2,329; 57.7%), followed by segmentectomy (N=437; 10.8%), wedge resection (N=168; 4.2%), and pneumonectomy (N=137; 3.4%). Only 5% of patients (N=193) underwent more complex procedures involving airway or chest wall resections. The type of surgery was missing for 19% of the patients (N=769). This high proportion is likely due to missing procedure codes in the administrative databases.

Table 4. Overall survival rate at 5 years according to baseline patient characteristics of the study cohort[*]

Patient Characteristics	N (%)	5-year OS% (95% CI)
All Subjects	4,033 (100)	67.4 (65.9, 68.8)
Age		†
< 60	1,522 (37.7)	78.4 (76.2, 80.4)
60 – 69	1,354 (33.6)	65.8 (63.2, 68.3)
≥ 70	1,157 (28.7)	54.8 (51.9, 57.6)
Sex		†
Female	1,808 (44.8)	73.8 (71.7, 75.7)
Male	2,225 (55.2)	62.2 (60.1, 64.2)
Income[§]		
High	1,370 (34.0)	69.2 (66.7, 71.6)
Middle	1,332 (33.0)	67.1 (64.5, 69.6)
Low	1,331 (33.0)	65.8 (63.2, 68.3)

Education#		†
High	1,356 (33.6)	70.4 (67.9, 72.8)
Middle	1,411 (35.0)	65.8 (63.2, 68.2)
Low	1,266 (31.4)	65.9 (63.3, 68.5)
Urbanicity		
Urban	2,304 (57.1)	67.6 (65.6, 69.4)
Sub-urban	1,089 (27.0)	67.2 (64.3, 69.9)
Rural/Remote	633 (15.7)	67.1 (63.3, 70.6)
Missing	7 (0.2)	57.1 (17.2, 83.7)
Charlson Comorbidity Index		†
0	1,700 (42.1)	72.4 (70.2, 74.5)
1	1,140 (28.3)	68.3 (65.5, 70.9)
2	676 (16.8)	62.6 (58.8, 66.1)
≥ 3	517 (12.8)	55.1 (50.7, 59.3)
Neo/Adjuvant Therapy		†
None	3,555 (88.2)	70.3 (68.8, 71.8)
≤ 3 months pre/post surgery	227 (5.6)	52.0 (45.3, 58.2)
> 3 months pre/post surgery	251 (6.2)	39.4 (33.4, 45.4)
Reoperations in < 30 days		
No	3,917 (97.1)	67.6 (66.1, 69.0)
Yes	116 (2.9)	60.3 (50.8, 68.6)
Surgeon's Experience		
≥ 20 years	2,297 (57.0)	66.3 (64.3, 68.2)
16 – 20 years	874 (21.7)	70.2 (67.1, 73.2)
10 – 15 years	244 (6.0)	66.4 (60.1, 71.9)
< 10 years	449 (11.1)	70.2 (65.7, 74.2)
Missing	169 (4.2)	61.5 (53.8, 68.4)
Type of Procedure		†
Pneumonectomy	137 (3.4)	51.8 (43.2, 59.8)
Lobectomy	2,329 (57.7)	66.2 (64.3, 68.1)
Wedge & segmentectomy	605 (15.0)	72.7 (69.0, 76.1)

Other	193 (4.8)	47.7 (40.5, 54.5)
Missing	769 (19.1)	74.4 (71.1, 77.3)
Postoperative Complications		‡
No	1,685 (41.8)	73.8 (71.6, 75.8)
Yes	2,348 (58.2)	62.8 (60.8, 64.7)
Type of Complication¶		‡
Non-infectious	1,550 (38.4)	64.1 (61.6, 66.4)
Minor infectious	420 (10.4)	64.0 (59.3, 68.4)
Major infectious♮	378 (9.4)	56.3 (51.2, 61.2)
Non-pulmonary$^{\theta}$	1,208 (29.9)	66.3 (63.6, 68.9)
Pulmonary$^{\theta}$	1,140 (28.3)	59.1 (56.2, 61.9)

* OS=Overall Survival; CI=Confidence Interval.
† Log-rank test within each category; $P < 0.05$.
‡ Log-rank test compared to patients without any complications; $P < 0.001$.
§ Average household income in the 6-digit postal code area of residence of each patient was estimated from Statistics Canada's 2001 censuses data and divided into tertiles.
# Educational level was approximated from Statistics Canada's 2001 censuses data using the proportion of people without a high school certificate in the 6-digit postal code area of residence of each patient.
¶ Patients may have more than one type of complication, but the categories were analyzed independently.
♮ Major infectious complications were considered to be: pneumonia, empyema, and mediastinitis.
θ The system-based complication categories include both infectious and non-infectious morbidities.

The overall 30-day postoperative complication rate was 58.2% (N=2,348) (Table 4). The major categories of postoperative complications were analyzed independently. Non-infectious complications were the most common (N=1,550; 38.4%), followed by non-pulmonary (N=1,208; 29.9%) and pulmonary complications (N=1,140; 28.3%). Infectious complications occurred in 798 patients and were further subdivided into two types: minor (e.g., wound infection and urinary tract infection; N=420) and major (pneumonia, empyema and mediastinitis; N=378). Atrial fibrillation was the most common of all postoperative complications (18%). Among the infectious complications, pneumonia was the most common (10.7%). The frequencies of the different complications are listed in Table 5.

Table 5. Distribution of postoperative complications among lung cancer patients [*]

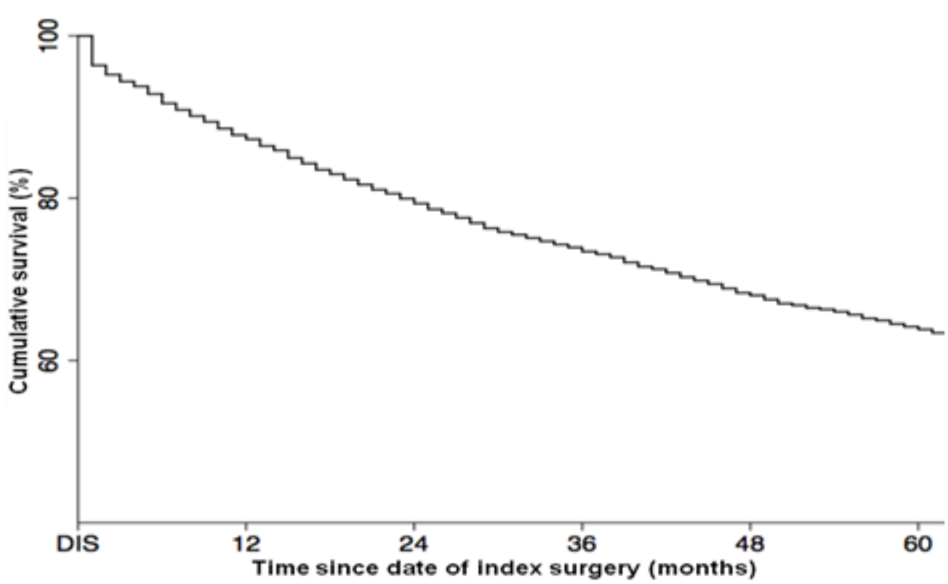
Complication Type (N=2,348)	**Category**	**N (%)**[†]
Pulmonary		
	Atelectasis	338 (14.4)
	ARDS and respiratory failure	267 (11.4)
	Pneumonia[‡]	251 (10.7)
	Empyema[‡]	135 (5.7)
	Pulmonary embolism	124 (5.3)
	Pulmonary edema	73 (3.1)
	Chylothorax	10 (0.4)
	Mediastinitis[‡]	7 (0.3)
	Unspecified	245 (10.4)
Non-pulmonary		
	Atrial fibrillation	422 (18.0)
	Urinary tract infection[§]	338 (14.4)
	Heart failure and cardiac arrest	301 (12.8)
	Wound infection[§]	131 (5.6)
	Hemorrhage	128 (5.4)
	Renal complications	49 (2.1)
	Wound dehiscence	30 (1.3)
	Shock	16 (0.7)
	Neurological complications	8 (0.3)
	Unspecified	866 (36.9)

* ARDS=Acute Respiratory Distress Syndrome.
† The frequencies do not add up to the total number of complications because each patient may have more than one postoperative complication.
‡ Pneumonia, empyema, and mediastinitis were considered major infectious complications.
§ Wound infection and urinary tract infection are considered minor infectious complications.

5.2. Kaplan-Meier Cumulative Survival

The cumulative 5-year OS for the final study cohort was 63.8% from the date of index lung surgery (Figure 2). The comparative postoperative mortality rates for the entire study cohort from the date of index surgery using different cut-offs (postoperative day 30, 90, 180, and 365) were 3.6%, 5.6%, 8.3%, 12.7%, respectively. The mortality rates were significantly different at all the cut-offs, when stratified analysis was performed based on the occurrence of the complications (*P* < 0.001). Comparative mortality rates and the respective 95% CI for the entire study cohort the date of index surgery are tabulated in Table 6.

