# Evaluating Patient Selection for Surgery in Older Patients with Non-Metastatic Colorectal Cancer in Ontario: a Population-Based Cohort Study

Richard Hu

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School of Epidemiology and Public Health
Faculty of Medicine

University of Ottawa

# ABSTRACT

## BACKGROUND

Surgeons are faced with an increasing number of patients over the age of 80 presenting with non-metastatic colorectal cancer (CRC). Justifying major surgery in a comorbid and frail population requires individualized decision making and remains a challenge for surgeons. Few studies compared survival in these patients with and without surgery, but all had important biases. In addition, no study has evaluated survival from a surgeon's case selection perspective. This study evaluated the quality of patient selection in Ontario octogenarians and nonagenarians with non-metastatic colorectal cancer by comparing survival by surgery status in important patient subgroups.

## METHODS

A retrospective population-based cohort study was conducted using population-based health administrative data in Ontario, Canada from 2010 to 2020. We included all patients aged 80 and over with stage I-III colorectal cancer. We first conducted an unadjusted analysis using methods described by Simon and Makuch, then we used a proportional hazards model to measure the association of surgical cancer resection with all-cause survival adjusted for: patient age, sex, and frailty; cancer stage and location; and year. Surgical status was a binary variable expressed as a time-dependent covariate. Interactions between surgical status and all other covariates were included. These results were visualized using heat maps.

## RESULTS

We identified 5782 patients; 4779 underwent elective colorectal surgery and 1003 did not. The surgery group was younger (84.4± 4.5 vs 86.9± 3.6), had more colon/recto-sigmoid cancer (83.7% vs 62.6%) and the difference in frailty between the two groups was small (standardized difference 0.21). Patients selected for surgery had significantly improved survival in almost all subgroups including stage I to II colon and rectal cancer and almost all patients with stage I-III colon cancer. Survival benefit of surgery was greatest in stage 1 disease and progressively decreased with stage 2 and 3 disease. Both male and female patients with stage III rectal cancer having increased levels of frailty undergoing surgery did not have better survival. The most important covariates associated with survival (from most to least important) were surgery, frailty, age, stage, and sex. Tumor type had the smallest independent influence on survival.

## CONCLUSION

Surgeons in Ontario are very good at identifying older patients with colorectal cancer in whom surgery improves survival. Age and frailty alone should not preclude patients from being considered for surgery.

# TABLE OF CONTENT

# A.INTRODUCTION

### *A1. Surgical Stress in the Older Population*

Major surgery can be conceptualized as an acute "controlled trauma". This "trauma" is followed by a complex interplay of neuroendocrine, metabolic, coagulatory, inflammatory, and immune system cascades that result in the body healing.[1-3] Aging alters the physiological responses to surgical stress. Advanced age is associated with a proinflammatory state, decreased adaptive immunity, and increased innate immunity which can all decrease one's ability to heal.[4, 5] Understanding the impact of surgical stress on the older population is important since the decision to offer invasive surgery depends partially on the individual's ability to recover from surgery.

Frailty has emerged as an important factor in assessing a patient's fitness for surgery and represents an important metric of operative risk.[6] Frailty is a multidimensional syndrome defined by a progressive reduction in physical reserve, energy, and cognitive breadth that coexists with other age-related and disease-related deficits which accumulate within multiple domains. Frailty impairs an individual's ability to cope with stressors such as surgery.[7, 8] It is most prevalent in the older population, with age being most strongly associated with frailty.[9, 10] Data show that a frail patient is more likely to experience many adverse outcomes including: serious surgical complications; prolonged hospital stay; higher 30-day readmission rate following surgery; loss of independence with increased likelihood of being discharged to an institutional facility; and reduced 1-year survival.[11-14] One of the surgeon's major roles is to understand a patient's fitness for surgery and avoid offering surgery to those with reduced physiological reserve who have an unacceptably high probability of succumbing to perioperative complications. This concept is illustrated in Figure 1.

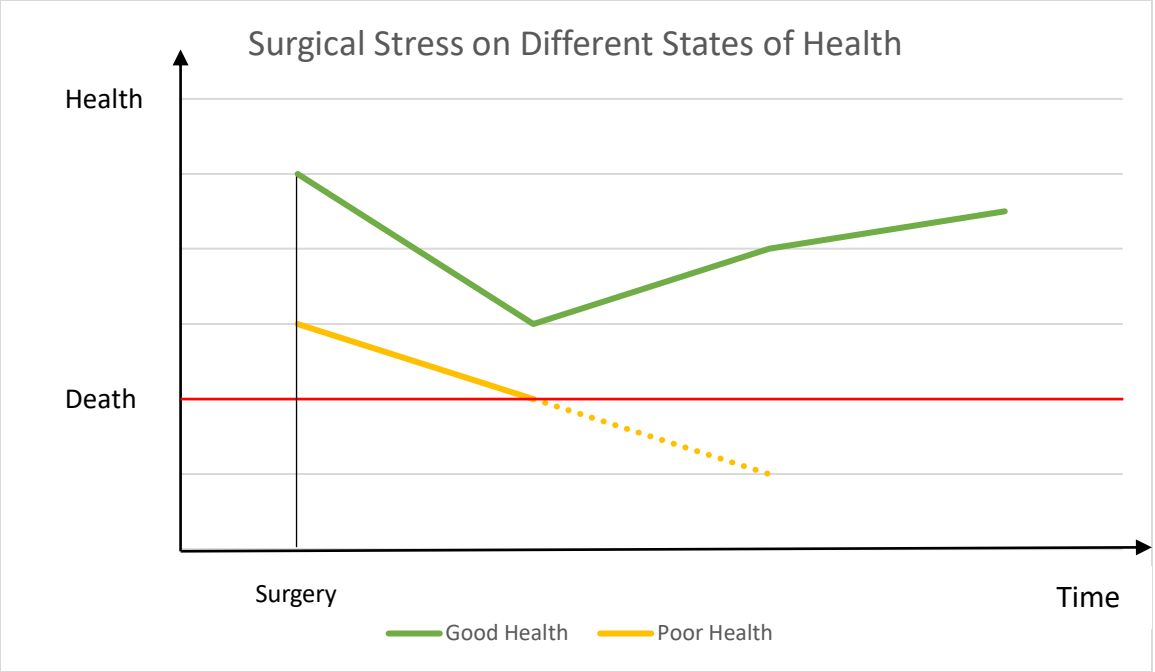



**Figure 1:** The vertical axis patient health levels with death occurring when they fall below the horizontal red line. The horizontal axis represents time. Following surgery, all patients experience a drop in their health. While patients with good health (green line) have enough health reserve to recover, those with poor health (yellow line) do not and can succumb to the health stress of surgery.

### *A2. Aging Population and Colorectal Cancer*

In the 2021 Statistics Canada census, 4.5% of Canadians were aged 80 years and older.[15] Globally, the number of people in this age range is projected to increase more than threefold between 2017 and 2050, from 137 million to 425 million.[16] Concurrently, it is estimated that 6.2% of all Canadians will develop colorectal cancer (CRC) during their lifetime, with incidence risk rising sharply with age.[17, 18] The combination of an aging population and increased CRC with age means that CRC prevalence will continue to rise with more elderly people having the disease.

Rising volumes of older people with CRC will increase the prevalence of difficult decisions regarding whether surgery should be used to treat CRC in older patients. Treatment algorithms for CRC are well established in today's literature. However, as discussed in Section A1, treatment decisions in older people are more complex due to an increased prevalence of co-

morbidity and greater frailty causing higher rates of postoperative morbidity and mortality.[19, 20] The International Society of Geriatric Oncology (SIOG)-2013 task force aimed to update the existing expert recommendations regarding CRC treatments in older patients and reviewed data on geriatric assessments of oncology patients.[21] They identified a paucity of data in this patient population with inadequate data available to make recommendations. They therefore urged the development of a separate treatment guideline for older patients with CRC.

Colorectal cancers, like most solid tumors, are usually staged with a system devised by the American Joint Committee on Cancer (AJCC). It is composed of T stage (whose value indicates the depth of penetration across the intestinal wall), N stage (indicating nodal status) and M stage (coding the presence of distant metastasis). Each potential combination of these 3 variables is grouped into 1 of 4 stages.[22] Cancer staging systems convey prognosis to both patients and clinicians and serves as the basis for treatment decisions, clinical trial eligibility, and surveillance programs.

In the current surgical literature, the only cure for non-metastatic colorectal cancer (M0 disease) involves a radical surgical resection.[23] As clinicians encounter a growing number of older patients with non-metastatic colorectal cancer, justifying major surgery in a potentially comorbid and frail population with a possibly limited life expectancy requires individualized decision making. As indicated in the SIOG-2013 task force report, there is a paucity of literature around natural disease progression without surgical intervention to guide the treatment discussions.

### *A3. Current Literature on Survival Comparisons in Older Colorectal Cancer Patients*

Very few studies have examined outcomes in patients over the age of 80 with non-metastatic colorectal cancer. A recent systematic review of published studies comparing non-operative to operative management of resectable colorectal cancer in the very old (80 and older) demonstrated very limited outcome data in the non-operative group.[24] This systematic review identified only 4 studies that measured survival in elderly patients with non-metastatic disease by surgical management (Table 1). Among the 4 studies, two used national cancer registries (SEER and IKNL-Netherlands),[25, 26] and the other were single-center retrospective analyses.[27, 28] Bhangu et al. used the SEER database to investigate the 5 year cancer-specific survival and overall survival of adult patients over the age of 18 with rectal cancer. In their subgroup of

patients over the age of 80, they found significantly worse outcomes in patients with non-operative treatment with hazard ratios for death of 6.78 (95%CI 1.05-5.56), 3.46 (2.88- 4.16), and 2.05 (1.60-2.64) for stages 1, 2, and 3, respectively. These hazard ratios were adjusted for sex, grade, year, total lymph node harvested and radiotherapy use. Due to the limitation of SEER data, important variables such as comorbidity and frailty were not measured. Similarly, Mazzotti et al. used the Dutch IKNL-Netherlands administrative database to measure potential years of life lost (YLL) due to colorectal cancer in a nationwide cohort of patients aged over 80. The YLLs were consistently and significantly *greater* in the non-operative group for stage 1-3, for patients between 80-85 and 86-90+. For example in 80-85 year olds with stage 1 disease, the surgical group YLL was 0.2 compared to 4.4 in the non-operative group (Table 1). Again, the analysis was limited because of the absence of patient comorbidity data due to the inherent limitation of this database. Franklyn et al. performed a single-center retrospective analysis to establish the natural history of patients over the age of 80 with non-metastatic colorectal cancer who underwent non-operative management in comparison with those who underwent operative management. They found that regardless of comorbidity (Charlson comorbidity index [CCI]), survival was better in the operative group in stage 1-2. However, they found that in patients with stage 3 disease with significant comorbidity (CCI of 9 or above), survival was not statistically different between the two groups. In Kim et al.'s single-center retrospective analysis, surgery group had significantly better survival than the no surgery group but the surgery group had better ECOG performance status with lower ASA grades. No subgroups were analysed to control for these confounders.

As expected, these non-randomized studies found that outcomes are better in the operative group. However, two major biases in these survival analysis studies must be considered when comparing outcomes for operative and non-operative patients. **First**, as discussed above, these studies are at risk of unresolved confounding between treatment groups due to poor adjustment of baseline factors – such as baseline functionality and frailty – that can influence outcomes in cancer patients. In fact, a surgeon's decision to *not* offer surgery to a patient with a surgically curable disease likely reflects their identification of high-risk patient characteristics that will increase the risk of poor post-operative outcomes to unacceptable levels. The factors driving such decisions are likely difficult, if not impossible, to obtain from health administrative data, disease registries, or even chart review. Two of the 4 studies comparing

outcomes by surgical status in elderly CRC patients (Table 1) adjusted for patient comorbidity using Charlson and ASA scores. However, these values are weak frailty measures.[29] Therefore, directly adjusting for frailty is important to help address selection bias when comparing operative to non-operative patients with resectable disease.

