Can recent health service use predict postoperative complications in seniors undergoing colon cancer surgery?

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Abstract

Introduction: Colon cancer surgery is associated with high morbidity, particularly in seniors. There is currently a lack of tools for accurately assessing vulnerable patients at risk of postoperative adverse events. The aim of this study was to identify predictors of severe postoperative complications in seniors undergoing colon cancer surgery based on recent health service use data.

Methods: A historical prospective cohort of colon cancer patients aged ≥ 65 years was assembled from hospitalization data provided by Quebec's provincial healthcare insurance provider (2000–2006). For each patient, health administrative claims were used to document domains of the Comprehensive Geriatric Assessment tool. 30-day postoperative severe complications were assessed using the Clavien-Dindo classification (grades III-V). A multivariate Cox model was used to evaluate associations between complications and patient characteristics.

Results: 3,789 patients were included (median age: 76; female 54.3%). 24.2% of cases were emergency procedures. Postoperative complications were observed in 29% of the cohort. Grade III, IV, or V complication were experienced in 17.3%, 12.6%, and 5% of the cohort, respectively (median time to first complication: 6 days). The incidence of postoperative emergency room visits and readmissions were 17.8% and 11.3%, respectively. Multivariate analysis indicated that the following variables were significantly associated with complications: male gender (HR = 1.28, CI = 1.13-1.45), age ≥ 85 years (HR = 1.25, CI = 1.03-1.52), ≥ 10 active medications prescribed in the 6 months preceding surgery (HR = 1.24, CI = 1.03-1.49), recent care for renal insufficiency or cardiovascular disease (HR = 1.43, CI = 1.02-1.99; HR = 1.25, CI = 1.10 – 1.43), and emergency procedures (HR = 1.39, CI = 1.22-1.59).

Conclusion: A large number of newly prescribed medications, recent care for renal insufficiency or cardiovascular disease, and emergency procedures were associated with severe postoperative complications. This study demonstrates the potential of developing assessment tools using recent health service use to identify vulnerable seniors at risk of postoperative complications.

Keywords: Seniors, colon cancer surgery, postoperative complications, Clavien-Dindo classification

Résumé

Introduction: La chirurgie pour un cancer du colon est associée à un taux élevé de morbidité, particulièrement chez les personnes âgées. Il y a présentement un manque d'outils d'évaluation pour les patients vulnérables à risque de complications postopératoires. Le but de cette étude était d'identifier des prédicteurs de complications postopératoires graves chez les personnes âgées subissant une chirurgie pour cancer du colon, basé sur des données provenant de statistiques récentes sur l'utilisation des services de santé.

Méthodes: Une cohorte prospective historique de patients atteints de cancer du colon âgés de 65 ans ou plus a été assemblée à partir de données d'hospitalisation provenant du fournisseur d'assurance de soins de santé de la province du Québec (2000-2006). Les réclamations administratives pour soins de santé de chaque patient ont été utilisées pour documenter les sections de l'Outil d'évaluation gérontologique (*Comprensive Geriatric Assessment*). Les complications postopératoires graves à 30 jours ont été évaluées à l'aide de la classification Clavien-Dindo (échelons III-V). Les associations entre complications et les caractéristiques des patients ont été évalués à l'aide d'un modèle Cox.

Résultats: 3,789 patients ont été inclus (âge médian : 76; 54,3% féminin). 24,2% des cas étaient des chirurgies d'urgence. Des complications postopératoires ont été décelées dans 29% de la cohorte. Des complications d'échelon III, IV ou V ont été décelées dans 17.3%, 12.6% et 5% de la cohorte, respectivement (délai médian avant la première complication : 6 jours). Le taux d'incidence de visites postopératoires en salle d'urgence et de réadmission était de 17.8% et 11.3%, respectivement. Certaines variables furent associées de manière significative aux complications grâce à une analyse multivariée : sexe masculin (RR = 1.28, ICI = 1.13-1.45), âge ≥ 85 ans (RR = 1.25, IC = 1.03-1.52), plus de 10 médicaments actifs prescrits dans les 6 mois

précédent la chirurgie (RR = 1.24, IC = 1.03-1.49), soins récents pour insuffisance rénale ou maladie cardiovasculaire (RR = 1.43, IC = 1.02-1.99; RR = 1.25, IC = 1.10 – 1.43), et chirurgie d'urgence (RR = 1.39, IC = 1.22-1.59).

Conclusions: Une quantité importante de medicaments nouvellement prescrits, des soins récents pour insuffisance rénale ou maladies cardiovascuaires, et des chirurgies d'urgence ont tous été associés avec des complications postopératoires graves. Cette étude démontre la pertinence du développement d'outils d'évaluation basées sur des données provenant de statistiques d'utilisation des services de santé, dans le but d'identifier des populations âgées vulnérables à risque de complications postopératoires.

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Contribution: developed the original research question for this thesis with me, and obtained the data used for the historical cohort study.

List of abbreviations

AHF: American Hospital Formulary

AJCC: American Joint Committee on Cancer

ASCO: American Society of Clinical Oncology

CC: Colon cancer

CEA: Carcinoembryonic antigen

CGA: Comprehensive geriatric assessment

CI: Confidence interval

CNS: Central nervous system

CT: Computed Tomography

DIN: Drug identification number

DNA: Deoxyribonucleic acid

EGFR: Epidermal growth factor receptor

ERV: Emergency room visit

HR: Hazard ratio

IC: Intermediate care

ICD-9: International Classification of Diseases – Version 9

ICD-10: International Classification of Diseases – Version 10

ICU: Intensive care unit

K-RAS: a type of oncogene, the activating mutations of which play a key role in neoplastic progression, especially in colorectal, pancreatic and lung cancer

MRI: Magnetic resonance imaging

MUHC: McGill University Healthcare Center

NAM: Numéro d'assurance-maladie

NCCN: National Comprehensive Cancer Network

OR: Odds ratio

PCP: Primary care physician

PET: Positron emission tomography

RAMQ: Régie de l'assurance-maladie du Québec

TNM: Tumor, node, metastasis

Introduction

1. COLON CANCER

1.1 Canadian colon cancer statistics in 2013

Colorectal cancer is the third most commonly diagnosed cancer, the second leading cause of death from cancer in men and third leading cause of death from cancer in women in Canada. It is estimated that in 2013, 23,900 Canadians were diagnosed with colorectal cancer and 9,200 Canadians died from it. This represents 13% and 12% of all new cancer cases and all cancer deaths occurred in 2013, respectively.[1]

1.2 Colon cancer types

Colorectal cancer causes are classified into hereditary, sporadic, or familial forms.[2] Hereditary forms of colorectal cancer have been extensively described and are characterized by young age at onset, family history, and the presence of other specific tumors and defects. Familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer are examples of hereditary forms.[3, 4] Sporadic colorectal cancer occurs in the absence of family history, generally affects an older population (≥ 65 years of age), and usually presents as an isolated colon lesion.[2] The most common form of colon cancer (CC) is sporadic in nature.[5] Lifetime risk for colorectal cancer increases for members in families in which the index case is young (<50 years) and the relative is close (first-degree). The risk increases as the number of family members with colorectal cancer rises. An individual who is a first-degree relative of a patient diagnosed with colorectal cancer before the age of 50 years is twice as likely as an individual in the general population to develop the cancer. Genetic polymorphisms, environmental factors, and

low-penetrance loci have all been implicated in various forms of familial colorectal cancer.[6] Tumor suppressor genes, Deoxyribonucleic acid (DNA) mismatch repair genes, and proto-oncogenes all contribute to colorectal neoplasia, in the sporadic and inherited forms. The use of different diagnostic and therapeutic modalities separate colonic from rectal cancers and influence both treatment outcomes and occurrence of adverse events. Therefore, this study will focus exclusively on CC.

1.3 Clinical features of colon cancer

CC may present in three different ways: patients with suspicious signs and symptoms, asymptomatic individuals discovered by routine screening and emergency admission with complications (e.g. intestinal obstruction, peritonitis or acute gastrointestinal bleed). In early stages, the majority of patients will present without symptoms and are diagnosed by screening program. Symptomatic patients are results of tumor growth reflecting an advanced stage of cancer.[7, 8] Patients' symptoms are different depending on tumor location. A change in bowel habits and hematochezia, which is the appearance of red blood in the stool, are more common presenting symptoms in left-sided CC. Sigmoid cancers can mimic diverticulitis, presenting with pain, fever, and obstructive symptoms. Sigmoid cancers can also cause colovesical or colovaginal fistulas. Right-sided CC is more commonly associated with otherwise unexplained iron deficiency anemia from unrecognized blood loss.[9, 10] One of the unusual presentations is fever of unknown origin, as well as intra-abdominal, retroperitoneal, abdominal wall or intrahepatic abscesses due to a localized perforated CC.[11, 12] Also, CC can be detected as an incidental finding for a workup for liver metastases that were detected upon studying the gallbladder or kidney by ultrasound or a computed tomography (CT) scan for evaluation of other symptoms.

1.4 Diagnosis of colon cancer

Colonoscopy is the gold standard for establishing the diagnosis of CC. It permits biopsy of the tumor to verify the diagnosis while allowing inspection of the entire colon to exclude synchronous CC or metachronous polyps or cancers.[13-15] Synchronous CC is defined as two or more distinct primary tumors diagnosed within six months of an initial CC diagnosis, separated by normal bowel, and not due to direct extension or metastasis, occur in 3 to 5 percent of patients. Whereas metachronous cancer is defined as a tumor located in a different part of the large intestine, so as to not represent a recurrence, diagnosed 6 months after the operation for the primary lesion. In patients with tumors causing complete obstruction, the diagnosis is best established by resection of the tumor without the benefit of preoperative colonoscopy. A water-soluble contrast enema is often useful in such circumstances to establish the anatomic level of the obstruction. Incomplete diagnostic colonoscopy in symptomatic patients is approximately 11 to 12 percent.[16, 17] The inability of the colonoscope to reach the tumor or to visualize the mucosa proximal to the tumor may be related to several technical reasons (e.g. partially or completely obstructing cancer, tortuous colon, poor preparation) and patient intolerance of the examination. In this setting, CT colonography is highly sensitive for the detection of the tumor and can provide a radiographic diagnosis, although it can misdiagnose stool as masses in poorly distended or poorly prepared colons; it also lacks the capability for biopsy or removal of polyps.[18-22]

Patients, with tumors that do not require emergent surgery, should undergo a thorough evaluation for metastatic disease. This includes a thorough physical examination, chest x-ray, liver function tests, and measurement of the carcinoembryonic antigen (CEA) level. Most surgeons now perform CT or magnetic resonance imaging (MRI) to inspect the liver more

thoroughly for metastases and search for other intra-abdominal pathology.[23, 24]

1.5 Staging of colon cancer

Staging may be defined as the process whereby objective data are assembled to try to define the state of progression of the disease. Once the diagnosis of CC is established, the local and distant extent of disease is determined to provide a framework for discussing therapy and prognosis. The stage of the tumor is assessed by the following factors: the depth of penetration of the tumor into the bowel wall (T stage), the extent of lymph node involvement (N stage), and the presence or absence of distant metastases (M stage).[25] This classification, known as the TNM (tumor, node, metastasis) system, combines clinical information obtained preoperatively with data obtained during surgery and after histologic examination of the specimen. There have been numerous and significant modifications in the system since its introduction in 1987; the seventh edition of the American Joint Committee on Cancer (AJCC) Staging Manual (2010) has taken into account survival and relapse data that refine the prognostic value of accurate staging of colorectal cancer.[25]

Clinical Staging is a clinical assessment of the stage of disease (cTNM) that is based on evidence obtained by medical history, physical examination, and endoscopy. Examinations designed to detect metastatic disease (M) include chest x-rays, CT (including pelvis, abdomen, chest), MRI, and positron emission tomography (PET) or fused PET-CT scans.

Pathologic Staging is the pathologic examination of the resected specimen (pTNM) that provides a basis for prognosis and consideration for the need of further (adjuvant) treatment. Patients who were given a clinical stage (cTNM) prior to the initiation of preoperative neoadjuvant treatment will have a modified pathologic stage assessed after examination of the surgically resected specimen; that stage is indicated by the “y” prescript (ypTNM). Cancer cells

confined within the glandular basement membrane (intraepithelial) or lamina propria (intramucosal) with no extension through the muscularis mucosae are not associated with a risk of metastasis and are defined as in situ carcinoma −pTis. T4 cancers that penetrate to the surface of the visceral peritoneum (pT4a) have a better prognosis than tumors that directly invade or adhere to other organs (pT4b), and the staging classification has been refined to reflect this. In addition, it is recognized that increasing numbers of involved lymph nodes are associated with a worsening prognosis, and the most recent classification system takes this into account. The recent AJCC manual also recognizes prognostic factors in addition to serum CEA levels that should be ascertained. These include the following: tumor deposits, the number of satellite tumor deposits discontinuous from the edge of the cancer that are not associated with a residual lymph node; a tumor regression grade that permits the pathologic response to neoadjuvant therapy to be graded (when applicable), the circumferential resection margin, the distance from the edge of tumor to the nearest dissected margin of the surgical resection; microsatellite instability; perineural invasion, histologic cancerous invasion of the regional nerves); and K-RAS mutation status. The K-RAS mutation is a type of oncogene, the activating mutations of which play a key role in neoplastic progression, especially in colorectal, pancreatic and lung cancer. The K-RAS mutation has been shown to be associated with lack of response to treatment with monoclonal antibodies directed against the epidermal growth factor receptor (EGFR) in patients with metastatic CC.

