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FACULTY OF HEALTH AND MEDICAL SCIENCES

PhD Thesis

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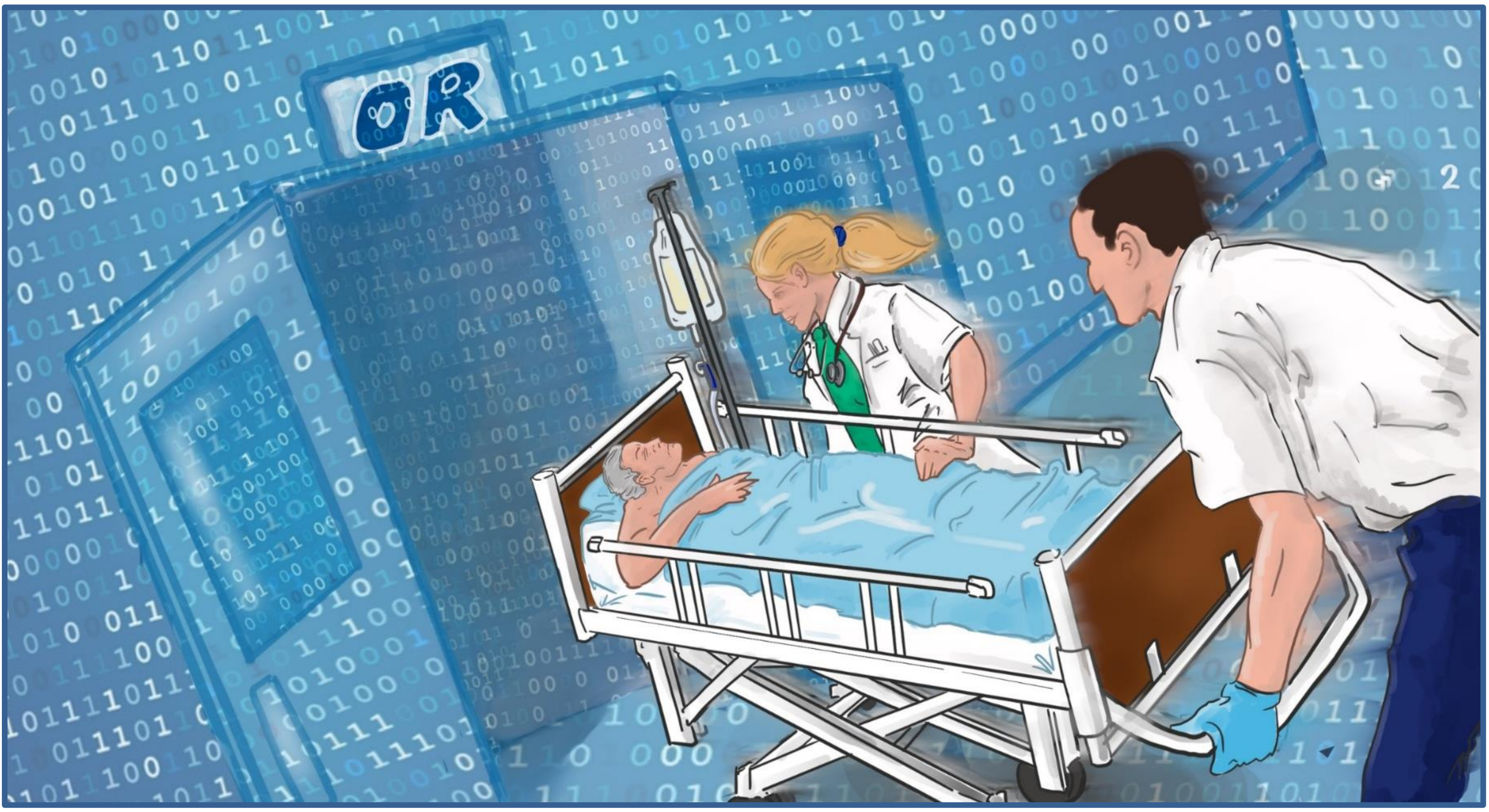
Short-term outcome after acute colorectal cancer surgery –risk factors and prediction



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Thea Helene Degett, February 2019

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1. List of publications

The following manuscripts are included in the thesis

Study I

Degett TH, Roikjær O, Iversen LH, Gögenur I. A model predicting operative mortality in the UK has only limited value in Denmark. Int J Colorectal Dis. 2018 33:141-147.

Study II

Degett TH, Dalton SO, Christensen J, Søgaard J, Iversen LH, Gögenur I. Mortality after emergency treatment of colorectal cancer and associated risk factors -a nationwide cohort study. Int J Colorectal Dis. 2019 34:85-95

Study III

Degett TH, Christensen J, Thomsen LA, Iversen LH, Gögenur I, Dalton SO. A nationwide cohort study of the impact of education, income and social isolation on survival after acute colorectal cancer surgery. Submitted BJS open

Study IV

Degett TH, Christensen J, Dalton SO, Bossen K, Frederiksen K, Iversen LH, Gögenur I. Prediction of postoperative mortality after acute colorectal cancer – development and validation of a prediction model.

2. List of abbreviations

ACPGBI: Association of Coloproctology of Great Britain and Ireland

AIC: Akaike Information Criterion

APE: Abdominoperineal excision

ASA: American Society of Anaesthesiologists

BMI: Body mass index

CCI: Charlson Comorbidity Index

CI: Confidence interval

CRS: Civil Registration System

DCCG.dk: Danish Colorectal Cancer Group

DAG: Directed Acyclic Graph

EWS: Early Warning Score

ERAS: Enhanced Recovery After Surgery

HR: Hazard Ratio

MAR: Missing At Random

MCAR: Missing Completely at Random

MNAR: Missing Not At Random

NCEPOD: National Confidential Enquiry into Patient Outcome and Death

NPR: National Patient Registry

OR: Odds Ratio

POSSUM: Physiological and Operative Severity Score for the enumeration of Mortality and morbidity

P-POSSUM: Portsmouth-POSSUM

CR-POSSUM: Colorectal-POSSUM

SEMS: Self-expanding Metallic Stent

UICC: Union for International Cancer Control

3. Introduction

Colorectal cancer is a major global health problem with an annual incidence of 1.7 million worldwide [1]. Around 6.3 million people in the world live with colorectal cancer which is the second most diagnosed cancer estimated to have caused around 860,000 deaths in 2018 [1, 2]. It is also a disease associated with a high rate of morbidity and loss of healthy life years [3]. In Denmark, 4856 patients were diagnosed with colorectal cancer in 2017, and 3649 patients underwent surgery [4]. In some patients, the disease presents with acute symptoms caused by perforation, obstructions or bleeding, *Figure 1* [5, 6]. Of all patients operated for colorectal cancer, between 10%-30% present with acute symptoms of the disease; a life-threatening condition [7-12].

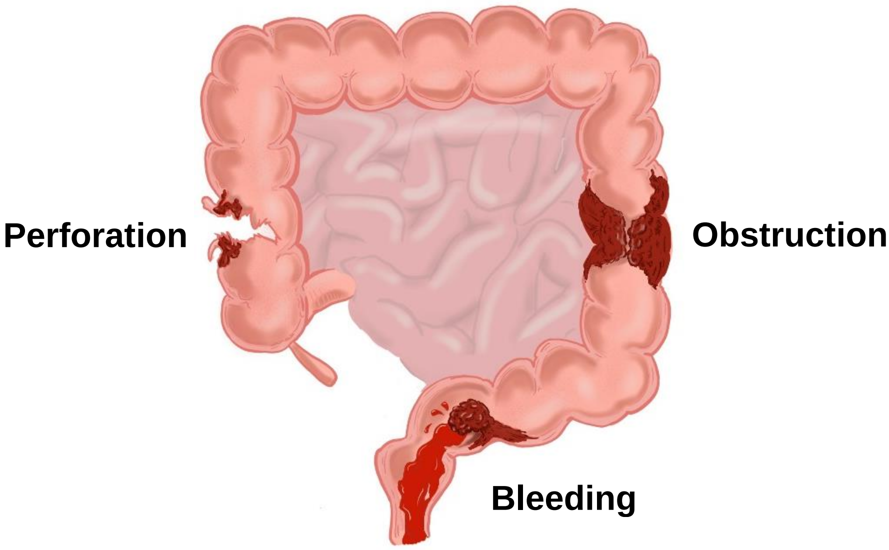


Figure 1. Acute presentation of colorectal cancer is caused by perforation, obstruction, or bleeding.

The postoperative mortality after acute colorectal cancer surgery varies from 6%-22% [7, 10, 12-15]. In Denmark, the 30-day and 90-day mortality after acute surgery for colorectal cancer was 11% and 21% in 2016, respectively [8]. Compared with elective surgery, the 30-day and 90-day postoperative mortality was only 1.4% and 3% [8]. The risk of postoperative complications is also increased in acute surgery compared with elective surgery, and medical complications after acute surgery are highly correlated to postoperative mortality [10, 14]. In the long-term perspective, acute surgery is associated with lower overall survival, disease-free survival, and higher rate of recurrence of the cancer disease [10, 16-18]. Previous studies have found that patients with low social economic status have a higher risk of acute surgery compared with elective surgery for colorectal cancer [19]. This PhD study was initiated to improve knowledge about the acutely operated patients with colorectal cancer. Even though it is a relatively small group of patients, their risk of postoperative mortality is high and the literature lacked larger studies focusing on this patient group only.

Overall survival after colorectal cancer has improved over the last 10 years both on short- and long-term basis [4, 20-22]. However, the postoperative mortality rate remains high after acute surgery and continuous focus on how to improve survival is important. Prediction models could be useful to help physicians identify patients at high risk of postoperative mortality. The word prediction means to forecast a future event and knowing the operative mortality risk after colorectal cancer surgery has several benefits [23, 24]. First, it is a tool to strengthen the physician's clinical decision-making and not a substitute for medical knowledge and experience [23, 25, 26]. If the surgeon knows the absolute operative risk of an acute surgical procedure, it could influence the choice of timing of surgery, surgical approach, perioperative care, postoperative care, and follow-up. Furthermore, the estimated prediction of an event can help the patient understand the critical circumstances and strengthen shared decision-making. Prediction models can also help comparing outcome at different hospitals adjusted for case mix [23, 25-27].

4. Background

4.1 Colorectal cancer

Colorectal cancer is defined as malignant tumours in the colon or rectum, distributed on approximately 2/3 and 1/3 of diagnosed patients, respectively [22]. About 95% of the colorectal tumours are adenocarcinomas from glandular epithelium. In Denmark, 46% of patients with colon cancer and 37% of patients with rectal cancer are women [8]. The median age for the diagnosis of colon cancer is 72 years and 69 years for rectal cancer [8].

4.2 Acute colorectal cancer surgery

Acute colorectal cancer surgery in this thesis is defined as primary surgery of undiagnosed cancer due to obstruction, perforation, or bleeding. This is based on the definition in the primary data source in this thesis, the Danish Colorectal Cancer Group (DCCG.dk) database [28, 29]. Only since 2014, is has been obligatory for the surgeon to register the intended time from decision to initiation of the acute surgical procedure with the options <6 hours or <36 hours in the database. In the UK, the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) strictly defines acute surgery in two categories [30]. Immediate surgery is life, limb, or organ-saving and usually carried out within minutes of decision to operate [30]. Urgent surgery is performed in potentially life-threatening conditions within hours of decision to operate [30]. In a retrospective Swedish study, 40% of all patients registered with acute colorectal cancer surgery had the procedure more than three days after decision to operate [31]. These differences imply the importance of a well-defined terminology of acute colorectal cancer surgery, both in terms of symptoms and time from decision to initiation of the surgical procedure.

Surgical treatment of colorectal cancer presenting acutely depends on the symptoms and clinical condition. The most common symptom is tumour obstruction occurring in around 70%-80% of all acute onsets and is often located in the distal colon [7, 32-34]. Left-sided obstructive tumours are treated with either a diverting stoma, self-expanding metallic stent (SEMS), or bowel resection with primary anastomosis or end colostomy (Harman's procedure) [5, 35]. Meta-analysis of randomized, controlled trials have not shown differences in short or long-term survival comparing surgical resection with SEMS or diverting stoma [36, 37]. In right-sided obstruction, the most common surgical treatment is resection with primary anastomosis but SEMS is also an option; if technically possible [38]. Limited evidence show that there might be worse long-term oncological outcome with an increased risk of recurrence after SEMS [39-41]. This should be kept in mind in younger patients with obstructive, non-metastatic disease. Perforation of the bowel is the second most common cause of acute surgery and associated with a high postoperative mortality risk and an increased risk of local recurrence [6, 14]. Treatment with SEMS is contraindicated in patients with perforation [5].

The pathophysiological mechanisms leading to development of colorectal cancer as an acute condition is not comprehensive [5, 42]. A diagnosis with acute symptoms can be interpreted as a result of delay in diagnosis of the disease; further divided into patient-related delay, disease-related delay or healthcare-related delay, and subsequently increased time for tumour progression, *Figure 2* [42, 43]. The patient's appraisal and management of symptoms may affect the delay [43]. Patient delay, also known as the patient interval, is the time between the patient's first notification of a symptom and first doctor consultancy [43-45]. In colorectal cancer, the most common reason for patient delay is not recognizing the seriousness of the first symptoms such as altered bowel habits and rectal bleeding [44]. Lack of knowledge about cancer symptoms, denial of symptoms, and fear of a cancer disease also prolong patient delay [44, 46]. Low educational level and living in rural areas are associated with increased patient delay in colorectal cancer patients, while having social support and comorbidities are associated with short patient delay [44, 47, 48]. Other known barriers to seeking healthcare include negative thoughts about cancer, e.g. cancer is a death sentence, worry about what the doctor might find, and worry about wasting the doctor's time [48, 49].

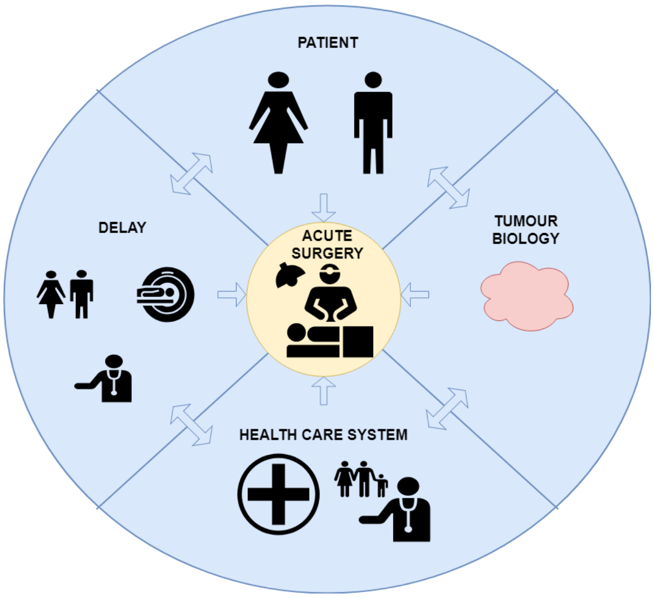


Figure 2. Possible mechanisms leading to acute colorectal cancer surgery.

The tumour itself is also suggested to be important in acute presentation of cancer due to variation in aggressiveness in tumour subtypes. Previous studies have shown that acute presentation of colorectal cancer is associated with high-grade tumours and advanced Union for International Cancer Control (IUCC) stage at the time of diagnosis compared with colorectal cancers electively operated [9, 10, 50]. Access to general healthcare could also affect the risk of having acute presentation of cancer due to delay in diagnosis and treatment. In colorectal cancer, tumours are thought to grow slowly and previous literature did not find an association between neither diagnostic nor treatment delay and overall survival [51-53].

Acute colorectal cancer surgery is associated with increased risk of short-term mortality and postoperative complications, both medical and surgical [10, 12, 14]. In addition, long-term prognosis is inferior after acute surgery with decreased long-term overall survival, decreased disease-free survival and increased risk of recurrence compared with elective surgery [10, 16-18]. Acute surgery also reduces the chances of getting the golden standard surgical and oncological treatment with removal of more than 12 lymph nodes and oncological treatment before or after surgery, if indicated [10, 29, 54, 55].

4.3 Socioeconomic position

Low socioeconomic position is associated with a higher risk of acute colorectal cancer surgery [56]. Socioeconomic position can be defined as a concept that aggregates both resource-based and prestige-based measures and refers to the position an individual or a group holds in the society [57, 58]. Measurements of socioeconomic position should not be interpreted as a risk factor, but rather interconnected pathways that help or harm health status in individuals or groups [57]. Different exogenous exposures can affect health such as living standards, social and psychological relations at work, at home or in society [57]. Some of the common measures of socioeconomic position are educational level and income [58]. Ten years ago, a Danish study showed that high income, high educational level and living in an owner-occupied versus rental housing were associated with improved 30-day mortality after elective colorectal cancer surgery [59]. The last 10 years, differences in 5-years relative survival from colorectal cancer between individuals with high and low socioeconomic position has increased to approximately 10%-units in Denmark [60]. Furthermore, a Danish study showed that individuals in the low-income groups with short educational level, unemployed persons, and non-western immigrants were less likely to join the screening programme for colorectal cancer [61]. Diagnosis via screening might improve the chances of having an early-diagnosed cancer and prevent acute presentation of the disease [4, 11]. In a

Swedish study, short education was associated with a decrease in five-year survival after colorectal cancer surgery [62]. The same association of socioeconomic position on long-term outcome has been investigated in the US where living in areas with a high poverty rate and being African-American are associated with a higher risk of acute surgery [9]. Another US study found an association between being African-American and presentation of more advance disease in colorectal cancer [19]. Results from a systematic review reported a global problem with increased mortality rate from colorectal cancer in individuals with low socioeconomic position [63].