A second unaddressed bias in all Table 1 studies is time-dependent bias, also known as the immortal-time bias. This bias occurs when there is a delay between diagnosis and treatment group allocation, in this case surgical vs. non-surgical. [30, 31] All patients without surgery are assigned to the non-surgical group. Therefore, any patient who dies before being operated upon – or even assessed for operation – would be assigned in the analysis to the non-surgical group. As a result, all such deaths will be assigned to the non-surgical group. This will make outcomes in the non-surgical group appear worse than those in the surgical group and return a biased benefit of the intervention. One can attempt to account for time-dependent bias by expressing the intervention as a time-dependent covariate. Failure to account for time-dependent nature of treatment group classification is termed 'time-dependent bias'; it is common in published survival analyses.[30]

As such, patient selection understandably represents a significant challenge for surgeons. A surgeon's decision to offer a major abdominal surgery for colorectal cancer depends on different factors including patient preference, tumor characteristics, patient co-morbidity, and – perhaps most importantly – the surgeon's "end-of-bed" assessment of patient's ability to tolerate surgery. This decision likely goes beyond the arithmetic of frailty indices, survival nomograms, performance status scales (such as the Eastern Cooperative Oncology Group scale), or other measures calculating patient's surgical risks.[7, 32]

All patients who receive operative treatments in colorectal cancer survival studies have passed a surgeon's "eye test"; their surgeon concluded that the morbidity of an invasive abdominal, irrespective of that patient's comorbidities, could be survived by that patient making surgical tumour resection the best path of action. As a result, patients undergoing surgery likely include those with a better baseline health status. This observation represents a selection bias that is almost impossible to account for in observational studies that compare outcomes by surgical status in elderly colorectal cancer patients.

### *A4. Rationale for This Study and Its Objectives*

As surgeons encounter an increasing number of patients aged over 80 with non-metastatic colorectal cancer, the decision to offer surgery becomes increasingly complex as these older patients have increased frailty and greater likelihood of perioperative complications. Current studies (Table 1) suggest that surgery is associated with improved outcomes; however the lack of accounting for time-dependent bias and unresolved confounding makes these comparisons potentially and severely flawed. While the first bias (time-dependent bias) can be addressed with proper analytical technique, the latter (unresolved confounding) cannot be solved. Therefore, it is likely impossible to conduct an unbiased observational study comparing outcomes in older patients with non-metastatic colorectal cancer patients by surgical status.

Instead, we will use the survival data comparing these two groups by surgical status to measure the quality of patient selection for surgery in this population in Ontario. In other words, do the elderly patients chosen by surgeons to undergo surgery live longer compared to their non-surgical counterparts? Are there groups of patients who were operated upon who did not significant improvement in outcomes? These questions have not been examined in the currently surgical literature.

As such, this study will use population-based administrative data to compare the outcomes of octogenarians and nonagenarians diagnosed with non-metastatic colorectal cancer who underwent surgical resection of their cancer to those who did not undergo surgery. By comparing these outcomes, the study will evaluate the quality of patient selection by surgeons and referring physicians. We are especially interested in whether subgroups of patients exist in whom surgery does not improve survival.

**Table 1**. Summary of studies measuring outcomes in octogenarian patients with non-metastatic colorectal cancer by surgical status

| 1st Author (Year) | Country | Data type | Sample size | | Adjusting Covariates | Time - dependent analysis | Out-comes | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | Surg-ery | No Surg-ery | | | | |
| Bhangu[25] (2014) | USA | Population-based cancer registry (SEER) | 7440 | 1679 | Age, surgical resection type, histology, differentiation, AJCC stage, radiotherapy use, total lymph nodes harvest | No | CSS OS | • Rectal cancer only<br>• OS worse in non-operative group for all stages<br>• No comorbidity or frailty data |
| Mazzotti[26] (2019) | Nether-lands | Population-based cancer registry (IKNL) | 22114 | 4492 | Age, gender, tumor stage, year of diagnosis, location and morphology, chemotherapy or radiation therapy | No | Year life lost (YLL), OS | • *describe difference in YLL b/w groups*<br>• No comorbidity or frailty data |
| Franklyn[28] (2020) | UK | Prospective cancer registry | 275 | 132 | Age, sex, TNM stage, location, **Charlson comorbidity index, ASA score** | No | OS | • Worse OS in non-operative group *except* with high comorbidity index (6-8) and stage 3 |
| Kim[27] (2021) | Korea | Retrospective chart review | 65 | 19 | Age, sex, **comorbidity disease** (1- cardiovascular, 2- cerebral, 3- pulmonary, 4-renal), BMI, hemoglobin, | No | OS | OS worse at 3 years in non-operative group |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | CEA, **ECOG** performance status, **ASA**, tumor location, clinical stage, lymph node status, histology type, perforation | | | |

SEER= The Surveillance, Epidemiology, and End Results Program (US) ; AJCC= American Joint Committee on Cancer ; CSS= Cancer Specific Survival; OS= Overall Survival; CEA= Carcinoembryonic Antigen ; ECOG= Eastern Cooperative Oncology Group; ASA= American Society of Anesthesiologists; IKNL= Netherlands Comprehensive Cancer Organization; TNM= T- extent of the tumor, N- extent of spread to lymph nodes, M- presence of metastasis;

# B. METHODS

### *B1. Datasets Used for the Analysis*

This is a population-based retrospective cohort study using linked health administrative data from the province of Ontario, Canada. The province has a population of over 13 million residents. All hospital and physician services are covered by publicly funded health insurance. Data generated during the provision of Ontario health care is stored at ICES, an independent, non-profit research institute that collates these patient data for health system evaluation and research. The data linkage and extraction were conducted by an ICES information specialist and an ICES scientist (CvW). All dataset linkages were deterministic (i.e. non-probabilistic) using encrypted health card numbers that were common to all datasets. Appendix 1 summarizes all datasets used in the analysis.

### *B2. Inclusion and Exclusion Criteria*

The cohort included all Ontarians diagnosed with colon or rectal cancer between January 1st, 2010, to December 31st, 2020 who were aged 80 or greater at the time of diagnosis. These people were identified in the Ontario Cancer Registry (OCR) as all patients with a diagnosis of colorectal cancer (OCR.TOPOG_CD). OCR captures all primary cancers in Ontarians.

We excluded several groups of patients from this cohort. **First**, we only included patients whose diagnosis of colorectal cancer was based on tissue. This was determined using the variable OCR.TOPOG_CD having a value of C18*, C19*, C20. Patients without histopathological evidence of disease were excluded because tissue diagnosis is needed to confirm malignancy. **Second**, we excluded patients without valid encrypted health card numbers since these were required to link to other datasets to create the analytical dataset.

**Third,** patients whose colorectal disease had a stage other than 1 through 3 were excluded. Disease stage is captured in OCR in the OCR.BEST_STAGE_GRP variable. Patients with AJCC stage 0 disease, meaning adenocarcinoma confined to the muscularis mucosa layer (i.e. malignant polyps), were excluded because best treatments of these lesions are unclear. Patients with AJCC stage 4 disease were excluded because surgery is typically not offered. OCR records **tumor AJCC-TNM stage** for almost 90% of all tumors. *Clinical stage* is that determined by physical examination, endoscopic evaluation, and different imaging modalities

such as computed tomography (CT) or magnetic resonance imaging (MRI). *Pathological stage* is determined by the surgical resection specimen and is only available for those who having surgery. OCR was tasked by provincial health authorities with staging CRC at the population level. Both pathological and clinical staging were captured from hospital medical records or regional cancer center records. From 2010-2017, OCR used the Collaborative Stage (CS), which is an adaptation of AJCC- TNM staging 7$^{th}$ edition that produced a "best" TNM classification using both clinical and pathological staging. Since 2018, OCR directly stages CRC using the AJCC- TNM staging 8$^{th}$ edition.

**Fourth**, we excluded patients who had their cancer diagnosed *following* a formal surgical resection. This would occur in patients who proceeded directly to surgical resection based on clinical data (e.g. symptoms or radiological findings) without histopathological confirmation of colorectal cancer. These patients were excluded since the study aimed to compare outcomes in patients based on surgical status following their diagnosis of colorectal cancer. Patients who had their cancer diagnosed *following* a formal surgical resection were identified by linking with DAD to identify all hospitalizations having a colorectal resection occurring in the 4 weeks *prior to* the histopathological diagnosis date of colorectal cancer. Typically, final pathology reports are generated within 1-2 weeks of sampling; therefore, 4 weeks would account for any delay from surgical resection to the final pathology report. Hospitalizations during which a laparotomy and colorectal resection occurred were identified as those having CCI code values of 1NM87*, 1NM89*, 1NM91*, 1NQ87*, 1NQ89*, 1NQ90* in variable DAD.INCODE.

**Fifth,** we excluded all patients who received their cancer surgery during emergent or urgent admissions. Surgical emergencies for cancer are difficult to treat and indications for surgery in these situations are difficult to determine using administrative data. In addition, emergency surgery is associated with significantly worse outcomes compared to elective surgery. As such, all surgeries with admissions category in SDS. ADMCAT having values of "E" (emergency) and "U" (urgent) were excluded.

**Finally,** we excluded patients who underwent radiotherapy as the initial treatment following diagnosis of colorectal cancer. Rectal cancer treatment has been evolving, especially over the last decade. Pre-operative radiation with chemotherapy, also termed "neoadjuvant treatment", has become a mainstay treatment for rectal cancer and is generally indicated for all T3+ disease.[33] In the event of complete tumor response to neoadjuvant treatment, there is

mounting research and acceptance to use a "watch and wait" approach, in which patients are monitored closely over time without surgical resection. Therefore, patients who received neoadjuvant treatment to the rectum were excluded since this approach is now considered curative. Patients with neoadjuvant therapy were identified by the variable ALR.INTENT_OF_RADIATION_TREATMENT, where the value is "N".

### *B3. Outcomes*

The study included one main outcome, ***all-cause survival***. All-cause survival was calculated as the number of days from the date of cancer diagnosis (OCR.DXDATE) to the end of observation. The end of observation was the earlier of death date (RPDB.DTHDATE) or the day patient observation was censored (due to end of study or last day of contact with the health care system). Patient observation was never censored prior to a death.

### *B4. Primary exposure covariate – colorectal resection*

The primary exposure variable of interest was whether patient underwent colorectal surgical resection with curative intent for their stage 1-3 colorectal cancer. These procedures varied between colon and rectal cancer due to differences in their treatment guidelines. Patients with **colon cancer** (including cancer localized to the sigmoid) were classified with surgical resection if any of the procedures listed in Appendix 1 were recorded in DAD within 6 months of cancer diagnosis. Colon cancer patients not meeting these criteria for surgical resection were classified as non-operative. Patients with **rectal cancer** were classified with surgical resection if any of the procedures listed in Appendix 1 were recorded in DAD within 12 months of diagnosis. Rectal cancer patients not meeting these criteria for curative surgical resection were classified as non-operative.

### *B5. Secondary Covariates*

Patient **age and sex** was determined from OCR at the time of colorectal cancer diagnosis.

**Tumor location** is important because it is a primary determinant of oncological surgical resections. For example, a colon cancer in the cecum undergoes a right hemicolectomy, whereas a cancer in the descending colon undergoes a left hemicolectomy, and a colon cancer near the rectosigmoid junction requires a low anterior resection. The surgical techniques for each of these

surgeries differ and are associated with different complication profiles. For this analysis, all tumors with locations in the rectum were classified as rectal cancers; all remaining tumours were classified as colonic including rectosigmoid cancers. OCR records topographic data of colorectal cancers (left colon, right colon, sigmoid colon, rectum) starting 2010, the date chosen as the start date for study inclusion. 2020 was chosen as the end date for study inclusion to allow sufficient follow-up time all cases.