1.6 Surgical treatment of colon cancer

Surgical resection continues to be the gold standard treatment for early cancer stage. The goal of the resection is to remove the primary cancer with adequate margins, regional lymphadenectomy, and restore the gastrointestinal tract continuity. The extent of resection is

determined by the location of the cancer, its blood supply and draining lymphatic system, and presence or absence of direct extension into adjacent organs. Proximal and distal resection margins should be at least 5 cm from the tumor.[26] These margins should allow for an adequate resection of the appropriate segment of the bowel with its vascular supply and associated lymphatics. Regional lymphadenectomy, along the course of major mesenteric vessels and the vascular arcades of the marginal artery, provides prognostic information and guides postoperative management, such as chemotherapy administration. There is a direct correlation between the number of lymph nodes evaluated per patient after surgical resection and survival.[27] In addition, the consensus guidelines recommend that at least 12 lymph nodes be assessed for adequate staging.[26, 28] The American Society of Clinical Oncology (ASCO) encourages the use of adjuvant chemotherapy for patients with node-negative CC if there are fewer than 12 nodes in the surgical specimen.[29] Resectable colorectal liver metstases can be potentially cured by hepatic resection.[30]

For lesions involving the cecum, ascending colon, and hepatic flexure, a right hemicolectomy is the procedure of choice.[31] This involves removal of the bowel from 4 to 6 cm proximal to the ileocecal valve to the portion of the transverse colon supplied by the right branch of the middle colic artery. An anastomosis is fashioned between the terminal ileum and transverse colon. An extended right hemicolectomy is the procedure of choice for most transverse colon lesions; this involves division of the right and middle colic arteries at their origin, with removal of the right and transverse colon supplied by these vessels.[31] The anastomosis is fashioned between the terminal ileum and proximal left colon. A left hemicolectomy (resection from the splenic flexure to the rectosigmoid junction) is the procedure of choice for

tumors of the descending colon, whereas a sigmoidectomy is appropriate for tumors of the sigmoid colon.[2]

Abdominal colectomy (sometimes called *subtotal colectomy* or *total colectomy*) entails removal of the entire colon from the ileum to the rectum, with continuity restored by an ileorectal anastomosis. Because of loss of the absorptive and storage capacity of the colon, this procedure causes an increase in stool frequency. Patients younger than 60 years generally tolerate this well, with gradual adaptation of the small bowel mucosa, increased water absorption, and an acceptable stool frequency of one to three movements daily. In older individuals, however, abdominal colectomy may result in significant chronic diarrhea. Abdominal colectomy is indicated for patients with multiple primary tumors and occasionally for those with completely obstructing sigmoid cancers. The chances that the patient has been cured by an operation performed to remove a CC are dependent on several factors. These include technical aspects of the operation, such as the complete removal of all tumor, certain biologic properties of the cancer that are poorly understood, and stage of the disease.

1.7 Prognosis of colon cancer

Patients treated with appropriate resection for stage I, II, III, and IV CC generally have a 5-year survival rate of approximately 93.2%, 82.5%, 59.5%, and 8.1%, respectively and overall 5-year survival is 65.2%.[32] Further treatment and follow-up of patients treated by segmental colectomy for CC is directed by the stage of the disease. Approximately 80% of recurrences are detected within 2 years of the time of resection, so follow-up strategy should be especially intensive during that period.[33] The ASCO [34] and National Comprehensive Cancer Network (NCCN)[35] have established guidelines of follow-up testing aim to detect early recurrence that is amenable to treatment. Different studies have demonstrated different chemotherapeutics

advantages for selected patient populations with specific tumor stages and characteristics but this is beyond the scope of this thesis.[29, 36-39]

2. SENIORS IN CANADA

The 2011 Census captured 4,945,060 people aged 65 and older in Canada, an increase of more than 609,810 or 14.1%, between 2006 and 2011. This rate of growth was more than double in comparison to the 5.9% increase for the Canadian population as a whole. Seniors accounted for 14.8% of the population in 2011, up from 13.7% five years earlier. This proportion has steadily increased since the end of the 1960s for two reasons: lower replacement fertility levels (the number of children per woman needed for a population to replenish itself in the absence of migration, which is 2.1) and longer life expectancy. From 2006 to 2011, the proportion of seniors increased faster in the Atlantic provinces (+1.7 percentage points) and Quebec (+1.6), compared to Ontario (+1.1), the Prairie provinces (0.0), British Columbia (+1.1) and the territories (+1.1)[40].

In patients age ≥65 years, 70% of cancer mortality and 60% of all cancers occur in this group of age[41]. Increased life expectancy has led to elevating the mean age of patients at the time of diagnosis of CC and subsequent treatment[42, 43].

2.1 Challenges in optimizing senior care in colon cancer

Advanced age has long been an exclusion criterion for many research studies in the past, resulting in a paucity of information pertaining to best care for the elderly[44, 45]. Age bias is also evident in clinical care. For example, approaches to the diagnosis and treatment of breast cancer differ significantly in older women[46]. Another example is suggested by an age-related decline in elective inguinal hernia repairs whereas rates of emergency repair increase

exponentially[47]. Risk assessment is typically more challenging and time-consuming than in younger patients and more often involves a multidisciplinary team approach. For example, comorbidity increases with age and is a major contributor to adverse events in hospital and to mortality. Dementia and other cognitive impairments are associated with increased mortality in elderly surgical patients. Other variables that predict clinical outcomes in various settings are nutritional status, voluntary handgrip strength and the presence of a spouse or adult child. Clearly, the risks associated with surgical illness are far greater in the frail, institutionalized, elderly person with multiple medical problems than in the healthy, community-dwelling person who is physically, mentally and socially active. At 75 and 85 years of age, the number of additional years of life expected is 10 and 5 respectively on average for men in Canada, and 12 and 7 years for women. Thus, major surgical procedures with a long-term perspective may be appropriate in selected, fit elderly patients[43].

2.2 Colon cancer surgery complications

Although there has been a tremendous improvement and evolvement of surgical techniques along with preoperative assessments, surgical procedures are not without any risk, especially CC surgeries in seniors, and complications continue to occur. These surgical complications are classified into systemic versus local complications. Systemic complications include but not limited to fever of unknown origin, any type of shock, pulmonary embolism, pneumonia, congestive heart failure, coronary artery disease, renal failure, and hepatic failure. Some of these systemic complications could be related to patient's health status. For example, development of cardiovascular complications in a patient who already had a history of coronary artery disease could be minimized or prevented by optimizing patient care preoperatively.

Indeed, patients who have multiple comorbidities and require multiple medications (polypharmacy) can be optimized before surgery to reduce drug-drug interaction or adverse drug reaction. On the other hand, local complications include superficial or deep infections, wound dehiscence, bleeding, anastomotic leak, stricture, fistulae, and injury to surrounding structures (e.g. small bowel, spleen, pancreas, and genitourinary). In literature, the rate of major morbidity ranged from 20 to 35 percent[48, 49] and the 30-day mortality rate from 2 to 9 percent.[48-53]

2.3 Effect of postoperative complications on colon cancer outcomes

The importance of postoperative complications is not only guided to patients' care but also to their outcomes and health cost. A prospective study of 1,722 patients undergoing colorectal cancer resection found a significantly higher five-year mortality rate in patients with a leak compared with those without a leak (56 versus 36 percent).[54] In a prospective study of 306 patients with resectable CC, patients with an anastomotic leak had, at 48 months follow-up, significantly higher rates of both tumor recurrence (45 versus 30 percent) and cancer-specific mortality (53 versus 31 percent) compared with patients without an anastomotic leak.[55] In contrast, a meta-analysis of three prospective studies that included 1,990 patients with CC only, found a non-significant increased risk of local recurrence with an anastomotic leak compared with patients with no leak (8.8 versus 6.6 percent, odds ratio (OR) = 2.16 95% CI 0.88–5.29).[56] On the other hand, in a series of nine patients with rectovaginal fistulas following colorectal surgery, four required permanent fecal diversion to manage their fistula.[57] Colocutaneous fistulas are generally low output fistulas and have an almost 50% chance of spontaneously closing. In contrast, high output fistulas are associated with mortality rates between 5 to 20 percent [58, 59]and fistulas that do not spontaneously close are associated with a

high morbidity rate.[58] In addition, Postoperative complication is associated with increased risk of readmission (OR=1.17, $p<0.01$)[60] ultimately, linked to higher 1-year mortality rate of 16%.[61] Importantly, postoperative complications are encountered in 60% of patients > 70 years of age (seniors) versus 30% in the general patient population.

2.4 Classification of postoperative complications

The lack of consensus on how to define and grade postoperative complications has greatly hampered the evaluation of surgical procedures. A classification of complications, initiated in 1992 by Clavien and Dindo is based on the type of therapy needed to manage the complication. The principle of the classification is simple, reproducible, flexible, and applicable. Therefore, the Clavien-Dindo classification appears reliable and may represent a compelling tool for assessing complications from physician claims data, which contains records for all therapy received by patients.[62, 63] Hence, we used this classification system to classify our cohort postoperative complications. We focused on grades III-V as they represent the more severe complications that can be captured by procedures codes, intensive care unit (ICU) admission or death for grades III, IV, and V, respectively. Grade III is any radiology, endoscopic or surgical interventions that are required to treat the complication. Grade IV is any ICU admission with single or multiple organ failures. Grade V is death within 30 days postoperatively. We excluded grades I and II as these involve less interventions but rather medications to treat symptoms (grade I) or medically manageable conditions (grade II).

HYPOTHESIS

Recent healthcare utilization may be a valuable tool in assessing severe postoperative Clavien-Dindo complications (grades III-V) in seniors undergoing CC surgery.

OBJECTIVES

1. Select and verify a cohort of colon cancer patients using the medical services and hospital discharge databases.
2. Assess the incidence of severe postoperative complications using physician claims.
3. Classify postoperative complications according to the Clavien-Dindo classification system using administrative data.
4. Identify predictors of Clavien-Dindo complications after CC surgery in senior population reflecting recent health service use.
5. Assess reasons for emergency room visits after CC surgery using diagnoses billed procedure claims from Régie de l'assurance-maladie du Québec's (RAMQ) medical services database.

Methods

Parts of the methodology of this study have been concurrently developed for another parallel study and are reported elsewhere.[64, 65]

SETTINGS AND DATA SOURCES

Data for this study was acquired through anonymous linkage of the following RAMQ's databases:

1) ***Registrants' database***, which provides demographic and socioeconomic data for registered patients which covers up to 99% of the population.[66]
2) ***Medical services database***, which contains physician fee-for-service claims (encrypted physician license number, specialty, service code and date, location of service

delivery (community health services center, hospital, etc.) and primary diagnosis using the international classification for diseases version 9 and 10 (ICD-9 & ICD-10)[67].

3) ***Quebec's hospital abstract discharge database*** which captures data on hospitalizations, including admission and discharge dates, length of stay, principal and secondary diagnoses (ICD-9 and ICD-10), intra-mural procedures and locations for services and discharges[68].

4) ***Drug insurance eligibility database*** contains start and end dates of patient eligibility for public drug insurance as well as the type of drug plan they are covered under[69].

5) ***Prescription claims database*** contains claims for prescribed medications dispensed to all Quebec residents insured under the public drug plan. It includes encrypted physician license number; drug dispensed (Drug Identification Number or DIN), date the medication was dispensed, quantity dispensed and duration of the prescription[67]. Our group has shown that the accuracy of this database in identifying the correct drug dispensed is around 90%[70].

These databases were originally linked for the purpose of investigating the relationship between physicians' scores on licensing exams (1993-1996) and their practice performance in primary care over time[71-75]. The database includes patients (> 5 million), recruited at random, upon encountering a physician from the original cohort of study physicians and followed through time. At least one year of prior medical history was provided by the RAMQ and patients were followed-up until they died, were lost to follow-up, or the physician study ended (2007). Since submission of claims for medical services has monetary incentives for physicians, the accuracy and validity of claims is very high.[76] The RAMQ linked the aforementioned data sources using

the numéro d'assurance-maladie (NAM), a unique identifier attributed to each Quebec resident and common to these databases. An encrypted patient identifier was attributed to each patient before the data was provided to the researchers ensuring data anonymity (Figure1). Appropriate clearance was obtained from the Commission d'accès à l'information du Québec for the use of these population databases.

COHORT SELECTION

Senior patients (aged ≥ 65 years) with a surgical claim and diagnosis related to CC, billed between January 1st, 2000 and December 31st, 2006, were selected from the existing dataset of RAMQ medical services, that had been used for the physician study (Appendix A, Table 1 and Figure 2). Surgical procedures included the surgical removal of malignant neoplasms of the caecum, right, transverse, left and sigmoid colon (Appendix A, Table 2). Patients without medical claims for up to a year before or 30 days after CC surgery were excluded, unless death occurred before the 30-day follow-up had elapsed. Patients without continuous drug insurance in the year before surgery were also excluded. The cohort was then verified using the hospital discharge database, where only patients with a corresponding hospitalization for CC (primary diagnosis, Appendix A, Table 3) and a matching date and type of surgery (Appendix A, Table 2) claim were further included. Patients with metastatic diagnoses in the year before surgery were excluded. The date of the colon surgery was considered the index date. Each step was established after extracting multiple random patient samples prior to the exclusion and manually searching their codes to verify that the selection pathway was valid.