4.4 Prediction models

With a prediction model, it is possible to estimate the absolute risk of a specific outcome based on several predictor variables [23, 64]. The main purpose of a prediction model is to help physicians in clinical, shared decision-making and give an objective estimation of e.g. the surgical risk [64]. Using prediction models in decision-making is not routinely applied in colorectal cancer [35, 65, 66]. In other medical specializations, prediction models are used as a tool to direct treatment strategies and guidelines. An example is the CHA_2DS_2-VASc score recommended worldwide to predict the risk of ischemic stroke in patients with atrial fibrillation [67, 68]. The Apgar score is widely used in new-borns to guide the health professionals in the level of monitoring and resuscitation [69]. Before initiating the studies included in this PhD, the author group made an overview of existing models predicting postoperative mortality after colorectal cancer surgery [70]. A systematic review evaluated the use of the Physiological and Operative Severity Score for the enumeration of Mortality and morbidity (POSSUM) model and its modification colorectal (CR-POSSUM) and Portsmouth (P-POSSUM) models in the literature to predict the postoperative mortality and morbidity risk in colorectal cancer surgery [71]. The P-POSSUM model performed well with a rate of observed and estimated risk of 0.90 (95% CI: 0.88-0.92) [71]. Unfortunately, it was not possible to evaluate the performance of the POSSUM models with available data due to lack of data on predictor variables in the DCCG.dk database. In US, the Cleveland Clinic Foundation had also developed a promising model to predict 30-day mortality postoperatively that was not possible to validate with the DCCG.dk database [72]. The Association of Coloproctology of Great Britain and Ireland (ACPGBI) model was developed in 2003 to predict 30-day mortality after colorectal cancer surgery [24] and in 2007, the association updated the model [73]. All data in the original and revised ACPGBI model was available in the DCCG.dk database and the model was validated in study I.

4.5 Development of a prediction model

It is unlikely that one single variable can predict an outcome and a multivariable approach is essential when creating a prediction model [64]. In the development of a prediction model, the first consideration is how the model is to be used and the clinical context, e.g. if the model is not automatically retracting data from the patient file, the number of variables has to be limited to achieve compliance from physicians using it [74]. It is also essential that the predicted outcome in the model is important for the patient and not a proxy for an outcome the patients cannot relate to [64]. Prediction models deviate from classical epidemiological research in various ways. All variables that adds predictive value to the model could be included. If two variables describe comorbidity in two different ways and both add predictive value to the model, they could both be included. In prediction, no apriori assumption of causal inference is needed for a predictor to be included. However, if a changeable predictor variable is to change the risk of a predicted outcome there has to be a causal relation between the predictor variable and the outcome. E.g. if exercise before surgery might be a good predictor for postoperative survival, implementation of exercise before surgery will only change the risk of postoperative death if the exercise has an impact on survival. The appropriate statistical method in development of a prediction model depends on the outcome. Logistic regression is used in models with binary outcomes [75]. For time-to-event data, Cox proportional regression model, which includes adjustment of the baseline risk of the outcome over time, is the preferred model [74].

5. Objective of the thesis

The primary aim of this thesis was to identify predictors for short-term mortality after acute colorectal cancer surgery. The four studies aimed to answer the following hypotheses separately:

- Study I. The aim was to validate the ACPGPI model in the Danish population and investigate if this model was able to predict 30-day mortality after colorectal cancer surgery.
- Study II. The aim was to investigate if survival had improved in Denmark between 2005 and 2015 after acute colorectal cancer surgery and to identify factors associated with decreased survival.
- Study III. The aim was to investigate if low socioeconomic position was associated with increased risk of having acute surgery for colorectal cancer compared with elective surgery and subsequently if low socioeconomic position was associated with decreased survival after acute colorectal cancer surgery.
- Study IV. The aim was to develop a prediction model for 90-day mortality after acute colorectal cancer surgery and subsequently to validate the model in patients undergoing acute colorectal cancer surgery in 2015.

6. Methods

6.1 Data sources (study I-IV)

In Denmark, there is a long history of registries dating back to 1875 where The Danish Register of Cause of Death was established [76]. Registries and databases in Denmark are linked together with a unique personal identification number (CPR-number) held by all persons with a permanent residence in Denmark [76]. The CPR-number contains information on sex and date of birth [77]. The Danish clinical quality databases were established with the aim to collect data within specific diseases and to monitor clinical quality [78]. Statistics Denmark is an administrative platform that holds data on some of the Danish administrative registries, all registered companies in Denmark, and data from taxation authorities among other things [79].

The Danish Civil Registration System (CRS) is a Danish register established in 1968 and was used to collect taxes from all citizens of Denmark and Greenland based on the personal CPR-number [77]. The register includes information on CPR-number, full name, date and place of birth, identity of parents and children, place of residence, date of migration and disappearing and is continuously updated on vital status. The register has a high validity and coverage with an ongoing validation of data contained in the register. It is required by law to have a CPR-number and the Danish Civil Registration System is interpreted as having complete coverage and it is not possible to be retracted from the register [77].

The Danish Colorectal Cancer Group (DCCG.dk) database is a clinical quality database established in 2001 and includes all Danish citizens aged >18 years diagnosed with colorectal adenocarcinoma and seen in a surgical department [80]. The database does not include information about recurrence, metachronous disease, and other histological cancer types than primary adenocarcinoma, mucinous adenocarcinoma, signet ring cell carcinoma, medullary carcinoma, and undifferentiated carcinoma. The database has a completeness proportion of all patients with colorectal cancer of 95% before 2010 and 99% since 2010 [80]. Data are collected at the surgical department where the patient is seen. Patients undergoing surgical procedures have data collected at three time points. Patient-related data are registered before surgery, intraoperative data are registered after surgery, and postoperative complications of any kind are registered 30 days after surgery. Follow-up on vital status after 30 days from a surgical procedure is carried out by linking to the CRS.

The Danish National Patient Register (NPR) was established in 1977 and holds both administrative and clinical data on all admissions and from 1994 also outpatient visits at somatic, psychiatric, and emergency wards [81]. Time and date of admission and surgery, and diagnosis at discharge are also registered in the NPR. The NPR was originally established to monitor diseases in Denmark. However, registration in the NPR was also the basis of payment for specific treatments at public and private hospitals from 2000 [81].

The Danish Education Registry holds information from all Danish educational programs, some established as early as 1910 [82]. Data are collected by the Danish Ministry of Education from several institutions and available through Statistics Denmark. The Income Statistics Register was established in 1970 and contains more than 160 variables on income composition of the Danish population, employment, taxation, and pension [83].

6.2 Setting (study I-IV)

All individuals included in this thesis had undergone surgery for colorectal cancer in a Danish hospital. In the full study period of inclusion, 29 public hospitals carried out acute colorectal cancer surgery, all financed by tax. No private hospitals perform colorectal cancer surgery in Denmark. The volume of patients per year at each hospital range from 1-425 in the years 2005-2015, when counting both elective and acute surgery. During the period of all four studies, several national initiatives were implemented to improve survival in colorectal cancer such as clinical guidelines and national cancer plans [84].

6.3 Definition of acute colorectal cancer surgery (study II, III and IV)

In the DCCG.dk database, only the definitive surgical procedure is registered resulting in suboptimal information about colorectal cancer surgery performed in more than one step. In patients with a primary acute procedure and subsequently tumour resection as an elective procedure (bridge to surgery), date of surgery and perioperative data are only registered for the elective procedure in the DCCG.dk database. Since most elective surgery is performed in one step, this is not a problem for the majority of the patients in the DCCG.dk database. However, perioperative data are not registered in patients with acute diverting stoma or SEMS as bridge to a definitive elective tumour resection and in patients with more than one acute procedure. In 2014, a new variable was introduced in the DCCG.dk database describing if SEMS, diverting stoma, damage control surgery, or any other procedure was performed before the definitive procedure [28]. However, the date of this first acute procedure is not registered and it is not possible to use for calculating postoperative mortality. When initiating study II, an algorithm was developed to include the patients with diverting stoma or SEMS prior to definitive surgery in the population. It will be referred to as the acute population algorithm in this thesis. The acute population algorithm included patients registered in the NPR, with a SEMS or diverting stoma as the main procedure within 72 hours after an emergency admission at any department. Furthermore, the patient had to be registered in the DCCG.dk database with a diagnosis of colorectal cancer. The first procedure registered in either DGGG.dk or in the NPR was defined as the primary procedure. The operation codes included in the NPR for diverting stoma were KJFF10, KJFF11, KJFF20, KJFF21, KJFF23, KJFF24, KJFF26, KJFF27, KJFF30, and KJFF3; and for SEMS KJFA68 and KJGA58A. The acute population algorithm increased the completeness rate of patients with acute colorectal cancer surgery. No perioperative data is available in the DCCG.dk database regarding the procedures included via the acute population algorithm.

6.4 Population selection (study I-IV)

In all four studies, the populations were selected through the DCCG.dk database study and entry time was date of surgery. The particular population in each study varied according to the study question and available data. Data from the DCCG.dk database was continuously updated throughout this thesis and consequently the latest studies include more recent study years.

Study I

In study I, the original and the revised ACPBGI models were validated and patients were included according to inclusion criteria in both models [24, 85]. Patients who underwent elective or acute colorectal cancer surgery from 2007-2013 and registered in the DCCG.dk database were included (31,370 patients). Only patients who underwent procedures included in the revised ACPBGI model were included in the validation of both models (right hemicolectomy, transverse colectomy, left hemicolectomy, sigmoid colectomy, subtotal/total colectomy, anterior resection, abdomino-perineal excision of rectum (APE), Hartmann’s procedure, palliative stoma, and only examination under anaesthesia/laparotomy/laparoscopy) [85]. We excluded patients with incomplete data on any predictor variable of both models (1437 patients).

Study II

In study II, it was investigated if postoperative mortality after acute colorectal cancer surgery has improved within the last decade and the risk factors for decreased mortality were identified. All patients undergoing acute colorectal surgery according to the DCCG.dk database or the acute population algorithm from 2005-2015 and registered in the DCCG.dk database were included in the study (6147 patients). Patients were excluded if they underwent local procedures (transanal endoscopic microsurgery, polypectomy etc.) or abdomino-perineal excision (17 patients), if an elective procedure was registered prior to the acute procedure (226 patients), or if they had migrated or disappeared within the follow-up time of 90-days (2 patients).

Study III

In study III, we investigated the association between socioeconomic position and acute surgery and subsequently 1-year survival after acute surgery. All patients undergoing colorectal cancer surgery from 2007-2015 according to the DCCG.dk database or the acute population algorithm and registered in the DCCG.dk database were included (35,661 patients). Only acutely operated patients were eligible for the survival analysis (5310 patients). Patients were excluded if they had missing information on surgical priority (11 patients), income (31 patients), cohabitation or urbanicity (85 patients), had migrated within one year after acute surgery (one patient), or were registered with a date of death prior to the date of surgery (12 patients).

Study IV

In study IV, a prediction model for 90-day mortality after acute surgery was developed and validated. Two populations were defined; one for development of the prediction model and one for validation of the developed model. For development of the model, all patients with acute colorectal cancer surgery in 2014 according to the DCCG.dk database and the acute population algorithm were included (535 patients). For validation of the developed model, all patients with acute colorectal cancer surgery in 2015 according to the DCCG.dk database and the acute population algorithm were included (554 patients). Exclusion criteria in both the development and validation population were elective surgical procedure prior to acute surgery (19 patients), registered with a death date prior to surgical date (two patients), migration or disappearing within the first 90-days after acute surgery (zero patients) and local resection or APE (two patients).

6.5 Indicators for socioeconomic position (study III)

In study III, education was selected as the primary investigated indicator for socioeconomic position based on the hypothesis that educational level is achieved early in adult life and affects other measurements of an individual's socioeconomic position, *Figure 3*. Education represents knowledge-related assets, which is strongly related to parental characteristics and reproduces through generations [58, 86]. The highest attained educational level is interpreted as a reflection of both material and intellectual resources of family origin and indirectly a measurement for health exposures in childhood [58]. It might also be related to cognitive functions and education can directly affect income level and place of residence, *Figure 3* [58]. Data on educational level were obtained from the Danish Education Registry October 1st, the year before the colorectal cancer surgery was performed [82]. Short educational was defined as seven or nine years of mandatory schooling for persons born before and after January 1st 1958, respectively. Medium educational level was 10-12 years of schooling corresponding to upper secondary school or vocational education. Long education was defined as more than 12 years of education corresponding to higher education, Appendix 1.

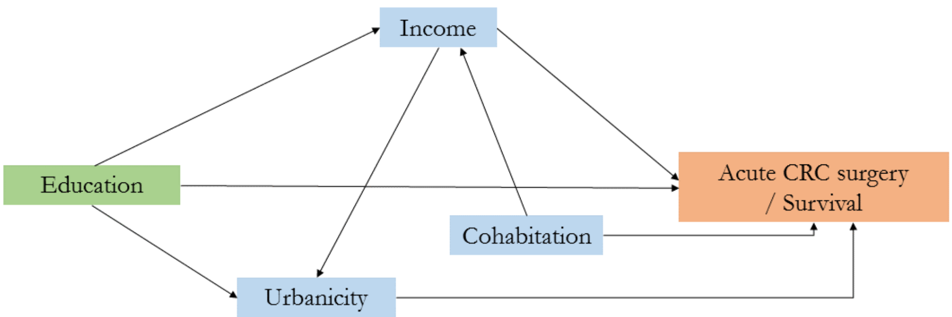


Figure 3: Hypothetical causal pathways between the four socioeconomic indicators.

Income was adjusted for sex, age and year of surgery and divided into quintiles for each income year to adjust for inflation and overall changes in income over the study period. To avoid the possible influence of a colorectal cancer diagnosis on income, the variable was retracted from the Income Statistics Registry the year before colorectal cancer surgery. Income represents financial capacity and the possibility of living a healthy lifestyle [58].

Urbanicity was the third socioeconomic indicator investigated. In Denmark, there are 98 municipalities and the Danish Business Authority (Erhvervsstyrelsen) made a composite indicator for urbanicity after the previous municipal reform in 2007 [87]. The categorisation of the specific municipalities is published in the DMCG benchmarking report from 2000 [22], *Appendix II*. Urbanicity was divided into the four categories; city, town, rural, and peripheral based on a composite of indicators such as population density, employment rate, number of jobs, distance to a highway, age, income, educational level etc. [87]. Urbanicity represents the effect of living far from the main hospitals diagnosing colorectal cancer and performing colorectal cancer surgery.

The last indicator for socioeconomic position investigated in study III was cohabitation. This indicator represents social and structural support while receiving a cancer diagnosis and treatment. Living with a partner could influence the support and initiative to contact a doctor when early signs and symptoms of the disease occur. Cohabitation could also affect the psychological support while in hospital and after discharge. Cohabitation was divided into living with a partner (married or cohabitating) or living without a partner (single, widow or divorced).

Before investigating socioeconomic position, causal pathways between the four indicator variables were considered, *Figure 3*. The pathways were taken into account when building the models of association between socioeconomic position and both acute surgery and 1-year survival. Educational level was the primary exposure of interest tested in the first model step. In the second model, it was investigated if income had an isolated effect on acute surgery or survival after adjusting for educational level. In the third model step, we investigated if urbanicity was associated with acute surgery or survival, when educational level and income were taken into account. Due to cheaper housing in the peripheral areas, individuals with low income might be more likely to live in these areas. In the last model step, we investigated the effect of cohabitation when adjusting for the effect of all the other three socioeconomic indicators.

6.6 Prediction models (study I and IV)

Before developing a prediction model, it is important to investigate existing models and gain knowledge about universal predictors. Several existing models predicted postoperative risk after colorectal cancer [70]; however, due to lack of clinical variables in the DCCG.dk database, only the ACPBGI model was possible to validate. In study I, validation of the APPGBI model showed suboptimal ability to predict 30-day mortality after colorectal cancer surgery, especially among the acutely operated (further details in section 8). The author group decided to develop a new model for postoperative mortality after acute colorectal cancer surgery (study IV). No model of this kind existed at the time study IV was initiated.

Development (study IV)

In study IV, the predicted outcome was 90-day mortality after acute colorectal cancer surgery. We chose 90-day mortality instead of 30-day mortality based on knowledge from study II showing a relevant increase in mortality between postoperative day 30 and day 90 from 16% to 25%. The model is thought to be implemented as a bedside score at the time it is decided to perform acute colorectal cancer surgery. Predictor variables were limited to factors known bedside at the time of arrival and no postoperative data could be included. Variables were selected for inclusion with backwards selection according to the minimum value of Akaike Information Criterion (AIC). The model was shrunken by bootstrapping to avoid over-fitting of the model in an external population [74]. A shrinkage factor and intercept were generated and added to the model before internal validation.

Validation (study I and IV)

An internal validation of a prediction model is an evaluation of how well the model predicts the outcome in the population the model was developed on. External validation is a test of the external validity of the prediction model in patients not included for development [88]. Validation is evaluated with various measurement, the most important being discrimination and calibration [88]. Discrimination is a measurement of the model's ability to predict the outcome in the patients who experience an outcome (sensitivity) and predict no outcome in patients who do not get an outcome event (specificity) [89]. Discrimination is measured by the area under the curve (AUC) of a receiver operating characteristic (ROC) curve. An AUC from 0.90 to 1.00 is considered an excellent discrimination, an AUC from 0.8 to 0.9 is considered a good discrimination and an AUC of 0.70 to 0.8 is considered a fair discrimination [90]. Calibration is a measurement of how well the model managed to assign a correct probability of the outcome. A calibration plot illustrates the relation between the observed and predicted risk of the primary outcome. Patients are divided into deciles according to the predicted value plotted on the x-axis and the corresponding observed value of the outcome on the y-axis. The optimal calibration plot is a line with a slope of one and an intercept in (0, 0) [88]. To test a significant difference between the observed and the estimated outcome in ten risk groups, the Hosmer-Lemeshow goodness-of-fit test is used in study I. However, in study IV, missing values were handled with multiple imputation which is not applicable in the goodness-of-fit test [88].