Figure 2. Cumulative survival experience for the study cohort from the date of index surgery *



* The cumulative 5-year overall survival for the entire study cohort using the date of index lung surgery as the starting time; K-M=Kaplan-Meier; DIS=Date of Index Surgery.

Table 6. Cumulative risk of postoperative mortality using different cut-offs and stratified on the occurrence of complications*

	N (%)	Cumulative Mortality % (95% CI)
POD 30		†
Full cohort	4,289 (100.0)	3.6 (3.1, 4.2)
No complications	1,722 (40.2)	0.8 (0.4, 1.3)
Any complications	2,567 (59.8)	5.6 (4.7, 6.5)
POD 90		†
Full cohort	4,289 (100.0)	5.6 (5.0, 6.3)
No complications	1,722 (40.2)	1.8 (1.3, 2.5)
Any complications	2,567 (59.8)	8.2 (7.2, 9.3)
POD 180		†
Full cohort	4,289 (100.0)	8.3 (7.5, 9.2)
No complications	1,722 (40.2)	3.9 (3.1, 5.0)
Any complications	2,567 (59.8)	11.3 (10.1, 12.5)
POD 365		†
Full cohort	4,289 (100.0)	12.7 (11.8, 13.8)
No complications	1,722 (40.2)	7.2 (6.1, 8.5)
Any complications	2,567 (59.8)	16.5 (15.1, 18.0)

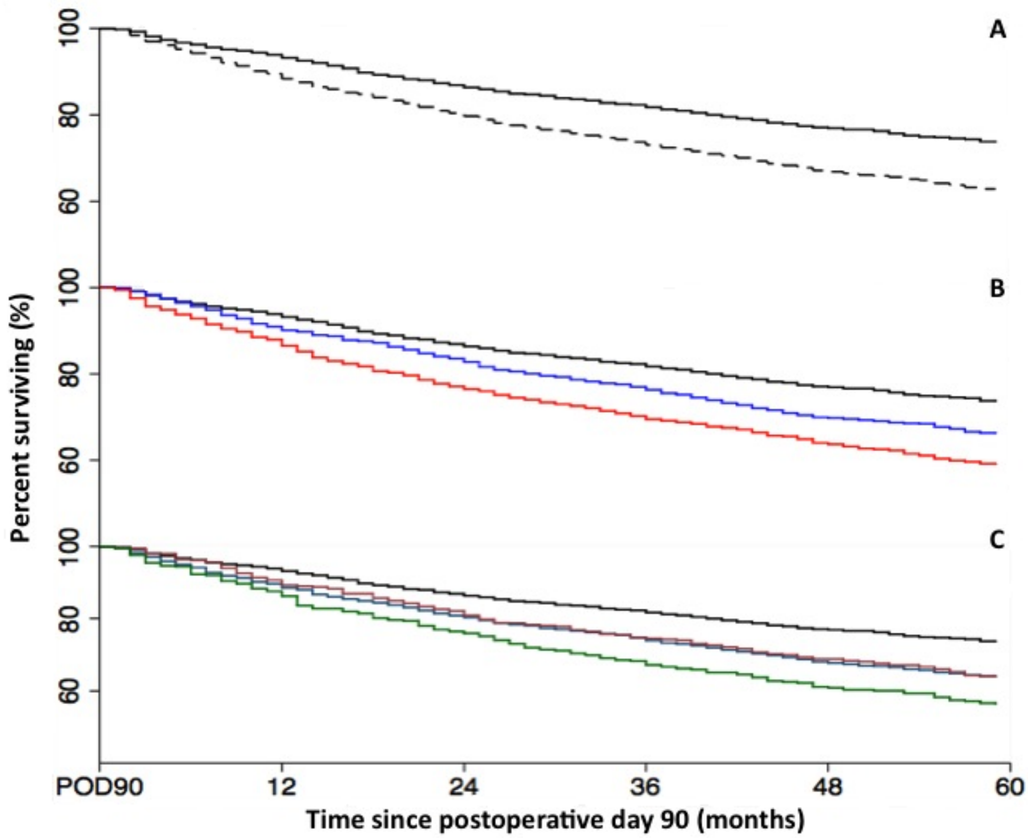
* The full cohort refers to all the patients in the study cohort from the date of the index surgery; CI=Confidence Interval; POD=Postoperative day.

† Log-rank test comparing mortality rates stratified on the occurrence of the postoperative complications using different cut-offs; $P < 0.001$.

Using postoperative day 90 as the starting point for the survival analyses, the unadjusted 5-year OS was found to be significantly lower for those who had a postoperative complication (62.8%) compared to those without (73.8%; $P < 0.001$; Figure 3A). For patients with pulmonary and non-pulmonary complications the OS rates were 59.1% and 66.3%, respectively, both significantly lower than that for those without complications ($P < 0.001$; Figure 3B). Among patients with an infectious complication, those with a major infectious type had a significantly worse OS compared to those with minor infectious and non-infectious complications (56.3%, 64.0% and 64.1% respectively; $P < 0.001$; Figure 3C). Likewise, patients with infectious complications had a significantly lower OS than those without complications (73.8%; $P < 0.001$; Figure 3C).

The above findings concerning differences in OS by presence and type of complication remained statistically significant even if the starting time was chosen at postoperative day 30 or at the date of index surgery.

Figure 3. Cumulative survival experience according to type of postoperative complication



A. By presence of any postoperative complication: (dashed black line) vs. no complications (solid black line). B. Pulmonary (red line) vs. non-pulmonary complications (blue line) (no complications: solid black line). C. Infectious complications: major infectious (green line), minor infectious (maroon line), non-infectious (navy line), no complications (solid black line). Survival distributions by Kaplan-Meier method; POD90=Postoperative day 90.

5.3. Multivariate Analysis

Occurrence of postoperative complication was an independent negative predictor of survival after adjusting for age, sex, income, education, area of residence (urbanicity), comorbidities, neo/adjuvant therapy, 30-day reoperations, and surgeon's years of experience, as shown in Model I (HR=1.37, 95% CI:1.21–1.54; Table 7). Adjusted estimates for non-pulmonary and pulmonary complications were (HR=1.21, 95% CI: 1.05–1.39; HR=1.54, 95% CI:1.34–1.77), respectively.

When classified based on occurrence and intensity of infections, major infectious complications had the highest adjusted effect measure (HR=1.67, 95% CI:1.39–2.01). The estimates for minor infections and non-infectious complications were (HR=1.27, 95% CI:1.05–1.54; HR=1.31, 95% CI:1.15–1.50), respectively. The sociodemographic parameters (income, education, urbanicity), 30-day reoperations, and experience in years of the treating surgeon were not found to be significantly associated with survival (Table 7).

Postoperative complications remained significantly associated with survival even after controlling for the empirical confounders (age, sex, comorbidities, neo/adjuvant therapy, and surgeon's years of experience, congestive heart failure, peripheral vascular disease, diabetes, and renal disease) in Model II (HR=1.32, 95% CI:1.17–1.49). Among the postoperative complication, major infections also remained the most important negative predictor of survival (HR=1.63, 95% CI:1.35–1.96; Table 7).

Four individual components of the CCI were found to be empirical confounders using Model II (congestive heart failure, peripheral vascular disease, diabetes, renal disease). Only heart failure and peripheral vascular disease were significantly associated with lower survival (HR=1.53, 95% CI:1.24–1.88 and HR=1.21, 95% CI:1.00–1.47 respectively; Table 7). Other than the estimates for CCI the effect measures stayed effectively unchanged using Model II.