PATIENT CHARACTERISTICS AND INTRAOPERATIVE VARIABLES

Several tools have been used to evaluate the senior population[77-80], however the majority of these tools are time consuming, or subjective. One of these tools include the comprehensive geriatric assessment (CGA) tool, which aims to assess physical functioning, co-morbidity, polypharmacy, nutrition, cognition, and emotional status in elderly patients and has been gaining popularity among onco-geriatric patients. It is very complex, time-consuming[81], difficult to use in practice and require extensive validation in oncology.[82] The comorbidities selected for assessment have shown to adversely affect an individual's ability to function independently.[83] We constructed variables corresponding to domains traditionally assessed through CGA (Appendix B, Table 1).

Patient characteristics

1) **Age:** Age at the index date calculated using the date of birth from the registrant database that includes patients' age ≥65.
2) **Gender:** extracted from the registrant database.
3) **Average household income in the residential area:** The average income for an individual's residential area was determined using Statistics Canada Census data, which was independently linked by the provincial healthcare insurance program, RAMQ, using 6-digit postal codes. This variable serves as a surrogate for socioeconomic status. If the average income for an individual's residential area was missing (7% of cohort), it was estimated using adjacent years' available data by multiple imputation methods (see below).

4) **Education estimates**:

   The percent of individuals that have completed a high school diploma in an individual's residential area was used to represent an individual's education level. This was again determined using Statistics Canada Census data. For missing data (6% of cohort), it was estimated using adjacent years' available data by multiple imputation methods (see below).

5) **Place of residence:** Whether an individual resided in an urban or rural region, the second digit of their postal code determined it. The residence of each patient was classified as rural or urban if the second digit of his or her postal code was 0 or not, respectively, in accordance with the forward sortation area of the first segment of the Canadian Postal Code Structure[84]. For missing data (4% of cohort), it was estimated using adjacent years' available data by multiple imputation methods (see below).

   For the above mentioned multiple imputation method, we imputed (revenue, education, or place of residence) by carrying forward or backward the available value from the closest adjacent year (either before or after the surgery year, whichever one is closer) regardless of change in postal code (postal code would usually contains 6 digit). If there is still missing data (i.e. no 6 digit postal code information from the closest adjacent years), then these missing data were computed using the mean from the 3 digit postal code in the closest year, or from the 2 digit postal code in the closest year.[85]

6) **Type of admission:** It is divided into elective versus emergent admission. Elective admission is any patient in whom the surgery index date was not preceded by emergency room visit (ERV). On the other hand, an emergency admission is any hospital admission accompanied by an ERV on the same day.

7) **Number of unique medications used in the past 6 months (polypharmacy)**: This was established through the prescription database, by calculating the number of unique drugs used in the 6 months before surgery, including the surgery date. This variable aims to evaluate the impact of using multiple different medications closer to the surgery index date.

8) **Use of cognition-altering drugs:** Participants were believed to have a history of consuming these drugs if at least one of the specified medications (Appendix B, Table 2) had been dispensed to that patient in the year prior to their CC surgery using the American Hospital Formulary (AHF) class codes. The utilization of various psychotropic medications (i.e. benzodiazepines) may impact a patient's ability to function independently in the community, increase their risk of experiencing an adverse outcome related to inappropriate drug use[86]. This may, in turn, impact an individual's likelihood of experiencing either an unplanned hospitalization after surgery, or ERVs.

9) **Geriatric Syndromes:**

   This included diabetes, renal insufficiency, osteoporosis, respiratory illness, cardiovascular disease and urinary incontinence, all of which have been cited as having an important impact on an individual's ability to function independently[83]. All these syndromes have been assessed in the year prior to and including the surgery date.

   a) ***Urinary incontinence***: A patient was considered to have urinary incontinence if the patient had ICD-9 related codes in their medical claims or ERVs (Appendix B, Table 3).

b) ***Anemia***: A patient was considered to have anemia if the patient had the following ICD-9 codes (285.2, 285.9, 280.0 and 281.0) in their medical claims or ERVs.

c) ***Arthritis***: A patient was considered to have arthritis if the patient had ICD-9 related codes in their medical claims or ERVs (Appendix B, Table 4).

d) ***Depression***: Depression is also highly prevalent in seniors, although those are commonly unreported or undiagnosed.[87] To identify those individuals with depression, we used both ICD-9 and drug codes. If an individual had at least one of the specified ICD-9 codes (Appendix B, Table 5) or had been dispensed at least one of the specified antidepressants (AHF code 28.16.04), they are deemed to have depression.

e) ***Osteoporosis***: It is an aging-process disease. This was identified by physician billing service use or procedure for osteoporosis (ICD-9 code 733) or were dispensed medication used in the treatment of osteoporosis and related conditions (Appendix B, Table 6).

f) ***Cardiovascular disease***: This can be established by being hospitalized in the year prior to but including the surgery with one of the ICD-9 codes as a primary diagnosis or visited the emergency room (establishment code 0X7) for one of the reasons corresponding to the ICD-9 (Appendix B, Table 7).

g) ***Dementia***: In order to identify individuals that have experienced cognitive decline, a combination of ICD-9 codes and drug codes were used. If an individual had at least one of the specified ICD-9 codes in their physician claims history, they were considered to have dementia. If they had been

dispensed at least one of the specified medications (Appendix B, Table 8), they were also considered to have been affected by dementia.

h) ***Diabetes***: Individuals were identified as having diabetes if in their medical history they had an ICD-9 code of 250 or had been dispensed one of the medications known to treat diabetes (Appendix B, Table 9).

i) ***Renal insufficiency***: As a reliable method of identifying patients with renal insufficiency or renal failure using health administrative databases does not currently exist, we consulted a McGill University Healthcare Center (MUHC) faculty member in the nephrology division for this definition: A history of at least one visit with a nephrologist (specialty code 34) in combination with one of the following ICD-9 (584, 585 and 586) or billing claims procedure codes (i.e. dialysis catheter insertion, renal transplantation, etc.) as shown in Appendix B, Table 10.

j) ***Respiratory illness***: This can be established by a record of hospitalization in the year prior to the surgery with one of the ICD-9 or ICD-10 codes as a primary diagnosis or visited the emergency room (establishment code 0X7) for one of the reasons corresponding to the ICD-9/10 listed in Appendix B, Table 11.

10) **Complete annual physical exam:** In many Western countries, such as United States, the primary care physician (PCP) or general practitioner is the main health care provider and gatekeeper to secondary care.[88] Coordinating care for multiple comorbidities, especially in seniors, is one the main tasks of the PCP.[89] Moreover, psychological and social aspects may also play a role in the aftercare of patients with cancer and need

special attention.[90] As such, this represented an important variable to account for in this study. Patients were considered to have had an annual exam performed if they had, in their physician billing claims history, a complete detailed examination (Appendix B, Table 12) performed in the year prior to their surgery, performed by a general practitioner in an outpatient setting.

11) **Health Care Utilization:**

This includes number of previous hospitalization prior to surgery index date, number of colon cancer-related ERVs within 30-days prior to surgery (Appendix B, Table 13) and number of ERVs unrelated to CC within a year prior to surgery index date. We assumed that these could indicate the severity of patients' health status up to a year prior to surgery.

12) Hospital setting: Defined as academic or non-academic, based on assignations from the Ministry of Health.

Intraoperative variables

I. **Elective ICU admission:** Patients who were admitted to the ICU were identified by billing codes (0X6 or 4X6) as a location for the billing. If these patients were admitted within the first 48-hour window after surgery or an admission, before the surgery, proceeded by angiography procedures they were considered an elective ICU admission. On the other hand, if the ICU admission occurred later than 48 hours, it was considered a grade IV Clavien-Dindo complication that had led to an ICU admission.

II. **Total Length of stay:** It is the hospital stay from the admission date till the discharge date including any type of transfers, e.g. inter and intra-hospital transfers.

III. **Length of postoperative stay:** The hospital abstract discharge database was used to identify the number of days patients remained hospitalized after the index date including any type of transfers, e.g. inter and intra-hospital transfers.

IV. **Discharge destination:** It is the destination after patient discharge from the hospital to home, Local Community Service Centre, or others (e.g. psychiatry ward)(Appendix A, Table 4).

OUTCOMES

- **All cause mortality:** Date of death was captured from the registrant's database for patient who died within 90 days and 1-year from the index date.
- **Severe postoperative complications:** Severe complications were defined as those that were grades III, IV and V according to the Clavien-Dindo morbidity and mortality classification[63]. Grade III included patients who had a complication requiring surgery, endoscopy or interventional radiology regardless of the type of anesthesia within 30 days from surgery, excluding the date of surgery and ICU stay. Grade IV complications include RAMQ procedures codes: 0693, 04825 or a non-elective ICU admission (establishments: 0X6, 4X6) within 30 days. A non-elective ICU admission refers to an admission occurring at least 48 hours after surgery and not proceeded by angiography procedures. As it is well known, some angiographic procedures will require elective ICU admissions for close monitoring[91-93]. These are mainly cardiac catheterization, and would be included as grade III complications. Individuals that experienced grade V complications were patients who died within 30 days of surgery, including the surgery date (Appendix C, Tables 1 and 2).

- **Postoperative ERVs reasons:**

  These include any postoperative ERV happened within 30 days of discharge from surgical admission. We used ICD-9 classification system for postoperative ERV categorization[94]. We included ICD-9 categories from 1-17 main categories (infectious and parasitic diseases, neoplasms, "endocrine, nutritional and metabolic diseases, and immunity disorders", disease of blood and blood-forming organs, mental disorders, diseases of the nervous system and sense organs, diseases of the circulatory system, diseases of the respiratory system, diseases of the digestive system, diseases of the genitourinary system, diseases of the skin and subcutaneous tissue, diseases of the muscloskeletal system and connective tissue, injury and poisoning) except 11 (Complications of pregnancy, childbirth and the puerperium), 14 (congenital anomalies), 15 (Certain conditions originating in the perinatal period) and 16 (Symptoms, signs, and ill-defined conditions) as well as supplementary classification.[95] For any codes within section 16, we match each code with its corresponding system. For example, symptoms involving respiratory system were included in respiratory system. For our research purpose, we added two categories: wound and non-specified general symptoms. All corresponding codes for the same system were collected and then systems were subdivided into subcategories (Appendix C, Table 3a and 3b).

STATISTICAL ANALYSIS

There were 390 physicians who performed the 3,789 surgeries (with median of 6 patients per surgeon, range = 1-53). Cox univariate analysis was used to assess the unadjusted associations between each predictor and severe postoperative complications (Clavien-Dindo Grade III-V). Subsequently, a multivariate Cox model was constructed to assess the association

between predictor variables and severe postoperative complications within 30 days after taking into account clustering of patients within physician[96]. Collinearity between variables was assessed via a Pearson correlation matrix and, as a result, education, number of colon cancer-related ERVs in the month before surgery and number of ERVs unrelated to CC in the year before were left out of the model due to their correlations (coefficient of ≥0.5) with income, type of surgical admission and number of hospitalizations respectively. Stepwise variable selection was then carried out but no major changes in the hazards ratio estimates were observed. All *P*-values are for two-tailed tests with statistical significance defined as $P \leq 0.05$. SAS software (SAS version 9.3, Institute, Inc., Cary, North Carolina) was used for all analyses.

Results

COHORT CHARACTERISTICS

This study included 3,789 patients with CC that were surgically treated. Of the 3,789 patients, 54.3% were females. The median age of the cohort was 76 years old. The majority of patients lived in an urban area (82.5%). The most common claims for geriatric syndromes during the year prior to surgery were: anemia (49.1%), cardiovascular problems (33.5%), arthritis (24.4%) and diabetes (19.7%). Other socioeconomic characteristics and risk factors are presented in Tables 1A, 1B and 2.

Median length of hospital, postoperative and elective ICU stays were 13 (ranging 1-266), 10 (ranging 0-265) and 2 days (ranging 1-30) respectively. Emergency admissions were encountered in 24.2%. The occurrence of the first complication per patient per grade level III, IV, and V were 16%. 10.3% and 2.7%, respectively. Home was the destination after discharge from the hospital for 71% of the cohort (n=2689). The incidence of postoperative ERVs and hospital readmissions were 17.8% (n= 650 patients) and 11.3%, respectively. These patients with

postoperative ERV (650 patients) encountered 795 total postoperative ERVs and these visits created 3,720 repetitive reasons in which 1,463 unique reasons where used for descriptive statistics. The three most common complaints requiring postoperative ERVs were infections, gastrointestinal and cardiovascular problems (Table 3). Interestingly, the incidence of all-cause mortality nearly doubled during each period of time. For example, the 30-day overall mortality rate was 5%, whereas 90-day and 1-year mortality rates were 8.58% and 19.24%, respectively. Severe postoperative complications were experienced by 29% of the cohort (median time to first complication of 6 days), with 17.3%, 12.6%, and 5% experiencing grade III, IV, and V complications, respectively.