6.7 Statistics

Missing data

Before dealing with missing data, one first has to consider why data are missing and how this may bias the results [91, 92]. Missing data are classified in three groups depending on the reason for missing values. Data are missing completely at random (MCAR) if the missing data do not depend on neither unobserved nor observed data. Data are missing at random (MAR) if the missing values do not depend on the unobserved data conditional on the observed data. Data are missing not at random (MNAR) if the probability of data being missing depends on the unobserved data, conditional on the observed data [93]. It is not possible to test the mechanism behind missing values and knowledge about data collected is necessary to categorize missing in MCAR, MAR, or MNAR [94]. In the DCCG.dk database, missing values are most frequently seen in patient-related variables like BMI, alcohol, smoking, and performance status. There is no reason to believe that missing data depend on the unobserved data, e.g. that only the smokers were not asked about smoking status because they smoked, and the missing values are considered to be missing at random in all four studies.

Missing data can be handled by exclusion of all patients with missing values in any of the model variables, a complete case analysis (study I), by using a missing data indicator and categorize the missing values (study II), or by multiple imputation (study III and IV). In a complete case analysis and missing categorized as an indicator, there is a risk of biased results if patients with missing data deviate from the complete cases [95]. Excluding a proportion of the complete population can also result in loss of power [92].

Multiple imputation (Study III and IV)

In multiple imputation, the distribution of observed values are used to generate plausible values for missing data multiple times, which assimilate variation of the missing value [92]. Multiple imputation is a three-step process, *Figure 4*. In the first step, the original data set is copied *n* times with *n* imputed values for each missing. In this process, all other covariates included in the final model and the outcome are included. In the second step, the parameter estimated for each imputed data set is analysed. In the third step, the estimates from all *n* imputed data sets are combined using the Rubin's rule to generate one parameter estimate with a 95% confidence interval (94% CI) [91].

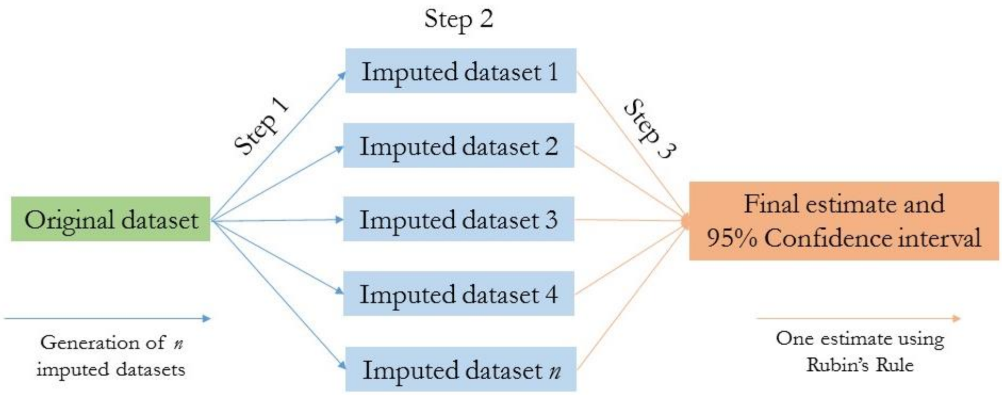


Figure 4. The three steps in multiple imputation

Logistic regression model and Cox proportional Hazard

In all four studies in this thesis, the primary outcomes were binary and subsequently all associations were investigated with either a logistic regression model or a Cox proportional Hazard regression model. Logistic regression was the statistical model used when time-to-event was not considered important, e.g. postoperative 90-day mortality. In study III, Cox proportional Hazard regression model was used to investigate the association between socioeconomic position and 1-year survival after acute colorectal cancer surgery because time-to-event was considered important.

In model testing, all continuous variables were tested for linearity and modelled as splines or in categories if not linear. Interactions between the primary exposure and pre-specified other covariates were considered in each study. An interaction between covariates indicates that the effect of the exposure depends on the another covariate [96], e.g. the effect of a treatment depend on the sex.

In study I, SPSS version 22 was used for statistical analysis. In study II-IV, data management, analysis, and graphs were conducted using SAS software 9.4. In study III, Rstudio was used to create the figures.

7. Ethics

All data in this thesis originate from registries and databases. We obtained approval for the project from the Danish Data Protection Agency, Statistics Denmark and the DCCG.dk database before initiation of the studies. Danish law does not require approval from The Danish National Committee on Health Research Ethics in register-based studies. All data were handled with strict confidentiality; data were stored safely and pseudo-anonymously with restricted access only for people involved in statistical analysis or data management. In register-based studies, it is not required to collect informed consent from the included patients according to Danish law [97]. However, it is required to present the result without the possibility to identify individual patients. In this thesis, patients with surgical procedures are included from 2005 and onwards. It would be impossible to obtain informed consent in a patient group with a high operative mortality risk.

8. Results

8.1 Study I

Aim

The aim of study I was to investigate if the original and revised ACPGBI model could predict 30-day mortality after colorectal cancer surgery in Denmark.

Methods

Patients undergoing colorectal cancer surgery from 2007 to 2013 were included, restricted to surgical procedures included in the revised ACPGBI model. Only patients registered in the DCCG.dk database were included. The predicted 30-day mortality was calculated according to the original model by information on age, American Society of Anaesthesiologist (ASA) score, cancer stage, cancer resection, and operative urgency, and with the revised model by information on age, ASA score, cancer stage, operative urgency and operative procedure. The discrimination of both models was evaluated with the AUC. Calibration was evaluated with the Hosmer-Lemeshow goodness-of-fit test. A subgroup analysis of only acutely operated patients was performed (only presented in the thesis).

Results

In total, 21,370 patients were included for analysis and 1437 patients were excluded due to missing values of minimum one of the model predictors. Thirty-day mortality was 5%, estimated to be 7% with the original model and 4% in the revised model. The ratio of observed over estimated mortality was 0.71 in the original model and 1.25 in the revised model. This indicates that the original model had a tendency of overestimating mortality while the revised model underestimated the mortality risk. A significant difference between the observed and estimated mortality was found in both models with the goodness of fit test. In the original ACPGBI model, no difference in observed and estimated 30-day mortality was found in high-risk patients with an estimated risk of more than 25%. Discrimination was good in both models with an AUC of 0.83 (95% CI 0.82-0.84) in the original model and an AUC of 0.83 (95% CI 0.82-0.84) in the revised model.

Among the included patients, 12% underwent acute colorectal cancer surgery. The 30-day mortality was 17% after acute surgery. In the subgroup analysis, a significant difference between observed and estimated 30-day mortality risk was found with the goodness-of-fit test in both models, $p = 0.0002$ in the original and $p < 0.0001$in the revised model, *Figure 5 and Figure 6*. The AUC decreased to 0.77 (95% CI 0.75-0.79) for the original model and AUC of 0.78 (95% CI 0.76-0.80) in the revised model when restricting the analysis to patients undergoing acute colorectal cancer, *Figure 5 and Figure 6*.

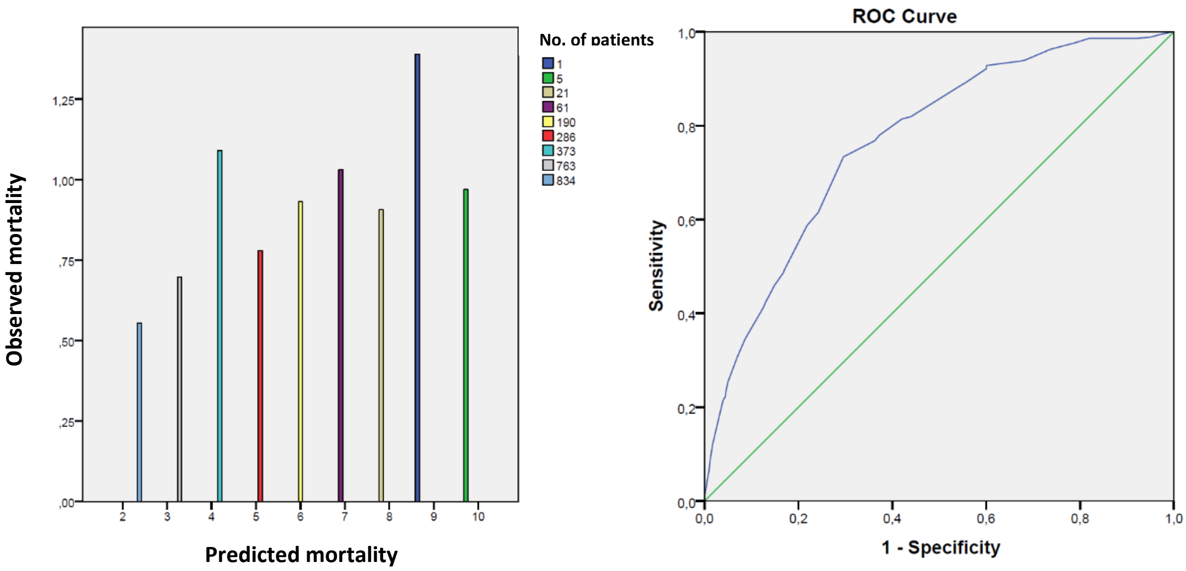


Figure 5. Calibration and discrimination of the original ACPGBI model, only for acutely operated patients.

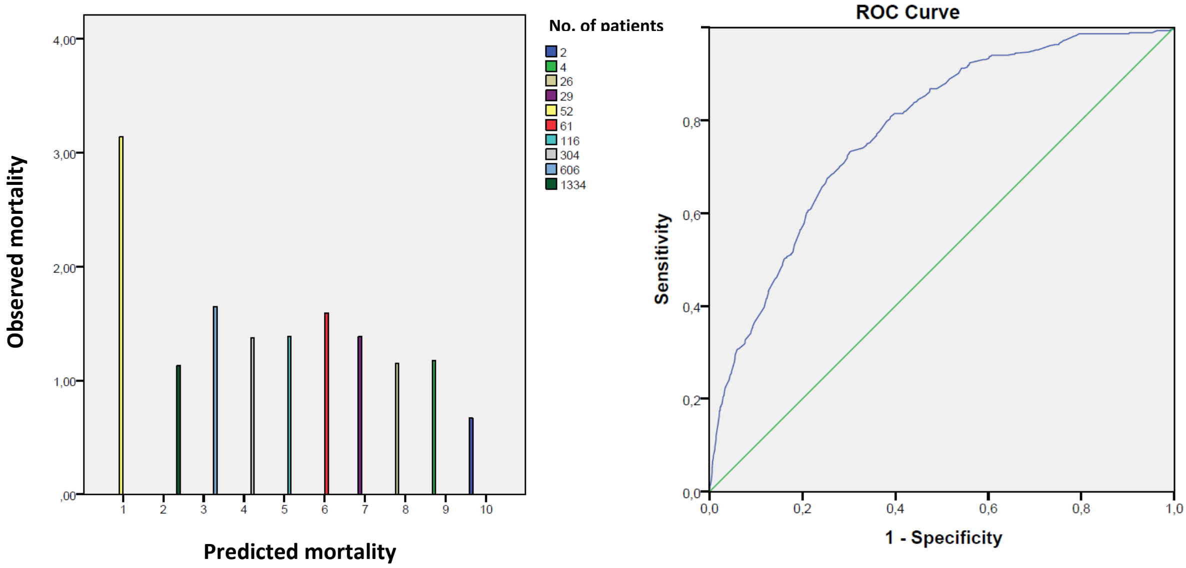


Figure 6. Calibration and discrimination of the revised ACPGBI model in, only for acutely operated.

Conclusion

In conclusion, neither the original nor the revised ACPGBI model had the ability to predict the 30-day mortality after colorectal cancer surgery in Denmark. However, both models had good discrimination both in the total population and in the subgroup of acutely operated patients.

Strengths and limitations

In the ACPGBI model, the primary outcome is 30-day mortality. This is not an optimal measure for operative mortality risk. In study II, we found that the mortality increased from 16% to 25% from postoperative day 30 to day 90. Our hypothesis is that improved intensive care treatment keeps patients alive longer postoperatively and that 90-day mortality is a better measure of surgical mortality risk. It is a strength in this study that we validated an existing prediction model already promising in other external validations [73, 85, 98-100]. Studies from Turkey, UK, China and the Netherlands all found good discrimination with an AUC from 0.70 to 0.87 and good calibration with no difference between the observed and the ACPBGI-model estimated 30-day mortality in four out of five studies [73, 85, 98-100]. This implicates good external validity of the model. The ACPBGI model was developed more than ten years ago and postoperative mortality after colorectal cancer surgery has improved in this period [8]. It is a limitation of study I that we did not recalibrate the original and revised model in our population to predict 30-mortality more accurately. Since the predictors are promising in external validation, a recalibration of the model could improve the calibration in a Danish context. The ACPGBI models are not possible to use preoperatively because the variable UICC stage is not known at the time of surgery. If this model was to be recalibrated in the Danish population to predict the operative mortality risk before surgery, the UICC has to be removed from the model.

It is a major limitation in study I that patients with missing data on any of the variables were excluded. A total of 6% of eligible patients were excluded due to missing data which is acceptable in terms of power when the population is already large. The main problem was that the excluded patients had a 30-day mortality of 14% versus 5% in the included patients. This difference indicates a selection bias of the healthiest patients for inclusion. It would have been better to include all patients and handle missing values with multiple imputation if the model was to be implemented in a clinical setting. Thus, the excluded patients had a high mortality risk and would be the most important to identify with a prediction model.

8.2 Study II

Aim

The aim of this study was to investigate if 90-day mortality after acute colorectal cancer surgery has improved from 2005 to 2015 in Denmark and to identify risk factors for 90-day postoperative mortality.

Methods

Patients undergoing acute colorectal cancer surgery according to the DCCG.dk database or the acute population algorithm and registered in the DCCG.dk database with a colorectal cancer diagnose from 2005 to 2015 were included in study II. We defined a surgical procedure as either a surgical resection, stent or diverting stoma. The association between year of surgery and postoperative mortality was investigated in a logistic regression model including possible confounding factors. Missing data were handled by categorizing the missing values within each variable. A subgroup analysis was performed in patients who underwent surgery excluding diverting stoma and SEMS. It was investigated if surgical specialization, operative approach or hospital volume was associated with 90-day mortality in patients undergoing surgical procedures other than SEMS and diverting stoma.

Results

In study II, 6147 patients were included for analysis. The overall 90-day mortality was 25% whereof 16% died within the first 30 days. The 90-day mortality rate improved with a yearly odds ratio (OR) trend of 0.94 (95% CI: 0.92-0.95, P< 0.0001). In 2015, the odds ratio for 90-day mortality was 0.65 (95% CI: 0.48-2.89) compared with 2005. The mortality rate improved already within the first 30 days after acute surgery from 2005 to 2015. Age was associated with 90-day mortality with an increased OR in the four age groups of 1.03 (95% CI: 1.02-1.05), 1.09 (95% CI: 1.06-1.12), 1.08 (95% CI: 1.02-1.13), and 1.07 (95% CI: 1.03-1.11) per year; thus, age was non-linear and included in the model as splines with 3 knots. Comorbidity also increased the risk of 90-day mortality for patients with a Charlson comorbidity index (CCI) score of one, two, and 3+ compared with a CCI score of zero with an OR of 1.57 (95% CI: 1.32-1.87), 1.86 (95% CI: 1.52-2.28), and 1.96 (95% CI: 1.66-2.31), respectively. Metastatic colorectal cancer (OR = 3.10, 95% CI: 1.80-5.36) compared with stage I disease and diverting stoma (OR =1.86, 95% CI: 1.53-2.27) compared with surgery as the primary procedure was also associated with 90-day postoperative mortality. SEMS as primary procedure was inversely associated with postoperative mortality (OR = 0.53, 95% CI: 0.45-0.64) compared with surgery. Having open surgery compared with minimal invasive surgery, was the only factor associated with 90-day mortality in the subgroup analysis (OR = 1.66, 95%CI: 1.23-2.23).

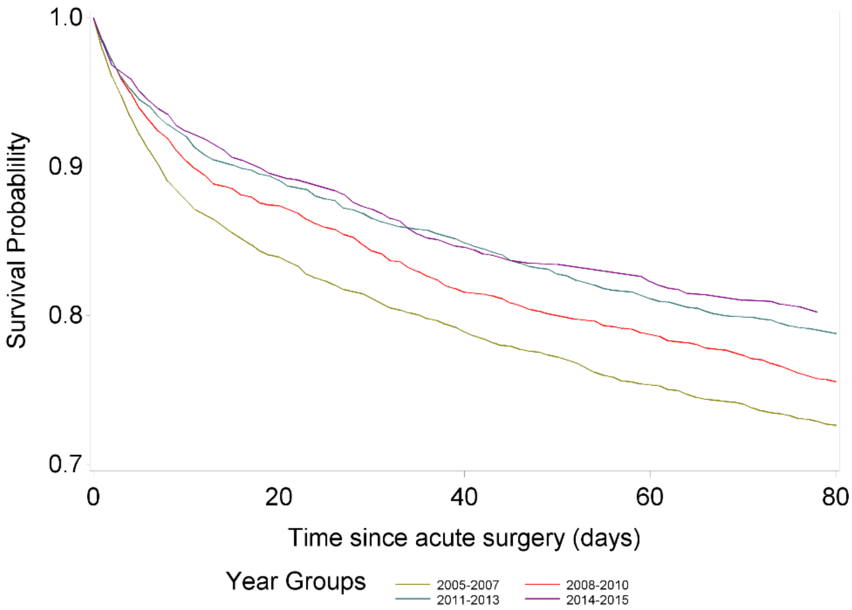


Figure 7. Kaplan-Meier curve for 90-day mortality according to year of surgery

Conclusion

In conclusion, the 90-day postoperative mortality have improved in Denmark from 2005 to 2015. High age, comorbidity, metastatic disease and diverting stoma as primary procedure were all associated with postoperative mortality. SEMS improved the operative mortality risk.