Table 7. Multivariable predictors of survival after curative-intent surgery for lung cancer*

	Crude $^{\theta}$	*Model I* †	*Model II* ‡
Predictors	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Patient Characteristics			
Age			
< 60	Ref.	Ref.	Ref.
60 – 69	1.70 (1.47, 1.96)	**1.54 (1.33, 1.78)**	**1.52 (1.31, 1.76)**
≥ 70	2.39 (2.09, 2.75)	**2.03 (1.76, 2.36)**	**2.01 (1.73, 2.33)**
Sex			
Female	Ref.	Ref.	Ref.
Male	1.57 (1.40, 1.75)	**1.35 (1.20, 1.52)**	**1.31 (1.16, 1.48)**
Charlson Comorbidity Index			
0	Ref.	Ref.	Ref.
1	1.17 (1.02, 1.35)	1.12 (0.97, 1.29)	1.06 (0.92, 1.23)
2	1.45 (1.25, 1.69)	**1.20 (1.02, 1.41)**	1.10 (0.93, 1.30)
≥ 3	1.83 (1.56, 2.14)	**1.38 (1.17, 1.63)**	1.14 (0.94, 1.39)
Heart Failure#	1.93 (1.60, 2.34)	-----	**1.53 (1.24, 1.88)**
Peripheral Vascular Disease#	1.63 (1.37, 1.94)	-----	**1.21 (1.00, 1.47)**
Diabetes#	1.42 (1.22, 1.66)	-----	1.06 (0.89, 1.26)
Renal Disease#	2.05 (1.47, 2.85)	-----	1.37 (0.96, 1.96)
Socioeconomic Status			
Income			
High	Ref.	Ref.	
Middle	1.08 (0.95, 1.24)	1.00 (0.85, 1.15)	
Low	1.12 (0.98, 1.28)	1.07 (0.92, 1.25)	
Education			
High	Ref.	Ref.	
Middle	1.18 (1.03, 1.35)	1.10 (0.95, 1.27)	
Low	1.17 (1.02, 1.34)	1.08 (0.92, 1.27)	

Urbanicity			
Urban	Ref.	Ref.	
Sub-urban	1.01 (0.89, 1.14)	1.05 (0.92, 1.20)	
Rural/Remote	1.02 (0.87, 1.19)	0.97 (0.82, 1.15)	
Treatment Characteristics			
Neo/Adjuvant Therapy			
None	Ref.	Ref.	Ref.
≤ 3m pre/post surgery	1.98 (1.63, 2.42)	**1.85 (1.47, 2.29)**	**1.97 (1.59, 2.45)**
> 3m pre/post surgery	2.81 (2.37, 3.34)	**2.64 (2.21, 3.15)**	**2.67 (2.24, 3.20)**
Reoperations in < 30 days			
No	Ref.	Ref.	
Yes	1.27 (0.94, 1.70)	1.34 (0.90, 2.00)	
Surgeon's Experience			
≥ 20 years	Ref.	Ref.	Ref.
16 – 20 years	0.86 (075, 0.99)	0.86 (0.74, 1.00)	0.85 (0.73, 1.00)
10 – 15 years	1.00 (0.80, 1.26)	0.96 (0.76, 1.21)	0.98 (0.78, 1.24)
< 10 years	0.87 (0.72, 1.04)	0.82 (0.68, 1.00)	0.83 (0.69, 1.00)
Main Exposures			
Post-operative Complications			
No[♮]	Ref.	Ref.	Ref.
Yes	1.53 (1.36, 1.72)	**1.37 (1.21, 1.54)**	**1.32 (1.17, 1.49)**
Type of Complication[¶]			
Non-infectious	1.47 (1.30, 1.66)	**1.31 (1.15, 1.50)**	**1.27 (1.12, 1.45)**
Minor infectious	1.45 (1.21, 1.75)	**1.27 (1.05, 1.54)**	**1.23 (1.02, 1.49)**
Major infectious[§]	1.89 (1.58, 2.26)	**1.67 (1.39, 2.01)**	**1.63 (1.35, 1.96)**
Non-pulmonary	1.34 (1.18, 1.54)	**1.21 (1.05, 1.39)**	**1.18 (1.02, 1.35)**
Pulmonary	1.74 (1.53, 1.98)	**1.54 (1.34, 1.77)**	**1.49 (1.30, 1.71)**

* OS=Overall Survival; HR=Hazard Ratio; CI=Confidence Interval; Ref=Reference category.
θ Crude refers to the unadjusted hazard ratios.
† Model I is the full model that includes all the *a priori* chosen confounders.
‡ Model II is based on empirical confounders that exerted a minimum of a 2% change in the estimates of the main exposure variables.

The individual components of CCI that were found to be empirical confounders and included in Model II.
♮ The category of patients without any postoperative complications is the fixed reference group for all the categories pertaining to the different types of complications.
¶ Patients may have more than one type of complication, but the categories are analyzed independently.
§ Major infectious complications are considered to be: pneumonia, empyema, and mediastinitis.

Furthermore, adjacent contrasts made using previous category as referent revealed pulmonary complications to be significantly associated with lower survival compared to non-pulmonary complications (HR=1.27, 95% CI:1.11–1.46; Table 8). Major infections were also associated with lower survival with reference to a minor infection (HR=1.31, 95% CI:1.04–1.65). However, this was not the case when minor infections were compared to non-infectious complications (Table 8). The estimates corresponding to the adjacent contrasts among the different categories of postoperative complications remained virtually the same when using Model II.

Table 8. Adjacent contrasts of the different types of postoperative complications*

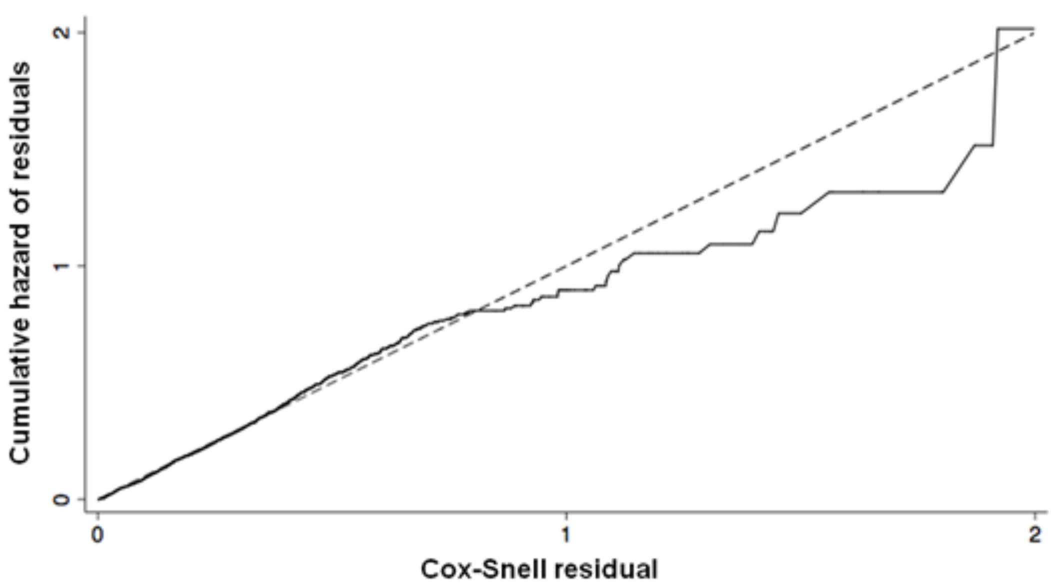
	Model I †	*Model II* ‡
Type of complication	**HR (95% CI)**	**HR (95% CI)**
None	1.00	1.00
Non-pulmonary	**1.21 (1.05, 1.39)**	**1.18 (1.02, 1.35)**
Pulmonary	**1.27 (1.11, 1.46)**	**1.27 (1.10, 1.45)**
None	1.00	1.00
Non-infectious	**1.31 (1.15, 1.50)**	**1.27 (1.12, 1.45)**
Minor infectious	0.97 (0.80, 1.17)	0.97 (0.80, 1.16)
Major infectious§	**1.31 (1.04, 1.65)**	**1.32 (1.05, 1.66)**

* The hazard ratios are estimated using a moving referent within each category, providing adjacent contrasts which compares each group to the one above; HR=Hazard Ratio; CI=Confidence Interval.
† Model I is the full model that includes all the *a priori* chosen confounders.
‡ Model II is based on empirical confounders that exerted a minimum of a 2% change in the estimates of the main exposure variables.
§ Major infectious complications are considered to be: pneumonia, empyema, and mediastinitis.

5.4. Goodness-of-Fit

The goodness-of-fit of the full model (Model I) was graphically depicted using the Cox-Snell residuals in Figure 4. The hazard function follows the 45-degree line very closely except for large values of time, which is a common finding for models especially at large values of time and should not cause much concern. Overall the Model I fits the data very well.

Figure 4. Graphical depiction of the goodness-of-fit using the Cox-Snell residuals*



* The graph shows the goodness-of-fit of the Cox proportional hazard regression model (Model I) and graphically depicts any deviation from the proportionality of hazard assumption; Nelson-Aalen cumulative hazard (solid black line) and

Cox-Snell residual (dashed black line). Overall, the model seems to be a good fit for the data.

6. DISCUSSION

6.1. Summary of Main Findings

We found that the death rate among patients who suffered from any postoperative morbidity after a curative-intent lung cancer surgery was almost 40% higher than that for those with no complications up to postoperative day 30. This effect was more profound in patients in whom the complication was due to a major infection; their death rate was nearly 70% greater than for those with no complications and 30% higher than those with minor infections. Such substantial prognostic effects persisted even after accounting for several potential and real confounders. Pneumonia, empyema and mediastinitis were the major infections. They are considered greatly pro-inflammatory in nature and result in high levels of bacteremia. Thus, our findings are in line with the wealth of basic science work linking both systemic inflammation and bacterial antigens with cancer progression [10-13,58,120] and mounting clinical evidence linking an inflammatory state with cancer causation, recurrence and survival in several types of malignancies [121-124].