CLAVIEN-DINDO CLASSIFICATION OF SEVERE POSTOPERATIVE COMPLICATIONS RISK ASSESSMENT

Upon conducting a univariate Cox analysis, significant non-modifiable risk factors included male gender and age ≥ 85 years (Hazard Ratio (HR) = 1.28, Confidence Interval (CI) = 1.14 – 1.44, $p < 0.0001$; HR = 1.35, CI = 1.12 – 1.62, $p = 0.001$). Other risk factors significantly associated with postoperative complications included: having ≥ 10 medications prescribed in the 6 months prior to surgery (HR = 1.39, CI = 1.19 – 1.61, $p < 0.0001$), recent care for cardiovascular disease (HR = 1.44, CI = 1.27 – 1.62, $p < 0.0001$), recent care for diabetes (HR = 1.21, CI = 1.05 – 1.39, $p = 0.009$) and recent care for renal insufficiency (HR = 1.78, CI = 1.29 – 2.46, $p = 0.001$). Other geriatric syndromes presented in Table 4 were not significantly associated with higher risk of complications. The number of hospital admissions (≥ 2) as well as emergency procedures in the year prior to surgery increased complications with HR = 1.27 (CI= 1.05 – 1.53, $p<0.014$) and HR = 1.44 (CI= 1.27 – 1.64, $p<0.0001$), respectively. On the other hand, a complete physical exam during the year prior to surgery and teaching status of the

hospital were not associated with a significant risk of complications, HR = 0.97 (CI= 0.84 – 1.13, p= 0.716) and HR = 1.01 (CI= 0.89 – 1.15, p= 0.852), respectively (Table 4).

These variables were subsequently used for multivariate analysis (Table 4), with the exception of diabetes and the number of hospital admissions prior to index date. Male gender and age ≥ 85 years were significantly associated with a higher risk of experiencing postoperative complications (HR = 1.28, CI = 1.13 – 1.45, $p < 0.000$; and HR = 1.25, CI = 1.03 – 1.49, p = 0.021, respectively). Recent care for renal insufficiency or cardiovascular disease a year prior to surgery, ≥ 10 medications prescribed 6 months prior to surgery, and emergency procedures were also associated with a significantly increased risk of experiencing complications (HR = 1.43, CI = 1.02 – 1.99, p = 0.036; HR = 1.25, CI = 1.10 – 1.43, p = 0.001; HR = 1.24, CI = 1.03 – 1.49, p = 0.026; and HR = 1.39 CI = 1.22 – 1.59, $p < 0.0001$, respectively).

Discussion

Although surgery is the most effective treatment for CC and despite improvements in surgical techniques and perioperative management, surgeons continue to encounter large numbers of postoperative complications. Recognizing these problems and effectively treating them is critical to achieving better outcomes and survival for patients. In fact, trying to identify risk factors to these complications and minimizing their occurrence is even more crucial. More than half of newly diagnosed cancer cases (53%) and cancer related deaths (69.1%) occur among seniors. An age of ≥ 65 is associated with a greater incidence (60.1%) and death (70.9%) from colorectal cancer [97]. Studies have shown that seniors are at increased risk of experiencing postoperative complications [48, 98, 99]. Morbidity rates after CC surgery are higher in the elderly population, 60% for > 70 years of age versus 30% in the younger population. Also, studies [100-102] have demonstrated that seniors have been under-represented in cancer clinical

trials exposing them to inaccurate risk assessments.[103] Postoperative complications have proven to adversely affect disease-free survival and overall survival in seniors with CC [104, 105]. There are several studies that correlate an increased local tumor recurrence and decreased recurrence-free survival of colorectal adenocarcinoma with postoperative complications, especially an anastomotic leak.[106-108] However, this leakage rate is lower in CC surgery in comparison with rectal cancer. On the other hand, the septic consequences were more severe and the operative mortality was significantly higher from anastomotic leak after CC surgery. This is because of intraperitoneal anastomotic leak, which usually leads to generalized peritonitis and severe sepsis, requiring reoperation and resulting in higher mortality.[106]

There is a lack of an effective, accurate, and time-sensitive pre-operative risk-assessment tool for senior CC patients. Several tools have been used to evaluate the senior population[77-80], however these tools are time consuming and subjective. There are different scoring systems that have been used to predict morbidity and mortality relevant to patients and surgeons. These scores include ColoRectal-Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity,[109] The Association Française de Chirurgie [110] and the Cleveland Clinic Foundation colorectal cancer model.[50] However, most of these scoring systems predict mortality rather than morbidity and they lack accuracy and feasibility.[111] Also, Grosso[98] et al described the postoperative complications as medical versus surgical complications. We used the Clavien-Dindo[63, 112] system to classify 30-day postoperative complications, a method that has been used and validated extensively in the literature[113-124].

In this large cohort study of a representative sample of patients with cancer from Quebec[66, 125], we identified pre-operative risk factors for severe postoperative complications in seniors undergoing CC surgery. The use of representative population data with universal

coverage and advanced health care provision augment our findings. In addition, administrative healthcare utilization is simple, accurate, and valuable in assessing preoperative risk factors in seniors undergoing CC surgery. The rate of complications within 30 days of surgery in our cohort was 29% with a mortality of 5%. These findings are similar to others where the rate of postoperative complications ranged from 18-37% and mortality 2-9%.[48]

Recent administrative claims are an accurate estimate of patients' healthcare utilization [126-130]. They can be used to identify predictors of complications related to CC surgery. Our study showed that seniors having received healthcare services within 1 year for renal disease or cardiovascular insufficiency, male gender, and polypharmacy within 6 months of surgery were at a higher risk of experiencing adverse postoperative events. The same was true for patients' ≥ 85 years of age as well as those seniors who underwent emergency surgical procedures for acutely symptomatic CC.

Two non-modifiable risk factors that were adversely associated with postoperative complications were male gender and age ≥ 85 years. Kirchhoff, et al [131] showed that male patients have a higher risk of complications after colorectal surgery, but Grosso et al[98] did not find any. This could be explained by anatomical differences in the narrower male pelvis for very low CC surgery[132] and the recently shown hormonal differences that influence the intestinal microcirculation.[133] Studies have shown that seniors with different age groups are associated with increased risk of experiencing postoperative complications. Grosso et al[98] revealed >65 years of age is associated with significant risk (OR=2.75, 95% CI= 1.67-4.52) for postoperative complications. A large study looking at predictors of postoperative complications found age >70 years to be associated with significant higher risk of experiencing the complications.[48] Indeed, a recent study demonstrate that patient age >75 years was independently and directly linked to

specifically transfusion and reoperation complications.[99] Kirchhoff[131] and his colleagues have shown that age > 75 years is significant in predicting an increase of postoperative complications. For men in North America aged 75 and 85 years the expected number of additional years of life is 10 and 5, whereas for women the years expected are 12 and 7, respectively[43]. Thus, major surgical procedures may be appropriate in selected fit elderly patients. However, life expectancy is more limited in patients with significant comorbidities or functional impairments [43]. Thus, some surgeons would try not to operate based on their eyeballing (surgeons' gut feeling) phenomenon due to patients multiple comorbidities. Although these are non-modifiable risk factors but knowing them helps the surgeon to choose the safest treatment option for the patient and to be aware of the increased risk.

Our study found that having recent care for renal insufficiency or cardiovascular disease was associated with a significant increased risk of experiencing complications. Several studies have shown similar findings. Alves, et al[48] demonstrated that neurologic and cardiopulmonary comorbidities, hypoalbuminemia, long operative times and peritoneal contamination adversely affected outcomes. In another study, operating time, shock, renal insufficiency, and intra-abdominal contamination were associated with postoperative complications [134]. Conversely, Kirchhoff, et al [131], using a multivariate analysis showed that renal insufficiency and vascular disease were not associated with postoperative complications. Although we found recent claims for renal insufficiency are the most significantly associated risk factor with postoperative complications, regardless of the onset of the disease (chronic versus an acute one), similar studies found an association between mortality and chronic or end-stage renal disease.[135-137]

Another plausible way to risk-profile patients undergoing CC surgery is to assess the number of medications which they are being prescribed [138]. Moreover, polypharmacy

significantly increases the risk of adverse drug reactions and interactions.[139] Ultimately, these reactions lead to hospitalization, surgery, loss of productivity, and death. Thus, these are considered a major problem on the individual as well as on the health system level.[140-144] Polypharmacy means that a patient uses multiple medications, especially if the medications are unnecessarily numerous or complex.[145] According to Goldberg et al, the risk of experiencing drug interactions is approximately 38 % when taking 4 medications concurrently and may increase up to 82 % in individuals using 7 or more medications.[146] Polypharmacy can be accurately assessed through the provincial drug insurance and prescription databases [68, 69]. The closer the time to the surgery, the higher the impact of these interactions could be. Therefore, assessed medications were those prescribed within a 6-month period preceding surgery. Over 60% of the study cohort used 5 or more medications and approximately 20% used ≥ 10 medications. Seniors using ≥ 10 different medications were at higher risk (HR = 1.24, CI = 1.03 – 1.49, $p = 0.026$) of experiencing complications. Seniors use, on average, 3-6 medications on a daily basis, making medication reconciliation a very crucial tool in this population [147]. Also, age-related processes, e.g. cognitive decline, account for a large proportion of adverse drug events that lead to postoperative complications and ERVs [86]. In sum, many drug reactions due to polypharmacy are preventable.[139]

This study also showed that emergency procedures were associated with an increased risk of experiencing postoperative complications. Similarly, other studies have shown an association between emergency surgery and long and short-term morbidity and mortality. [148-151] This association has proven to be very crucial, since proximal diversion and/or the use of stents may be better options in emergency situations. [149] Especially in left-sided CC, self-expanding stents have led to significantly improved outcomes with a decrease in rates of permanent stomas

and surgical site infections [152]. On the other hand, patients presented with generalized peritonitis and perforation of the left colon may benefit from primary anastomosis and protective ileostomy rather than Hartman's procedure (where surgical resection of the affected colon with closure of the distal stump and formation of an end colostomy proximally).[153, 154]

Diabetes, although associated with complications in our univariate analysis, did not demonstrate a significant association with complications after adjusting for other variables. This could be partially due to the fact that patients who are diabetic, may also suffer from cardiovascular disease (i.e. myocardial infarction or peripheral vascular disease as well as renal insufficiency, combined or separately. This is why we think diabetes was correlated with them and did not show any significance when adjusting for other variables. Kirchhoff et al[131] found similar results where diabetes was associated with increased risk of complications but without statistical significance ($p = 0.05$) when performing a univariate analysis and did not show any statistical significant on multivariate. Another study found no association between diabetes and complications neither on uni nor multi-variate analyses.[155]

Most of hospital admissions are usually related to medical problems, thus, may occur prior to surgery. This could explain why previous hospitalization was not a significant risk factor when adjusting for comorbidities as these patients may encounter hospitalization due to their comorbidities, which was already a separate section of variables in our cohort. In our univariate analysis, having had 2≥ hospitalization within a year prior to surgery was strongly associated with postoperative complications (HR = 1.27, CI = 1.05 - 1.53, $p = 0.014$) but this association was not significant when a multivariate analysis was performed. Although studies have suggested referral to highly specialized centers could improve quality of care and outcomes[156-158], we could not find any association between postoperative complications and teaching

hospitals, which are typically considered to be highly specialized center, in either univariate or multivariate analyses.

Study limitations

The study encountered several limitations. First, members of this cohort were limited to procedures performed between 2000 and 2006. Since this time, there may have been a number of changes in the perioperative management of patients. In addition, comorbidities were assessed with varying levels of accuracy based on ICD-9 and/or drug codes. This raises the issue of misclassification bias, in which some individuals who truly had a given disease or comorbidity were not labeled as such, e.g. dementia misdiagnosed based on the ICD-9 (3.3%) vs. use of cognitive drugs (46.8%). However, based on the findings of relevant validation studies, the use of ICD-9 and ICD-10 codes offers an accurate and reliable way of identifying comorbidities [159]. We also lacked data on disease recurrence and cause of death. Our ability to assess patients' overall health was limited to what we could abstract from the claims and hospital databases within a year from patient's surgery. Although we were able to abstract specific comorbidities, we found little relationship between the presence of specific comorbidities and overall survival, even for those comorbidities, which would be hypothesized to be associated with poor outcomes (such as complicated diabetes). This may reflect the fact that although the presence of the comorbidity was captured in the billing record, there is no information available regarding the severity of that comorbidity or it has been correlated with other comorbidities as mentioned earlier. Furthermore, we were unable to assess whether a patient's nutritional status played an important role in predicting adverse cancer-related outcomes as compared to other studies [48, 149, 160]. Future integration of electronic health records and valuable sources of

administrative healthcare data is also easily conceivable and will likely enhance risk-profiling in the senior surgical cancer population.

Conclusion

Our study found that recently prescribed medications, recent care for renal insufficiency or cardiovascular disease, and emergency procedures, were significantly associated with postoperative complications. These factors are easily tracked through administrative claims providing a risk assessment prior to CC management decisions. Ultimately, this tool may reduce patient's morbidity and minimize healthcare cost. However, future development of risk assessment tools and their validation through prospective studies will explore the potential benefit of utilizing such tools prior to CC surgeries.