Strengths and limitations

It was a limitation in study II that missing data were categorized within each variable. In the variables with a high rate of missing values, information is lost about the effect of the variable, which may bias the results and warrant careful interpretation. Multiple imputation would have been a more accurate way to handle missing data, even though not a perfect solution.

Another limitation in study II was that the investigated risk factors could represent confounding by indication [101]. In this case, the variable itself is not a risk but it is rather the pathways in treatment, e.g. the patients characterized by this variable were selected to a specific treatment. An example from study II, is the increased mortality risk in patients with diverting stoma as the primary procedure. If diverting stoma is a risk factor, this procedure should not be recommended. However, if diverting stoma is the primary procedure chosen for the patients in a bad clinical condition, it might be the right approach. In conclusion, recommendation of the choice of primary procedure cannot be given by this observational study due to the risk of confounding by indication. In the DCCG.dk treatment guidelines diverting stoma and SEMS are recommended equally in acute obstruction of colorectal cancer [35].

The risk of residual confounding in study II is also a limitation. Patients included with this algorithm did not have the same detailed perioperative information, as did the patients with registration of acute surgery in DCCG.dk. The reason for acute surgery is one of the variables important for short-term survival and lacking this information could cause residual confounding. Patients who have a perforation of the colon or rectum are at high risk of postoperative mortality [14]. The increased risk of 90-day mortality in patients with diverting stoma as the primary procedure could have been confounded by the reason for acute surgery if patients with perforation was more likely to have diverting stoma than patients with obstruction. Lifestyle factors such as BMI, smoking and alcohol intake were not included in the model due to a high rate of missing values. This might also create residual confounding in our results.

It is a strength in study II that we had a high completeness of all patients undergoing acute colorectal cancer surgery as primary procedure due to the acute population algorithm. In the yearly report of the DCCG.dk database, it seems like the rate of acutely operated is decreasing. In contrast, our study shows that the annual number of acutely operated patients was quite stable from 2005 to 2015. In concordance, the proportion of patients included through the acute population database increased over the study period. This probably reflects that more patients get bridge to elective surgery in 2015 compared with 2005 and only the final procedure is registered in the DCCG.dk database.

8.3 Study III

Aim

The aim of study three was to investigate if low socioeconomic position was associated with the likelihood of being operated acutely for colorectal cancer. Secondly, to investigate if low socioeconomic position was associated with 1-year survival after acute colorectal cancer surgery.

Methods

In study III, all patients undergoing colorectal cancer surgery from 2007 to 2015 according to the acute population algorithm and registered with a diagnosis in the DCCG.dk database were included. Patients were excluded if they had missing information on surgical priority, income, urbanicity, or cohabitation; had migrated or disappeared within the first year after acute surgery, or were registered with a date of death before the date of surgery.

The association between social economic position and the likelihood of having acute surgery was investigated in a logistic regression model. Missing data were handled with multiple imputation, generating 10 imputed data sets. We tested for interaction between education and age and between education and CCI.

We applied a Cox regression to investigate the association between socioeconomic position and 1-year survival after acute colorectal cancer surgery. Missing data were handled with multiple imputation with the generation of 10 imputed datasets. We tested for interaction between education and age and between education and CCI.

Results

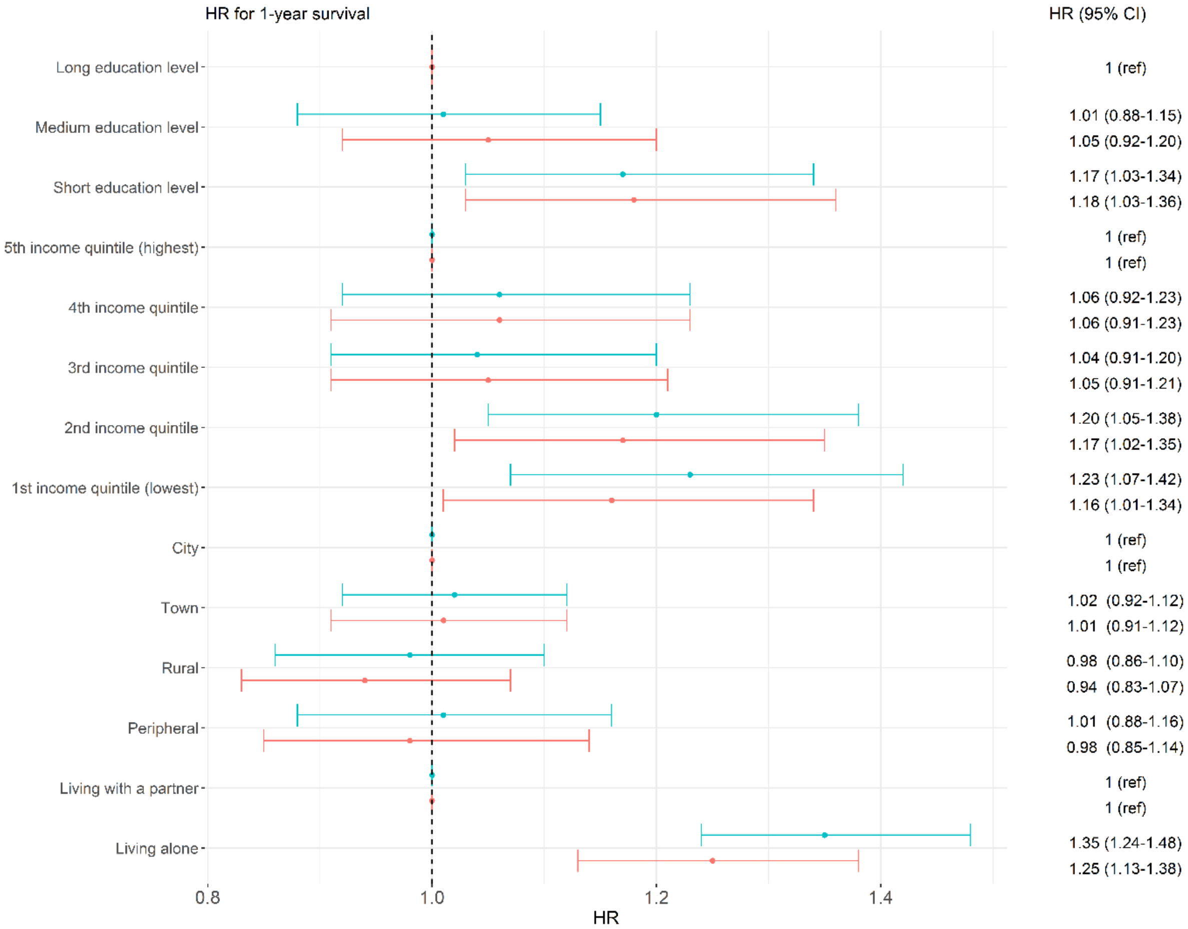
In study III, 35,661 patients were included whereof 5310 patients (15%) underwent acute colorectal cancer surgery. We excluded 140 patients in accordance with the exclusion criteria. In patients aged < 65 years, short and medium educational level was associated with an increased risk of acute surgery. For short education the OR was 1.58 (95% CI: 1.32-1.91) and for medium educational level the OR was 1.34 (95% CI: 1.15-1.55) for acute surgery. Independently of age, being in the second lowest income quintile and living alone were also associated with acute colorectal cancer surgery (OR =1.12, 95% CI: 1.01-1.24 and OR=1.35, 95% CI: 1.26-1.46, respectively), *Figure 8*.

Short education, low income and living alone were associated with decreased 1-year survival after acute colorectal cancer surgery. The hazard ratio (HR) for 1-survival for short education was 1.18 (95% CI: 1.03-1.36), for the lowest income quintile the HR was 1.16 (95% CI: 1.01-1.34), and for patients living alone the HR was 1.25 (95% CI: 1.13-1.38).

Conclusion

Low socioeconomic position measured by education, income and cohabitation was associated with a higher likelihood of acute surgery and subsequently a decreased risk of 1-year survival among patients treated with acute surgery.

Figure 8. Association between socioeconomic position and 1-year survival after acute colorectal cancer surgery.



Blue line: adjusted for sex, age and year of surgery. Red line: Adjusted for sex, age, year of surgery, Charlson Comorbidity Index score, BMI, smoking, drinking, UICC stage, and localization. Income additionally adjusted for education. Urbanicity additionally adjusted for education and income. Cohabitation additionally adjusted for education, income and urbanicity.

Strengths and limitations

Study III is the first to show socioeconomic disparities in survival after acute colorectal cancer surgery. Previous studies have primarily focused on mortality after elective colorectal cancer surgery or on the socioeconomic gradient in acutely versus electively operated patients with colorectal cancer [56, 59].

Socioeconomic position is an indicator for unequal health conditions and is associated with particular health outcome. In study III, we tested if UICC stage at surgery, smoking, alcohol, or BMI could explain the socioeconomic gradient. None of these variables had a high impact on the estimate neither in the association with acute surgery nor with 1-year survival after acute surgery. We may lack identification on other factors potentially mediating the socioeconomic gradient and thus explain why patients with a short education live shorter after acute colorectal cancer surgery. This introduces residual confounding or mediation in our results. The clinical condition at the time of surgery is a possible unmeasured confounder. If patients with short education, low income, and living alone wait longer from onset of acute symptoms to contact of medical support, the acute condition can become more critical leading to a poor postoperative outcome [14]. However, the mortality also increase remarkably in the acutely operated from 24% 90 days after surgery to 41% 1 year postoperatively and unmeasured confounding or mediation in this time-gab should be investigated. In order to investigate the causal relation between the socioeconomic gradient and 1-year survival, the cause of death is needed. To prevent early and 1-year mortality it is crucial to find out what patients died from.

8.4 Study IV

Aim

The aim of study IV was to develop a prediction model for 90-day mortality after acute colorectal cancer surgery and subsequently validate the model.

Methods

The prediction model was developed and validated in patients undergoing acute colorectal cancer surgery in 2014 and 2015, respectively. We tested age, sex, performance status, BMI, smoking, alcohol, educational level, cohabitation, localization of the tumour and primary procedure as possible predictor variables. Missing data were handled with multiple imputation, by generating 10 imputed data sets. The model was developed with a logistic regression model and variables included in the model were selected with backwards selection according to the lowest AIC. After variable selection, the model was shrunken by 1000 bootstrapping samples creating a shrinkage factor and intercept integrated in the final model to minimize the risk of overfitting. The model was validated both internally, on the patients the model was developed on and externally on the patients operated in 2015. Accuracy was evaluated with a Brier score, discrimination with the AUC and calibration was evaluated with a calibration plot.

Results

In study IV, 535 patients were included for development of the prediction model, while 554 patients were included for validation. In the final model, the predictor variables age, performance status, smoking, alcohol and primary procedure were included, *Figure 9*.
The 90-day mortality was 18% in 2014 and 24% in 2015. In the internal validation, the Brier score was 0.12, and the AUC was 0.80. The calibration slope had an intercept of 1.0 and the slope 1.0. In the external validation, the Brier score was 0.16 and the AUC was 0.72. The calibration slope had an intercept of 1.0 and the slope 1.0.

Figure 9. Model for predicting 90-day mortality after acute colorectal cancer surgery

	Risk group	Score
Age		
	<65	0.00
	>65-70	0.92
	>70-75	1.08
	>75	1.67
Performance Score		
	0	0.00
	1	1.11
	2	1.45
	3-4	2.14
Alcohol (weekly recommendation)[1]		
	Below	0.00
	Above	0.78
Smoking		
	Never smoked Former smoker[2] Smoker	0.00 0.45 0.89
Primary procedure		
	Stent Surgery	0.00 0.48

1. Above weekly recommendation is defined as >14 units/week for women and >21 units/week for men.
2. Not smoked for minimum weeks.

$\text{In}(R/1-R) = -4.66788 + (\text{score})$, where R is the risk of death

Conclusion

We developed a prediction model for 90-day mortality after acute colorectal cancer surgery. The final predictor variables included in the model were age, performance status, smoking, alcohol, and primary procedure. The internal validation showed a good Brier score, good discrimination and poor calibration. In the external validation, the Brier score was good, the AUC was only acceptable and the calibration was poor.

Strengths and limitations

A major limitation of this study is that predictor candidates are limited to the variables collected by the DCCG.dk. Previous prediction models have shown that paraclinical tests such as haemoglobin and leucocytes are important predictors for postoperative outcome after colorectal cancer surgery [71, 72]. It would have been relevant and possible to test some of these predictor variables in the model if the predictor variables were collected prospectively for the purpose of this study. Another limitation of the study is that patients might already have been selected to surgery or no surgery. If the model is to be used as a tool in shared, clinical decision-making, this selection of patients is relevant if the surgeon and patients decide to withdraw from surgery. When we have not included patients with acute presentation who were not operated, the mortality risk was probably underestimated assuming that the oldest patients with comorbidities were the ones selected for no surgery. There is a problem with the power in the development of the prediction model. In total, 94 patients died within the first 90-days postoperatively and 11 predictor variables with 31 degrees of freedom are tested eligible for the model. The general rule of thumb is that there should be 10 cases for each degree of freedom in the development of a prediction model. This might explain the suboptimal calibration.

In study IV, the first prediction model for 90-day mortality after acute colorectal cancer surgery was developed. It is a strength that we have including all patients undergoing colorectal cancer surgery in Denmark. The model had a good ability to discriminate between patients who died and patients who survived 90 days after surgery with an AUC of 0.72 in the external validation. The developed model was not ideal but a reasonable basis for further development.

In future studies it might be interesting to include patients with benign abdominal emergencies as well. Even though the cancer is important for the surgical procedure, many preoperative predictors for postoperative mortality are probably the same in benign acute colorectal surgery. From a clinician's perspective, it would be meaningful to treat patients with an abdominal emergency the same and then include the information about malignancy in the model. It is also more likely that the model will be used, if it involves all patients with obstruction and perforation and not only the few cases where cancer is causing the symptoms.

9. Discussion

The overall findings of this PhD thesis were that 90 day-mortality among patients operated acutely for colorectal cancer has improved in Denmark within the last 10 years, but the 90-day mortality rate remains as high as 25% in 2015. High age, comorbidity measured with the Charlson Comorbidity Index, metastatic diseases, and diverging stoma were associated with increased risk of postoperative 90-day mortality. Socioeconomic indicators associated with decreased 1-year survival mortality were short education, low income and living alone. The same socioeconomic indicators were associated with the likelihood of acute versus elective surgery for colorectal cancer.

In order to predict the postoperative mortality after colorectal cancer surgery, the ACPGBI prediction model was tested inferior, especially among the acutely operated. In this thesis, we developed the first prediction model for postoperative mortality after acute colorectal cancer surgery. The external validation showed a model with acceptable discrimination and poor calibration. The accuracy measured by the Brier score was also good.

9.1 Bias due to the observational study design.

A strength in this thesis is that the internal validity was high due to the data of registers and a database. First, all studies have a relatively large sample size and study II-IV are some of the largest published cohorts regarding acute colorectal cancer only. Furthermore, there is a high completeness rate of 95%-99% of all colorectal cancer patients in Denmark in the DCCG.dk database [80]. The acute population algorithm improved the completeness rate of the acutely operated. This resulted in a minimized risk of selection bias and very few exclusion criteria, which is only possible when the whole population constitutes the base population [102]. All studies had an almost complete follow-up of vital status on all included patients continuously updated in the NPR, which strengthened the internal validity. Only the few patients who migrated or disappeared were lost to follow-up. A strength of this thesis is also that data were registered prospectively in the registries independently of the study hypotheses, which eliminated the risk of recall bias. In retrospective studies, recall bias is an important bias risk and describes the phenomena that patients developing a disease remember an exposure better than the control group [103].

Confounding by indication is a relevant potential bias in all four observational studies of this thesis. This type of bias indicates that patients were not randomly designated to one treatment or the other, as is the case in a randomized controlled trial [101, 104]. The selection of treatment is rather subjective and depends on the patient characteristics, the disease characteristics and the surgeon's clinical experience or preferences. Keeping confounding by indication in mind is important when interpreting the results of all four studies. The variable "primary surgical procedure" is an example of how to interpret carefully. In study II, diverting stoma was a risk factor for increased postoperative mortality. It is not possible to recommend one treatment over the other based on this finding due to the risk that the patients at high operative risk were selected for this treatment. In study IV, diverting stoma was also identified as an important predictor variable for postoperative 90-day mortality. This indicates that patients selected for diverting stoma were predicted to have a higher risk of postoperative mortality. However, we cannot conclude that a change of procedure from diverting stoma to resection would give the patient a better postoperative survival because we believe that the relation between diverting stoma and mortality is not causal.

It is a limitation in this thesis that data were restricted to the variables available in the databases and registries, but a strength that data were not pre-collected by the research group with the purpose of answering the specific project hypotheses which minimize the risk of information bias [102]. The registries and databases collected the variables and controlled the completeness and accuracy of data. There could have been mistakes in the registered data that are hard to identify and correct. In the acute population algorithm, it was conditioned that the patient was registered with an acute admission. The variable "type of admission" had many missing values in the NPR and this might have affected the completeness of the population. Important confounders or mediators may also be unavailable in the registries or databases causing residual confounding. In our studies, it would have been valuable to collect data on the clinical condition of the patient at the time of surgery [105, 106]. Some of the known mediators for poor survival in acute colorectal surgery are sepsis, colon perforation, and white blood cell count [14, 107]. These mediators could have affected the results in study II-IV. Some variables available in the DCCG.dk, like perforation, has a high proportion of missing values and the patients included with the acute population algorithm did not have perioperative data. Unmeasured confounding is less important in randomized trials because randomization in principle should ensure equally distributed of known and unknown confounders in the groups. If a suspected confounder is available in some of the patients in observational studies, a sensitivity analysis with this subgroup is a way of testing for residual confounding [108].

Unfortunately, it was not possible to validate the acute population algorithm. All data were pseudo-anonymized and data from Statistics Denmark cannot be retracted. It would have been valuable to validate the algorithm by going into patient files and investigate the validity of the algorithm.