**Patient frailty** can be defined as a "progressive decline marked by loss of function, loss of physiological reserve, increased risk of falls, delayed illness recovery, more frequent and longer hospital stays, and mortality." [6] There are several indices at ICES which use administrative data to directly or indirectly measure frailty including the Hospital Frailty Risk Score (HFRS), the hospital-patient one-year mortality risk (HOMR),[34] and the Charlson comorbidity index. The preoperative Frailty Index (pFI) is a frailty index developed by McIsaac et al. in 2019 that builds on the HOMR score.[35] It has been validated in both elective and emergency surgery settings and has been shown to be robust to missing data and variable substitution. The index is a continuous linear variable which includes 30 deficits spanning multiple domains (comorbidity, sensory, cognitive, psychosocial, disability, pharmaceutical). It is calculated by summing the points assigned for each deficit and dividing this number by 30 (the total number of deficits measured), as shown in Appendix 3. The pFI ranges from 0 to 1 with higher numbers indicating greater frailty. The pFI was calculated using %getpFI macro.

### *B6. Analysis*

All analyses and data manipulation were performed using SAS 9.4 (for Windows, SAS Institute, Cary NC). Study cohort was described by surgical status. Standardized differences were used to gauge differences between groups by covariates (age, sex, year of diagnosis, frailty score, cancer type and stage). Standardized differences (StD), also known as Cohen's S, is a measure to quantify the difference between the means of two groups, taking into consideration the standard deviation of each group. It is suggested that an StD of 0.2 represents a "small" effect, and SMD of 0.5 represents a "medium" effect, and StD of 0.8 represents a "large" effect.[36, 37]

Multivariable logistic regression was used to measure the independent association of all covariates (including patient age, frailty, patient sex, tumor location, tumor stage, and diagnosis year) with likelihood of undergoing surgery. Fractional polynomials were used to model non-linear associations between continuous covariates and the outcome. The %MFP8 algorithm from Sauerbrei et. al. was used to identify best fitting fractional polynomials.[38] This macro combines backward elimination with an adaptive transformation identification algorithm to select the best fractional polynomial transformation for each continuous variable's adjusted association with the outcome. Each polynomials included 1 term and consumed 2 degrees of freedom (1 for the algorithm and 1 for the variable).

To examine unadjusted association of surgery with time to death by other covariate levels, we used methods described by Simon and Makuch to adapt Kaplen-Meier methods for time-dependent variables. [39]

We conducted a survival analysis of time to all-cause death. Survival time was calculated as the number of days from cancer diagnosis to end of observation (the earliest of death date, censoring date [31 December 2020], or date of last encounter). Patient surgical status was a binary variable expressed as a time-dependent covariate. This means that each patient is assigned to 'no surgery' at the start of their observation. This status can change over time (i.e. it is 'time-dependent') if they subsequently underwent resection of their tumor subsequently in their observation. Cox proportional hazard regression models were used to obtain adjusted hazard ratios and 95% confidence intervals. We structured the analytical dataset using a counting-process format to model surgery, and its interaction with all other covariates as, as a time-dependent variable. We used a continuous variable transformation identification algorithm from Sauerbrei et. al.[21] to identify best transformations for modelling non-linear associations which had been modified to account for time-dependent covariates.[40] This algorithm combined backward elimination with an adaptive transformation identification algorithm to select the best fractional polynomial transformation for each continuous variable's adjusted association with time to death.

Our model building started by including all covariates and their interactions with surgery in the model. We then planned to exclude all interactions with p-value less than 0.2. Then the model was rerun, with main effects with p-values less than 0.4 being excluded. The contribution of each covariate to the final model was measured using the difference in the Akaike Information

Criterion (AIC) value of the complete model from that with the covariate of interest (and its interactions) removed. Variables strongly associated with time to death had greater difference values.

Our primary interest was to measure the independent association of surgical status with all-cause survival in all patient groups defined by covariates in the study (age, sex, cancer type (colon vs. rectal), cancer stage, and frailty score). This required measuring the *linear predictor* (i.e. the 'x-beta') of surgery in all patient subgroups. This was done by first creating a cohort of patients having all potential combinations of predictor variables (age 80 to 95, sex, frailty score 0 to 0.38, tumor type [colon or rectal], cancer stage [1 to 3], study year [2011 and 2019]). This dataset (containing 29 552 observations without any outcomes) was appended to the analytical dataset prior to running the final model; because they lacked outcomes, observations in the simulated data did not influence parameter estimates. The PROC PHREG step used to create the final model included an OUTPUT statement to output the linear predictor for all covariate combinations. Differences of this value between models with identical covariate values except surgical status returned the linear predictor of surgery for that subgroup. Exponentiating this value returned the hazard ratio for surgery's influence on survival in that subgroup. These values were visualized using heat maps.

# C. RESULTS

### *C1. Demographics:*

We identified 5782 individuals who were over the age of 80 between 2010 and 2020 diagnosed with stage I to III colon or rectal cancer (Table 2). The mean age was 84.9 years, with the "no surgery" group being slightly older (mean age 86.9 years [SD 4.5] vs. 84.4 years [SD 3.6]). The standardized difference for age was 0.61 which represents a medium- sized difference between the two groups. 54.7% of patients were female. Differences in frailty between surgical groups was surprisingly small, with a standardized mean difference in the preoperative frailty index pFI of only 0.23. There were 4626 patients (80%) with colon or rectosigmoid junction cancer while 1156 (20%) had rectal cancer. In total, 1003 (17.3%) of all patients did not undergo surgery; the majority of these patients (62.6%) had colon/rectosigmoid cancer. In contrast,

83.7% of patients getting surgery had colon/rectosigmoid cancer (StD= 0.49). Further characteristics of patients by surgical status are presented in Table 2.

**Table 2.** Cohort characteristics by surgery status

| **Characteristics** | **No Surgery** (N=1003) | **Surgery** (N=4779) | **Overall** (N= 5782) | **Standardized Difference*** |
|---|---|---|---|---|
| Mean Age (SD) | 86.9 (4.5) | 84.4 (3.6) | 84.9 (3.9) | 0.61 |
| Female | 567 (56.5%) | 2596 (54.3%) | 3163 (54.7%) | 0.04 |
| Preoperative Frailty Index Median (IQR) | 0.15 (0.08-0.22) | 0.12 (0.07- 0.18) | 0.12 (0.07- 0.18) | 0.12 |
| Colon or Rectosigmoid (vs Rectum). | 628 (62.6%) | 3998 (83.7%) | 4626 (80.0%) | 0.49 |
| Cancer Stage | | | | |
| I | 341 (34.0%) | 963 (20.2%) | 1304 (22.6%) | 0.32 |
| II | 369 (36.8%) | 2163 (45.3%) | 2532 (43.8%) | 0.17 |
| III | 293 (29.2%) | 1653 (34.6%) | 1946 (33.7%) | 0.12 |
| Median Observation Length in days (IQR) | 244 (75-643) | 1217 (547 – 2158) | 987 (370 – 1969) | 1.22 |

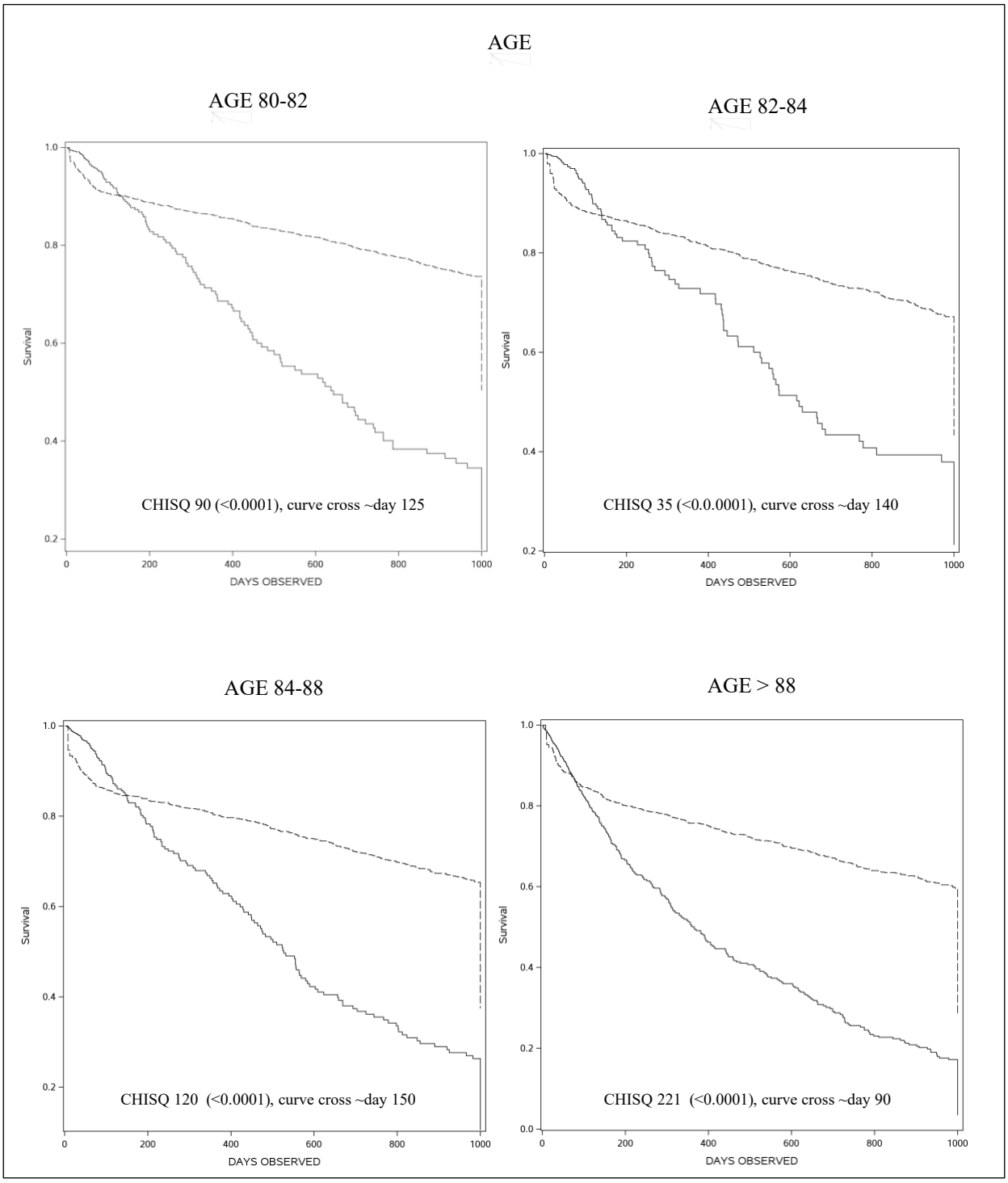
SD: standard deviation; IQR : interquartile range

*Standardized Difference interpretation: <0.2 very small; 0.2-0.5 small; 0.5-0.8 medium; >0.8 large

***C2. Survival by surgery status for all patients and sub cohorts***

Unadjusted associations between surgery and time to death was examined using the Simon and Kakuch method (an adapted Kaplan Meier analysis that accounts for time-dependent nature of stratification variables). Continuous variables (age and frailty) were analysed in quartiles (Appendix 5). Survival plots (with Chi square values to quantify survival differences between surgical groups) are presented in Figures 2a – 2e. Surgery was significantly associated with improved survival in all patients' groups defined by age, sex, frailty score, cancer type, cancer stage, and year. Each patient strata exhibited similar patterns regarding the influence of surgery on survival; survival in the surgery group initially dipped below that of those without surgery. However, between days 30 and 200 (as indicated on each figure), survival in the surgery group exceeded that of the no surgery group and remained superior throughout observation. In all groups, survival of those with surgery was significantly better than those without (with p-values of all chi-square values less than 0.0001). Of note, the surgery group's survival was better from day 0 in the stage 1 rectal cancer patients (Figure 2c).