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Tables

TABLE 1A: DEMOGRAPHICS AND CLINICAL CHARACTERISTICS OF PATIENTS

Characteristic	Value	
Age	**N**	**(%)**
65-74	1573	(41.5)
75-84	1759	(46.4)
≥85	457	(12.1)
Gender		
Female	2058	(54.3)
Male	1731	(45.7)
Mean income in area ($ CAD)		
<20,000	46	(1.2)
20,000-39,999	1432	(37.8)
40,000-59,999	1701	(44.9)
60,000-79,999	430	(11.3)
≥80,000	180	(4.8)
Proportion with high school diploma in area		
0-49	355	(9.4)
50-100	3434	(90.6)
Residence		
Urban	3126	(82.5)
Rural	663	(17.5)
Year of surgery		
2000	481	(12.7)
2001	516	(13.6)
2002	568	(15)
2003	585	(15.4)
2004	548	(14.5)
2005	529	[161]
2006	562	14.8)
Type of admission		
Elective	2872	(75.8)
Emergency	917	(24.2)

All variables assessed in the year before surgery unless otherwise specified, [1]Assessed in the 6 months before surgery, [2]Assessed in the 30 days before surgery, n = number, % = percentage

TABLE 1B: DEMOGRAPHICS AND CLINICAL CHARACTERISTICS OF PATIENTS

Characteristic	Value	
Number of unique drugs[2]		
<5	1378	(36.4)
5-9	1498	(39.5)
≥10	913	(24.1)
Median (range)	6	(0-35)
Use of cognition-altering drugs	1774	(46.8)
Geriatric comorbidities		
Urinary incontinence	55	(1.5)
Anemia	1862	(49.1)
Arthritis	926	(24.4)
Depression	602	(15.9)
Osteoporosis	526	(13.9)
Cardiovascular disease	1270	(33.5)
Dementia	125	(3.3)
Diabetes	748	(19.7)
Renal insufficiency	82	(2.2)
Respiratory illnesses	323	(8.5)
Complete physical exam	860	(22.70)
Health Care Utilization		
Hospital admissions		
0	2488	(65.7)
1	912	(24.1)
2	277	(7.3)
≥3	112	(3.0)
Number of emergency room visits related to colon cancer[3]	1481	(39.1)
Teaching status of hospital		
Academic	2439	(64.4)
Non-academic	1350	(35.6)

All variables assessed in the year before surgery unless otherwise specified, [1]Assessed in the 6 months before surgery, [2]Assessed in the 30 days before surgery, n = number, % = percentage

TABLE 2: SHORT AND LONG-TERM OUTCOMES

Outcomes	**Value**	
Total Length of stay (days) [Median (range)]	13	(1-266)
Length of postoperative stay (days) [Median (range)]	10	(0-265)
Elective ICU admission after surgery [n (%)]	900	(23.8)
Length of stay for elective ICU admission (days) [Median (range)]	2.0	(1-30)
Discharge destination [n (%)]		
Home	2689	(71.0)
Local Community Service Center (CLSC)	692	(18.3)
Other	408	(10.7)
Readmission within 30 days of discharge [n (%)]	428	(11.3)
ERVs within 30 days of discharge [n (%)]	674	(17.8)
Any complication (Clavien-Dindo grade III or higher) within 30 days of surgery [n (%)]	1099	(29.0)
Time to first complication after surgery (days) [Median (range)]	6.0	(0-30)
Clavien-Dindo grade of first complication [n (%)]		
Clavien-Dindo grade III	605	(16.0)
Clavien-Dindo grade IV	391	(10.3)
Clavien-Dindo grade V	103	(2.7)
Proportion with postoperative complications within 30 days of surgery[1] [n (%)]		
Clavien-Dindo grade III	656	(17.3)
Clavien-Dindo grade IV	476	(12.6)
Clavien-Dindo grade V[2]	189	(5.0)
All-cause mortality [n (%)]		
90-day	325	(8.58)
1-year	729	(19.24)

Footnote: ICU = intensive care unit; ERVs = emergency room visits; N = number; % = Percentage

TABLE 3: EMERGENCY ROOM VISIT CLASSIFICATIONS

System	**Frequency**	**Percentage**
Infection	301	20.57
Skin & soft tissue	116	38.54
Generalized infection	89	29.57
Genito-urinary tract infection	50	16.61
Digestive	264	18.05
Symptoms of GI tract	122	46.21
Intestinal obstruction	34	12.88
Other diseases of intestine	31	11.74
Cardiovascular	213	14.56
Diseases of peripheral circulation	58	27.23
Arrhythmias	46	21.60
Ischemic heart disease	28	13.15
Respiratory	129	8.82
Neoplasm	96	6.56
Injury & poisoning	58	3.96
Nonspecific general symptom	56	3.83
Wound	51	3.49
CNS	50	3.42
Unspecified codes	49	3.35
Missing codes	37	2.53
Genitourinary	34	2.32
Musculoskeletal	29	1.98
Mental disorders	28	1.91
Skin and soft tissue	26	1.78
Endocrine, metabolic, & nutritional	23	1.57
Hematology	19	1.3
Total	1463	100

TABLE 4: UNIVARIATE AND MULTIVARIATE ANALYSES

Factors	# of Patients	Complications %	Univariate Cox model[a] HR	95% CI		P	Multivariate Cox model[a] HR	95% CI		P
Gender										
Female	539	26.2	1.00	Reference			1.00	Reference		
Male	560	32.4	1.28	1.14	1.44	< 0.0001	1.28	1.13	1.45	0.000
Age										
65-74	427	27.1	1.00	Reference			1.00	Reference		
75-84	515	29.3	1.10	0.97	1.25	0.135	1.05	0.92	1.20	0.477
≥85	157	34.3	1.35	1.12	1.62	0.001	1.25	1.03	1.52	0.021
Number of unique drugs										
<5	367	26.6	1.00	Reference			1.00	Reference		
5-9	412	27.5	1.03	0.89	1.18	0.712	0.99	0.85	1.15	0.892
≥10	320	35.0	1.39	1.19	1.61	<.0001	1.24	1.03	1.49	0.026
Geriatric comorbidities										
Urinary incontinence	16	29.1	0.99	0.60	1.62	0.962	1.01	0.62	1.66	0.966
Anemia	560	30.1	1.08	0.96	1.22	0.138	0.99	0.88	1.12	0.909
Arthritis	257	27.8	0.94	0.82	1.08	0.387	0.90	0.78	1.04	0.141
Depression	190	31.6	1.12	0.95	1.30	0.171	1.09	0.92	1.28	0.328
Osteoporosis	134	25.5	0.85	0.71	1.02	0.851	0.93	0.76	1.13	0.443
Cardiovascular disease	446	35.1	1.44	1.27	1.62	<.0001	1.25	1.10	1.43	0.001
Dementia	39	31.2	1.15	0.84	1.59	0.379	1.02	0.74	1.42	0.893
Diabetes	247	33.0	1.21	1.05	1.39	0.009	1.08	0.93	1.25	0.342
Renal insufficiency	38	46.3	1.78	1.29	2.46	0.001	1.43	1.02	1.99	0.036
Respiratory illnesses	109	33.7	1.22	1.00	1.48	0.051	0.94	0.75	1.16	0.549
Complete physical exam	236	27.4	0.91	0.79	1.06	0.216	0.97	0.84	1.13	0.716
Hospital admissions										
0	689	27.7	1.00	Reference			1.00	Reference		
1	280	30.7	1.13	0.98	1.30	0.085	1.06	0.91	1.22	0.473
≥2	130	33.4	1.27	1.05	1.53	0.014	1.10	0.90	1.36	0.357
Type of admission										
Elective	769	26.8	1.00	Reference			1.00	Reference		
Emergency	330	36.0	1.44	1.27	1.64	<0.0001	1.39	1.22	1.59	<0.0001
Teaching status of hospital										
Academic	705	28.9	1.00	Reference			1.00	Reference		
Non-academic	394	29.2	1.01	0.89	1.14	0.938	1.01	0.89	1.15	0.852

Abbreviations: CI, confidence interval; HR, hazard ratio; P, p-value;

[a] Adjusted for clustering of patients within physicians (N=390), year of surgery, rural residence, and mean income in residence. The median cluster size was 6 patients, range: 1-53.

Figures

FIGURE 1: ANONYMOUS LINKAGE OF DATABASES

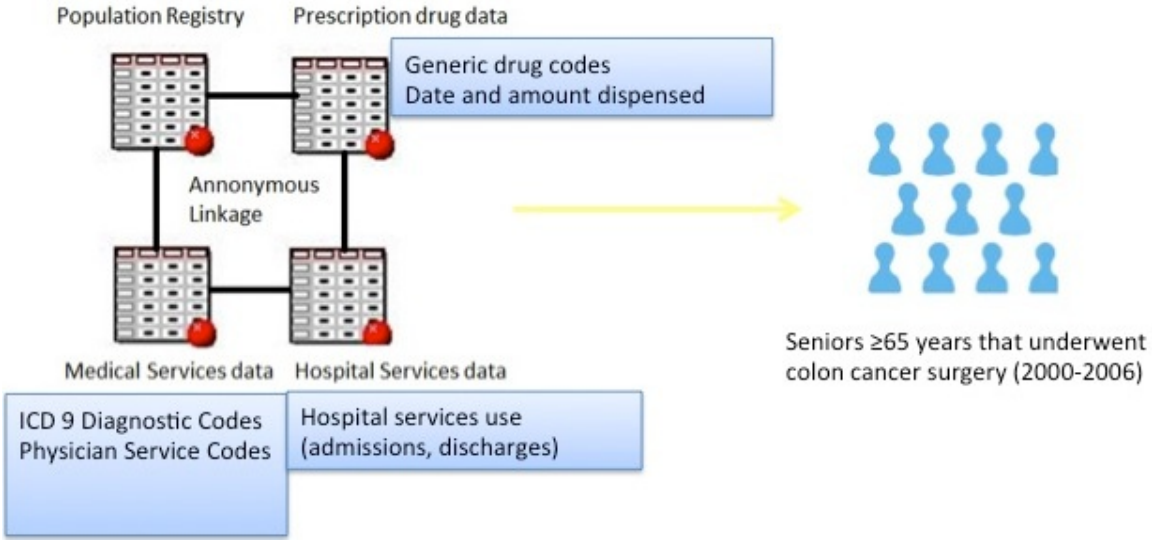
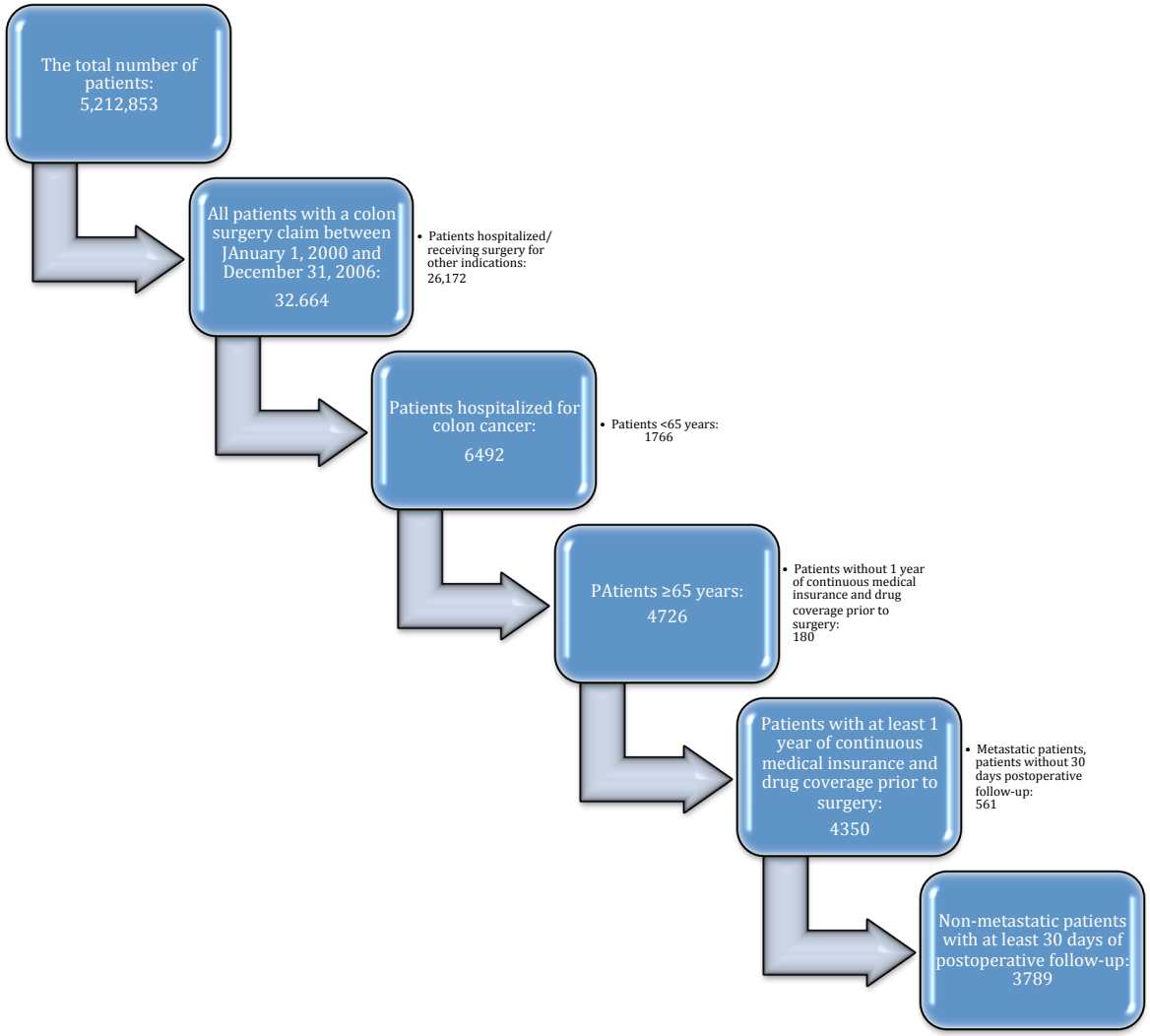