In the external validity of the study results, it is important to be aware that the studies only concern patients who undergo colorectal cancer surgery and cannot be extrapolated to generalize anything about patients who had acute presentation of colorectal cancer but did not undergo surgery.

9.2 Acute abdominal surgery

This thesis has confirmed that acute surgery for colorectal cancer is a major risk for operative mortality. It is crucial to establish what treatment strategies can improve survival in these patients. There is a lack of literature about perioperative treatment to improve survival after acute colorectal cancer surgery. Inspiration must be sought in the literature regarding acute surgery for non-malignant major abdominal crises. A Danish study initiated in 2013 implemented a standard care, multidisciplinary and multimodal intervention, on all patients admitted to a single centre with major abdominal pathology requiring acute surgery [109]. They included 600 consecutive patients and compared them with 600 historical controls. In the intervention group, standard of care was improved by early resuscitation after admission, early high-dose antibiotics, initiation of surgery within 6 hours after arrival, standardized analgesic treatment, early postoperative ambulation and nutrition. With these simple changes in perioperative care and management, the 30-day mortality rate decreased from 21.8% to 15.5% ($p = 0.005$) and 180-day mortality decreased from 29.5% to 22.2% ($p= 0.004$) [109]. In UK, a similar study on all acute laparotomies was conducted in 2015 with implementation of improved perioperative care [110]. This included Early Warning Score (EWS), early antibiotics, initiation of surgery less than six hours after decision, gold directed fluid therapy, and postoperative intensive care. This intervention reduced postoperative mortality from 15.6% to 9.6% ($p= 0.003$) comparing 427 patients in the intervention group with 299 historical controls. The relative mortality rate was 0.61 (95% CI: 0.45-0.85) [110]. A Chinese study investigated the effect of enhanced recovery after surgery (ERAS) programme after acute abdominal surgery [111]. They compared 556 patients in a modified ERAS programme with 483 patients treated with standard care and found an improved function of the intestine measured by time to first flatus ($P=0.002$), time to first defecation ($P=0.008$), and decreased prolonged ileus (p=0.016). Patients in the ERAS programme also had less surgical complications (P = 0.002) [111] .

The overall experience from previous studies indicate that a multimodal and multidisciplinary intervention probably is a substantial part of the solution to improve survival after acute colorectal cancer surgery. In study III, the mortality rate increased from 24% on day 90 postoperatively to 41% one year after surgery. With these findings, we have identified an important window for improvement of mortality. Some of the deaths might be unpreventable and caused by progression of the cancer disease. Further studies should investigate if some deaths could be prevented with close long-term follow-up or rehabilitation.

It is also important to investigate the core solution to avoid mortality after acute colorectal cancer surgery, which is how to prevent an acute presentation of the disease by identifying the patients earlier. Improving the screening of colorectal cancer in patients at high risk of acute presentation is one way of approaching this. In the annual report from the DCCG.dk from 2017, the crude 1-year and 4-year survival were improved in patients diagnosed through screening compared with patients diagnosed through other pathways, e.g. due to symptoms [4]. A British study from 2017 investigated the risk factors for acute colorectal cancer surgery in 286,591 patients diagnosed from 1997 to 2012 [11]. Introduction of screening in 2016 reduced by 40% the proportion of acutely operated from 23% to 15% ($p<0.001$). In Denmark, a screening program for colorectal cancer was implemented in 2014 including individuals aged 50 to 74 years. However, it is too early to evaluate a decrease in the proportion of acutely operated in our data in study II-IV. Previous studies found socioeconomic disparities in participation of colorectal cancer screening. Patients with a short education, low income and living alone were less likely to participate in the screening programme [61, 112]. This implies that even though the total number of acutely operated might be decreasing due to screening, this will probably not be to the benefit of the socioeconomically deprived. In 2017, the DCCG.dk registered only 250 patients with acute surgery as final procedure [4]. The decreased number could either be due to less acutely operated or because more patients are bridged to elective surgery. Another way of increasing the cancers diagnosed earlier, before acute symptoms occurs, is primary prevention such as national health campaigns for the population and for the doctors in primary care [42].

9.3 Socioeconomic position

In study III, we found that living alone was associated with both the likelihood of acute surgery for colorectal cancer and for a decreased risk of 1-survival subsequently. This can be interpreted as lack of social and psychological support encouraging an individual to seek medical advice. The decrease in 1-year survival, even after adjusting for cancer progression, might reflect the ability of self-care after discharge. A study from Ireland including 2750 patients with rectal cancer, similarly found that marriage was protective for acute presentation (OR = 0.85, 95% CI: 0.74-0-98) pointing to the importance of social support [50].

In the known literature on disparities in socioeconomic position, most studies found that the difference in cancer survival is partly mediated by comorbidity and cancer stage and to a lesser degree by treatment. One study regarding prostate cancer found that patients with low socioeconomic position had a decreased cancer specific survival (HR = 1.48, 95% CI: 1.03-2.13). The association was eliminated when adjusting for comorbidity and cancer stage which thought to mediate the association between short education and survival [113]. Also in cervical cancer, decreased overall survival in patients with short education level (HR = 1.46, 95% CI 1.20-1.77) was explained mainly by differences in screening participation, cancer stage and life style and no effect of socioeconomic position could be observed in the fully adjusted analysis [114]. In study III, none of the variables included in the models seemed to explain differences in socioeconomic position. We would have expected that advanced cancer stage, comorbidity or lifestyle factors would have mediated the socioeconomic gradient; however, the mechanism of difference in acute surgery and survival remains unknown in study III.

9.4 Prediction models

A prediction model should preferably be developed from a prospective cohort in order to include all variables known to be predictive from the literature [64]. In study IV, the predictor variables were restricted to those variables available in the DCCG.dk database. From the Cleveland Clinic Foundation and the POSSUM models, we know several paraclinical measures, like haemoglobin, lymphocytes, and haematocrit, which are predictors for postoperative mortality after colorectal cancer surgery. It is a limitation in study IV that data on blood tests are not available. However, it would be interesting to make a sensitivity analysis in a subpopulation to test the additive predictive value of known predictive blood tests. It is also possible that the developed prediction model in study IV should rather include all patients having major abdominal acute surgery because these patients have some of the same risk factors for mortality.

In order to evaluate the external validity of the prediction model developed in study IV, it would be interesting to make a validation in other countries with similar organization of the health system, like Sweden or the Netherlands.

9.5 Future perspectives

In order to improve survival in patients with acute colorectal cancer surgery, it would be interesting to test the prediction model developed in study IV in a cluster randomized controlled trial. In some centres, a multimodal predefined perioperative care programe with focus on survival during and after hospitalization would then be applied according to the risk prediction. This is the only way to validate whether a prediction model have an impact on the clinical outcome. It would also be interesting to develop a separate prediction model for the patients who have undergone elective colorectal cancer surgery, since the existing models all include variables known after surgery.

In study III, we found a 41% mortality rate within the first year after acute colorectal cancer surgery. This is an alarming high mortality rate and further studies are needed to investigate the cause of death to initiate possible preventive studies. A Danish study introduced daily visits from a nurse to help with basic needs after insertion of metallic stents in patients with non-resectable oesophagus cancer in a randomized trial (MB Mortensen, not yet published). Survival was improved significantly in the intervention group. It should be investigated if routinely home visits in patients at high mortality risk after acute colorectal cancer surgery could improve survival. Home visits constitute a simple intervention, it is relatively cheap and should be easy to implement in Denmark where the system already exists for elderly people. It is reasonable to hypothesise that both instrumental and psychosocial support could improve survival and quality of life among also vulnerable patients who may be older, living alone and who have few socioeconomic resources.

In study III, we found socioeconomic disparities in patients operated acutely for colorectal cancer. Previous studies have found socioeconomic disparities in participation of colorectal cancer screening. In some cases, acute presentation of colorectal cancer is possibly due to patient-delay and could be prevented if the cancer was detected in a screening programme. It would be interesting to make a more active screening surveillance in patients who do not attend the screening program and who are at high risk of acute surgery, e.g. individuals living alone and individuals with a short education.

10. Conclusion

This thesis has contributed with knowledge about patients operated acutely for colorectal cancer and identified predictors for 90-day postoperative survival. We have showed that survival has improved the last ten years, but that the 90-day mortality rate remains unacceptably high of 24%, increasing to 41% one year after surgery. Age, comorbidity, cancer stage, and diverting stoma was identified to increase the risk of postoperative mortality. This thesis is the first to show socioeconomic disparities in survival after acute colorectal cancer surgery. Short education, low income and living alone were associated with the likelihood of an acute operation and subsequently decreased 1-year survival. The studies have demonstrated a need to enhance focus on the patients acutely operated. To improve survival in patients operated acutely, it is beneficial to identify patients with a high risk of mortality. The ACPGBI prediction model was validated in this thesis and only showed acceptable discrimination and poor calibration. We developed a new model including age, performance score, smoking, alcohol and intended primary procedure to predict postoperative mortality after colorectal cancer. The discrimination was acceptable and the calibration showed underestimation of the mortality risk. The model will be adjusted further to improve the calibration before taking it into clinical practice.

11. English summary

Background

Colorectal cancer is one of the most common cancers with an estimated incidence of 1.7 million worldwide. Patients presenting with acute symptoms like tumour obstruction or bowl perforation, are operated acutely with a high risk of postoperative mortality. Around 10% of all colorectal cancer surgeries are performed as an acute procedure and the postoperative mortality varies from 6% to 22%.

Aim

The aim of this thesis was to investigate if the postoperative mortality after acute colorectal cancer surgery has improved in Denmark within the last ten years and to identify risk factors for early death. We furthermore aimed to investigate whether low socioeconomic position was associated with the risk of having colorectal cancer surgery as an acute procedure and subsequently if low socioeconomic position was associated with decreased 1-year survival. We aimed to validate if the Association of Coloproctology of Great Britain and Ireland (ACPGBI) model could predict 30-day mortality after colorectal cancer surgery in Denmark. The final aim of this thesis was to develop a model to preoperatively predict the risk of postoperative 90-day mortality in acutely operated patients with colorectal cancer.

Methods and result

All four studies of this PhD thesis were register-based historical cohort studies. Data were mainly collected from the Danish Colorectal Cancer Group database and the Danish National Patient Registry. Patients were included from 2005 to 2015. In the thesis, we found that the 90-day mortality has improved in Denmark within the last 10 years. Age, comorbidity, metastatic diseases and diverging stoma were associated with increased risk of postoperative mortality. Socioeconomic indicators associated with increased 90-day postoperative mortality were low educational level, low income and living alone. The same socioeconomic indicators were associated with the likelihood of acute versus elective surgery for colorectal cancer. The ACPGBI prediction model was not appropriate to identify patients at high mortality risk. In this thesis, the first model to preoperatively predict mortality in acutely operated patients with colorectal cancer is presented. In the external validation the model had a good accuracy, an acceptable discrimination and a calibration with underestimation of mortality.

Conclusion

The overall finding of this PhD thesis was that 90 day-mortality has improved in Denmark within the last 10 years but has remained as high as 24% in 2015. This thesis was the first to present the association between low socioeconomic position and decreased 1-year survival in acute colorectal cancer surgery. It was confirmed that also in Denmark, individuals with low socioeconomic position are more likely to have acute colorectal cancer surgery compared with elective. Finally, a model to predict 90-day mortality after acute colorectal cancer surgery was presented in this PhD thesis.

12. Danish summary

Baggrund

Kolorektalkræft er en af de mest almindelige kræftformer i verden med en anslået forekomst på 1,7 millioner om året. Patienter, hvis kræft debuterer med akutte symptomer som tumorobstruktion eller perforation, har en øget risiko for at dø postoperativt. Omkring 10 % af alle kolorektalkræft-operationer udføres som en akut procedure, og den postoperative dødeligheden er mellem 6% og 22%.

Formål

Formålet med denne Ph.d.-afhandling var at undersøge, om korttidsdødeligheden efter akut kolorektalkræft-kirurgi har forbedret sig i Danmark de sidste ti år, og hvilke risikofaktorer der var forbundet med en høj dødelighed. Det var desuden et formål at undersøge, om lav socioøkonomisk position var forbundet med en øget risiko for at blive opereret akut efterfølgende og for nedsat 1-års overlevelse efter akut kirurgi. Det var i afhandlingen et formål at validere om prædiktionsmodellen fra Association of Coloproctology of Britain og Ireland (ACPGBI) kunne forudsige 30-dages overlevelsen for patienter opereret for kolorektalkræft samt i en undergruppe af kun akutopererede. Det sidste formål med denne afhandling var at udvikle en model til præoperativt at forudsige risikoen for 90-dages dødelighed efter akut kolorektalkræft-kirurgi.

Metoder og resultat

Alle fire studier i denne ph.d.-afhandling var registerbaserede, historiske kohortestudier. Data blev primært indsamlet fra den danske kolorektalkræftgruppe (Danish Colorectal Cancer Group, DCCG.dk) databasen og Landspatientregistret. Patienter blev inkluderet fra 2005 til 2015. I afhandlingen fandt vi, at 90-dages dødelighed efter akut kolorektalkræft-kirurgi er forbedret i Danmark gennem de sidste 10. Alder, komorbiditet, metastaserende sygdomme og aflastende stomi som primær procedure var forbundet med øget risiko for død efter operationen. Socioøkonomiske indikatorer forbundet med øget 90-dages dødelighed var kort uddannelsesniveau, lav indkomst og det at bo alene. De samme socioøkonomiske indikatorer var forbundet med en øget sandsynlighed for akut versus elektiv kirurgi. ACPGBI-modellen var ikke optimal til at identificere patienter med høj dødelighed. I denne afhandling præsenteres den første model for præoperativ forudsigelse af dødelighed hos akutopererede patienter med kolorektalkræft. I den eksterne validering havde modellen en god nøjagtighed, en acceptabel diskrimination og en kalibrering med undervurdering af dødelighed.

Konklusion

Det overordnede fund i denne ph.d.-afhandling var, at 90-dages dødeligheden efter akut kolorektalkræft-kirurgi er forbedret i Danmark gennem de sidste 10 år, men dødeligheden er forblevet så høj som 24% i 2015. Denne afhandling var den første til at præsentere at der er en sammenhæng mellem lav socioøkonomisk position og nedsat 1-års overlevelse efter akut kolorektalkræft-kirurgi. Det blev bekræftet, at der også i Danmark er en association mellem lav socioøkonomisk position og akut kolorektalkræft-kirurgi sammenlignet med elektiv. Endelig præsenteres den første model til at forudsige 90-dages mortalitet efter akut operation for kolorektalkræft.

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14. Appendix

Appendix 1. Categorisation and translation of highest attained education

Categorisation:		Definition
i.	Short (10,15)	Mandatory school, corresponding to a maximum length of education of seven years for persons born before 1 January 1958, and nine years for persons born at or after this date.
ii.	Medium (20, 25, 35, 39)	Secondary school and vocational education, which approximate to a maximum of 10-12 years of schooling.
iii.	Higher (40, 50, 60, 65, 70)	Short, medium or long-term higher education, approximately over 12 years of education.

Translation to the Danish education vocabulary (references in the categorization)

Category	Type of education
Short	10 Grundskole 15 Forberedende uddannelser
Medium	20 Almene gymnasiale uddannelser 22 Grundskole længere end obligatorisk, for personer født før 1958. 25 Erhvervsgymnasiale uddannelser 30 Erhvervsfaglige grundforløb
	35 Erhvervsfaglige praktik og hovedforløb 39 Efteruddannelse af faglærte
Higher	40 Korte videregående uddannelser 50 Mellemlange videregående uddannelser 60 Bachelor 65 Lange videregående uddannelser 70 Forskeruddannelse

Appendix 2. Specification of the categorisation of urbanicity for each municipality from the bench marking report [22].

In translation of the Danish terminology the following word are used in the thesis Bykommune equals city, Mellemkommune equals town, Landkommune equals rural, Yderkommune equals peripheral.