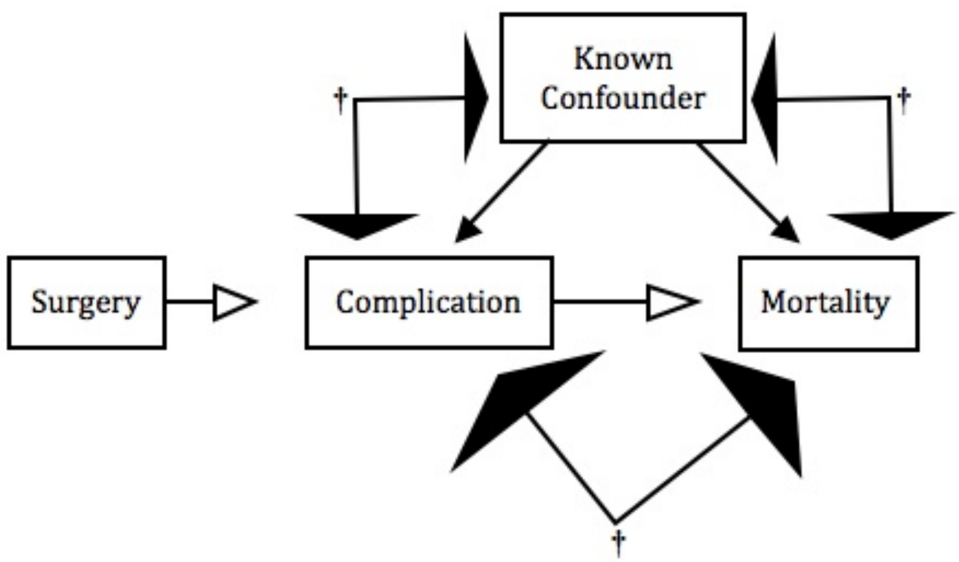
To our knowledge, there has been only one study showing a decreased long-term survival beyond postoperative day 30 for patients with stage I NSCLC who had complications [68]. It was a population-based study by Rueth et al. that used SEER data, which captures less than one-third of the population in the United States [69].

The need to link with the Medicare database to improve completeness of data restricted their population to 65 years and older. Further restriction was made to include stage I disease patients that only underwent a lobectomy, all of which decrease the generalizability of the results.

In addition to being a large province-wide study free of restrictions on the basis of age and disease burden, our investigation also demonstrated that postoperative morbidity not only influences early mortality, but its negative impact also lingers beyond the early postoperative phase with a lasting influence on the overall 5-year survival in lung cancer patients undergoing surgery. After controlling for several confounders (age, sex, socioeconomic status, Charlson Comorbidity Index, neo/adjuvant therapy, 30-day reoperations, and surgeon's years of experience) postoperative complications, particularly those pulmonary in origin and of a major infectious type, remained significant negative predictors of survival. Our findings remained the same even after controlling conservatively for all empirical confounders. This is the first study to assess at a population level and beyond the early postoperative period (90 days) the negative impact of major infectious complications, such as pneumonia, on long-term survival in lung cancer patients. The 90-day cut-off was chosen arbitrarily but as a conservative threshold in order to focus only on the long-term association between postoperative morbidity and survival. Our choice was based on the rationale that there is evidence that the immediate impact of postoperative morbidity exceeds the conventional 30-day period, thus supporting the use of 90 days as the limit for early postoperative events [14].

The current study was not designed to address whether the underlying mechanism for a negative impact of postoperative morbidity on survival could be due to a worse oncologic outcome associated with tumor recurrence either locally or at a distant site facilitated by inflammatory states and associated immunological phenomena [10,11,58,121-124]. Likewise, it was not our aim to verify, in the case of infectious complications, whether there is a prognostic mechanism through bacterial antigen-mediated processes, even though experimental data exist [12,13,120]. Alternatively, the detrimental effect of postoperative complications could be due to unmeasured confounders, which for instance can exert their effect via the proposed Directed Acyclic Graph (DAG) below.

Figure 5: Directed Acyclic Graph representing the impact of unknown confounding*



* The Directed Acyclic Graph (DAG) schematically shows how unknown and unmeasured confounders may explain a possible association between the main exposures and the outcome despite adjustments for known confounders.
† The symbol represents unknown and/or unmeasured confounders.

The negative impact of the postoperative complications on survival could also be explained by a more direct relationship between the two, through sequelae such as chronic postoperative respiratory compromise. Regardless of the mechanism, however, the above findings have clinical utility. Postoperative complications particularly those that are more pro-inflammatory (such as major infections, e.g., pneumonia) may be a proxy for the prognostic effect from unmeasured factors and thus efforts should be made to minimize postoperative morbidity for improved prognosis beyond short-term survival.

Several patient, tumor and therapeutic factors have been linked to greater postoperative morbidity in addition to being identified as negative predictors of long-term survival in patients with an early-stage NSCLC. Thus in order to appropriately address the issue of confounding in our study, an attempt was made to identify and include such factors in the analysis. Age at diagnosis (above 70), sex (male), comorbidities (higher CCI), and low socioeconomic status are among the recognized patient characteristics [71,73,74,80]. Tumor size, grade, histology and the stage of the cancer along with an incomplete resection, neo/adjuvant therapy, and access to a high-volume thoracic surgery center have also been identified as potential confounders [71,73,86,87,91]. We were not able to control for all these variables due to the limitations in using the provincial administrative health care databases, which are primarily constructed for remuneration purposes. Moreover, despite adjustments made for the measured confounders, there always remains the likelihood of residual confounding most notably in the case of comorbidities. This is once again a well-known limitation of using population administrative databases.

Nevertheless, our results confirmed advanced age, sex, Charlson Comorbidity Index, and neo/adjuvant therapy as negative predictors with all showing a dose-prognosis relationship. Using Model II (empirical confounders), only heart failure and peripheral vascular disease as individual components of CCI were found to be independent predictors of mortality. Similar findings have been reported in a study by Ambrogi et al., where cardiovascular comorbidities were found to be important negative predictors of both short and long-term outcomes in patients with an early stage NSCLC post resection [75]. Lower socioeconomic status (income, education and urbanicity) was not found to be significantly associated with poor survival. This finding is likely due to the universal access to health care in Canada for patients regardless of income, education, race or area of residence. The finding is consistent with a nation-wide study by Rich et al. on the effect of socioeconomic status on lung cancer therapy and survival in United Kingdom [125] where a universal health care system is also in place. Experience of the treating surgeon, as measured by years of practice, was used as a proxy for the volume of lung surgeries performed by the surgeon, and found not to be an independent predictor of survival. The proxy was used due to inability to calculate the true surgeon or hospital-specific surgical volume from the provincial administrative databases, which is mainly for the protection of both patient and doctor's confidentiality. Nevertheless, the finding likely demonstrates that the years of experience does not necessarily translate into proficiency in lung cancer surgery, rather it is the volume of surgical procedures that has been associated with improved short and long-term outcome after cancer surgery [91].

Thirty-day postoperative complications occurred at a high rate of 58% in our study cohort, which is higher than what has been reported [3,44,45]. However, most studies were based on voluntary reporting sources or on patients treated in single institutions or highly specialized cancer centers. We identified the postoperative complications from the provincial administrative databases using specific ICD9-CM diagnosis codes. Therefore, the estimated incidence rate of the 30-day postoperative complications represents documented outcome events for the entire population in the province of Quebec and a more realistic estimate of what happens at the provincial or even national level given that a large proportion of lung cancer surgery is performed by non-thoracic surgeons, which may lead to inferior outcomes [126]. Albeit, the high proportion of the "unspecified" postoperative complications, which could have been due to misclassification or coding error in the administrative databases may also represent a potential reason for such high complication rate. However, the postoperative complication rate for this Quebec study was comparable to that of the aforementioned study using SEER data (54%) [68].

The 30-day mortality in our study cohort was 3.6%, which is somewhat higher than expected (1.3%-3.2%) [4,5]. Inclusion of more advanced cases in the study cohort due to misclassification in the administrative datasets could explain the observed estimate. This mortality rate is also representative of a true region-wide study as opposed to one from a single specialized center.