FIGURE 2: COHORT SELECTION PROCESS

>>>>>



Appnedices

APPENDIX A

Table 1: Exclusion criteria

Exclusion criteria	**Number excluded**	**Number included after exclusion**
Patients with a colon cancer surgery claim outside the period from January 2000 to December 2006	5,180,189	32,664
Those who do not have a colon cancer surgery in hospitalization database	8,732	23,932
Those who do not have a same date surgery for colon cancer in hospitalization database in comparison with claims	1,610	22,322
Those who do not have a primary diagnosis of colon cancer for the surgical hospitalization	11,516	10,806
Those who do not have a specific diagnostic code for colon cancer billed for their surgery in RAMQ (either missing or different from colon cancer codes)	4,314	6,492
Patients less than 65 years of age	1,766	4,726
Patients without medical claims for one year before surgery	166	4,560
Patients without 30 days follow up postoperatively if they didn't die	14	4,546
Patients without continuous drug insurance coverage in the year before surgery	196	4,350
Metastatic patients	561	3,789

Table 2: Colon surgery procedure codes

Billing procedure codes	Description
5136	Intestinal resection without anastomosis: small intestine or colon resection with ileostomy including the closure of the distal end
5141	Bowel resection with anastomosis: terminal ileum, cecum
5142	Bowel resection with anastomosis: terminal ileum, cecum, ascending colon and hepatic flexure (right hemicolectomy)
5164	Left hemicolectomy
5232	Total colectomy with ileo-rectostomy
5165	Partial resection of the colon with colostomy and closure of the distal rectum (Hartman)
5166	Total resection of the colon with ileostomy and closure of the distal rectum
5154	Transverse colon or left colon segment

Table 3: ICD-9/10 codes for primary reason for the surgical hospitalization

ICD-9	Description
153.0	Malignant neoplasm of colon, hepatic flexure
153.1	Malignant neoplasm of colon, transverse colon
153.2	Malignant neoplasm of colon, descending colon
153.3	Malignant neoplasm of colon, sigmoid colon
153.4	Malignant neoplasm of colon, cecum
153.5	Malignant neoplasm of colon, appendix
153.6	Malignant neoplasm of colon, ascending colon
153.7	Malignant neoplasm of colon, splenic flexure
153.8	Malignant neoplasm of colon, other specified sites of large intestine
153.9	Malignant neoplasm of colon, unspecified
ICD-10	**Description**
C18.0	Malignant neoplasm of colon, cecum
C18.1	Malignant neoplasm of colon, appendix
C18.2	Malignant neoplasm of colon, ascending colon
C18.3	Malignant neoplasm of colon, hepatic flexure
C18.4	Malignant neoplasm of colon, transverse colon
C18.5	Malignant neoplasm of colon, splenic flexure
C18.6	Malignant neoplasm of colon, descending colon
C18.7	Malignant neoplasm of colon, sigmoid colon
C18.8	Malignant neoplasm of colon, overlapping lesion of colon
C18.9	Malignant neoplasm of colon, unspecified

Table 4: Discharge destination codes

Code	Description (en français)
2	C.H. public soins prolongés de convalescence
3	Centre d'hébergement et de soins de longue durée
5	C.H. privé soins de convalescence
6	C.H. privé soins de longue durée
8	C.H. fédéral - soins de longue durée
10	Centre d'hébergement et de soins de longue durée, hors province
13	Centre de réadaptation
14	Centre d'accueil d'hébergement
15	Centre d'accueil d'hébergement privé
20	Pavillon d'hébergement
21	Domicile
22	Domicile avec soins à domicile
26	Hôpital de jour
36	Transfert aux soins de longue durée (C.H. psychiatriques seulement)

Table 5: Canadian Classification of Health Interventions codes of hospitalization records for colon cancer surgery

CCI code	Description (en français)
1NM76DF	Pontage, gros intestin, approche endoscopique [par laparoscopie] par colocolostomie de diversion
1NM76DN	Pontage, gros intestin, approche endoscopique [par laparoscopie] par entérocolostomie de diversion
1NM76RE	Pontage, gros intestin, approche ouverte par entérocolostomie de diversion
1NM76RN	Pontage, gros intestin, approche ouverte par colocolostomie de diversion
1NM77EP	Pontage avec extériorisation, gros intestin, colostomie, approche endoscopique [par laparoscopie]
1NM77RS	Pontage avec extériorisation, gros intestin, colostomie, approche ouverte
1NM77RSXXG	Pontage avec extériorisation, gros intestin, caecostomie continente, approche ouverte avec lambeau pédiculé
1NM87DA	Excision partielle, gros intestin, approche endoscopique [par laparoscopie] procédure excisionnelle simple
1NM87DE	Excision partielle, gros intestin, approche endoscopique [par laparoscopie] anastomose colo-rectale
1NM87DF	Excision partielle, gros intestin, approche endoscopique [par laparoscopie] anastomose avec colocolostomie
1NM87DN	Excision partielle, gros intestin, approche endoscopique [par laparoscopie] formation d'abouchement et fermeture distale
1NM87DX	Excision partielle, gros intestin, approche endoscopique [par laparoscopie] formation d'abouchement et fermeture distale
1NM87DY	Excision partielle, gros intestin, approche endoscopique [par laparoscopie] formation d'abouchements avec création d'une fistule muqueuse
1NM87LA	Excision partielle, gros intestin, approche ouverte procédure excisionnelle simple
1NM87PN	Excision partielle, gros intestin approche endoscopique [par laparoscopie] télémanipulation robotisée d'outils [téléchirurgie]
1NM87RD	Excision partielle, gros intestin, approche ouverte anastomose colo-rectale
1NM87RE	Excision partielle, gros intestin, approche ouverte anastomose avec entérocolostomie
1NM87RN	Excision partielle, gros intestin, approche ouverte anastomose avec colocolostomie
1NM87TF	Excision partielle, gros intestin, approche ouverte formation d'abouchement et fermeture distale
1NM87TG	Excision partielle, gros intestin, approche ouverte formation d'abouchements avec création d'une fistule muqueuse
1NM89DF	Excision totale, gros intestin, approche endoscopique [par laparoscopie] anastomose iléo-rectale [endo-rectale, iléo-rectostomie]
1NM89DX	Excision totale, gros intestin, approche endoscopique [par laparoscopie] formation d'abouchement avec fermeture distale
1NM89RN	Excision totale, gros intestin, approche ouverte anastomose iléo-rectale [endo-rectale, iléo-rectostomie]
1NM89TF	Excision totale, gros intestin, approche ouverte formation d'abouchement avec fermeture distale
1NM91DE	Excision radicale, gros intestin, approche endoscopique [par laparoscopie] anastomose colo-rectale
1NM91DF	Excision radicale, gros intestin, approche endoscopique [par laparoscopie] anastomose avec colocolostomie
1NM91DN	Excision radicale, gros intestin, approche endoscopique [par laparoscopie] anastomose avec entérocolostomie
1NM91DX	Excision radicale, gros intestin, approche endoscopique [par laparoscopie] formation d'abouchement avec fermeture distale
1NM91DY	Excision radicale, gros intestin, approche endoscopique [par laparoscopie] formation d'abouchements avec création d'une fistule muqueuse
1NM91RD	Excision radicale, gros intestin, approche ouverte anastomose colo-rectale
1NM91RE	Excision radicale, gros intestin, approche ouverte anastomose avec entérocolostomie
1NM91RN	Excision radicale, gros intestin, approche ouverte anastomose avec colocolostomie
1NM91TF	Excision radicale, gros intestin,approche ouverte formation d'abouchement avec fermeture distale
1NM91TG	Excision radicale, gros intestin,approche ouverte formation d'abouchements avec création d'une fistule muqueuse

APPENDIX B

Table 1: Variable construction

CGA risk factor	Variable(s)	Data source(s)
Geriatric syndromes & comorbidities	Urinary incontinence, anemia, arthritis, depression, osteoporosis, cardiovascular disease, dementia, diabetes, renal insufficiency, and respiratory illness	Medical service claims Prescription claims
Polypharmacy	No. of unique medications used in the 6 months prior to colon cancer surgery	Prescription claims
Socioeconomic status	- Sex - Revenue (average household income of patient's residential area) - Education (% of individuals in residential area with high school diploma)	Registrants' database Statistics Canada Canada postal code structure
Cognition-altering drug use	e.g. benzodiazepines, antipsychotics	Prescription claims
Type of admission	- Elective: not preceded by ERV - Emergent: Preceded by ERV	Medical service claims
Complete annual physical exam	1 year look back window	General practitioner billing claims
Elective ICU admission	48 hours after the surgery or preceded by angiography	Medical service claims Procedure claims
Discharge destination	Home, Local Community Service Center, or others	Medical service claims Hospital abstract discharge database
Number of previous hospitalizations	1 year look back window	Hospital abstract discharge database

Table 2: AHF code used defining cognition-altering medications

AHF code	**Description (en français)**
28:08.08	Opiates (agonistes des opiacés)
28:08.12	Partial opiate agonists (agonistes partiels des opiacés)
28:12.04	Barbituates (barbituriques)
28:12.08	Benzodiazepines (benzodiazépines)
28:16.04	Antidepresssants (antidépresseurs)
28:16.08	Antipsychotics (antipsychotiques)
28:24.08	Anxiolytics, sedatives and hypnotics (anxiolytiques, sédatifs et hypnotiques)
28:24.92	Miscellaneous anxiolytics, sedatives and hypnotics (divers anxiolytiques, sédatifs et hypnotiques)
28:28	Other psychotropics (autres psychotropes)

Table 3: ICD-9 codes defining urinary incontinence.

ICD-9 codes	**Description**
625.6	Stress incontinence, female
788.2	Retention of urine
788.4	Frequency of urination and polyuria

Table 4: ICD-9 codes defining arthritis

ICD-9	Description
696.0	Psoriatic arthropathy
729.0	Rheumatism, unspecified and fibrositis
729.1	Myalgia and myositis, unspecified
729.3	Panniculitis, unspecified
729.5	Other disorders of soft tissue, pain in limb
729.9	Other and unspecified disorders of soft tissue
728.8	Other disorders of muscle, ligament, and fascia
095.7	Syphilis of synovium, tendon, and bursa
274.0	Gout
446.0	Polyarteritis nodosa and allied conditions
726.0	Peripheral enthesopathies and allied syndromes
727.0	Other disorders of synovium, tendon, and bursa
701.0	Other hypertrophic and atrophic conditions of skin
711.0	Arthropathy associated with infections
712.0	Crystal arthropathies
713.0	Arthropathy associated with other disorders classified elsewhere
714.0	Rheumatoid arthritis and other inflammatory polyarthropathies
715.0	Osteoarthrosis and allied disorders
716.0	Other and unspecified arthropathies
717.0	Internal derangement of knee
718.0	Other derangement of joint
719.0	Other and unspecified disorders of joint
720.0	Ankylosing spondylitis and other inflammatory spondylopathies
725.0	Polymyalgia rheumatica
880.0	Open wound of shoulder and upper arm
840.0	Sprains and strains of shoulder and upper arm

Table 5: ICD-9 codes defining depression.