Kommune Kode	Kommune Navn	Region Kode	Region Navn	Geokode
101	København	084	Hovedstaden	Bykommune
147	Frederiksberg	084	Hovedstaden	Bykommune
151	Ballerup	084	Hovedstaden	Bykommune
153	Brøndby	084	Hovedstaden	Bykommune
155	Dragør	084	Hovedstaden	Bykommune
157	Gentofte	084	Hovedstaden	Bykommune
159	Gladsaxe	084	Hovedstaden	Bykommune
161	Glostrup	084	Hovedstaden	Bykommune
163	Herlev	084	Hovedstaden	Bykommune
165	Albertslund	084	Hovedstaden	Bykommune
167	Hvidovre	084	Hovedstaden	Bykommune
169	Høje-Taastrup	084	Hovedstaden	Bykommune
173	Lyngby-Taarbæk	084	Hovedstaden	Bykommune
175	Rødovre	084	Hovedstaden	Bykommune
183	Ishøj	084	Hovedstaden	Mellemkommune
185	Tårnby	084	Hovedstaden	Mellemkommune
187	Vallensbæk	084	Hovedstaden	Bykommune
190	Furesø	084	Hovedstaden	Bykommune
201	Allerød	084	Hovedstaden	Bykommune
210	Fredensborg	084	Hovedstaden	Bykommune
217	Helsingør	084	Hovedstaden	Bykommune
219	Hillerød	084	Hovedstaden	Bykommune
223	Hørsholm	084	Hovedstaden	Bykommune
230	Rudersdal	084	Hovedstaden	Bykommune
240	Egedal	084	Hovedstaden	Bykommune
250	Frederikssund	084	Hovedstaden	Bykommune
253	Greve	085	Sjælland	Bykommune
259	Køge	085	Sjælland	Bykommune
260	Halsnæs	084	Hovedstaden	Mellemkommune
265	Roskilde	085	Sjælland	Bykommune
269	Solrød	085	Sjælland	Bykommune
270	Gribskov	084	Hovedstaden	Bykommune
306	Odsherred	085	Sjælland	Landkommune
316	Holbæk	085	Sjælland	Mellemkommune
320	Faxe	085	Sjælland	Mellemkommune
326	Kalundborg	085	Sjælland	Landkommune
329	Ringsted	085	Sjælland	Mellemkommune
330	Slagelse	085	Sjælland	Mellemkommune
336	Stevns	085	Sjælland	Mellemkommune
340	Sorø	085	Sjælland	Mellemkommune

350	Lejre	085	Sjælland	Bykommune
360	Lolland	085	Sjælland	Yderkommune
370	Næstved	085	Sjælland	Mellemkommune
376	Guldborgsund	085	Sjælland	Landkommune
390	Vordingborg	085	Sjælland	Landkommune
400	Bornholm	084	Hovedstaden	Yderkommune
410	Middelfart	083	Syddanmark	Mellemkommune
411	Christiansø	084	Hovedstaden	Yderkommune
420	Assens	083	Syddanmark	Landkommune
430	Faaborg-Midtfyn	083	Syddanmark	Landkommune
440	Kerteminde	083	Syddanmark	Landkommune
450	Nyborg	083	Syddanmark	Landkommune
461	Odense	083	Syddanmark	Bykommune
479	Svendborg	083	Syddanmark	Landkommune
480	Nordfyns	083	Syddanmark	Landkommune
482	Langeland	083	Syddanmark	Yderkommune
492	Ærø	083	Syddanmark	Yderkommune
510	Haderslev	083	Syddanmark	Landkommune
530	Billund	083	Syddanmark	Landkommune
540	Sønderborg	083	Syddanmark	Landkommune
550	Tønder	083	Syddanmark	Yderkommune
561	Esbjerg	083	Syddanmark	Landkommune
563	Fanø	083	Syddanmark	Landkommune
573	Varde	083	Syddanmark	Yderkommune
575	Vejen	083	Syddanmark	Landkommune
580	Aabenraa	083	Syddanmark	Landkommune
607	Fredericia	083	Syddanmark	Mellemkommune
615	Horsens	082	Midtjylland	Mellemkommune
621	Kolding	083	Syddanmark	Bykommune
630	Vejle	083	Syddanmark	Mellemkommune
657	Herning	082	Midtjylland	Landkommune
661	Holstebro	082	Midtjylland	Landkommune
665	Lemvig	082	Midtjylland	Yderkommune
671	Struer	082	Midtjylland	Yderkommune
706	Syddjurs	082	Midtjylland	Landkommune
707	Norddjurs	082	Midtjylland	Yderkommune
710	Favrskov	082	Midtjylland	Mellemkommune
727	Odder	082	Midtjylland	Mellemkommune
730	Randers	082	Midtjylland	Landkommune
740	Silkeborg	082	Midtjylland	Mellemkommune
741	Samsø	082	Midtjylland	Yderkommune
746	Skanderborg	082	Midtjylland	Bykommune
751	Aarhus	082	Midtjylland	Bykommune
756	Ikast-Brande	082	Midtjylland	Landkommune
760	Ringkøbing-Skjern	082	Midtjylland	Yderkommune

766	Hedensted	082	Midtjylland	Landkommune
773	Morsø	081	Nordjylland	Yderkommune
779	Skive	082	Midtjylland	Yderkommune
787	Thisted	081	Nordjylland	Yderkommune
791	Viborg	082	Midtjylland	Landkommune
810	Brønderslev-Dronninglund	081	Nordjylland	Landkommune
813	Frederikshavn	081	Nordjylland	Landkommune
820	Vesthimmerlands	081	Nordjylland	Yderkommune
825	Læsø	081	Nordjylland	Yderkommune
840	Rebild	081	Nordjylland	Landkommune
846	Mariagerfjord	081	Nordjylland	Landkommune
849	Jammerbugt	081	Nordjylland	Landkommune
851	Aalborg	081	Nordjylland	Bykommune
860	Hjørring	081	Nordjylland	Landkommune

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ORIGINAL ARTICLE

A model predicting operative mortality in the UK has only limited value in Denmark

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Abstract

Purpose Postoperative mortality from colorectal cancer varies between surgical departments. Several models have been developed to predict the operative risk. This study aims to investigate whether the original and the revised Association of Coloproctology of Great Britain and Ireland (ACPGBI) model can predict 30-day mortality after colorectal cancer surgery in Denmark.

Methods Data were collected from the Danish Colorectal Cancer Group database which has > 95% completeness. All patients operated on from January 2007 to December 2013 were included. The individual estimated operative risk was calculated with the original and revised ACPGBI models. Discrimination and calibration were evaluated with a Receiver Operating Characteristic (ROC) curve analysis and a Hosmer-Lemeshow test, respectively.

Results In total, 22,807 patients underwent open or laparoscopic colorectal cancer surgery. After excluding 1437 patients because of missing data, 21,370 patients were left for the analyses. The observed 30-day mortality was 5.0%. The original and revised ACPGBI models estimated an operative risk of 7.0 and 4.0%, respectively, with a significant difference in observed and estimated mortality in both models. However, in patients with an estimated risk of at least 26%, i.e., high-risk, good calibration was found with the original ACPGBI model. Discrimination was good with an AUC of 0.83 (95% CI 0.82–0.84) in both models.

Conclusion The original and revised ACPGBI models are not suitable prediction models for postoperative mortality in the Danish colorectal cancer population. However, the original model might be applicable in predicting mortality in high-risk patients.

Keywords Calibration · Colorectal cancer · Study population · Prediction model · ACPGBI · 30-day mortality

Introduction

Colorectal cancer is responsible for more than 700,000 deaths annually worldwide [1, 2]. In Denmark, more than 5000 people were diagnosed with colorectal cancer in 2015, of whom 85% underwent surgical resection of the primary tumor [3]. The postoperative mortality varies widely among European countries [4, 5]. In Denmark, the 30-day mortality rate in 2014 was 1.6% after elective surgery, but as high as 15.0% after acute surgery [3].

There is increasing focus on tailored surgical therapy and prehabilitation in patients with cancer scheduled for surgery. An increasing number of non-operative and endoscopic treatment options may challenge even further the process of shared decision-making for clinicians and patients. Therefore, knowing the operative risk is beneficial not only in order to optimize perioperative treatment, but also to improve counseling and guidance of the individual patient. Prediction models to estimate postoperative mortality may accomplish these tasks, but would also be useful for comparisons of mortality between hospitals, regions, and countries.

Several prediction models have been developed to estimate the risk of postoperative death from colorectal surgery [6–8]. In 2003, the Association of Coloproctology of Great Britain

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and Ireland (ACPGBI) developed a promising model based on a UK cohort [9]. A revised version of the model was available online in 2010 [10] and evaluated as an accurate prediction model in an external validation in 2011 [7]. No models have been tested in the Danish population, and we hypothesized that the ACPGBI model might be valuable in the Danish context to identify high-risk patients.

The aim of this study was to validate the original and revised ACPGBI prediction models in a Danish nationwide cohort.

Methods

Data source

Data were collected from a nation-wide database established in 2001 by the Danish Colorectal Cancer Group (DCCG) including all colorectal cancer patients diagnosed and/or treated at any surgical department in Denmark. Data for each patient concerning the disease, comorbidity, treatment, and postoperative complications are registered prospectively into the database with a national completeness rate of > 95% [3, 11]. Mortality data are continuously updated from the Danish National Registry of Patients (DNRP) by linkage with the unique, personal 10-digit Central Population Registry (CPR) number assigned to all Danish citizens.

The study population

The population consists of patients in the DCCG database operated on for primary colorectal cancer from January 2007 to December 2013. Only patients who underwent operative procedures included in the revised ACPGBI model were included (see Table 1), irrespective of surgical approach (open or laparoscopic) and operative priority (emergency or elective). Thus, patients undergoing minor procedures such as polypectomies or other kinds of local excisions were not included.

Patients with data insufficient to calculate either the original or the revised ACPGBI score were excluded.

Table 1 Parameters for calculating mortality for the ACPGBI models

Risk factor		Score original ACPGBI		Score revised ACPGBI
Age (yrs)	≤ 65	0		0
	65–74	0.7		0.356
	75–84	1.1		0.959
	85–94	1.3		1.347
	≥ 95	2.6		1.866
ASA status		Cancer resected[a]	Cancer not resected[a]	
	ASA I	0	1.7	0
	ASA II	0.8	1.8	0.462
	ASA III	1.6	2.1	1.159
	ASA IV/V	2.5	2.4	2.196
Cancer staging	Dukes A	0		0
	Dukes B	0		0.314
	Dukes C	0.2		0.498
	Dukes D or any	0.6		0.809
Operative urgency	Elective	0		0
	Urgent/emergency[c]	0.8		0.866
Operative procedure[b]	Right hemicolectomy			0
	Transverse colectomy			0.522
	Left hemicolectomy			0.039
	Sigmoid colectomy			0.301
	Subtotal/total colectomy			0.022
	Anterior resection			0.293
	APER			0.337
	Hartmann's procedure			0.129
	Palliative stoma			0.467
	EUA/laparotomy/laparoscopy only			0.286

[a] In the original ACPGBI model only

[b] In the revised ACPGBI model only

[c] We cannot distinguish between emergency and urgent in our data and assign the urgent score to all patients registered as "acute surgery"

APER Abdomino Perineal Excision of Rectum, *EUA* examination under anesthesia

Equation for calculation of risk of death:

Original ACPGBI score: ln(R/1-R) = − 4859 + (total ACPGBI score)

Revised ACPGBI score: ln(R/1-R) = − 5123 + (total ACPGBI revised score)

Data extraction

For each patient, we extracted data regarding age, American Society of Anesthesiology (ASA) grade, cancer stage according to the UICC classification, priority of operation (emergency or elective), surgical procedure, 30-day postoperative mortality, and surgical approach (open or laparoscopic).

The ACPGBI model categorizes acute surgery into two groups, emergency surgery (surgery within 1 hour) [12] and urgent surgery (surgery within 24 h), according to the classification of the National Confidential Enquiry into Perioperative Deaths (NCEPOD) in 2000 [12]. The DCCG database does not distinguish between these two categories; hence, all patients with acute presentation were given a score equivalent to urgent surgery.

Statistical analyses

The mortality risk was calculated for each patient using the original and the revised ACPGBI models [9, 10], see Table 1. Observed mortality was compared with estimated mortality, according to the original and revised ACPGBI models, by two statistical methods. First, we investigated the calibration of the model with the Hosmer-Lemeshow goodness-of-fit test [13]. Calibration refers to the model's ability to predict the correct mortality risk. Patients were divided into ten groups according to the estimated mortality with an increase of approximately 10% risk in each group. The mean rate of observed and estimated mortality (O/E ratio) was calculated for each group. When the estimated risk did not differ significantly from the observed risk, the O/E ratio was close to one with a p value of more than 0.05, indicating a good calibration. Secondly, discrimination was investigated with a Receiver Operated Characteristic (ROC) curve analysis [13, 14] that describes how well the model classifies patients who die within 30 days postoperatively. An area under the curve (AUC) between 0.7 and 0.8 is regarded as "fair discrimination," and values higher than 0.8 are regarded as "good discrimination" [14].

Subgroup analyses on laparoscopic and open surgery were assessed for both models. We also investigated if 30-day mortality of patients excluded because of missing values differed from that of included patients.

IBM SPSS version 22, Chicago, Illinois, USA was used for statistical analyses. The study was reported to the Danish Data Protection Agency with registration number 2014-331-0777. Under Danish law, registration with the Danish Ethical Committee was not required.

Results

A total of 22,807 patients registered in the DCCG database underwent operations for colorectal cancer between 2007 and 2013. Due to missing data for at least one variable in either of the models, 1437 (6%) of the patients were excluded from all statistical analysis, hence, the operative risk was estimated for 21,370 patients with the original and revised ACPGBI models.

The 30-day mortality was 5.0% for the included patients and 14% for the excluded patients. Demography of the included population is illustrated in Table 2. The median age was 71 years (25–75 percentile ranged from 63 to 78 years), and 5007 patients (23%) were in ASA classes III or IV. The number of patients included each year varied from 2949 to 3200. In total, 9874 (46%) of the surgical procedures were performed by laparoscopy, with a gradually increased implementation from 26% of all procedures in 2007 to 62% in 2013. The 30-day mortality rate was significantly higher after open surgery (7.2%) than after laparoscopy (2.4%), $p < 0.01$.

Table 2 Demographic characteristics of the study population

	Number of patients (%)	
Age (yrs)		
< 65	6075	(28.4)
65–84	13,395	(62.7)
> 84	1900	(8.9)
Sex		
Female	10,035	(47.0)
Male	11,335	(53.0)
Operative priority		
Elective	18,836	(88.1)
Acute	2534	(11.9)
Clinicopathologic stage[a]		
UICC I	3492	(16.3)
UICC II	7731	(36.2)
UICC III	6250	(29.3)
UICC IV	3897	(18.2)
ASA		
ASA I–II	16,363	(76.6)
ASA III–V	5007	(23.4)
Cancer site		
Colon	14,552	(68.1)
Rectum	6818	(31.9)
Surgical approach		
Open	11,496	(53.8)
Laparoscopy	9874	(46.2)
Observed mortality (all patients)		
30-day mortality	1062	(5.0)

ASA American Society of Anesthesiologists

[a] In the risk estimation, UICC stage was converted to Dukes stage. UICC I equals Dukes A, UICC II equals Dukes B, UICC III equals Dukes C, and UICC IV equals Dukes D

Calibration of the models

In the total population, the original ACPGBI model overestimated the risk of postoperative mortality, while the revised model underestimated this risk, see Table 3. There was no evidence of good calibration in either model when testing with the Hosmer-Lemeshow test ($p < 0.001$). This is illustrated in Fig. 1 by the bars of each risk group deviating from O/E = 1. Both the original and revised ACPGBI model lack the ability to predict the 30-day mortality for patients, with an estimated risk of up to 25%. However, in high-risk patients, i.e., those with an estimated risk of at least 26%, the original ACPGBI model was a good predictor for 30-day mortality after colorectal cancer surgery. Thus, there was a good calibration with no significant difference in observed and estimated mortality when analyzing only those patients with an estimated risk of 26% or more. The revised ACPGBI model did not have the same good calibration; thus, there was also a significant difference in observed and estimated mortality in the subgroup analysis of patients with an estimated risk of operative death of 26% or more. The high-risk cases comprised 1185 patients in the original model and 634 patients in the revised model.

In the stratified analyses by surgical approach (open or laparoscopic), the Hosmer-Lemeshow test showed significant difference in both models ($p < 0.001$) between the observed and estimated mortality after open surgery. In patients operated on with a laparoscopic approach, the revised ACPGBI model had a good calibration; thus there was no significant difference between the observed and estimated mortality, see Table 3. As for the total population, the original ACPGBI model showed good calibration in separate subgroup analyses of the open- and laparoscopic surgical approaches for high-risk patients.

Discrimination of the models

Discrimination was good in both the original and the revised ACPGBI models with an AUC of 0.83 (95% CI 0.82–0.84) and 0.83 (95% CI 0.82–0.84), respectively, see Table 2 and Fig. 2. In stratified analyses by surgical approach, both the original and revised models performed better in open surgery compared with a laparoscopic approach, with a "good" and "fair" discrimination, respectively, see Table 3.

Discussion and conclusions

This study is the first to validate the ACPGBI models in a Danish population-based cohort. We found that the original model overestimated the risk of postoperative mortality, while the revised model underestimated this risk, irrespective of the surgical approach. The original model, but not the revised one, was a good prediction model in high-risk patients. The revised model had good calibration in the stratified analysis of only those patients undergoing the laparoscopic approach. Discrimination was good in both models, indicating a good ability to identify the patients likely to die after surgery.