6.2. Limitations

Several factors need to be taken into consideration when interpreting our findings. Currently accepted 5-year survival for stage I NSCLC after a curative surgery with or without combination therapy varies from 51% to 83% and for stage II ranges from 30% to 60% [34,40,73]. However a common limitation to using the provincial administrative health care database is that it does not include cancer specific data such as cancer type and stage, tumor size, grade and histology, which prevented us from conducting stratified analyses on these characteristics and subsequently control for these potential sources of selection bias and confounding. Regarding selection bias and histology, NSCLC is the predominant histological subtype of lung cancer amenable to surgery (carcinoids represent less than 1-2% in most surgical series [127]) and the small cell lung cancer is highly invasive with a poor 5-year OS of less than 10% [19,128]. Hence, we are confident that the vast majority of patients in our cohort had NSCLC. To further counter this bias and select only those patients with an early stage disease amenable to a curative resection, we implemented conservative exclusion criteria, which even excluded some patients with Stage IIA, IIB and IIIA with node positive disease, who were still candidates for curative-intent surgery. We felt that this conservative approach was necessary to allow us to assess the impact of postoperative complications on long-term survival only in those patients with the best chance for both cure and long-term survival even though this restriction may have decreased the generalizability of the results (to all curative-intent surgeries). Furthermore, the 5-year OS of our study cohort was within the accepted survival range for patients with stages I and II NSCLC, who have undergone a curative resection and is comparable to that of the above SEER study [68], which demonstrates external validity and consistency of our findings. With respect to confounding, despite having data on the greater majority of the known confounders, as previously mentioned we were unable to gather information on some known prognostic factors, particularly the tumor-specific factors such as size, grade and histology. This again is a shortcoming of using the provincial administrative health care databases and the true impact of such confounding and its direction on the estimates from the multivariate regression analysis is unpredictable. However given the similar findings from the above SEER study [68], which had information on the tumor-specific characteristics, we can assume that there would likely be no material changes in the estimates even if we were able to measure the missing confounders.

An additional concern inherent in using the provincial administrative health care datasets is misclassification of data, as has been shown in the growing field of pharmacoepidemiology [129]. However, given the many advantages of the region-wide databases and by implementing proper study designs and analyses, such databanks are becoming increasingly used for epidemiologic studies [97]. We are also confident that by using hard outcome measures, such as mortality, our findings were less affected by outcome misclassification than if we had used disease-free survival or other “softer” outcomes.

Another limitation was our inability to calculate cancer-specific survival because the need to link to administrative healthcare data provided us only with all-cause mortality. That said, overall mortality is still valid and a commonly used outcome in population-based cancer survival studies [130].

6.3. Strengths

Despite the limitations, our study has a number of very important elements. The strengths of the study include the large sample size, broad population base, and use of province-wide administrative data that capture virtually all the healthcare procedures for the population, thus improving the generalizability of the findings.

We found that the immediate postoperative morbidity is an independent negative predictor of long-term survival for lung cancer patients undergoing curative-intent surgery. Most notably, we have demonstrated that the negative long-term impact of postoperative morbidity is highest for those complications that are infectious and highly pro-inflammatory in nature, such as pneumonia, empyema and mediastinitis. This finding supports the hypothesis linking bacterial-mediated acute systemic inflammation with poor cancer outcomes [10-13,58,120-124].

7. CONCLUSIONS

In practical terms, our findings emphasize the importance of achieving a lung resection with minimal postoperative complications, not only for a better immediate postoperative course, but also for a beneficial impact on long-term oncologic outcomes. The focus should predominantly be placed on limiting the postoperative morbidities with the highest negative impact on survival. The findings from this large cohort study identify pulmonary and major infectious complications as important targets to improve outcomes.

Different novel strategies can be utilized to diminish the burden of postoperative morbidity. One such perioperative preventive strategy is fast-track surgery, which implements a multi-disciplinary protocol involving anesthesia, surgery, nutrition, aggressive rehabilitation and ambulation with an aim to reduce the surgical stress endured by the patient, shorten the time to recovery, and decrease postoperative morbidity especially major infections such as pneumonia, which have been shown to be effective in intestinal surgeries [131-133].

Furthermore, the strong association between major infectious complications and survival after lung cancer surgery may open the door to investigational therapies targeting bacterial antigens in the perioperative period in patients undergoing lung cancer surgery.

8. REFERENCES

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61:69-90.

2. Molina JR, Yang P, Cassivi SD, Schild SE, Adjei AA. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. Mayo Clin Proc 2008;83:584-94.

3. Allen MS, Darling GE, Pechet TT, et al. Morbidity and mortality of major pulmonary resections in patients with early-stage lung cancer: initial results of the randomized, prospective ACOSOG Z0030 trial. Ann Thorac Surg 2006;81:1013-9; discussion 9-20.

4. Wada H, Nakamura T, Nakamoto K, Maeda M, Watanabe Y. Thirty-day operative mortality for thoracotomy in lung cancer. J Thorac Cardiovasc Surg 1998;115:70-3.

5. Boffa DJ, Allen MS, Grab JD, Gaissert HA, Harpole DH, Wright CD. Data from The Society of Thoracic Surgeons General Thoracic Surgery database: the surgical management of primary lung tumors. J Thorac Cardiovasc Surg 2008;135:247-54.

6. Mirnezami A, Mirnezami R, Chandrakumaran K, Sasapu K, Sagar P, Finan P. Increased local recurrence and reduced survival from colorectal cancer following anastomotic leak: systematic review and meta-analysis. Ann Surg 2011;253:890-9.

7. de Cassia Braga Ribeiro K, Kowalski LP, Latorre Mdo R. Perioperative complications, comorbidities, and survival in oral or oropharyngeal cancer. Arch Otolaryngol Head Neck Surg 2003;129:219-28.

8. Laurent C, Sa Cunha A, Couderc P, Rullier E, Saric J. Influence of postoperative morbidity on long-term survival following liver resection for colorectal metastases. Br J Surg 2003;90:1131-6.

9. Lerut T, Moons J, Coosemans W, et al. Postoperative complications after transthoracic esophagectomy for cancer of the esophagus and gastroesophageal junction are correlated with early cancer recurrence: role of systematic grading of complications using the modified Clavien classification. Ann Surg 2009;250:798-807.

10. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature 2008;454:436-44.

11. McDonald B, Spicer J, Giannais B, Fallavollita L, Brodt P, Ferri LE. Systemic inflammation increases cancer cell adhesion to hepatic sinusoids by neutrophil mediated mechanisms. Int J Cancer 2009;125:1298-305.

12. Doan HQ, Bowen KA, Jackson LA, Evers BM. Toll-like receptor 4 activation increases Akt phosphorylation in colon cancer cells. Anticancer Res 2009;29:2473-8.

13. Hsu RY, Chan CH, Spicer JD, et al. LPS-induced TLR4 signaling in human colorectal cancer cells increases beta1 integrin-mediated cell adhesion and liver metastasis. Cancer Res 2011;71:1989-98.

14. Bryant AS, Rudemiller K, Cerfolio RJ. The 30- versus 90-day operative mortality after pulmonary resection. Ann Thorac Surg 2010;89:1717-22; discussion 22-3.

15. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin 2009;59:225-49.

16. Canadian Cancer Society's Steering Committee on Cancer Statistics. Canadian Cancer Statistics 2011. In. Toronto, ON: Canadian Cancer Society; 2011.

17. The M.D. Anderson surgical oncology handbook. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2006.

18. Park BJ, Altorki NK. Diagnosis and management of early lung cancer. Surg Clin N Am 2002;82:457-76, v.

19. Sher T, Dy GK, Adjei AA. Small cell lung cancer. Mayo Clin Proc 2008;83:355-67.

20. Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. J Thorac Oncol 2007;2:706-14.

21. Groome PA, Bolejack V, Crowley JJ, et al. The IASLC Lung Cancer Staging Project: validation of the proposals for revision of the T, N, and M descriptors and consequent stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. J Thorac Oncol 2007;2:694-705.

22. Manser R, Wright G, Hart D, Byrnes G, Campbell DA. Surgery for early stage non-small cell lung cancer. Cochrane Database Syst Rev 2005:CD004699.

23. Robinson LA, Ruckdeschel JC, Wagner H, Jr., Stevens CW. Treatment of non-small cell lung cancer-stage IIIA: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 2007;132:243S-65S.

24. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg 1995;60:615-22; discussion 22-3.

25. Kirby TJ, Mack MJ, Landreneau RJ, Rice TW. Lobectomy--video-assisted thoracic surgery versus muscle-sparing thoracotomy. A randomized trial. J Thorac Cardiovasc Surg 1995;109:997-1001; discussion -2.

26. Rueth NM, Andrade RS. Is VATS lobectomy better: perioperatively, biologically and oncologically? Ann Thorac Surg 2010;89:S2107-11.

27. Darling GE, Allen MS, Decker PA, et al. Number of lymph nodes harvested from a mediastinal lymphadenectomy: results of the randomized, prospective American College of Surgeons Oncology Group Z0030 trial. Chest 2011;139:1124-9.