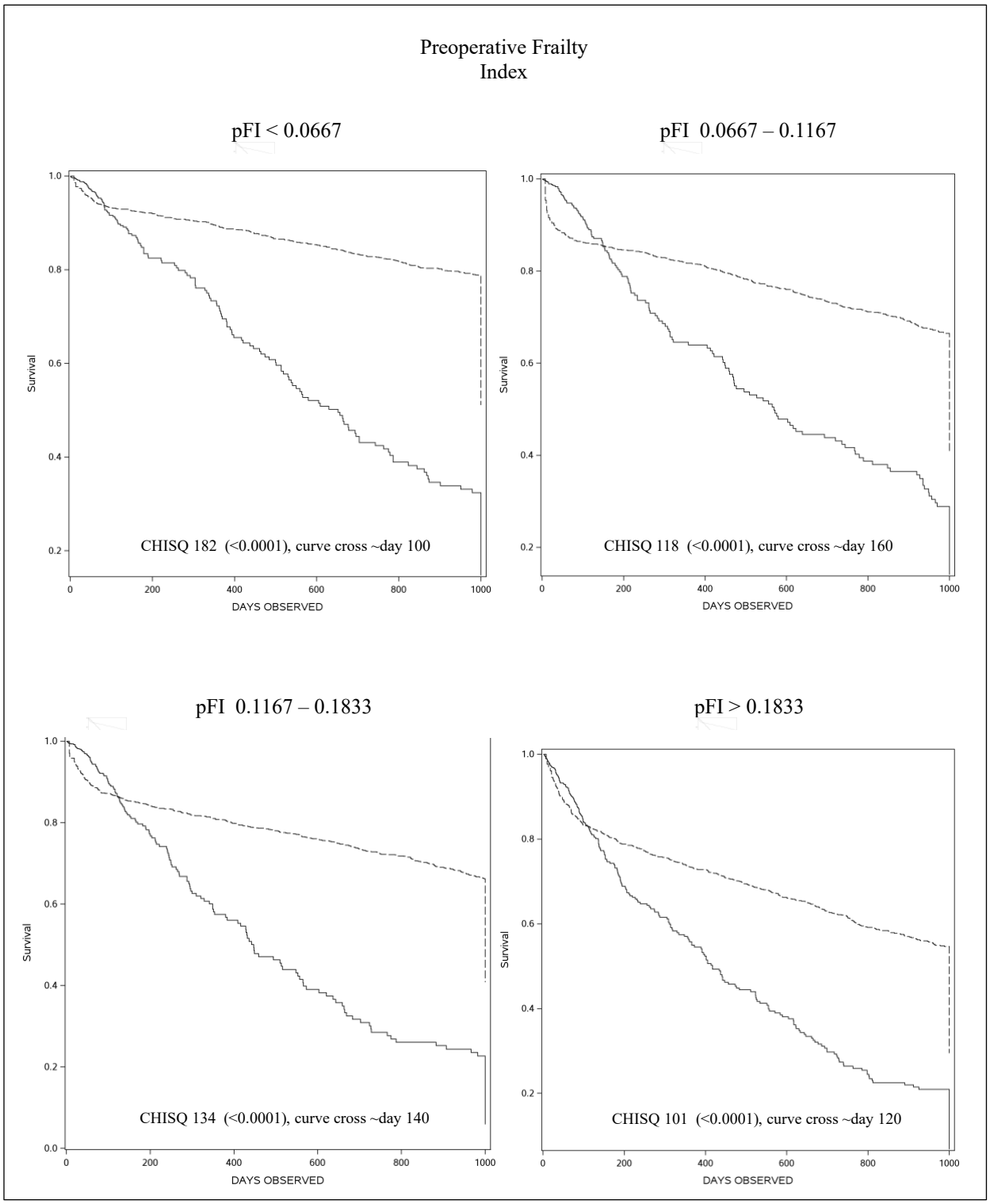
**Fig 2a.** Unadjusted survival by surgical status and age




x-axis: time in days; y-axis: proportion of people surviving

——— : no surgery group - - - - : surgery group

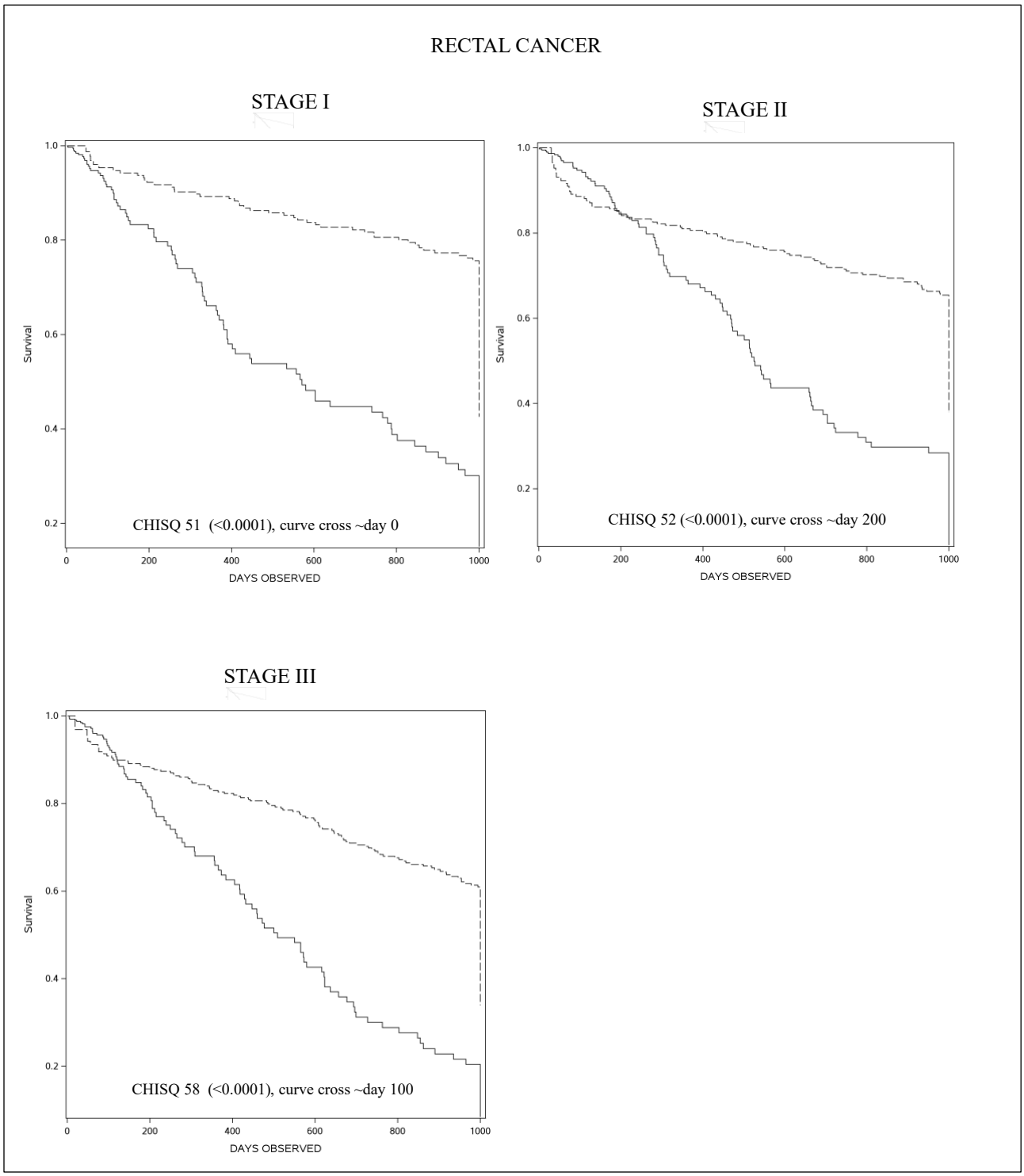
**Fig 2b.** Unadjusted survival by surgical status and frailty score




x-axis: time in days; y-axis: proportion of people surviving

——— : no surgery group - - - - : surgery group

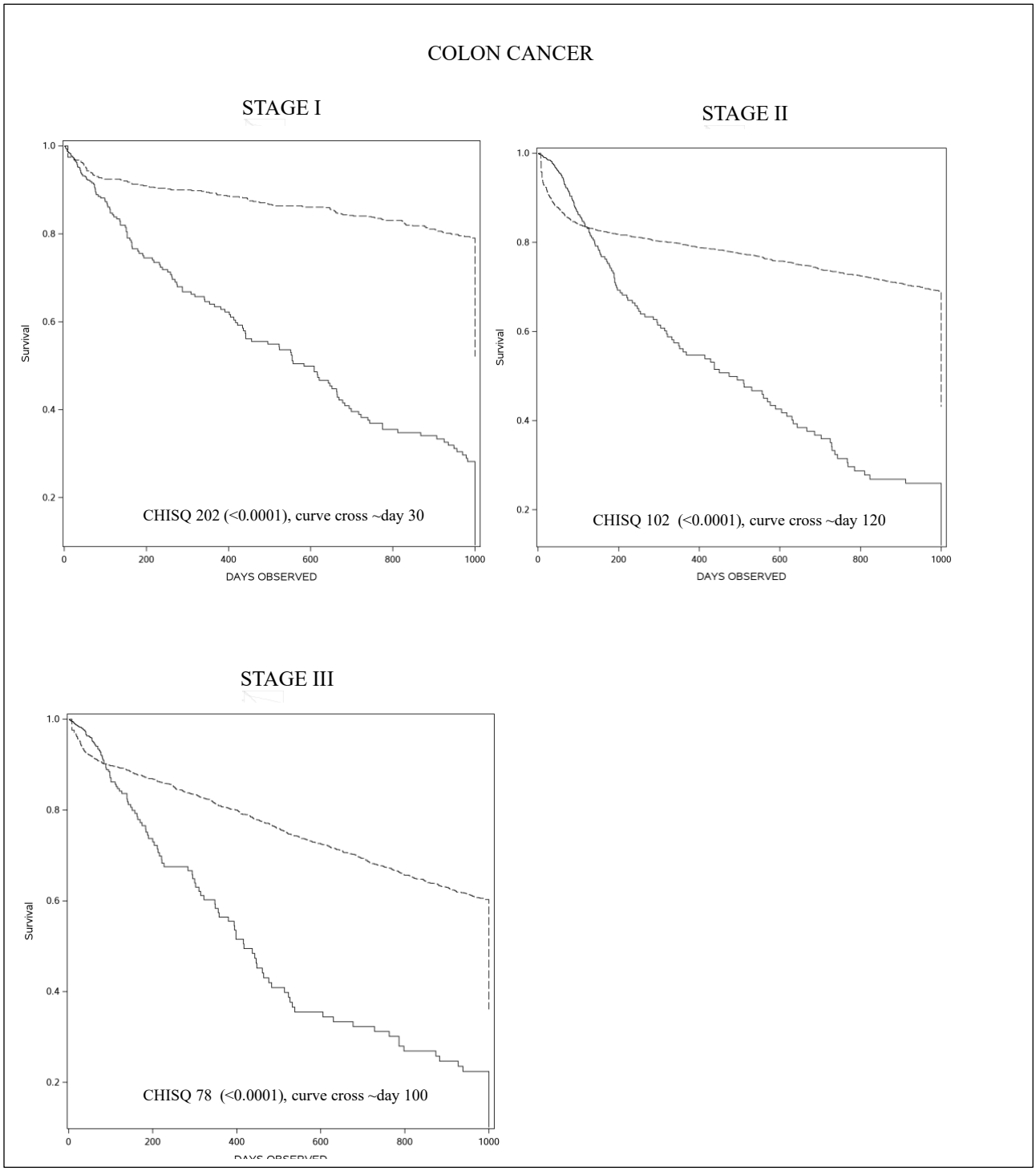
**Fig 2c.** Unadjusted survival by surgical status and rectal cancer stage