Previous studies have validated both the original and the revised ACPGBI models. The original model has been validated in two UK studies with 618 and 423 patients [6, 7], one Dutch study with 190 patients [15], and one Chinese study with 1695 patients [16] operated for colorectal cancer. Calibration was calculated in three of the studies [6, 7, 16],

Table 3 Comparison of the original and revised ACPGBI model for all patients, and subgroup analyses for patients undergoing open or laparoscopic surgery

Model	Observed 30-day mortality	Mean estimated 30-day mortality	Overall O/E	AUC	Calibration[a] (sum, p value with 8 degrees of freedom)
Original ACPGBI	5.0%	7.0%	0.71	0.83 (95% CI 0.82–0.84)	174.9, $p < 0.001$*
Revised ACPGBI		4.0%	1.25	0.83 (95% CI 0.82–0.84)	85.0, $p < 0.001$*
Open surgery Original ACPGBI	7.2%	8.6%	0.84	0.83 (95% CI 0.81–0.84)	54.5, $p < 0.001$*
Open surgery Revised ACPGBI		5.1%	1.41	0.83 (95% CI 0.82–0.84)	124.3, $p < 0.001$*
Laparoscopic Original ACPGBI	2.4%	5.2%	0.46	0.78 (95% CI 0.75–0.81)	148.2, $p < 0.001$*
Laparoscopic Revised ACPGBI		2.8%	0.88	0.78 (95% CI 0.75–0.81)	11.3, NS

NS not significant

*Indicates that observed mortality is significantly different from the estimated mortality, when divided into ten risk groups

[a] Calibration was calculated with a Hosmer-Lemeshow goodness-of-fit test after dividing the population into ten risk groups according to estimated mortality

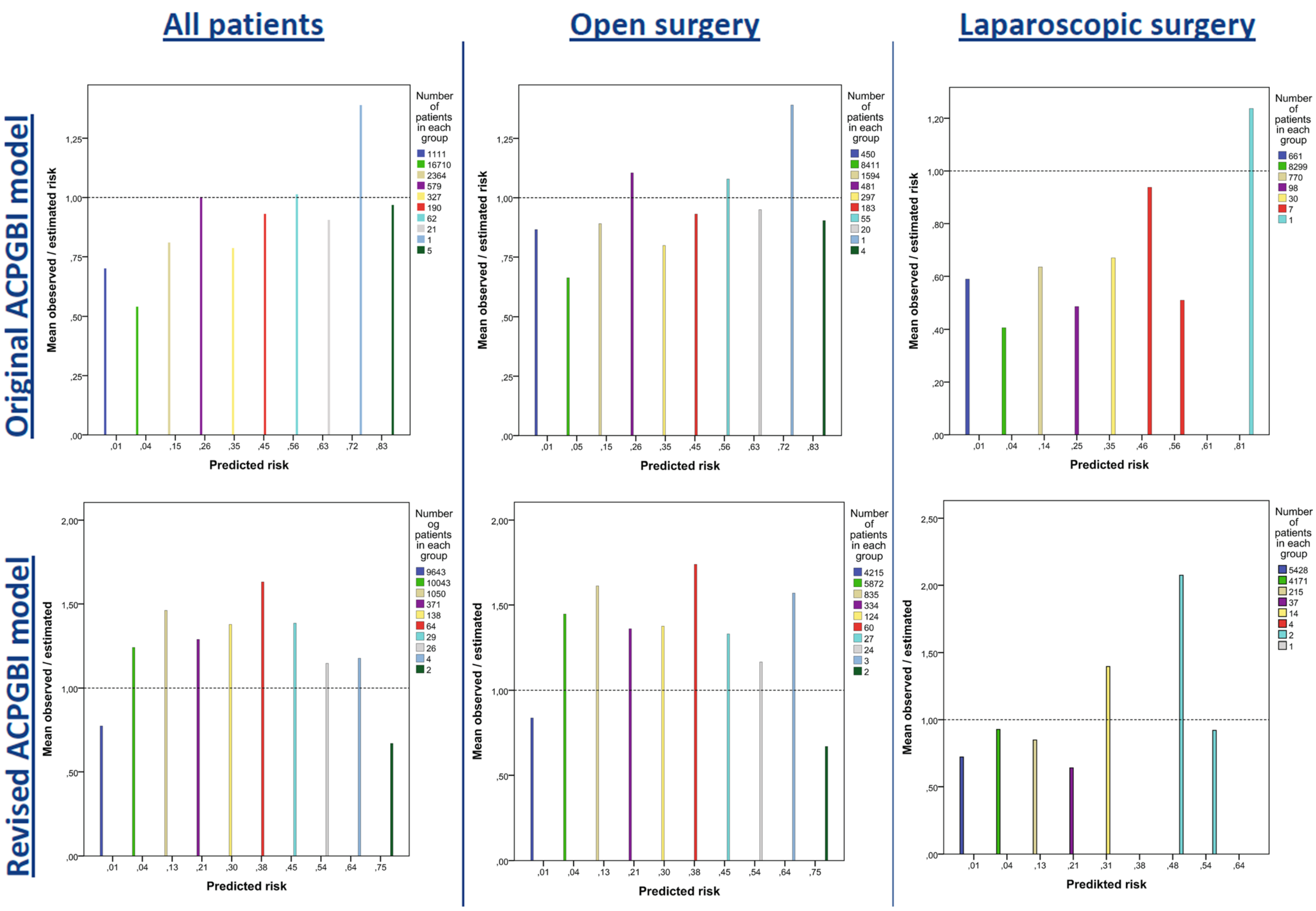

Fig. 1 Calibration of the model with a Hosmer-Lemeshow goodness-of-fit test

all showing a significant difference between the observed and estimated mortality. Discrimination was good in the Dutch and Chinese studies with an AUC of 0.85 (95% CI not reported) [15], and 0.87 (95% CI 0.87–0.91) [16], respectively. In the two UK studies, the discrimination was only fair with an AUC of 0.70 (95% CI 0.66–0.73) [6], and 0.76 (95% CI 0.68–0.84) [7], respectively. One of these studies also validated the revised ACPGBI model on 423 patients with a 30-day postoperative mortality rate of 4% [7]. The model showed good calibration with no significant different in observed and estimated mortality, and a fair discrimination with an AUC of 0.73 (95% CI 0.63–0.82) [7].

A model developed using UK patients might not be applicable in patient populations from other countries because of variations in postoperative mortality and causes of postoperative death [4, 5, 17]. Geographical differences are likely due to variations in organization of the health systems, perioperative care, access and quality of treatment, quality of reporting systems, and in general health in the population, such as high smoking rate, a high prevalence of obesity, comorbidity, and widespread low socioeconomic status [4, 5]. Organizational structures and perioperative optimization are important for improved postoperative survival. A recent Danish cohort study attributes the observed improvement in colorectal cancer survival in Denmark the past 15 years to several national initiatives [18]. Introduction of national guidelines, laparoscopic surgery, multi-disciplinary team conferences prior to elective surgery, specialization of colorectal cancer surgeons, and concentration of hospitals performing colorectal cancer surgery are some of the factors suggested to be responsible for the improved outcome. Geographical variations in national health care organization and treatment strategy of colorectal cancer are assumed to be the main reasons why results from validation of the ACPGBI models vary among the studies from the UK, the Netherlands, China, and Denmark. The different results emphasize the importance of an individual prediction model for each country tailored to the composition of the population and complexity of the treatment quality and access.

The first ACPGBI model was developed more than 10 years ago. Both perioperative and surgical standards have changed within that time [19]. One example is that the models were developed for open surgery; however, laparoscopy is gaining increasing ground as the standard surgical approach in Danish colorectal cancer surgery [3]. In 2014, 78% of colorectal cancer surgery was initiated with a laparoscopic

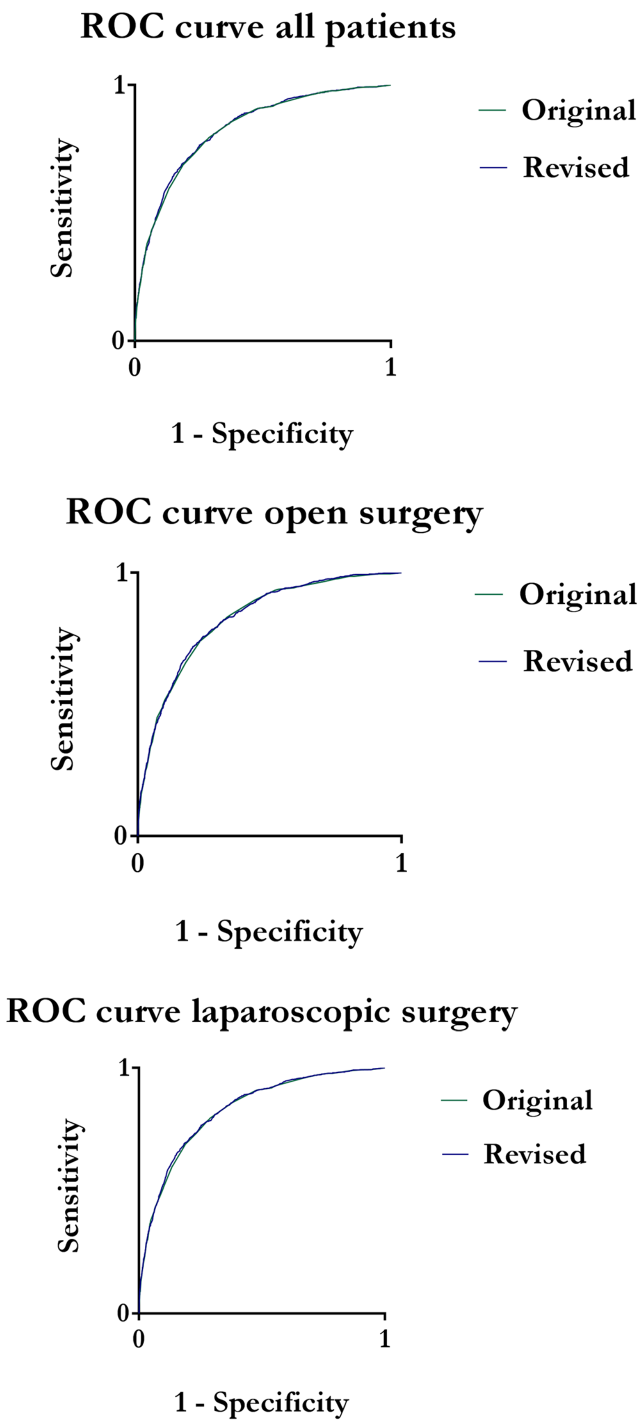

Fig. 2 Discrimination of the model with a ROC curve

approach in Denmark [3]. A previous study showed that the replacement of open surgery by laparoscopy was associated with a reduction of the 30-day mortality rate in Denmark [20]. Since the ACPGBI models were developed on patients undergoing open surgery [9], we would have expected the models to fit better in this subpopulation. In contrast, the revised ACPGBI model estimated the risk of death more accurately in the subpopulation undergoing laparoscopic surgery. An explanation for this might be that the laparoscopic subgroup had a low mortality rate of 2.4%, and the revised ACPGBI model performed well in estimating patients at low risk of operative death.

Both ACPGBI models include variables collected postoperatively, such as cancer stage and operative procedure, and cannot be used as preoperative prediction models. To our knowledge, no preoperative models have been developed yet. A randomized controlled trial would have to clarify if an intervention with perioperative optimization in high-risk patients could improve postoperative survival. So far, all existing prediction models integrate both preoperative and postoperative risk factors, such as cancer stage; thus, none of them is suitable to identify high-risk patients before surgery.

The major strength of the present study is the nationwide, population-based design with an almost complete coverage of clinical data. There is no loss to follow-up; thus, data on time of death are exact. The DCCG database provided almost complete data on all variables, however, with missing values in 1437 patients. This excluded group did not differ in any of the variables from the patients included for analyses. Data are collected prospectively for the DCCG database, thus minimizing the risk of recall bias. A weakness in our study is that the two models were developed more than 10 years ago, and might not represent current clinical practice. Furthermore, the excluded patients had a significantly higher mortality rate of 14.0 versus 5.0% in the included population. All the exclusions were due to missing data in at least one variable in either model; thus, a prediction score could not be calculated in these patients. Due to the power in this study, we do not expect the exclusion of 6% of the total population to affect our overall results.

In conclusion, both the original and revised ACPGBI models lack the ability to estimate the 30-day mortality in the majority of the population, i.e., those with a risk of operative mortality lesser than 26%. However, the original model succeeded in allocating a correct risk for patients at high risk of death within 30 days after colorectal cancer surgery. In order to predict the postoperative mortality in Denmark, a prediction model reflecting the multiple variables related to the Danish population and health care system is needed.

Author contribution Thea Helene Degett, Ole Roikjær, Lene Hjerrild Iversen, Ismail Gögenur; design

Ole Roikjær; statistics

Thea Helene Degett; manuscript writing

Thea Helene Degett, Ole Roikjær, Lene Hjerrild Iversen, Ismail Gögenur; manuscript reviewing

Thea Helene Degett, Ole Roikjær, Lene Hjerrild Iversen, Ismail Gögenur; final approval

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE

Mortality after emergency treatment of colorectal cancer and associated risk factors—a nationwide cohort study

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Abstract

Purpose The aim of this study was to investigate if postoperative mortality after acute surgical treatment of colorectal cancer has decreased in Denmark during this period and to investigate risk factors associated with early death.

Methods This is a nationwide and population-based cohort study. From the Danish Colorectal Cancer Group database and National Patient Registry, we collected data on all patients operated with bowel resection, diverting stoma only, or placement of an endoscopic stent from 2005 to 2015. Year of surgery was the main exposure variable and 90-day postoperative mortality the primary outcome.

Results We included 6147 patients. The incidence of patients per year was stable during 2005–2015. The 90-day mortality decreased from 31% in 2005 to 24% in 2015 with a significant time trend ($p < 0.0001$). Other factors associated with postoperative mortality were increasing age, presence of comorbidity (measured as Charlson comorbidity index score ≥ 1), and stage IV disease. Insertion of self-expanding metallic stent was protective for 90-day postoperative mortality compared with other surgical procedures.

Conclusion Ninety-day postoperative mortality from acute colorectal surgery has improved in Denmark from 2005 to 2015. Nevertheless, almost one out of four patients undergoing acute surgery for colorectal cancer dies within 90 days.

Keywords Colorectal · Cancer · Emergency · Surgery

Introduction

Worldwide, colorectal cancer is the third most common cancer with an incidence of around 1.4 million per year and an estimated 700,000 deaths annually [1]. In Denmark, the incidence is 5000 of which approximately 10% undergo acute therapy [2], due to complete obstruction, perforation, abscess formation, or diffuse peritonitis. Acute onset of colorectal cancer is associated with a high short-term mortality risk [3, 4]. In Denmark, postoperative 90-day mortality from acute colorectal cancer surgery is 21% versus only 3% after elective surgery [1]. Besides surgical intervention and diverting stoma, insertion of self-expandable metallic stents (SEMS) can be performed in chosen cases to recreate intestinal continuity as the only treatment or as bridge to surgery.

During the past 10 years, both short- and long-term survival after elective colorectal cancer surgery has improved in Denmark [5, 6]. Changes in short-term mortality after surgery depend on patient-related factors, clinical factors, and structural factors. For instance, changes in mortality can be a result of patient selection and perioperative treatment. The Danish Colorectal Cancer Group (DCCG.dk) and the Danish health authorities have since the 1990s taken several national initiatives to improve survival in patients with colorectal cancer [6]. Initiatives such as evidence-based guidelines, fast-track cancer pathways, cancer plans, and centralization of colorectal cancer surgery in fewer high-volume units [6].

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The aim of this study was to evaluate 90-day mortality rate after acute treatment of colorectal cancer within a period of 11 years in Denmark and associated risk factors. Resection, SEMS, and diverting stoma as bridge to surgery, and palliative surgery are all included as treatment strategies.

Method

Study design and setting

This study is a nationwide and population-based historical cohort study. Data are collected prospectively in the Danish national registries. We report the results according to the STROBE statement for cohort studies [7]. The study is based on data from the DCCG.dk database and the National Patient Registry (NPR) [8, 9]. All patients included in the study were operated at a surgical department in a public hospital in Denmark between 1 January 2005 and 31 December 2015.

All Danish residents have access to tax financed, free of charges hospital care. Information on services are registered for all residents and linked with a unique identification number in national registries, e.g., the NPR and population-based clinical quality databases, e.g., the DCCG.dk database. All patients were followed up for 90 days after acute surgery or stent placement. Information about postoperative mortality within this period was collected from the Danish Civil Registration Registry [10].

Registries

Data were collected from the DCCG.dk database, a national population-based, clinical quality database with a completeness proportion of 95–99% of all incident colorectal cancer patients in Denmark [9]. Patients included in the database were treated or diagnosed with colorectal cancer in a surgical department in Denmark. Patients with metachronous cancer, recurrence, and tumors of other histological origin than primary adenocarcinoma, mucinous adenocarcinoma, signet ring cell carcinoma, medullary carcinoma, or undifferentiated carcinoma are not registered in the DCCG.dk database. All clinical and pathological data are registered prospectively.

Only the definitive surgical procedure is registered in DCCG.dk [9]. Thus, patients who are acutely relieved with a diverting stoma or SEMS prior to an elective surgical resection, will only have a registration of the elective procedure in DCCG.dk, and data on these patients were extracted from the Danish NPR. The Danish NPR is the most comprehensive nationwide register worldwide [8]. From the Danish NPR, we use date of emergency admission, stoma as only procedure (KJFF10, KJFF11, KJFF20, KJFF21, KJFF23, KJFF24, KJFF26, KJFF27, KJFF30, and KJFF31), and insertion of endoscopic stent in colon or rectum (KJFA68 and KJGA58A) to include patients with diverting stoma or SEMS prior to elective resection. None of the codes for these variables changed within the study period. Using the unique identification number we obtained information on vital status by linking to the Danish Civil Registration System that holds continuously updated information on name, sex, date of birth, vital status, etc. on all Danish residents alive [10]. All patients included via the Danish NPR were also diagnosed with colorectal cancer in the DCCG.dk within the study period.

Participants

All patients registered in the DCCG.dk database with an acute surgical procedure between 2005 and 2015 were included. Procedures included right hemicolectomy, transverse colectomy, left hemicolectomy, sigmoid colectomy, Hartmann's procedure, other colectomy ± stoma, diverting stoma, intestinal bypass, subtotal/total colectomy, explorative laparotomy/diagnostic laparoscopy only, anterior resection ± stoma, proctocolectomy with ileostomy, or insertion of SEMS in colon or rectum. Furthermore, we included all patients registered in the Danish NPR with an acute insertion of SEMS or diverting stoma within 72 h after acute admission at any department from 2005 to 2015. If a patient was registered with more than one acute procedure in, e.g., one in the NPR and one in DCCG.dk, the first procedure was used for this analysis. All patients registered in the Danish NPR also needed to have a date of diagnosis in DCCG.dk within the study period. Patients were excluded if they emigrated within 90 days after the surgery, or had an elective surgical procedure for colorectal cancer before the acute procedure. Furthermore, we excluded all patients registered in the DCCG.dk database with acute surgery and one of the following procedures: abdominoperineal excision of rectum, transanal endoscopic microsurgery (TEM), and other local procedures including polypectomy.

Variables

The primary outcome was 90-day mortality after acute colorectal cancer surgery including insertion of SEMS. The secondary outcome was 30-day mortality. Acute surgery is defined in the DCCG.dk as indication of surgery due to suspected ileus, perforation, bleeding, or other acute reasons. Year of surgery was the primary exposure variable. We consider the following to be confounders: age, sex, comorbidity estimated with Charlson comorbidity index (CCI), UICC stage, and tumor localization (right, transverse or left colon, and rectum). Additionally, we adjusted for primary surgical procedure (SEMS insertion, acute surgery with resection, or acute surgery with only diverting stoma).