28. Arriagada R, Bergman B, Dunant A, Le Chevalier T, Pignon JP, Vansteenkiste J. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N Engl J Med 2004;350:351-60.

29. Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. N Engl J Med 2005;352:2589-97.

30. Visbal AL, Leighl NB, Feld R, Shepherd FA. Adjuvant Chemotherapy for Early-Stage Non-small Cell Lung Cancer. Chest 2005;128:2933-43.

31. Bogart JA, Aronowitz JN. Localized non-small cell lung cancer: adjuvant radiotherapy in the era of effective systemic therapy. Clin Cancer Res 2005;11:5004s-10s.

32. Rusch VW, Giroux DJ, Kraut MJ, et al. Induction chemoradiation and surgical resection for non-small cell lung carcinomas of the superior sulcus: Initial results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). J Thorac Cardiovasc Surg 2001;121:472-83.

33. Wright CD, Menard MT, Wain JC, et al. Induction chemoradiation compared with induction radiation for lung cancer involving the superior sulcus. Ann Thorac Surg 2002;73:1541-4.

34. Nesbitt JC, Putnam JB, Jr., Walsh GL, Roth JA, Mountain CF. Survival in early-stage non-small cell lung cancer. Ann Thorac Surg 1995;60:466-72.

35. Howlader N NA, Krapcho M, Neyman N, Aminou R, Waldron W, Altekruse SF, Kosary CL, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Eisner MP, Lewis DR, Chen HS, Feuer EJ, Cronin KA, Edwards BK. SEER Cancer Statistics Review, 1975-2008, National Cancer Institute.

36. Martini N, Bains MS, Burt ME, et al. Incidence of local recurrence and second primary tumors in resected stage I lung cancer. J Thorac Cardiovasc Surg 1995;109:120-9.

37. Thomas P, Doddoli C, Thirion X, et al. Stage I non-small cell lung cancer: a pragmatic approach to prognosis after complete resection. Ann Thorac Surg 2002;73:1065-70.

38. Ost D, Goldberg J, Rolnitzky L, Rom WN. Survival after surgery in stage IA and IB non-small cell lung cancer. Am J Respir Crit Care Med 2008;177:516-23.

39. Warren WH, Faber LP. Segmentectomy versus lobectomy in patients with stage I pulmonary carcinoma. Five-year survival and patterns of intrathoracic recurrence. J Thorac Cardiovasc Surg 1994;107:1087-93; discussion 93-4.

40. Sawabata N, Miyaoka E, Asamura H, et al. Japanese Lung Cancer Registry Study of 11,663 Surgical Cases in 2004: Demographic and Prognosis Changes Over Decade. J Thorac Oncol 2011;6:1229-35.

41. Fry WA, Phillips JL, Menck HR. Ten-year survey of lung cancer treatment and survival in hospitals in the United States: a national cancer data base report. Cancer 1999;86:1867-76.

42. Pairolero PC, Williams DE, Bergstralh EJ, Piehler JM, Bernatz PE, Payne WS. Postsurgical stage I bronchogenic carcinoma: morbid implications of recurrent disease. Ann Thorac Surg 1984;38:331-8.

43. Thomas PA, Jr., Rubinstein L. Malignant disease appearing late after operation for T1 N0 non-small-cell lung cancer. The Lung Cancer Study Group. J Thorac Cardiovasc Surg 1993;106:1053-8.

44. Watanabe S, Asamura H, Suzuki K, Tsuchiya R. Recent results of postoperative mortality for surgical resections in lung cancer. Ann Thorac Surg 2004;78:999-1002; discussion -3.

45. Deslauriers J, Ginsberg RJ, Piantadosi S, Fournier B. Prospective assessment of 30-day operative morbidity for surgical resections in lung cancer. Chest 1994;106:329S-30S.

46. Belda J, Cavalcanti M, Iglesias M, Gimferrer JM, Torres A. Respiratory infections after lung cancer resection. Clinical Pulmonary Medicine 2006;13 (1):8-16.

47. Martin RC, 2nd, Brennan MF, Jaques DP. Quality of complication reporting in the surgical literature. Ann Surg 2002;235:803-13.

48. Arozullah AM, Khuri SF, Henderson WG, Daley J. Development and validation of a multifactorial risk index for predicting postoperative pneumonia after major noncardiac surgery. Ann Intern Med 2001;135:847-57.

49. Schussler O, Alifano M, Dermine H, et al. Postoperative pneumonia after major lung resection. Am J Respir Crit Care Med 2006;173:1161-9.

50. Licker M, Cartier V, Robert J, et al. Risk factors of acute kidney injury according to RIFLE criteria after lung cancer surgery. Ann Thorac Surg 2011;91:844-50.

51. Zingg U, Smithers BM, Gotley DC, et al. Factors associated with postoperative pulmonary morbidity after esophagectomy for cancer. Ann Surg Oncol 2011;18:1460-8.

52. Roselli EE, Murthy SC, Rice TW, et al. Atrial fibrillation complicating lung cancer resection. J Thorac Cardiovasc Surg 2005;130 (2):438-44.

53. Dutta S, Crumley AB, Fullarton GM, Horgan PG, McMillan DC. Comparison of the prognostic value of tumour- and patient-related factors in patients undergoing potentially curative resection of oesophageal cancer. World J Surg 2011;35:1861-6.

54. Richards CH, Platt JJ, Anderson JH, McKee RF, Horgan PG, McMillan DC. The impact of perioperative risk, tumor pathology and surgical complications on disease recurrence following potentially curative resection of colorectal cancer. Ann Surg 2011;254:83-9.

55. Hara M, Yonei A, Ayabe T, Tomita M, Nakamura K, Onitsuka T. Postoperative serum C-reactive protein levels in non-small cell lung cancer patients. Ann Thorac Cardiovasc Surg 2010;16:85-90.

56. Pidgeon GP, Harmey JH, Kay E, Da Costa M, Redmond HP, Bouchier-Hayes DJ. The role of endotoxin/lipopolysaccharide in surgically induced tumour growth in a murine model of metastatic disease. Br J Cancer 1999;81:1311-7.

57. Harmey JH, Bucana CD, Lu W, et al. Lipopolysaccharide-induced metastatic growth is associated with increased angiogenesis, vascular permeability and tumor cell invasion. Int J Cancer 2002;101:415-22.

58. Orr FW, Warner DJ. Effects of systemic complement activation and neutrophil-mediated pulmonary injury on the retention and metastasis of circulating cancer cells in mouse lungs. Lab Invest 1990;62:331-8.

59. Khatib AM, Auguste P, Fallavollita L, et al. Characterization of the host proinflammatory response to tumor cells during the initial stages of liver metastasis. Am J Pathol 2005;167:749-59.

60. Fujita S, Teramoto T, Watanabe M, Kodaira S, Kitajima M. Anastomotic leakage after colorectal cancer surgery: a risk factor for recurrence and poor prognosis. Jpn J Clin Oncol 1993;23:299-302.

61. Law WL, Choi HK, Lee YM, Ho JW, Seto CL. Anastomotic leakage is associated with poor long-term outcome in patients after curative colorectal resection for malignancy. J Gastrointest Surg 2007;11:8-15.

62. de Melo GM, Ribeiro KC, Kowalski LP, Deheinzelin D. Risk factors for postoperative complications in oral cancer and their prognostic implications. Arch Otolaryngol Head Neck Surg 2001;127:828-33.

63. Ferri LE, Law S, Wong KH, Kwok KF, Wong J. The influence of technical complications on postoperative outcome and survival after esophagectomy. Ann Surg Oncol 2006;13:557-64.

64. Rizk NP, Bach PB, Schrag D, et al. The impact of complications on outcomes after resection for esophageal and gastroesophageal junction carcinoma. J Am Coll Surg 2004;198:42-50.

65. Crestanello JA, Deschamps C, Cassivi SD, et al. Selective management of intrathoracic anastomotic leak after esophagectomy. J Thorac Cardiovasc Surg 2005;129:254-60.

66. Hulscher JB, Tijssen JG, Obertop H, van Lanschot JJ. Transthoracic versus transhiatal resection for carcinoma of the esophagus: a meta-analysis. Ann Thorac Surg 2001;72:306-13.

67. Song SW, Lee HS, Kim MS, et al. Preoperative Serum Fibrinogen Level Predicts Postoperative Pulmonary Complications After Lung Cancer Resection. Ann Thorac Surg 2006;81 (6):1974-81.

68. Rueth NM, Parsons HM, Habermann EB, et al. The Long-term Impact of Surgical Complications After Resection of Stage I Nonsmall Cell Lung Cancer: A Population-based Survival Analysis. Ann Surg 2011;254:368-74.