x-axis: time in days; y-axis: proportion of people surviving

——— : no surgery group - - - - : surgery group

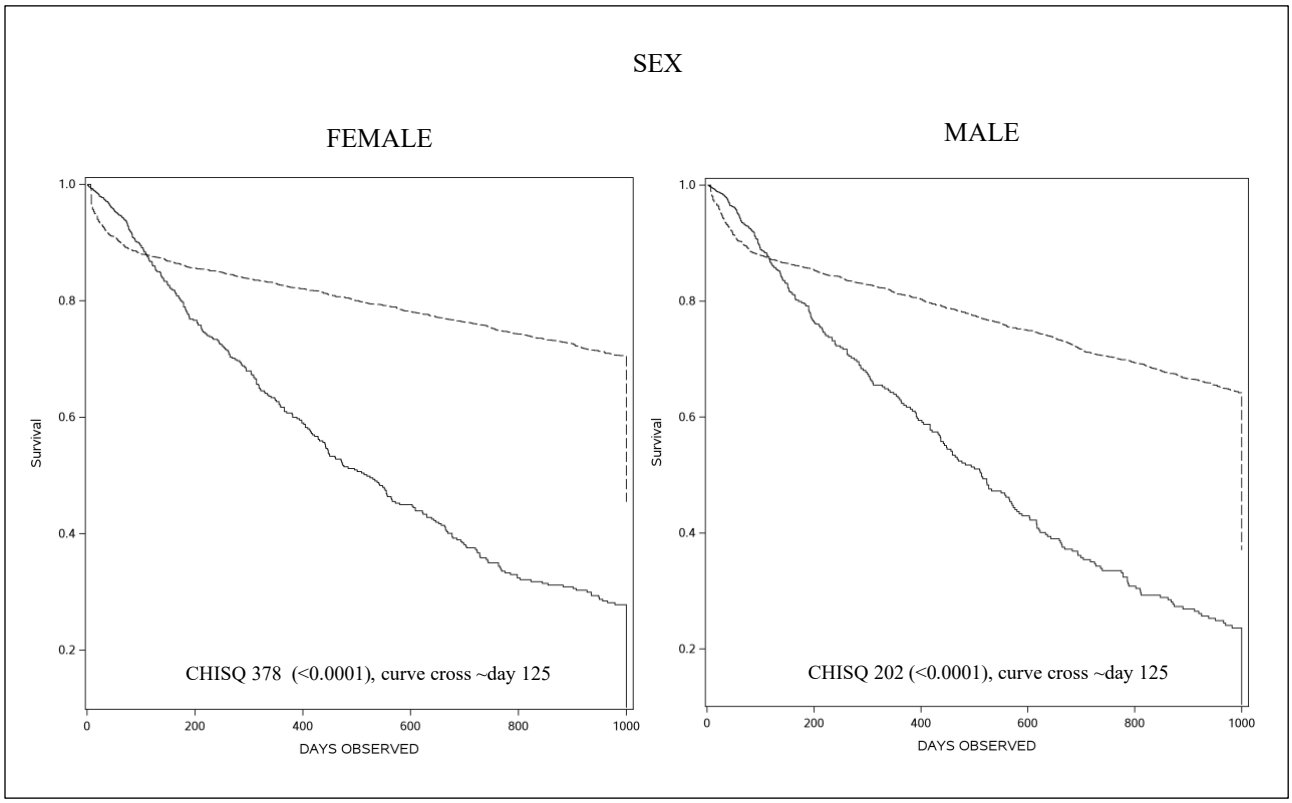
**Fig 2d.** Unadjusted survival by surgical status and colon cancer stage




x-axis: time in days; y-axis: proportion of people surviving

——— : no surgery group - - - - : surgery group

**Fig 2e.** Unadjusted survival by surgical status and sex




x-axis: time in days; y-axis: proportion of people surviving

——— : no surgery group - - - - : surgery group

### *C3. Adjusted influence of variables on time to death*

The adjusted final model is presented in Appendix 4. The table includes all included variables and their interactions terms, fractional polynomial transformations, parameter estimates, standard errors, chi-square statistics and hazard ratios. Since all the covariates are involved in interactions, interpretation of the parameter estimates (and their associated hazard ratio) is difficult. Section C5 presents these values graphically for each patient subgroup.

Having surgery, being female and more recent years of diagnosis were variables with a negative parameter estimate, which indicates that these variables had an adjusted association with *decreased* risk of death. In contrast, having colon (instead of rectal) cancer , stage 2 and 3 disease, increasing age and frailty had a positive estimate, meaning that these variables had an adjusted association with increased risk of death.

### *C4. Covariates ranked according to its adjusted association with time to death*

The importance of each variables adjusted association with time to death was measured by how much the Akaike Information Criterion (AIC) increased when that variable was removed from the complete model (Appendix 4); larger values in these AIC differences indicate a stronger association with all cause survival. The ranking is shown in Table 3, from the most important covariate (number 1) to least important (number 7). The most important variables associated with time to death were surgery, frailty, and age. Cancer stage was the fourth most important variable. Interestingly, location of the tumor (colon versus rectum) had the smallest independent association with all-cause survival in this cohort.

**Table 3.** Covariate influence on all-cause survival ranked

| Covariate and Rank | AIC | AIC Difference |
|---|---|---|
| 1- Surgery | 47617.0 | 382.1 |
| 2- Frailty | 47535.9 | 300.8 |
| 3- Age | 47492.0 | 257.8 |
| 4- Stage | 47328.5 | 93.4 |
| 5- Female | 47298.1 | 63.0 |
| 6- Year | 47274.0 | 38.9 |
| 7- Colon | 47247.6 | 12.4 |

Base Model AIC: 48460.7

### *C5. Survival heatmaps*

The association between surgery status and all-cause survival indicated by the final survival model was presented using heatmaps for each patient strata, shown the Figures 3a-d.

With few exceptions, all patients with **stage 1 and 2** cancers had significantly improved survival with surgery regardless of: cancer type; patient age or sex; frailty score; or surgical year. The only exception to this statement were males with stage 2 rectal cancer and very high frailty scores in the earlier surgical years (Figure 3c) whose survival benefit with surgery (HR~0.82) was not statistically significant.

All *female* patients with colorectal cancer having surgery had improved survival regardless of cancer type, age, sex, frailty score, or surgical year. This survival benefit of surgery

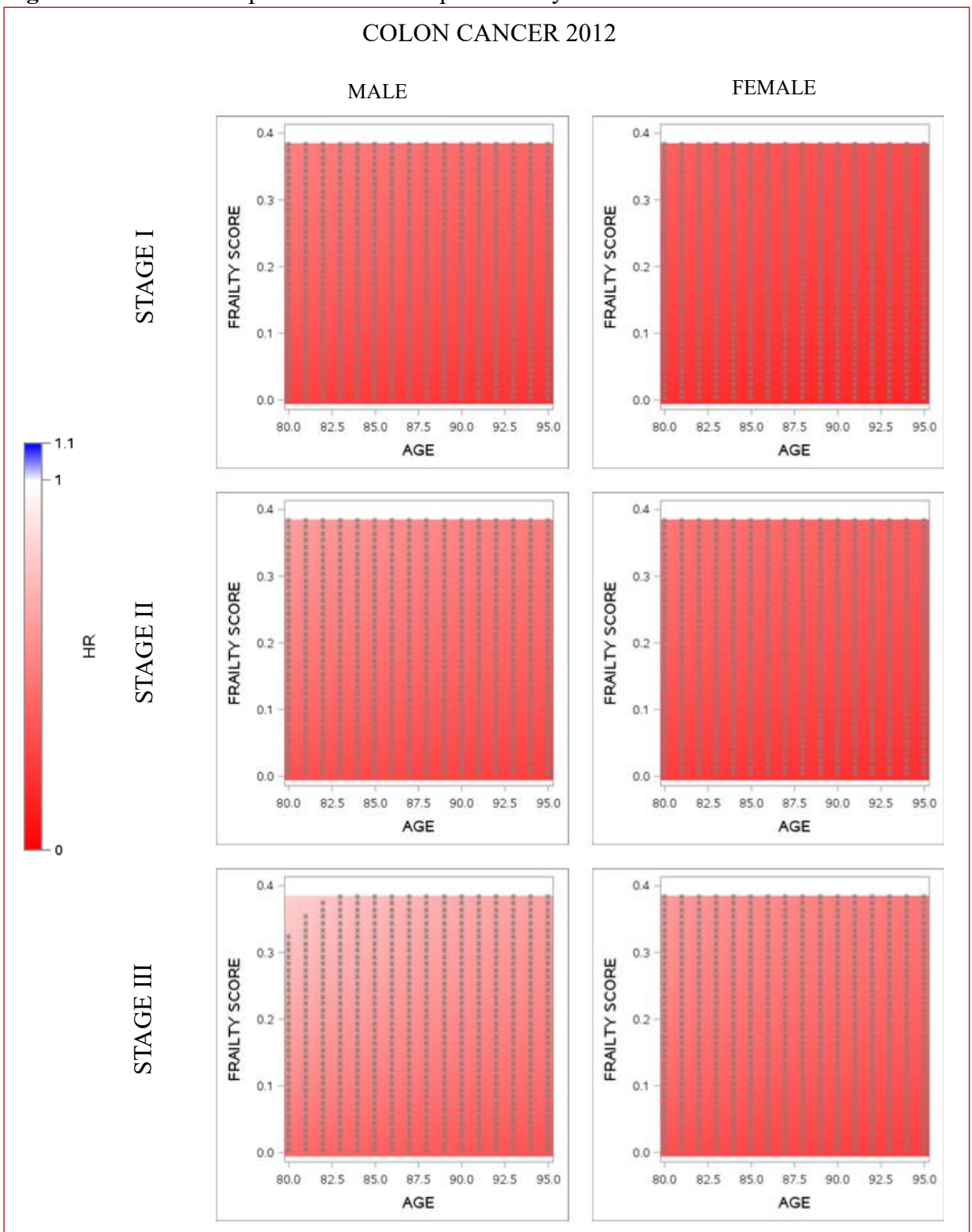
was statistically significant for all female patients except for the very frail with stage 3 rectal cancer in the early surgical years (Figure 3c).

All patients undergoing surgery for *colon cancer* had significantly improved survival regardless of age, sex, surgical year, and frailty score except for the very frail male patients in early years where statistical significance was lost (Figure 3a).

*Males* with **stage 3** rectal cancer undergoing surgery had significantly improved survival for all cancer type, age, sex, or surgical year when the frailty index was below 0.2; However, male patients with stage 3 rectal cancer did not have significantly better survival with surgery when frailty score exceeded 0.2 in younger patients.