ICD-9 codes	Description
296.2	Major depressive disorder, single episode
298.0	Depressive type psychosis
296.8	Other and unspecified bipolar disorders
296.3	Major depressive disorder, recurrent episode
296.5	Bipolar I disorder, most recent episode (or current) depressed
296.6	Bipolar I disorder, most recent episode (or current) mixed
296.9	Other and unspecified episodic mood disorder
300.4	Dysthymic disorder
300.5	Neurasthenia
301.1	Affective personality disorder
309.0	Adjustment reaction
311.0	Depressive disorder, not elsewhere classified

Table 6: Generic drug codes used in treating osteoporosis

Generic drug codes (Dénomination commune)	Description (en français)
46295, 47165	Alendronate monosodique
46631, 47339	Risédronate sodique
46510, 47340	Raloxifène ou chlorhydrate de raloxifène
40862, 46589	Calcitonine de saumon (synthétique)

Table 7: ICD-9 codes defining cardiovascular disease

ICD-9 codes	**Description**
429.2	Cardiovascular disease, unspecified
414.1	Aneurysm and dissection of heart
414.8	Other specified forms of chronic ischemic heart disease
414.9	Chronic ischemic heart disease, unspecified
415.1	Pulmonary embolism and infarction
416.9	Chronic pulmonary heart disease, unspecified
410.0	Acute myocardial infarction
414.0	Other forms of chronic ischemic heart disease
412.0	Old myocardial infarction
428.0	Heart failure
431.0	Intracerebral hemorrhage
432.0	Other and unspecified intracranial hemorrhage
433.0	Occlusion and stenosis of precerebral arteries
434.0	Occlusion of cerebral arteries
435.0	Transient cerebral ischemia
436.0	Acute, but ill-defined, cerebrovascular disease
437.0	Other and ill-defined cerebrovascular disease
438.0	Late effects of cerebrovascular disease
411.0	Other acute and subacute forms of ischemic heart disease
430.0	Subarachnoid hemorrhage

Table 8: ICD-9 and generic drug codes defining or used to treat dementia

ICD-9 codes	**Description**
294.1	Dementia in conditions classified elsewhere
046.1	Jakob-Creutzfeldt disease
333.4	Huntington's chorea
290.0	Dementias
331.0	Other cerebral degenerations
Generic drug codes (Dénomination commune)	**Drug name**
47352	Donepezil
47368	Rivastigmine
47542	Memantine
47415	Galantamine

Table 9: AHF codes for medications used in treating diabetes.

Generic drug codes (Dénomination commune)	Name of the medication (en français)
682004	Biguanides
682028	Thiazolidinediones
682020	Sulfonylureés
682016	Meglitindines
682002	Inhibiteurs des alpha-glucosidases
682008	Insulines

Table 10: Billing claims procedure codes defining renal failure.

Procedure codes	Description (en français)
147	Visites pour le contrôle du traitement par hémodialyse en centre satellite comprenant la revue du dossier de chaque dialyse, l'interprétation des résultats sanguins avant ou après chaque dialyse, le contrôle de l'anticoagulothérapie, la surveillance hebdomadaire d'une dialyse et le contrôle à distance des traitements, par mois, par patient
283	Visites pour le traitement pour dialyse péritonéale, incluant tous les soins, par patient pour les premières quarante-huit (48) heures
284	Visites pour le traitement pour dialyse péritonéale, incluant tous les soins, par patient après quarante-huit (48) heures, par jour
285	Visites pour le contrôle du traitement par dialyse péritonéale à domicile, par mois, par patient, comprenant la revue du dossier de chaque dialyse, l'interprétation des résultats sanguins avant et après chaque dialyse, le contrôle de l'anticoagulothérapie et revue de l'évolution du patient en plus de l'examen lors d'une visite périodique (patient de plus de seize (16) ans)
287	Visites pour le traitement par hémodialyse, incluant tous les soins, par patient (première)
288	Visites pour le traitement par hémodialyse, incluant tous les soins, par patient (subséquente, patient de plus de seize (16) ans)
290	Visites pour le contrôle du traitement par hémodialyse à domicile, par mois, comprenant la revue du dossier de chaque dialyse, l'interprétation des résultats sanguins avant et après chaque dialyse, le contrôle de l'anticoagulothérapie et revue de l'évolution du patient en plus de l'examen lors d'une visite périodique, par patient
311	Dialyses péritonéales (techniques chirurgicales): installation ou exrèse de cathéter type Tenckhoff ou d'Oreopoulos
332	Dialyses péritonéales (techniques chirurgicales): mise en place d'un tube par ponction, par trocart ou par incision
336	Dissection incluant ponction ou insertion de cathéter artérielle (périphérique)
337	Dissection incluant ponction ou insertion de cathéter veineuse
389	Mise en place d'un cathéter veineux ou artérielle pour hémodialyse ou toute autre technique d'épuration extrarénale, par voie transcutanée, tout site
419	Installation de canules artérielles et veineuses
426	Hémodialyse: revision ou réinstallation de cathéters (cathéter artériel ou veinuex)
427	Hémodialyse: revision ou réinstallation de cathéters (cathéter artériel et veinuex)
493	Dialyse péritonéales (techniques chirurgicales pour accès): installation d'un cathéter de type Tenckhoff ou d'Oréopoulos incluant l'exérèse d'un autre cathéter, le cas échéant
494	Dialyse péritonéales (techniques chirurgicales pour accès): omenectomie totale ou subttotale (au moins les deux tiers), supplement
495	Dialyse péritonéales (techniques chirurgicales pour accès): exérèse d'un cathéter de type Tenckhoff ou d'Oréopoulos
699	Thérapie immunosuppressive pour transplantation rénale, traitement complet pré et postopératoire
4032	Hémodialyse: creation d'une nouvelle fistule artério-veineuse au meme site qu'une ancienne fistule, avec ou sans greffe
4748	Hémodialyse: création de fistule artério-veineuse avec ou sans greffe
4749	Hémodialyse: exérèse de prothse vasculaire infectée
4752	Réparation de fistule artério-veineuse pour hémodialyse: thrombectomie par voie ouverte
4753	Réparation de fistule artério-veineuse pour hémodialyse: angioplastie par patch ou greffon our emplacement d'un segment avec or sans thrombectomie
4754	Réparation de fistule artério-veineuse pour hémodialyse: exérèse d'anévrisme sans réparation
4755	Réparation de fistule artério-veineuse pour hémodialyse: ligature de fistule artério-veineuse pour hémodialyse
4756	Réparation de fistule artério-veineuse pour hémodialyse: exérèse de prothèse infectée lors de creation de nouvelle fistule pour hémodialyse à un site different, supplément
6221	Transplanation rénale, excluant la thérapie immune-suppressive (un chirurgien)
6222	Transplanation rénale, excluant la thérapie immune-suppressive (équipe de deux chirurgiens), temps vasculaire
6223	Transplanation rénale, excluant la thérapie immune-suppressive (équipe de deux chirurgiens), temps urologique
9291	Visites pour le traitement par dialyse péritonéale, incluant tout les soins par un néphrologue pendant cette séance de dialyse par patient
9382	Hémofiltration artério-veineuse continue incluant tous les soins, sauf le premier examen et l'insertion du cathéter, trois (3) premiers jours, par patient, par jour
9489	Thérapie immunosuppressive pour transplantation complet pré et postopératoire
15035	Supervision du traitement par dialyse péritonéale à domicile par mois, par patient
15040	Supervision d'une unité de dialyse, par séance, par patient – dialyse initiale
15041	Supervision d'une unité de dialyse, par séance, par patient – dialyse initiale, patient de plus de 16 ans
15043	Hémodialyse débutant entre 17:00 heures et minuit, en semaine – patient de plus de 16 ans
15045	Hémodialyse débutant entre minuit et 07 :00 heures, en semaine – patient de plus de 16 ans
15047	Hémodialyse ayant lieu entre 00:00 heures samedi et 07:00 heures lundi, ou un jour férié – patient de plus de 16 ans
15050	Supervision du traitement par hémodialyse à domicile, par mois, par patient
15051	Supervision du traitement par hémodialyse en centre satellite, par mois, par patient

Table 11: ICD-9/ICD-10 codes defining respiratory disease.

ICD-9 codes	**Description**
466.0	Acute bronchitis and bronchiolitis
480.0	Viral pneumonia
481.0	Pneumococcal pneumonia [Streptococcus pneumoniae pneumonia]
482.0	Other bacterial pneumonia
483.0	Pneumonia due to other specified organism
486.0	Pneumonia, organism unspecified
487.0	Influenza
491.0	Chronic bronchitis
492.0	Emphysema
493.0	Asthma
494.0	Bronchiectasis
496.0	Chronic airway obstruction, not elsewhere classified
519.8	Other diseases of respiratory system, not elsewhere classified
ICD-10 codes	**Description**
J10.0	Influenza with pneumonia, other influenza virus identified
J11.0	Influenza with pneumonia, virus not identified
J12	Viral pneumonia, not elsewhere classified
J13	Pneumonia due to Streptococcus pneumoniae
J14	Pneumonia due to Haemophilus influenzae
J15	Bacterial pneumonia, not elsewhere classified
J16	Pneumonia due to other infectious organisms, not elsewhere classified
J18	Pneumonia, organism unspecified
J20	Acute bronchitis
J21	Acute bronchiolitis
J22	Unspecified acute lower respiratory infection
J41.0	Simple chronic bronchitis
J41.1	Mucopurulent chronic bronchitis
J41.8	Mixed simple and mucopurulent chronic bronchitis
J42	Unspecified chronic bronchitis
J43	Emphysema
J44	Other chronic obstructive pulmonary disease
J45	Asthma
J46	Status asthmaticus
J47	Bronchiectasis

Table 12: Billing procedure codes defining a complete physical exam

Billing claims procedure code	Description (en français)
11	Examen pour les patients de 60 ans mais de moins de 70 ans au cabinet complet
21	Examen pour les patients de 60 ans mais de moins de 70 ans au cabinet complet majeur
50	Examen pour les patients moins de 70 ans au cabinet complet, sans déplacement
52	Examen pour les patients moins de 70 ans au cabinet complet
56	Examen dans un centre hospitalier de soins de courte durée et dans un C.L.S.C. (patients de moins de 70 ans) complet patient inscrit sans déplacement
57	Examen dans un centre hospitalier de soins de courte durée et dans un C.L.S.C. (patients de moins de 70 ans) complet patient inscrit d'urgence avec déplacement
74	Examen pour les patients de 60 ans mais de moins de 70 ans à domicile, patient supplémentaire sous un même toit examen complet
93	Examen pour les patients moins de 70 ans, complète, à domicile, pour un patient supplémentaire
97	Examen dans un centre hospitalier de soins de courte durée et dans un C.L.S.C. (patients de moins de 70 ans) complet majeur patient inscrit sans déplacement
98	Examen dans un centre hospitalier de soins de courte durée et dans un C.L.S.C. (patients de moins de 70 ans) complet majeur patient inscrit d'urgence avec déplacement
8871	Examen (patients de moins de 70 ans) en cabinet (patients de moins de 60 ans) complet
8872	Examen (patients de moins de 70 ans) en cabinet (patients de moins de 60 ans) complet majeur
8874	Examen (patients de moins de 70 ans) à domicile (patients de moins de 60 ans) patient supplémentaire, sous le même toit examen complet
8879	Consultation et examen pour les patients de soixante-dix (70) ans ou plus examen (70 ans ou plus) à domicile patient supplémentaire, sous le même toit examen complet 70-79 ans
8881	Consultation et examen pour les patients de soixante-dix (70) ans ou plus examen (70 ans ou plus) à domicile patient supplémentaire, sous le même toit examen complet 80 ans ou plus
9035	Consultation et examen pour les patients de soixante-dix (70) ans ou plus examen (70 ans ou plus) au cabinet complet 70 - 79 ans
9036	Consultation et examen pour les patients de soixante-dix (70) ans ou plus examen (70 ans ou plus) au cabinet complet majeur 70 - 79 ans
9039	Consultation et examen pour les patients de soixante-dix (70) ans ou plus (réservé au médecin exerçant en anesthésie) au cabinet complet 80 ans ou plus
9040	Consultation et examen pour les patients de soixante-dix (70) ans ou plus examen (70 ans ou plus) au cabinet complet majeur 80 ans ou plus
9050	Examination of patients aged 70 and over, complete, outpatient, without travel
9051	Examination of patients aged 70 and over, complete, outpatient, emergency, with travel
9052	Examination of patients aged 70 and over, complete major, outpatient, without travel
9053	Examination of patients aged 70 and over, complete major, outpatient, emergency, with travel
9105	Examination of patients aged 70 and over, complete, office
9107	Examination of patients aged 70 and over, complete major, office
9116, 9117, 9119, 9120	Consultation et examen pour les patients de soixante-dix (70) ans ou plus

Table 13: Colon-cancer related symptoms (ICD-9 codes) used in identifying colon cancer-related ERVs.