69. Warren JL, Klabunde CN, Schrag D, Bach PB, Riley GF. Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. Med Care 2002;40:IV-3-18.

70. Nagasaki F, Flehinger BJ, Martini N. Complications of surgery in the treatment of carcinoma of the lung. Chest 1982;82:25-9.

71. Kozower BD, Sheng S, O'Brien SM, et al. STS database risk models: predictors of mortality and major morbidity for lung cancer resection. Ann Thorac Surg 2010;90:875-81; discussion 81-3.

72. Cerfolio RJ, Bryant AS. Optimal care of patients with non-small cell lung cancer reduces perioperative morbidity. J Thorac Cardiovasc Surg 2011;141:22-33.

73. Ou SH, Zell JA, Ziogas A, Anton-Culver H. Prognostic factors for survival of stage I nonsmall cell lung cancer patients : a population-based analysis of 19,702 stage I patients in the California Cancer Registry from 1989 to 2003. Cancer 2007;110:1532-41.

74. Battafarano RJ, Piccirillo JF, Meyers BF, et al. Impact of comorbidity on survival after surgical resection in patients with stage I non-small cell lung cancer. J Thorac Cardiovasc Surg 2002;123:280-7.

75. Ambrogi V, Pompeo E, Elia S, Pistolese GR, Mineo TC. The impact of cardiovascular comorbidity on the outcome of surgery for stage I and II non-small-cell lung cancer. Eur J Cardiothorac Surg 2003;23:811-7.

76. Schneeweiss S, Maclure M. Use of comorbidity scores for control of confounding in studies using administrative databases. Int J Epidemiol 2000;29:891-8.

77. Klabunde CN, Legler JM, Warren JL, Baldwin LM, Schrag D. A refined comorbidity measurement algorithm for claims-based studies of breast, prostate, colorectal, and lung cancer patients. Ann Epidemiol 2007;17:584-90.

78. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.

79. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45:613-9.

80. Birim O, Kappetein AP, Bogers AJ. Charlson comorbidity index as a predictor of long-term outcome after surgery for nonsmall cell lung cancer. Eur J Cardiothorac Surg 2005;28:759-62.

81. Strand TE, Rostad H, Damhuis RA, Norstein J. Risk factors for 30-day mortality after resection of lung cancer and prediction of their magnitude. Thorax 2007;62:991-7.

82. Wang CY, Lin YS, Tzao C, et al. Comparison of Charlson comorbidity index and Kaplan-Feinstein index in patients with stage I lung cancer after surgical resection. Eur J Cardiothorac Surg 2007;32:877-81.

83. Moro-Sibilot D, Aubert A, Diab S, et al. Comorbidities and Charlson score in resected stage I nonsmall cell lung cancer. Eur Respir J 2005;26:480-6.

84. Wisnivesky JP, Arciniega J, Mhango G, Mandeli J, Halm EA. Lymph node ratio as a prognostic factor in elderly patients with pathological N1 non-small cell lung cancer. Thorax 2011;66:287-93.

85. Iyoda A, Hiroshima K, Moriya Y, et al. Predictors of postoperative survival in patients with locally advanced non-small cell lung carcinoma. Surg Today 2010;40:725-8.

86. Shiono S, Yoshida J, Nishimura M, et al. Risk factors of postoperative respiratory infections in lung cancer surgery. J Thorac Oncol 2007;2 (1):34-8.

87. Fujita S, Katakami N, Takahashi Y, et al. Postoperative complications after induction chemoradiotherapy in patients with non-small-cell lung cancer. Eur J Cardiothorac Surg 2006;29 (6):896-901.

88. Bach PB, Cramer LD, Schrag D, Downey RJ, Gelfand SE, Begg CB. The influence of hospital volume on survival after resection for lung cancer. N Engl J Med 2001;345:181-8.

89. Schrag D, Panageas KS, Riedel E, et al. Surgeon volume compared to hospital volume as a predictor of outcome following primary colon cancer resection. J Surg Oncol 2003;83:68-78; discussion -9.

90. Verhoef C, van de Weyer R, Schaapveld M, Bastiaannet E, Plukker JT. Better survival in patients with esophageal cancer after surgical treatment in university hospitals: a plea for performance by surgical oncologists. Ann Surg Oncol 2007;14:1678-87.

91. Cheung MC, Hamilton K, Sherman R, et al. Impact of teaching facility status and high-volume centers on outcomes for lung cancer resection: an examination of 13,469 surgical patients. Ann Surg Oncol 2009;16:3-13.

92. Tamblyn R, Lavoie G, Petrella L, Monette J. The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Quebec. J Clin Epidemiol 1995;48:999-1009.

93. King MA, Purdie DM, Roberts MS. Matching prescription claims with medication data for nursing home residents: implications for prescriber feedback,

drug utilisation studies and selection of prescription claims database. J Clin Epidemiol 2001;54:202-9.

94. Muhajarine N, Mustard C, Roos LL, Young TK, Gelskey DE. Comparison of survey and physician claims data for detecting hypertension. J Clin Epidemiol 1997;50:711-8.

95. Tamblyn R, Reid T, Mayo N, McLeod P, Churchill-Smith M. Using medical services claims to assess injuries in the elderly: sensitivity of diagnostic and procedure codes for injury ascertainment. J Clin Epidemiol 2000;53:183-94.

96. Wilchesky M, Tamblyn RM, Huang A. Validation of diagnostic codes within medical services claims. J Clin Epidemiol 2004;57:131-41.

97. Suissa S. Novel Approaches to Pharmacoepidemiology Study Design and Statistical Analysis. In: Strom BL, ed. Pharmacoepidemiology. 3rd ed: John Wiley & Sons Ltd; 2000:785-805.

98. Regie de l'assurance-maladie du Quebec. Statistiques Annuelles. Quebec; 2004.

99. Ayanian JZ. Using administrative data to assess health care outcomes. Eur Heart J 1999;20:1689-91.

100. Quam L, Ellis LB, Venus P, Clouse J, Taylor CG, Leatherman S. Using claims data for epidemiologic research. The concordance of claims-based criteria with the medical record and patient survey for identifying a hypertensive population. Med Care 1993;31:498-507.

101. Mayo N DI, Carlton J, Scott S. Accuracy of hospital discharge coding for stroke. . Can J Cardiol 1993;9 (Suppl D):121D-4D.

102. Newton KM, Wagner EH, Ramsey SD, et al. The use of automated data to identify complications and comorbidities of diabetes: a validation study. J Clin Epidemiol 1999;52:199-207.

103. Rawson NS, Malcolm E. Validity of the recording of ischaemic heart disease and chronic obstructive pulmonary disease in the Saskatchewan health care datafiles. Stat Med 1995;14:2627-43.

104. Romano PS, Roos LL, Luft HS, Jollis JG, Doliszny K. A comparison of administrative versus clinical data: coronary artery bypass surgery as an example. Ischemic Heart Disease Patient Outcomes Research Team. J Clin Epidemiol 1994;47:249-60.

105. Rahme E, Barkun AN, Toubouti Y, Bardou M. The cyclooxygenase-2-selective inhibitors rofecoxib and celecoxib prevent colorectal neoplasia occurrence and recurrence. Gastroenterology 2003;125:404-12.

106. Huzel L, Roos LL, Anthonisen NR, Manfreda J. Diagnosing asthma: the fit between survey and administrative database. Can Respir J 2002;9:407-12.

107. Mapel D, Pearson M. Obtaining evidence for use by healthcare payers on the success of chronic obstructive pulmonary disease management. Respir Med 2002;96 Suppl C:S23-30.

108. Newschaffer CJ, Bush TL, Penberthy LT. Comorbidity measurement in elderly female breast cancer patients with administrative and medical records data. J Clin Epidemiol 1997;50:725-33.

109. Cleves MA, Sanchez N, Draheim M. Evaluation of two competing methods for calculating Charlson's comorbidity index when analyzing short-term mortality using administrative data. J Clin Epidemiol 1997;50:903-8.

110. Romano PS, Roos LL, Jollis JG. Adapting a clinical comorbidity index for use with ICD-9-CM administrative data: differing perspectives. J Clin Epidemiol 1993;46:1075-9; discussion 81-90.

111. Humphries KH, Rankin JM, Carere RG, Buller CE, Kiely FM, Spinelli JJ. Co-morbidity data in outcomes research: are clinical data derived from administrative databases a reliable alternative to chart review? J Clin Epidemiol 2000;53:343-9.

112. Levy AR, Tamblyn RM, Fitchett D, McLeod PJ, Hanley JA. Coding accuracy of hospital discharge data for elderly survivors of myocardial infarction. Can J Cardiol 1999;15:1277-82.

113. Cadieux G, Tamblyn R. Accuracy of physician billing claims for identifying acute respiratory infections in primary care. Health Serv Res 2008;43:2223-38.