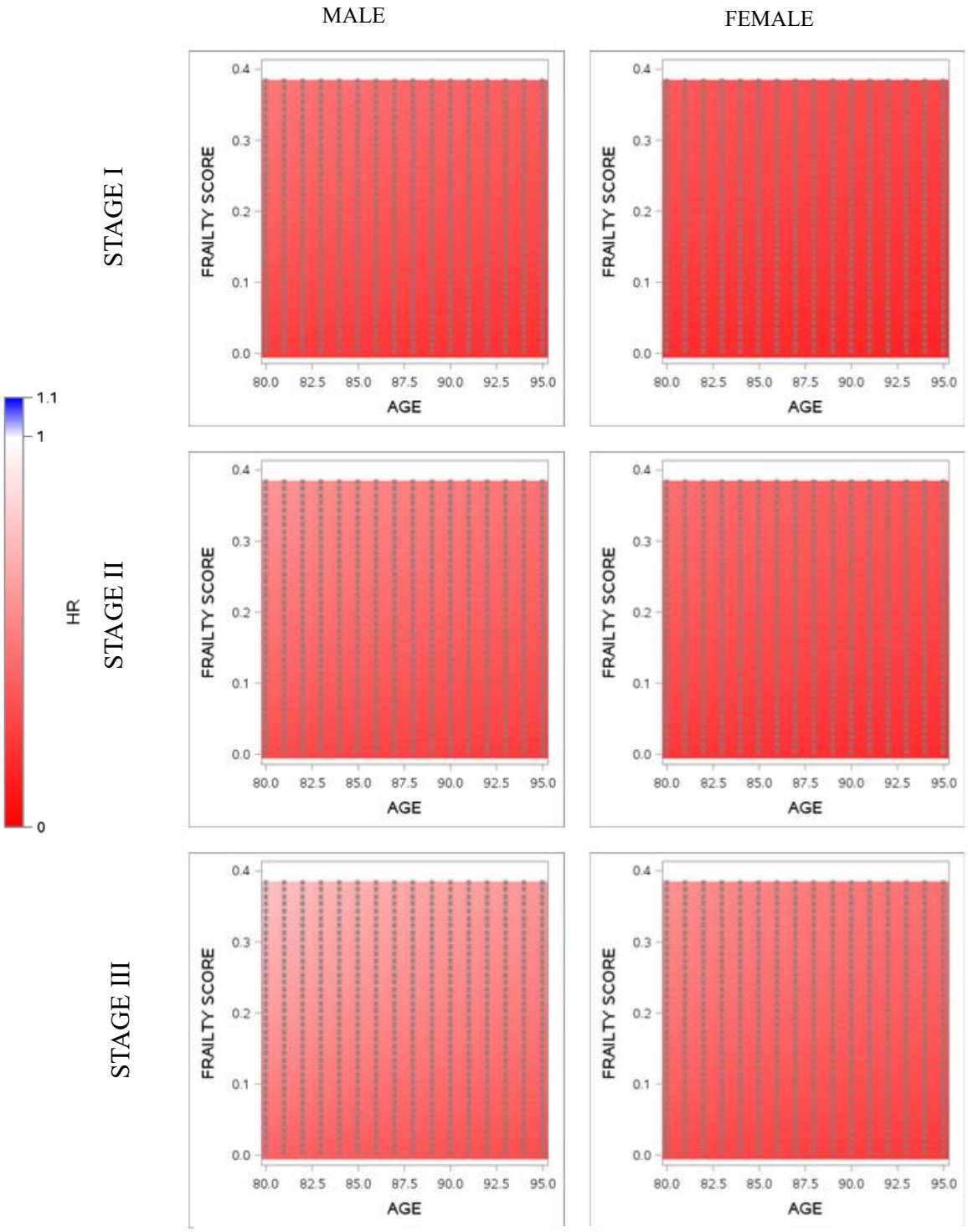
It is also important to note that despite statistical significance, the survival benefit associated with surgery decreased in both colon and rectal cancer with progressive stage, as well as progressive frailty in patients. This was shown with the shade of red, with deeper red signalling greater benefit.

**Fig 3a.** Survival heatmaps of colon cancer patients in year 2012



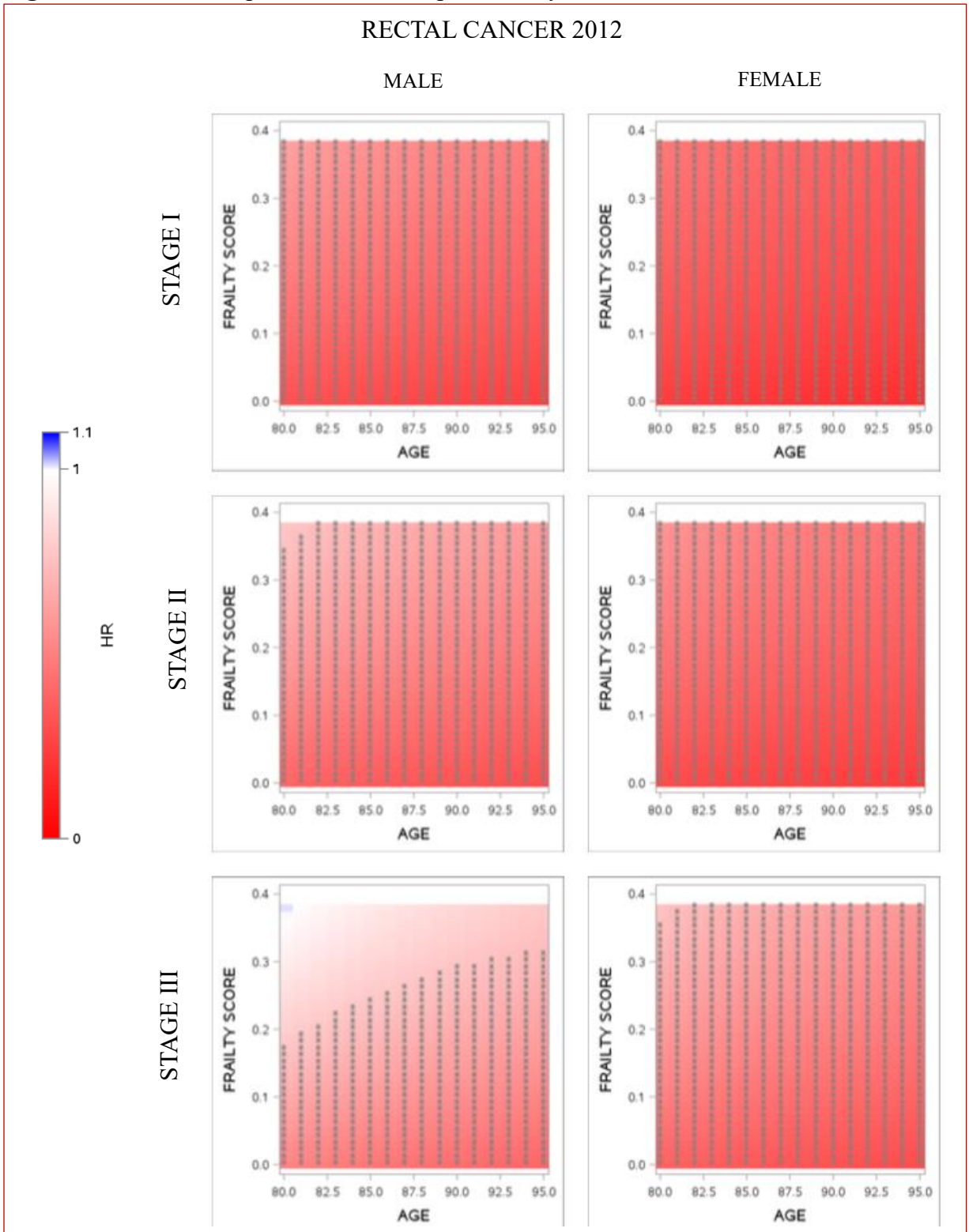

The x-axis: age; Y- axis: frailty. The colour at each x-y: the hazard ratio of surgery vs. no-surgery for that patient group. White representing a hazard ratio (HR) of 1. HR < 1 indicate improved survival *with* surgery with the reddest hue representing a hazard ratio of 0. HR > 1 indicate improved survival *without* surgery with the bluest hue representing a HR of 1.9. Coordinates with an asterixis indicate that HR has a p-value less than 0.05.

**Fig 3b.** Survival heatmaps of colon cancer patients in year 2019



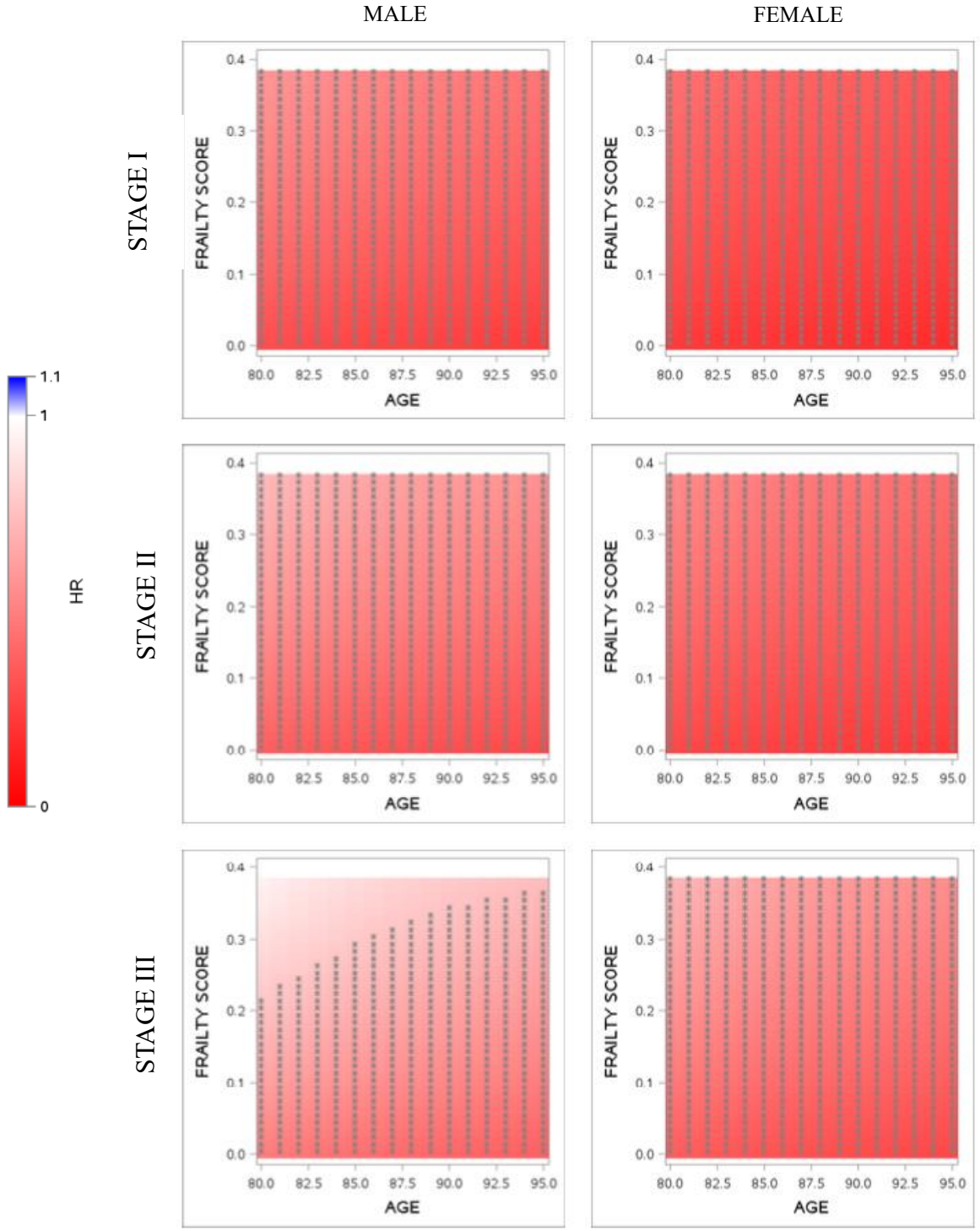

The x-axis: age; Y- axis: frailty. The colour at each x-y: the hazard ratio of surgery vs. no-surgery for that patient group. White representing a hazard ratio (HR) of 1. HR < 1 indicate improved survival *with* surgery with the reddest hue representing a hazard ratio of 0. HR > 1 indicate improved survival *without* surgery with the bluest hue representing a HR of 1.9. Coordinates with an asterixis indicate that HR has a p-value less than 0.05.