ICD-9 codes	Description
789	Other symptoms involving abdomen and pelvis
285	Other and unspecified anemias
153	Malignant neoplasm of colon
560	Intestinal obstruction without mention of hernia
578	Gastrointestinal hemorrhage
199	Malignant neoplasm without specification of site
569	Other disorders of intestine
562	Diverticula of intestine
558	Other and unspecified noninfectious gastroenteritis and colitis
455	Hemorrhoids
780	General symptoms
787	Symptoms involving digestive system
280	Iron deficiency anemias
428	Heart failure
535	Gastritis and duodenitis
540	Acute appendicitis
239	Neoplasms of unspecified nature
541	Appendicitis, unqualified
555	Regional enteritis
281.9	Unspecified deficiency anemia
230	Carcinoma in situ of digestive organs
458.9	Hypotension, unspecified
211	Benign neoplasm of other parts of digestive system
575	Other disorders of gallbladder
751.9	Unspecified anomaly of digestive system
154	Malignant neoplasm of rectum, rectosigmoid junction, and anus
155	Malignant neoplasm of liver and intrahepatic bile ducts
159	Malignant neoplasm of other and ill-defined sites with the digestive organs and peritoneum
564	Functional digestive disorders, not elsewhere classified
152	Malignant neoplasm of small intestine, including duodenum
532	Duodenal ulcer
533	Peptic ulcer, unspecified
535	Gastritis and duodenitis
783.2	Abnormal loss of weight and underweight
751.1	Atresia and stenosis of small intestine
151	Malignant neoplasm of stomach
530	Diseases of esophagus
568	Other disorders of peritoneum
458.0	Hypotension
537	Other disorders of stomach and duodenum
553	Other hernia of abdominal cavity without mention of obstruction or gangrene
565	Anal fissure and fistula
573	Other disorders of liver
150	Malignant neoplasm of esophagus
225	Benign neoplasm of brain and other parts of nervous system
229	Benign neoplasm of other and unspecified sites
234	Carcinoma in situ of other and unspecified sites
531	Gastric ulcer
536	Disorders of function of stomach
556	Ulcerative colitis
566	Abscess of anal and rectal regions
579	Intestinal malabsorption
142	Malignant neoplasm of major salivary glands
158	Malignant neoplasm of retroperitoneum and peritoneum
235	Neoplasm of uncertain behavior of digestive and respiratory systems
281.2	Folate-deficiency anemia
286.5	Hemorrhagic disorder due to intrinsic circulating anticoagulants
287	Purpura and other hemorrhagic conditions
533	Peptic ulcer, site unspecified
567	Peritonitis and retroperitoneal infections
009	Ill-defined intestinal infections

APPENDIX C

Table 1: Clavien-Dindo Classification system of postoperative complications

Grade	Description
I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications Blood transfusions and total parenteral nutrition are also included.
III	Requiring surgical, endoscopic or radiological intervention a. Intervention not under general anesthesia b. Intervention under general anesthesia
IV	Life-threatening complication (including CNS complications) requiring IC/ICU management a. Single organ dysfunction (including dialysis) b. Multiorgan dysfunction
V	Death of a patient

Abbreviations: CNS: central nervous system, IC: Intermediate care, ICU: intensive care unit

Table 2: Identifications and classification of severe postoperative complications using procedure codes

Complication	Definition
Grade V	**Death of patient** Death within 30 days from the surgery date, including the surgery date
Grade IV	**Life-threatening complication (including CNS complications), requiring CC/ICU management** RAMQ procedures codes: 0693, 04825 or a non-elective ICU admission (establishments: 0X6, 4X6) within 30 days. A non-elective ICU admission refers to an admission occurring at least 48 hours after surgery and not preceded by angiography procedures.
Grade III	**Any deviation from the normal postoperative course requiring surgical, endoscopic, or radiological intervention** RAMQ procedure codes corresponding to **angiography** (20506, 09492-09496, 09446-09448, 09440-09444, 09436-09438, 09432, 09433, 09422, 09420, 09361, 09360, 09355, 09345, 08440-08449, 08434-08439, 08408-08423, 08400-08405, 00883-00888, 00866, 00846, 00756-00758, 00690, 00685, 00648, 00630, 00621, 00619, 00617, 00597, 00575, 00570, 00567, 00566, 00565, 00564, 00560, 00545, 00542, 00540, 00535, 00525, 00488, 00487, 00409, 00408, 00294, 00243-00246, 00233, 00219, 00191, 00141-00143, 00139, 00129-00135, 00126, 00108, 00102) or the management of other grade III complications [(**radiology codes:** 20598, 20075, 20072, 20064, 20063, 09472-09474, 09464-09470, 09449-09458, 09439, 00854, 00790, 00765, 00730, 00435, 00418, 00416, 00324, 00299, 00298, 00252, 00247, 00212, 00178, 00154, 00124, 00123), (**endoscopy codes:** (**bronchoscopy and/or laryngoscopy**: 20085, 20015, 09484, 09401, 09400, 09366-09369, 09362-09364, 09344, 00812, 00811, 00801, 00800, 00782, 00753, 00724, 00716, 00707, 00140, 009365, 009353, 009352, 009351, 00724, 00723, 00644-00646, 00519, 00512, 00511, 00471, 00413, 00412, 20594, 20016, 09384, 00978-00882, 00799, 00654, 00559, 00547, 00521-00524, 00515-00517, 00275), (**GI endoscopy**: 20039-20084, 20037, 20036, 20030, 20024, 09488, 09486, 09485, 09373-09381, 09337-09340, 08182, 00877, 00876, 00874, 00862-00870, 00754, 00750, 00749, 00706, 00700-00703, 00697, 00692, 00691, 00634-00636, 00620, 00571-00574, 00569, 00568, 00563, 00562, 00548, 00390, 00391, 00365, 00364, 00349, 00346, 00338, 00304, 00303, 00122), (**gynecology endoscopy**: 06462, 06460, 06434, 06404, 06075, 06074), (**urinary endoscopy**: 09407, 09311, 09310, 00731, 00726, 00709, 00652, 00651, 00372-00374, 00325-00327, 00314-00320, 00302), or (**surgery**: 01415, 01414, 01024, 01013-01020, 01328, 01327, 01325, 01323, 01322, 01320, 01317, 01316, 04655, 04600-04606, 04540, 04539, 03365, 03038, 03031-03034, 02066, 18152, 18120, 18107, 18106, 18084, 18065, 18064, 18041-18043, 18012, 09589-09592, 07507, 02921, 02912, 02911, 02770, 02769, 02742, 02740, 02739, 02736, 02735, 02725, 02721, 02714-02716, 02694-02696, 02688-02690, 02680, 02673, 02667, 02665, 02661, 02655, 02654, 02652, 02651, 02649, 02636, 02633, 02631, 02624, 02581, 02580, 02554, 02041, 02021, 02020, 02011, 02008, 05812, 05805-05807, 05803, 05505, 05437, 05434, 05432, 05426, 05422, 05421, 05418, 05408-05413, 05405, 05404, 05400, 05397, 05393, 05382-05390, 05375-05379, 05373, 05369, 05363-05366, 05361, 05304, 05291-05294, 05279-05282, 05253, 05250, 05248, 05246, 05238-05244, 05231-05235, 05226, 05209, 05205-05207, 05201, 05192, 05186, 05183, 05182, 05164-05166, 05154, 05152, 05144, 05140-05142, 05136, 05121, 05114, 05110, 05108, 05098, 05097, 05094, 05093, 05090, 05067, 05052, 05050, 05045, 05044, 05039, 05038, 05036, 05030, 05029, 05025-05027, 05023, 05022, 04257, 04251, 04250, 04235, 04166, 01227, 01220-01225, 01217, 01197, 01196, 05506, 05486, 05485, 05453, 05450, 05445-05448, 05442, 05439, 05435, 05431, 05429, 05425, 05424, 05419, 05416, 05299, 05295-05298, 05277, 05273, 05272, 05268-05270, 05265, 05264, 05263, 05259, 05251, 05219, 05218, 05188, 05174, 05169, 05155-05157, 05145-05148, 05137, 05122, 05075, 05059, 05057, 05056, 05053, 05005, 05507, 05487-05489, 05483, 05482, 05480, 05477-05479, 05471-05475, 05466-05469, 05462, 05460, 05459, 05455-05457, 05452, 05267, 05266, 05194-05197, 05191, 05190, 05119, 05118, 05084, 05080, 05077, 05073, 05061-05064, 05054, 05011, 05010, 06804, 06454, 06450, 06446-06449, 06423, 06417, 06403, 06402, 06384, 06383, 06366-06374, 06362, 06358, 06357, 06352, 06350, 06350, 06346-06348, 06344, 06343, 06341, 06340, 06339, 06327-06337, 06322-06325, 06320, 06318, 06315, 06312, 06311, 06305-06308, 06302, 06301, 06295-06298, 06277, 06219-06223, 06217, 06215, 06211, 06210, 06205, 06204, 06200, 06199, 06190, 06168, 06162, 06161, 06159, 06113-06115, 06109-06111, 06101, 06100, 06084, 06057, 06052, 06049, 06047, 06046, 06044, 06042, 06041, 06029-06039, 06002-06025, 06000, 06424-06427, 06419-06422, 06414-06416, 06410-06412, 06408, 06406, 06405, 06400, 06381, 06279, 06278, 06276, 06271-06274, 06225, 07595-07598)] within 30 days from surgery, excluding the date of surgery and outside of periods spent in the ICU.

Table 3a: ERV reasons identifications and classification

System	Subcategory	ICD-9 Codes
Infectious	Skin and soft tissue	6829, 6822, 6820, 9583, 6869
	Generalized infection	7806, 9985, 1369, 389, 388
	Genitourinary tracts infection	5990, 5959, 5950, 5901, 6143,1121
	Respiratory tract infection	4639, 4661, 340, 4609, 119, 4869, 4859, 4871
	Gastrointestinal tract infection	99, 93, 91, 90, 92
	Nonspecific organisms	419, 1023, 1024, 88
	Peritonitis	5672 and 5671
Neoplasms	Colorectal neoplasm	1539, 1538, 1536, 1533, 1531, 1530, 1975, 1540, 1548
	Unspecified neoplasm	2349, 2398, 1991
	Intestine neoplasm unspecified	2113, 1529, 1599, 1590
	Respiratory neoplasm	1629
	Hematology neoplasm	2020
Endocrine, nutritional and metabolic diseases, and immunity disorders	Glucose disorder	2512 and 2500
	Other metabolics disorder	2769, 2765, 2768, 2767, 2740, and 2749
Disease of blood and blood-forming organs	Anemia	2859
	Other disease of blood	2890, 2899 and V182
	Coagulation defect	2869 and 2865
	Disorder of white blood cell	2889
Mental disorders	Neurotic, personality, and nonpsychotic disorders	3000, 3078, 3091, 3092, 3109, 7805, 3129
	Psychosis	2900, 2902, 2909, 2910, 2949, 2989
Diseases of the nervous system and sense organs	Symptoms of nervous system	7800, 7802, 7819, 7803, 7804, 7809, 7810, 7840
	Eye, ear, nose and throat	3699, 3810, 3820, 3804, 3892
Diseases of the circulatory system	Diseases of peripheral circulation	4479, 4409, 4439, 4449, 4553, 4590, 4571, 4599, 4580, 4589, 4519, 4511, 4512, 4510, 4518
	Arrhythmia	4278, 4273, 4275, 4279, 4270
	Ischemic heart disease	4119, 4139, 4149, 4140, 4109
	Cerebrovascular disease	4369, 4359, 4340, 4349, 4371,4379
	Symptoms of circulatory system	7855, 7851, 7852, 7989, 7981
	Heart failure	4289, 4281, 4280
	Hypertensive disease	4029, 4019, 4011, 4010
	Disease of pulmonary circulation	4151
	Other forms of heart disease	4249, 4291, 4299
	Mitral valve disease	3940
Diseases of the respiratory system	Symptoms of pulmonary system	7860, 7865, 7862, 7991
	Chronic pulmonary obstructive disease	4909, 4919, 4929, 4930, 4960,4969
	Other disease of pulmonary system	5184, 5185, 5188, 5119, 5191
Diseases of the digestive system	Symptoms of gastrointestinal system	7511, 7870, 7879, 7890
	Intestinal obstruction	5603 and 5609
	Other diseases of intestine and peritoneum	5621, 5699, 5640, 5693, 5641
	Noninfectious gastroenteritis	5589
	GI bleed	5789, 5781, 5780
	Disease of upper GI	5273, 5301, 5339, 5350, 5361, 5374, 5355, 5368, 5309, 5354, 5369
	Anorectal disease	5651, 5691, 5694, 5650
	Hernia of abdominal cavity	5529, 5509, 5532, 5539
	Noninfectious Peritonitis	5678 and 5679
	Hepatopancreaticbiliary system	5751, 5779, 5715, 5760
	Appendicitis	5419
Diseases of the genitourinary system	Symptoms of urinary system	5997, 7882, 7881
	Renal failure	5869, 5849, 5859
Diseases of the skin and subcutaneous tissue	Symptoms of skin system	7821 and 7823
	Skin disorder	7089, 6860, 7099, 6923
Diseases of the musculoskeletal system and connective tissue	Rheumatism	7273, 7289, 7291, 7295
	Dorsopathy	7242, 7245, 7249
	Arthropathy	7169, 7159, 7199
	Other disorder of bone & cartilage	7339

Table 3b: ERV reasons identifications and classification

System	Subcategory	ICD-9 Codes
Injury and poisoning	Injury to nerve and spinal cord	9598 and 9599
	Complication of surgical and medical care	9973 and 9989
	Contusion with intact skin surface	9249, 9232, 9229, 9245, 9222
	Unspecified effect of external causes	9953
	Fractures of extremity	8140, 8120, 8248, 8208, 8209, 8210
	Internal injury of thoracic, abdomen & pelvis	8636, 8640, 8690
	Fracture of unspecified bone	8299 and 8290
	Fracture of skull	8020
	Fracture of chest	8074
	Fracture of pelvis	8080
	Sprains of joint and adjacent muscle	8470
	Injury to blood vessel	9018
	Toxic effect of substances	9899
Wound	Nonspecific wound	8798, 8797, 8799, 9983, 8792, V583
	Open wound of extremity	8809 and 8949
	Intracranial and skull injury	8540 and 8730
Non specific General symptoms		7807, 7992, 7993, 7979,V700
Unspecified codes		V999, V725, V589, V728, V670, V729, 7893, 7899, V250, V819
Missing		No code