114. Wyse JM, Joseph L, Barkun AN, Sewitch MJ. Accuracy of administrative claims data for polypectomy. CAMJ 2011;183:E743-7.

115. Quan H, Parsons GA, Ghali WA. Validity of procedure codes in International Classification of Diseases, 9th revision, clinical modification administrative data. Med Care 2004;42:801-9.

116. Fisher ES, Whaley FS, Krushat WM, et al. The accuracy of Medicare's hospital claims data: progress has been made, but problems remain. Am J Public Health 1992;82:243-8.

117. Cox DR. Regression models and life-tables. J Roy Stat Soc B Met 1972;34:187-220.

118. Mickey RM, Greenland S. The impact of confounder selection criteria on effect estimation. Am J Epidemiol 1989;129:125-37.

119. Commission d'accès à l'information. (Accessed at http://www.cai.gouv.qc.ca/index-en.html.)

120. Molteni M, Marabella D, Orlandi C, Rossetti C. Melanoma cell lines are responsive in vitro to lipopolysaccharide and express TLR-4. Cancer Lett 2006;235:75-83.

121. Siemes C, Visser LE, Coebergh JW, et al. C-reactive protein levels, variation in the C-reactive protein gene, and cancer risk: the Rotterdam Study. J Clin Oncol 2006;24:5216-22.

122. Pine SR, Mechanic LE, Enewold L, et al. Increased levels of circulating interleukin 6, interleukin 8, C-reactive protein, and risk of lung cancer. J Natl Cancer Inst 2011;103:1112-22.

123. Lagiou P, Trichopoulos D. Inflammatory biomarkers and risk of lung cancer. J Natl Cancer Inst 2011;103:1073-5.

124. Engels EA. Inflammation in the development of lung cancer: epidemiological evidence. Expert Rev Anticancer Ther 2008;8:605-15.

125. Rich AL, Tata LJ, Stanley RA, et al. Lung cancer in England: information from the National Lung Cancer Audit (LUCADA). Lung cancer 2011;72:16-22.

126. Schipper PH, Diggs BS, Ungerleider RM, Welke KF. The influence of surgeon specialty on outcomes in general thoracic surgery: a national sample 1996 to 2005. Ann Thorac Surg 2009;88:1566-72; discussion 72-3.

127. Travis WD. Pathology of lung cancer. Clin Chest Med 2002;23:65-81, viii.

128. Jackman DM, Johnson BE. Small-cell lung cancer. Lancet 2005;366:1385-96.

129. Collet JP, Boivin JF. Bias and confounding in pharmacoepidemiology. In: Strom BL, ed. Pharmacoepidemiology. 3rd ed: John Wiley & Sons Ltd; 2000:765-84.

130. Sarfati D, Blakely T, Pearce N. Measuring cancer survival in populations: relative survival vs cancer-specific survival. Int J Epidemiol 2010;39:598-610.

131. Akutsu Y, Matsubara H. Perioperative management for the prevention of postoperative pneumonia with esophageal surgery. Ann Thorac Cardiovasc Surg 2009;15:280-5.

132. Spanjersberg WR, Reurings J, Keus F, van Laarhoven CJ. Fast track surgery versus conventional recovery strategies for colorectal surgery. Cochrane Database Syst Rev 2011:CD007635.

133. Serclova Z, Dytrych P, Marvan J, et al. Fast-track in open intestinal surgery: prospective randomized study (Clinical Trials Gov Identifier no. NCT00123456). Clin Nutr 2009;28:618-24.

9. APPENDIX

Appendix 1: RAMQ and MED-ECHO procedure codes for lung resections*

Type of Surgery	RAMQ Code	MED-ECHO Code
Wedge resection	3122; 3140	4429
Segmentectomy	3124; 3126	4439
Lobectomy	3125; 3127; 3132	4449; 4499
Pneumonectomy	3162; 3138	4459
Other	3128-3131; 3133-3139	

* RAMQ=Régie de l'Assurance Maladie du Québec; MED-ECHO=Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière.

Appendix 2: ICD9-CM diagnosis codes for postoperative complications*

Postoperative Complication	ICD9-CM Code
Atelectasis	518.0
Pneumonia	997.31-9; 481-2; 482.0-4; 482.8-9; 485-6
Empyema	510; 510.0; 510.9
ARDS & Respiratory Failure	518.5; 518.81
Pulmonary Embolism	415.1; 415.11
Airleak & Bronchopleural fistula	998.6
Chylothorax	457.8
Mediastinitis	519.2
TRALI	518.7
Pneumothorax	512.1
Acute Pulmonary Edema	518.4
Wound Infection	998.5; 998.51; 998.59
Wound Dehiscence	998.3; 998.30-2
Urinary Tract Infection	599.0; 996.64
Atrial Fibrillation & Flutter	427.3
Hemorrhage	998.1; 998.11-3
Shock	998.0
Heart Failure & Cardiac Arrest	997.1
Renal Complication	997.5
Neurologic Complication	997.0; 997.00-09
Unspecified Complication	997.3; 997.9; 998.2; 998.4; 998.7-9

* ICD9-CM=International classification of diseases, 9th revision-clinical modification; ARDS=Acute Respiratory Distress Syndrome; TRALI=Transfusion-Related Acute Lung Injury.

Appendix 3: Charlson Comorbidity Index conditions*

Comorbid Condition	ICD9-CM Code	Description	CCI Score
Myocardial Infarction	410 – 410.9	Acute myocardial infarction	1
	412	Old myocardial infarction	
Congestive Heart Failure	428 – 428.9	Heart failure	1
Peripheral Vascular Disease	443.9	Peripheral vascular disease, including IC	1
	441 – 441.9	Aortic aneurysm	
	785.4	Gangrene	
	V43.4	Blood vessel replaced by prosthesis	
Cerebrovascular Disease	430 – 438	Cerebrovascular disease	1
Dementia	290 – 290.9	Senile and presenile dementia	1
Chronic Pulmonary Disease	490 – 496	Chronic pulmonary obstructive disease	1
	500 – 505	Pneumoconioses	
	506.4	Chronic respiratory conditions due to fume & vapor	
Rheumatologic Disease	710.0	Systemic lupus erythematosus	1
	710.1	Systemic sclerosis	
	710.4	Polymyositis	
	714.0 – 714.2	Adult rheumatoid arthritis	
	714.81	Rheumatoid lung	
	725	Polymyalgia rheumatica	
Peptic Ulcer Disease	531 – 534.9	Gastric, duodenal, & gastrojejunal ulcers	1
	531.4 – 531.7	Chronic forms of peptic ulcer disease	
	532.4 – 532.7		
	533.4 – 533.7		
	534.4 – 534.7		
Mild Liver Disease	571.2	Alcoholic cirrhosis	1
	571.5	Cirrhosis without mention of alcohol	
	571.6	Biliary cirrhosis	
	571.4 – 571.49	Chronic hepatitis	
Diabetes	250 – 250.3	Diabetes +/- acute metabolic disturbances	1
	250.7	Diabetes with peripheral circulatory disorders	
Diabetes with Chronic Complications	250.4 – 250.6	Diabetes with renal, ophthalmic, or neurological manifestations	2

Hemiplegia or Paraplegia	342 – 342.9 344.1	Hemiplegia Paraplegia	2
Renal Disease	582 – 582.9 583 – 583.7 585 586 588 – 588.9	Chronic glomerulonephritis Nephritis and nephropathy Chronic renal failure Renal failure, unspecified Disorders resulting from impaired renal function	2
Any malignancy, including Lymphoma & Leukemia†	140 – 172.9 174 – 195.8 200 – 208.9	Malignant neoplasms Malignant neoplasms Lymphoma and leukemia	2
Liver Disease (Moderate to Severe)	572.2 – 572.8 456.0 – 456.21	Hepatic come, portal hypertension, other sequalae of chronic liver disease Esophageal varices	3
Metastatic Solid Tumor‡	196 – 199.2	Secondary malignant neoplasm of lymph nodes & other organs	6
AIDS	042 – 044.9	HIV infection with related specified conditions	6

* ICD9-CM=International classification of diseases, 9th revision-clinical modification; CCI=Charlson Comorbidity Index; IC=Intermittent claudication; AIDS=Auto-immune deficiency syndrome; HIV=Human immunodeficiency virus.

† All patients in the study cohort were diagnosed with lung cancer (ICD9-CM codes 162.3 – 162.9); thus the presence of the respective diagnosis codes was not used in calculating the CCI score.

‡ All patients with ICD9-CM codes corresponding to metastatic solid tumors either prior to or on the date of index surgery were removed from the study cohort; hence the metastatic solid tumors were not contributing to the calculation of the CCI score.