**Fig 3c.** Survival heatmaps of rectal cancer patients in year 2012




The x-axis: age; Y- axis: frailty. The colour at each x-y: the hazard ratio of surgery vs. no-surgery for that patient group. White representing a hazard ratio (HR) of 1. HR < 1 indicate improved survival *with* surgery with the reddest hue representing a hazard ratio of 0. HR > 1 indicate improved survival *without* surgery with the bluest hue representing a HR of 1.9. Coordinates with an asterixis indicate that HR has a p-value less than 0.05.

**Fig 3d**. Survival heatmaps of rectal cancer patients in year 2019




The x-axis: age; Y- axis: frailty. The colour at each x-y: the hazard ratio of surgery vs. no-surgery for that patient group. White representing a hazard ratio (HR) of 1. HR < 1 indicate improved survival *with* surgery with the reddest hue representing a hazard ratio of 0. HR > 1 indicate improved survival *without* surgery with the bluest hue representing a HR of 1.9. Coordinates with an asterixis indicate that HR has a p-value less than 0.05.

# E. Discussion

## E1. Summary

In this retrospective population-based cohort study, we identified 5782 Ontarians over the age of 80 who were diagnosed with stage I to III colon or rectal cancer from 2010 to 2020. Within this cohort, 4779 underwent surgery and 1003 did not. We found surgical status was the variable that had the strongest independent influence on survival, with survival significantly improving when surgery was provided in almost all patient subgroups defined by age, sex, year, cancer stage, and frailty. These data indicate that methods used to select which older patients with colorectal cancer should undergo surgery is very effective; with few exceptions, all patients offered and having surgery had better survival. Exceptions include: the very frail younger male patients with stage III colon cancer in the earlier years, the very frail younger male patients with stage II rectal cancer in the earlier years, and stage III rectal cancer (most notable in males with frailty index over 0.2). These data demonstrate that age and frailty alone should not preclude patients from being considered for elective colorectal cancer surgery and a surgeon's clinical judgement of a patient's candidacy for surgery is a key prognostic factor.

## E2. Notable Aspects of the Study

This study presents a framework to evaluate the quality of surgeons' case selection at a population level. In fact, no existing studies in the literature used survival outcomes to assess patient selection for a surgical intervention. A recent nomogram was developed using the QResearch database from the UK by Hippisley-Cox et al. that included both surgery and no surgery patients where "surgery" was analysed as a major covariate. Although the primary objective was not to assess surgeon's case selection, the difference in survival between the surgery and non-surgery group for different combination of variables (age, stage, comorbidity, etc) could be measured.[41] These data showed improved survival with surgical patients. Some studies have used similar framework to assess case selection but for different objectives; for example Guidry et al. looked the relationship of a surgeon's experience and their patient selection in respect to their surgical outcomes[42]; Wallis et al. used population data to evaluate patient selection and outcome differences between male and female surgeons in Ontario.[43] In sum, this is the first study to use administrative data to evaluate patient selection at a population level, and provides a framework for future similar work in this field.

This study used a multi-variate model that included interactions between surgery and all other important covariates, while treating surgery as a time-dependent variable. This allowed us to measure the outcome based on different combination of covariates. Heatmaps were used to visualize the trends in outcome based on variation of these covariates.

**E3. Study Issues to be Considered in its Interpretation**

As our results show, most patients selected by surgeons to undergo surgery had better survival than those who did not undergo surgery. This holds true in most patients irrespective of their age and frailty. Thus, a surgeon's decision to offer surgery is the most important factor associated with better survival. However, the details of this decision-making process are not captured in administrative data; therefore, we cannot determine the rationale behind the decisions for no surgery. These reasons can either be patient-driven due to personal choices in respect to their goals of care, or surgeon-driven where factors, not identified through administrative data, led the surgeons to believe that the patient would be a poor candidate for surgery.

Another limitation to this study is the accuracy of staging for patients who never had surgery. The Ontario Cancer Registry collects data through hospital medical records or regional cancer center records; as such clinical staging is most often based on imaging, which is inherently not as accurate as pathological staging from surgical specimens (gold standard). A recent systematic review by Nerad et al. investigated the diagnostic accuracy of CT for local staging of colon cancer and found good accuracy for T staging (sensitivity of 90%, specificity of 69%), however less accurate for nodal staging (sensitivity of 71% and specificity of 67%).[44] Underestimating the nodal stage, hence the staging of the non- surgery patients would favor the surgery group, representing a limitation that cannot be adjusted for in our study.

Our data may have also missed some important prognostic factors in our analysis such as tumor markers, treatment with systemic therapy/ immunotherapy, molecular biology of tumors (microsatellite instability status), perioperative factors (e.g blood loss, laparoscopic versus open, length of the operation, etc). These unaccounted covariates could affect our results in an unpredictable way.

**E4. Next Steps**

This study focused one main outcome – all-cause survival. Other outcomes include quality of life outcomes, which are being seen as increasingly important patient-centered outcomes and should be explored especially in an old and frail population in future studies. Additional outcomes could include unplanned readmission, days-alive-at-home (an emerging measure of independence at home and patient satisfaction), and healthcare cost. These latter outcome measures are available through ICES datasets and could be used in future studies.

This current study measured case selection at a population level. Future analyses could be done at the surgeon level. For example, the quality of patient selection for surgery can be compared between academic and community hospitals, between surgeons with colorectal fellowship/ surgical oncology fellowship trained surgeons vs. non-fellowship trained surgeons, and between distinct regions in Ontario. By doing so, it might be possible to identify groups where case selection is inferior; this information could help us understand factors potentially influencing better case selection by surgeons. However, such analyses might be limited by decreased sample sizes.

As mentioned previously, the decision to not undergo surgery can be influenced by patient-level or surgeon-level factors. Population-based data do not have the ability to distinguish between the two. This would require prospective data collection at the time of clinic encounter where the discussions around the diagnosis and treatments are had between the patient and the surgeon. Such an exercise could identify the factors driving the decision to forego surgery, which could be informative to our study as well. A qualitative study at the time of the clinic encounter can also be performed to understand the patient-important factors in their decision-making during the treatment discussion.

# Conclusion

Faced with an aging population with stage I-III colorectal cancer, Ontario surgeons are excellent at identifying those who can benefit from elective abdominal surgery even in the older and frailer patients. The survival comparison favors the surgery group in almost all colorectal cancer patients except for stage III rectal cancer with high frailty index. Our study suggests that Ontario surgeon's "end-of-bed" assessment is the most important factor associated with better survival. We consider our analysis a novel strategy at measuring the quality of patient selection for surgery at a population level and believe that it could be used to evaluate patient selection for surgery in other conditions as well as in other health systems with similarly stored large administrative data. Future studies should include patient-centered outcomes such as quality of life outcome measures.

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Appendix 1

| ABBREV-IATION | NAME | CONTENTS | UNIT OF RECORD | KEY VARIABLES USED IN ANALYSIS |
|---|---|---|---|---|
| CCRS | Continuing Care Reporting System | Clinical and demographic information on all Ontarians receiving facility based continuing care in long-term care and rehabilitation centres. Also captures geriatric assessments, respite care and palliative care. | Each stay at a facility based continuing care services | 1) LENGTH_OF_STAY_DISCHARGED – patient length of stay in long term and respite care |
| DAD | Discharge Abstract Database | Demographic and clinical data for all inpatient hospitalizations to all 175 acute care facilities in Ontario. | Each hospital stay - After every discharge, a medical records coder at the hospital draws up an abstract from the chart, compiling administrative and clinical data on that particular stay. | 1) INDATE – date of the surgical intervention<br>2) INCODE –stores codes indicating surgical procedure; used to identify all colorectal resections<br>3) AMDATE – admission date<br>4) ADMCAT – admission type (elective vs. emergency vs. urgent)<br>5) LOS – total length of hospital stay including acute and alternate level of care<br>6) SCUADMDATE – date of admission to a special unit (ICU, Surgical step down ICU) |

| | | | | |
|---|---|---|---|---|
| | | | | 7) SCUDDATE – date of discharge from a special unit |
| NACRS | National Ambulatory Care Reporting System | Data regarding all emergency department visits. | Each visit to hospital and community based ambulatory care, outpatient clinics, emergency departments. | 1) ED_ENCOUNTERS – Records ED visit dates |
| NRS | Nation Rehabilitation Reporting System | Data on all rehabilitation facilities and participating individuals in the inpatient setting. | Each stay at an adult inpatient rehabilitation facility or program | 1) DDATE – date of discharge from rehab during a hospital stay<br>2) ADMDATE – date of admission to in hospital rehab |
| OHIP | Ontario Health Insurance Plan Claims Database | Records all services and procedures from healthcare providers remunerated under OHIP. | Each record represents a single service, identified by feecode | 1) FEECODE – indicates billed service; used to determine the ASA status of those who underwent a surgical resection |
| SDS | Same Day Surgery Database | Records all same-day surgeries. | Every record corresponds to one same-day surgery or procedure stay | 1) *INCODE – includes the code of the intervention*<br>2) ADMCAT – determines the type of procedure (L= elective; E= Emergency; U= Urgent) |
| RPDB | Registered Persons Database | Contains data on vital status of all Ontarians having OHIP. | Each individual with an Ontario healthy card number | 1) Place and date of death |

| | | | | |
|---|---|---|---|---|
| OCR | Ontario Cancer Registry | Captures all primary cancer diagnosis identified on pathology reports in all Ontarians. | Every malignant neoplasm diagnosed in Ontario | 1) SEX – sex of the patient<br>2) DXDATE – date of cancer diagnosis on pathology (biopsy or surgical specimen)<br>3) TOPOG_CD – determines the site of the primary tumor on diagnosis from cecum to rectum<br>4) AGE – age of the patient<br>5) AJCC_TNM_CLIN/ AJCC_TNM_PATH/ CHEST_STAGE – determines the stage of the tumor. Study only includes tumor stage 1-3<br>6) RESCODE – site of residence at the time of diagnosis |
| ALR | Cancer Activity Level Reporting | Records all cancer treatment activities including radiation and systemic therapy. | Each delivery of cancer related services, e.g radiation, chemotherapy, outpatient oncology clinic visits | 1) INTENT_OF_RADIATION _TREATMENT – determines if a rectal cancer patient received neoadjuvant (“N”) in the predetermined region of radiation |

Appendix 2

| Code (CCI) | Description |
|---|---|
| 1NM87* | 1NM87 = Excision partial, large intestine<br>1NM87BA = Excision partial, large intestine endoscopic per orifice approach Simple excisional technique<br>1NM87DA = Excision partial, large intestine endoscopic [laparoscopic, laparoscopic-assisted, hand-assisted] approach simple excisional technique<br>1NM87DE = Excision partial, large intestine endoscopic [laparoscopic, laparoscopic-assisted, hand-assisted] approach colorectal anastomosis technique<br>1NM87DF = Excision partial, large intestine endoscopic [laparoscopic, laparoscopic-assisted, hand-assisted] approach colocolostomy anastomosis technique<br>1NM87DN = Excision partial, large intestine endoscopic [laparoscopic, laparoscopic-assisted, hand-assisted] approach enterocolostomy anastomosis technique<br>1NM87DX = Excision partial, large intestine stoma formation and distal closure<br>1NM87DY = Excision partial, large intestine endoscopic [laparoscopic, laparoscopic-assisted, hand-assisted] approach stoma formation with creation of mucous fistula<br>1NM87GB = Excision partial, large intestine endoscopic [laparoscopic, laparoscopic-assisted, hand- assisted] approach special excisional technique (without anastomosis)<br>1NM87LA = Excision partial, large intestine open approach Simple excisional technique<br>1NM87PN = Excision partial, large intestine endoscopic [laparoscopic, laparoscopic-assisted, hand-assisted] approach robotic assisted telemanipulation of tools [telesurgery]<br>1NM87RD = Excision partial, large intestine open approach Colorectal anastomosis technique<br>1NM87RE = Excision partial, large intestine open approach Enterocolostomy anastomosis technique<br>1NM87RN = Excision partial, large intestine open approach Colocolostomy anastomosis technique<br>1NM87TF = Excision partial, large intestine open approach Stoma formation with distal closure<br>1NM87TG = Excision partial, large intestine open approach Stoma formation with creation of mucous fistula<br>1NM87WJ = Excision partial, large intestine open approach special excisional technique (without anastomosis) |
| 1NM89* | 1NM89 = Excision total, large intestine<br>1NM89DF = Excision total, large intestine endoscopic [laparoscopic, laparoscopic-assisted, hand-assisted] approach ileorectal [endorectal, ileoproctostomy] anastomosis technique<br>1NM89DX = Excision total, large intestine endoscopic [laparoscopic, laparoscopic-assisted, hand-assisted] approach stoma formation with distal closure<br>1NM89GB = Excision total, large intestine endoscopic [laparoscopic, laparoscopic-assisted, hand-assisted] approach special excisional technique without anastomosis<br>1NM89RN = Excision total, large intestine open approach using Ileorectal [endorectal, ileoproctostomy] anastomosis technique<br>1NM89TF = Excision total, large intestine open approach Stoma formation with distal closure<br>1NM89WJ = Excision total, large intestine open approach special excisional technique without anastomosis |
| 1NM91* | 1NM91 = Excision radical, large intestine<br>1NM91DE = Excision radical, large intestine endoscopic [laparoscopic, laparoscopic-assisted, hand-assisted] approach colorectal anastomosis technique<br>1NM91DF = Excision radical, large intestine endoscopic [laparoscopic, laparoscopic-assisted, hand-assisted] approach |

| | |
|---|---|
| | colocolostomy anastomosis technique<br>1NM91DN = Excision radical, large intestine endoscopic [laparoscopic, laparoscopic-assisted, hand-assisted] approach enterocolostomy anastomosis technique<br>1NM91DX = Excision radical, large intestine endoscopic [laparoscopic, laparoscopic-assisted, hand-assisted] approach stoma formation with distal closure<br>1NM91DY = Excision radical, large intestine endoscopic [laparoscopic, laparoscopic-assisted, hand-assisted] approach stoma formation with creation of mucous fistula<br>1NM91RD = Excision radical, large intestine open approach Colorectal anastomosis technique<br>1NM91RE = Excision radical, large intestine open approach Enterocolostomy anastomosis technique<br>1NM91RN = Excision radical, large intestine open approach Colocolostomy anastomosis technique<br>1NM91TF = Excision radical, large intestine open approach Stoma formation with distal closure<br>1NM91TG = Excision radical, large intestine open approach Stoma formation with creation of mucous fistula |

Appendix 2

| Code (CCI) | Description |
|---|---|
| 1NQ87* | 1NQ87 = Excision partial, rectum<br>1NQ87BA = Excision partial, rectum endoscopic per orifice approach closure by apposition technique [e.g. suturing, stapling] or no closure required (for tissue regeneration)<br>1NQ87BAFA = Excision partial, rectum endoscopic per orifice approach encirclage device<br>1NQ87CA = Excision partial, rectum perineal [e.g. pull through, transanal, sacral or sphincteric] approach closure by apposition technique [e.g. suturing, stapling] or no closure required (for tissue regeneration)<br>1NQ87CAFA = Excision partial, rectum per orifice approach [e.g. perineal, pull through, transanal, sacral or sphincteric] encirclage device (banding)<br>1NQ87DA = Excision partial, rectum endoscopic [laparoscopic, laparoscopic-assisted, hand-assisted] approach closure by apposition technique [e.g. suturing, stapling] or no closure required (for tissue regeneration)<br>1NQ87DE = Excision partial, rectum endoscopic [laparoscopic, laparoscopic-assisted, hand-assisted] approach colorectal anastomosis technique<br>1NQ87DF = Excision partial, rectum endoscopic [laparoscopic] approach colorectal anastomosis technique<br>1NQ87DX = Excision partial, rectum endoscopic [laparoscopic, laparoscopic-assisted, hand-assisted] approach stoma formation with distal closure<br>1NQ87LA = Excision partial, rectum open abdominal [e.g. anterior] approach closure by apposition technique [e.g. suturing, stapling] or no closure required (for tissue regeneration)<br>1NQ87PB = Excision partial, rectum perineal (e.g. pull through, transanal, sacral or sphincteric) approach colorectal anastomosis technique<br>1NQ87PF = Excision partial, rectum posterior [e.g. entering through incision between coccyx and anal verge with proctotomy] approach closure by apposition technique [e.g. suturing, stapling] or no closure required (for tissue regeneration)<br>1NQ87PN = Excision partial, rectum endoscopic [laparoscopic, laparoscopic-assisted, hand-assisted] approach robotic assisted telemanipulation of tools [telesurgery]<br>1NQ87RD = Excision partial, rectum open abdominal [e.g. anterior] approach colorectal anastomosis technique<br>1NQ87TF = Excision partial, rectum open abdominal approach [e.g. anterior] stoma formation with distal closure |

| | |
|---|---|
| 1NQ89* | 1NQ89 = Excision total, rectum<br>1NQ89AB = Excision total, rectum, stoma formation with distal closure, combined endoscopic [laparoscopic] abdominoperineal approach<br>1NQ89GV = Excision total, rectum combined endoscopic [abdominal] with perineal approach coloanal anastomosis technique<br>1NQ89KZ = Excision total, rectum abdominoperineal approach coloanal anastomosis technique<br>1NQ89KZXXG = Excision total, rectum abdominoperineal approach pouch formation<br>1NQ89LH = Excision total, rectum abdominoperineal approach Stoma formation with distal closure<br>1NQ89LHXXG = Excision total, rectum abdominoperineal approach Continent ileostomy formation<br>1NQ89RS = Excision total, rectum abdominal [anterior] approach Stoma formation with distal closure<br>1NQ89RSXXG = Excision total, rectum abdominal [anterior] approach Continent ileostomy formation<br>1NQ89SF = Excision total, rectum abdominal [anterior] approach coloanal anastomosis technique<br>1NQ89SFXXG = Excision total, rectum abdominal [anterior] approach pouch formation |
| 1NQ90* | 1NQ90 = Excision total with reconstruction, rectum<br>1NQ90LAXXG = Excision total with reconstruction, rectum using open approach with ileum [for construction of pouch] |

## Appendix 3

Scoring rubric for frailty index. The preoperative frailty index (pFI) is calculated by adding the score for each deficit measured and dividing this number by the total number of deficits measured (i.e. 30Su).

| Variable | Source | Points | | |
|---|---|---|---|---|
| | | 0 | 0.5 | 1 |
| Anticholinergic risk scale | ODB[a] | 0 | 1–2 | >2 |
| Arrhythmia | Elixhauser | None | | Present |
| Cancer | Elixhauser | None | | Present |
| Cerebrovascular disease | Elixhauser | None | | Present |
| COPD | COPD algorithm | None | | Present |
| Dementia | Elixhauser | None | | Present |
| Dental | ADG | None | | Present |
| Dermatologic | ADG | None | | Present |
| Diabetes mellitus | Diabetes algorithm | None | | Present |
| Dialysis | Elixhauser | None | | Present |
| Drug or alcohol abuse | Elixhauser | None | one | Both |
| Heart failure | Heart failure algorithm | None | | Present |
| Hemiparesis | Elixhauser | None | | Present |
| History of falls | ICD-10 code[b] | None | | Present |
| Home oxygen | ADP | None | | Present |
| HOMR Score | Calculated | 0–21 | 22–55 | >55 |
| Hypertension | Hypertension algorithm | None | | Present |
| Injury | ADG | None | minor | Major |
| Liver disease | Elixhauser | None | | Present |
| Multimorbidity | Charlson score | 0 | 1–2 | >2 |
| Myocardial Infarction | Myocardial infarction algorithm | None | | Present |
| Peripheral vascular disease | Elixhauser | None | | Present |
| Psychosocial (minor or stable) | ADG | None | minor/stable | Major |
| Resource use band 4–5 | ADG | 0–1 | 2–3 | 4–5 |
| Rheumatic disease | Elixhauser | None | | Present |
| Socioeconomic status | Census | Top 2 quintiles | middle quintile | Bottom 2 quintiles |
| Ear, nose, throat | ADG | None | stable | Unstable |
| Eye | ADG | None | stable | Unstable |
| Supported living environment | CCRS/HCD/LTC | None | | Present |
| Weight loss | Elixhauser | None | | Present |

a Calculated according to methods of Rudolph and colleagues.[24]

b Any inpatient or emergency department record with a diagnosis code W0–W19. ADG, Aggregated Diagnosis Group; ADP, Assistive Devices Program; CCRS, Continuing Care Reporting System; COPD, chronic obstructive pulmonary disease; HCD, Home Care Database; ICD-10, International Classification of Diseases, 10th Edition; ODB, Ontario Drug Benefits Program.

**Appendix 4**. Final regression all-cause survival model

| VARIABLES/ INTERACTIONS | VARIABLE VALUE / TRANS-FORMATION | ESTIMATE | STANDARD ERROR | CHI SQ | HAZARD RATIO |
|---|---|---|---|---|---|
| Surgery Status | Surgery= 1<br>No surgery= 0 | -3.589 | 1.064 | 11.3711 | 0.028 |
| Female | Female= 1<br>Male= 0 | -0.060 | 0.070 | 0.7223 | 0.942 |
| Colon Cancer | Colon cancer =1<br>Rectal cancer= 0 | 0.010 | 0.073 | 0.0192 | 1.010 |
| Stage 2 | Stage 2 = 1<br>Stage 1= 0 | 0.005 | 0.083 | 0.0036 | 1.005 |
| Stage 3 | Stage 3 =1<br>Stage 1= 0 | 0.085 | 0.087 | 0.9574 | 1.089 |
| Diagnosis Year | Year – 2009 | -0.036 | 0.010 | 14.2394 | 0.964 |
| Standardized Age | Range 1 to 2 | 1.878 | 0.204 | 85.0447 | 6.543 |
| Frailty | $[\text{Frailty (range 1 to 2)}]^2$ | 0.519 | 0.073 | 50.4369 | 1.681 |
| Age x Frailty | $[\text{age * frailty}]^3$ | -0.027 | 0.008 | 12.0713 | 0.973 |
| Surgery x Female | Surgery * female | -0.286 | 0.083 | 11.9735 | 0.752 |
| Surgery x Colon | Surgery * colon | -0.221 | 0.093 | 5.7139 | 0.802 |
| Surgery x Stage 2 | surgery * stage 2 | 0.207 | 0.103 | 4.0676 | 1.230 |
| Surgery x Stage 3 | surgery * stage 3 | 0.468 | 0.107 | 19.2773 | 1.596 |
| Surgery x Year | $[\text{surgery * year} +1]^{-2}$ | 0.631 | 0.361 | 3.0549 | 1.880 |
| Surgery x Age | $[\text{surgery *age} +1]^{-0.5}$ | 1.994 | 1.172 | 2.8957 | 7.343 |
| Surgery x Frailty | $[(\text{surgery * frailty}) + 1]^{-2}$ | -4.816 | 1.172 | 16.8920 | 0.008 |

Appendix 5. Quartiles of continuous variables used in unadjusted analysis

| Variable | Label | 25th percentile | 50th percentile | 75th percentile |
|---|---|---|---|---|
| AGE | | 82 | 84 | 87 |
| Frailty | pFI index | 0.0667 | 0.1167 | 0.1833 |