Subgroup analysis

Patients that directly undergo surgery, and not SEMS, represent a certain risk group and we therefore performed a subgroup analysis of these patients. We did a stepwise analysis, first including surgical specialization, then operative approach and finally hospital volume to investigate if the effect of these variables on 90-day postoperative mortality. Surgery was performed by a specialist if either the surgeon, or the assistant, was specialized in surgical gastroenterology or was a certified colorectal cancer surgeon. The operative approach was either laparotomy or minimal invasive (laparoscopic or robot-assisted). Hospital volume was calculated as the total numbers of surgical colorectal cancer procedures per year, both acute and elective. Volume intervals were based on quartiles of the procedures with 25%, 50%, and 75%, which gave the cut points: < 150 per year, 150–220 per year, 220–280 per year, and > 280 per year.

Additionally, we described the subgroup of patients who had an acute stent or diverting stoma as either bridge to elective surgery with curative attend or compromised resection, or as a palliative procedure without bridge to elective surgery.

Statistical analysis

Association between year of surgery and 90-day postoperative mortality was analyzed using a logistic regression model. We reported the *p* value of the trend in year of surgery with the chi square test. *P* values < 0.05 were considered significant. We adjusted analyses for sex, age, CCI score, primary procedure, tumor localization, and UICC stage. Missing data were categorized within each variable. Quantitative variables were tested for linearity by inserting a squared term in the model. Age was found non-linear and was included as a linear spline with cut points at the tertiles. Kaplan-Meier curves were used to illustrate the survival over the calendar periods, after diverting the study period in to four groups.

Interaction was tested in the full model between age and comorbidity (CCI), and between year of surgery and comorbidity (CCI).

A subgroup analysis was performed to investigate the association between 90-day mortality and hospital volume, surgical specialization, and surgical approach with a multiple regression model adjusting for year of surgery, sex, age, CCI, year of surgery, primary procedure, tumor localization, and UICC stage.

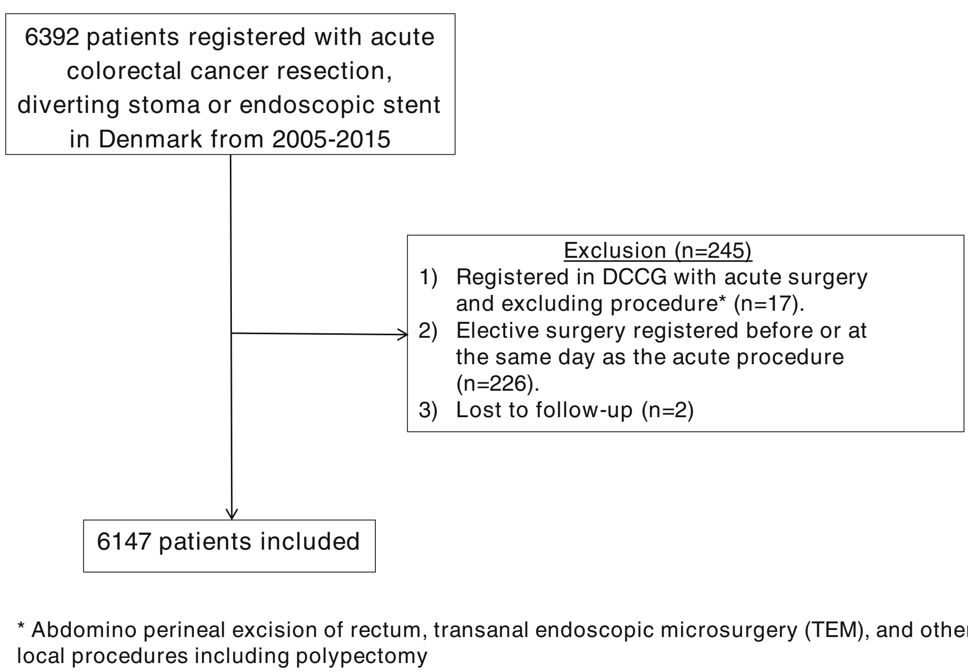
All analyses were performed using SAS software, version 9.3. This study was reported to the Danish Data Protection Agency with registration number 2015-41-3726. Under Danish law, registration with the Danish Ethical Committee was not required.

Results

Participants

We included 6147 patients admitted and treated with acute surgery for colorectal cancer in Denmark in 2005 through 2015. We excluded 245 patients, Fig. Fig. 1. No difference was found in the gender distribution, and the mean age was 72 years (SD ± 12). Nineteen percent had a CCI score of three or more, while 52% of the participants had

Fig. 1 Flowchart of patient exclusion



no comorbidity. The number of patients operated each year varied from 501 to 631 with a median of 560. Surgical resection was the most common surgical procedure, and most tumors were localized in the left side. Metastatic disease was found in 42% of the patients and local disease (stage I–II) in only 26%. Of the right-sided tumors, 86% were treated with surgery as primary procedure, 3% with SEMS and 11% with diverting stoma. Among the left-sided tumors, 47% were treated with surgery, 44% with SEMS and 9% with diverting stoma. The tumors localized in transverse colon and rectum were mainly treated with surgery (64%) and diverting stoma (45%), respectively. As expected, few variables included in the analysis had missing values. The variables sex, age, CCI, year of surgery, and 90-day mortality had no missing values, while stage had most missing values (8%).

Mortality

The 90-day overall mortality was 25% after acute surgery, insertion of SEMS, or diverting stoma, whereas 30-day mortality was 16%, Table 1. Of the patients, aged 85 years or more, 46% died within 90 days after the acute procedure, whereas this rate was 14% for patients less than 70 years old.

The Kaplan-Meier plot illustrates the unadjusted 90-day survival in the four different periods, Fig. Fig. 2.

Risk factors for postoperative mortality after acute colorectal cancer surgery

The year of surgery was associated with 90-day postoperative mortality also when adjusting for confounders, Table 2. From 2012 to 2015, the mortality was reduced significantly compared with 2005 and the trend in the total period was significantly reduced with an OR of 0.94 per year (95% confidence interval, 0.92–0.96, $p < 0.0001$).

Increasing age, comorbidity, and UICC stage IV were all significant independent risk factors for postoperative 90-day mortality, Table 2. SEMS, as the primary treatment of acute colorectal cancer, was protective for postoperative mortality compared with other surgical interventions, Table 2.

No interaction was found between age and comorbidity nor year of surgery and comorbidity.

Subgroup analysis

We included 4354 patients in the subgroup analysis not including SEMS. The 90-day mortality was 28% whereof 18% died within the first 30 days after surgery. In adjusted analysis, specialization of the surgeon was associated with 90-day mortality, OR = 1.16 (95% CI, 0.99–1.35), however not significant. When adjusting for specialization of the surgeon, open surgery was associated with an increased risk of 90-day postoperative mortality, OR = 1.66 (95% CI, 1.23–2.23). There was a decreased 90-day mortality in hospitals with a low annual volume of colorectal cancer surgery; however, only significant in hospitals with 150–220 procedures per year, Table 3.

We described the demography of 854 patients in the second subgroup of patients undergoing acute stent or diverting stoma prior to elective resection with a curative intent or compromised resection, and the 1777 patients with stent or stoma as palliative procedure, Table 4. The 90-day mortality in patients with further bridge to surgery 2% compared with 38% in the palliative procedure group. In the patients having bridge to surgery, mean age was 69 years (SD ± 11), 64% had no comorbidity (CCI = 0), 76% of the patients had stage II or III disease, 75% of the tumors were localized in left colon, and the majority had an SEMS procedure (98%). In comparison, patients having a stent procedure or diverting stoma as a palliative procedure mean age was 73 (SD ± 12), 48% had no comorbidity (CCI = 0), 89% had stage IV disease or missing stage, 53%of the tumors were localized in the rectum, and 58% had SEMS as primary procedure.

Discussion

In this present Danish population-based study, 6147 patients operated in an acute setting for colorectal cancer from 2005 to 2015 and the overall postoperative 90-day mortality decreased from 31 to 24%. The 90-day mortality decreased significantly in the latest years from 2012 to 2015 and mortality was reduced with an OR of 0.94 per year (95% CI, 0.92–0.95). Other risk factors for postoperative mortality after acute colorectal cancer surgery were high age, comorbidity, stage IV disease, and diverting stoma. SEMS was associated with reduced risk of mortality.

The primary limitation in this study is the observational design enabling a description of correlation between the year of surgery and postoperative mortality without proving causality. Several individual factors could determine how the patients were treated which can introduce confounding by indication. One example of this is that our results indicate that patients treated with SEMS have a reduced risk of postoperative mortality than the patients treated with surgical resection or diverting stoma. This result could reflect confounding by indication meaning that the patients in the less acute clinical condition like bowel obstruction only were chosen for SEMS and the high-risk patients with, for instance, perforation and peritonitis needed surgical resection or a diverting stoma only. However, there could also be an actual benefit of SEMS in short-term survival, which is a less invasive procedure that prolong the period for medical optimization. Surprisingly, diverting stoma did not have the same protective effect on

Table 1 Demography of the population

	Patients		Deaths within 90 days	
	No	(%)	No	(%)
Total	6147			
90-day mortality	1530	(25)		
30-day mortality	966	(16)		
Year or surgery				
2005	501	(8)	154	(31)
2006	542	(9)	165	(30)
2007	521	(8)	133	(26)
2008	558	(9)	158	(28)
2009	511	(8)	129	(25)
2010	607	(10)	149	(25)
2011	631	(10)	158	(25)
2012	578	(9)	130	(22)
2013	563	(9)	114	(20)
2014	575	(9)	105	(18)
2015	560	(9)	135	(24)
Sex				
Men	3015	(49)	734	(24)
Women	3132	(51)	796	(25)
Age				
Mean (SD)	72	(± 12)		
< 70	2637	(43)	376	(14)
> 70–80	1869	(30)	473	(25)
> 80–85	866	(14)	322	(37)
> 85	775	(13)	359	(46)
ASA				
1	893	(15)	83	(9)
2	2741	(45)	433	(16)
3	1841	(30)	685	(37)
4–5	356	(6)	221	(62)
Missing	316	(5)	108	(34)
CCI				
0	3192	(52)	564	(18)
1	1128	(18)	326	(29)
2	673	(11)	220	(33)
≥ 3	1154	(19)	420	(36)
Tumor localization				
Right colon[a]	1857	(30)	476	(26)
Transverse colon	557	(9)	155	(28)
Left colon[b]	2991	(49)	678	(23)
Rectum	666	(11)	193	(29)
Missing	76	(1)	28	(37)
Stage				
I	107	(2)	18	(17)
II	1501	(24)	251	(17)
III	1504	(24)	229	(15)
IV	2570	(42)	820	(32)
Missing	465	(8)	212	(46)

Table 1 (continued)

	Patients		Deaths within 90 days	
	No	(%)	No	(%)
Primary procedure[c]				
Surgery[d]	3516	(57)	836	(24)
Stent insertion	1793	(29)	319	(18)
Diverting stoma	838	(14)	375	(45)

[a] Includes the cecum, ascending colon and hepatic flexure

[b] Includes the splenic flexure, descending colon and sigmoid colon

[c] The initial treatment regardless of later surgical interventions

[d] Includes right hemicolectomy, transverse colectomy, left hemicolectomy, sigmoid colectomy, Hartmann's procedure, other colectomy ± stoma, intestinal bypass, subtotal/total colectomy, examination under anesthesia only, anterior resection ± stoma, proctocolectomy with ileostomy

mortality even though it is an alternative procedure to SEMS and have the same benefits of postponing the final procedure. This could reflect confounding by indication between patients who get SEMS and diverting stoma. For instance, diverting stoma may be chosen in more severe cases if SEMS was not possible and/or in case of an advanced tumor or massive carcinomatosis. Two previous meta-analysis of 334 and 382 patients, and overlapping studies, showed that treatment of malignant, left-sided colon obstruction did not find any advantages of SEMS compared with emergency surgery [11, 12]. A Dutch cohort study with 1860 treated for obstruction of the proximal colon showed that stent was possible in 2.4% as bridge to surgery and resulted in improved in the unadjusted 30-day mortality and morbidity [13]. In the long-term perspective, some studies have, however, reported an increased risk of recurrence and decreased disease-free survival after SEMS [14–16].

Lack of information about the clinical condition at the time of surgery, e.g., sepsis or perforation of the tumor associated with a high postoperative mortality [17], can introduce residual confounding in our results. Furthermore, information about life style factors such as smoking, alcohol intake, and BMI could also affect postoperative mortality. Sufficient data on these variables were not available in our study. However, through adjusting for comorbidity, we indirectly account for some of the effect of lifestyle factors.

Previous studies have focused on acute colorectal cancer surgery as a risk factor for early postoperative death and analyzed differences in patient and clinical related characteristics in acute versus elective surgery [18–20]. This study is, to our

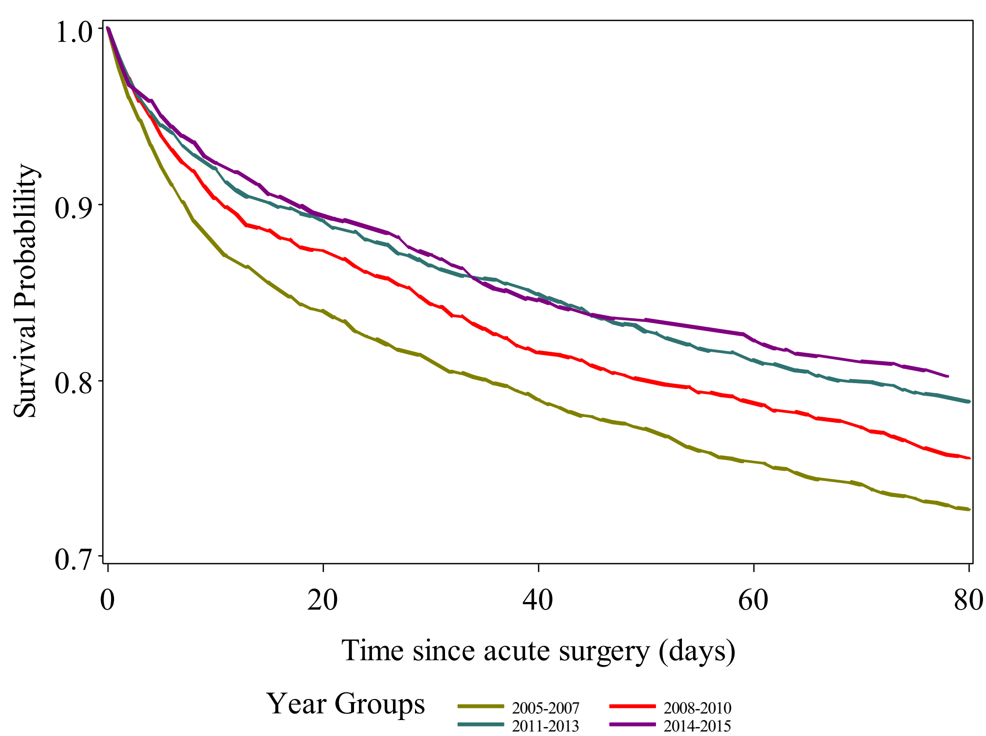


Fig. 2 Kaplan-Meier plot illustrating the unadjusted 90-day survival in the four different periods

Table 2 The risk factors associated with 90- and 30-day mortality after initial treatment with surgery, diverting stoma or SEMS, analyzed with a multiple logistic regression model

	Adjusted analysis 90-day mortality			Adjusted analysis 30-day mortality		
	OR	(95% CI)	*p*	OR	(95% CI)	*p*
Per year	0.94	(0.92–0.95)	< 0.0001	0.94	(0.92–0.96)	< 0.0001
Year or surgery						
2005	1	Ref	< 0.0001	1		< 0.0001
2006	1.14	(0.85–1.52)		1.18	(0.85–1.63)	
2007	0.77	(0.57–1.04)		0.78	(0.55–1.09)	
2008	1.00	(0.74–1.34)		0.97	(0.70–1.35)	
2009	0.85	(0.63–1.15)		0.92	(0.65–1.29)	
2010	0.81	(0.60–1.08)		0.75	(0.54–1.05)	
2011	0.83	(0.62–1.11)		0.70	(0.50–0.99)	
2012	0.66	(0.49–0.89)		0.74	(0.53–1.05)	
2013	0.61	(0.45–0.83)		0.65	(0.45–0.93)	
2014	0.43	(0.32–0.59)		0.47	(0.33–0.67)	
2015	0.65	(0.48–0.89)		0.67	(0.47–0.96)	
Sex						
Men	1	Ref	0.1168			
Women	0.90	(0.79–1.03)				
Age						
Mean (SD)						
< 70	1.03[e]	(1.02–1.05)	< 0.0001			
> 70–80	1.09[e]	(1.06–1.12)	< 0.0001			
> 80–85	1.08[e]	(1.02–1.13)	0.0055			
> 85	1.07[e]	(1.03–1.11)	0.0009			
CCI						
0	1	Ref	< 0.0001			
1	1.57	(1.32–1.87)				
2	1.86	(1.52–2.28)				
≥ 3	1.96	(1.66–2.31)				
Tumor localization						
Right colon[a]	0.94	(0.80–1.11)	0.0545			
Transverse colon	1.22	(0.98–1.54)				
Left colon[b]	1	Ref				
Rectum	1.00	(0.80–1.25)				
Missing	1.80	(1.05–3.09)				
Stage						
I		Ref	< 0.0001			
II	1.11	(0.64–1.94)				
III	1.15	(0.66–2.01)				
IV	3.10	(1.80–5.36)				
Missing	3.43	(1.93–6.12)				
Primary procedure[c]						
Surgery[d]	1	Ref	< 0.0001			
Stent insertion	0.53	(0.45–0.64)				
Diverting stoma	1.86	(1.53–2.27)				

All variables were included in the adjusted analysis

[a] Includes the cecum, ascending colon and hepatic flexure

[b] Includes the splenic flexure, descending colon and sigmoid colon

[c] The initial treatment regardless of later surgical interventions

[d] Includes right hemicolectomy, transverse colectomy, left hemicolectomy, sigmoid colectomy, Hartmann's procedure, other colectomy ± stoma, intestinal bypass, subtotal/total colectomy, examination under anesthesia only, anterior resection ± stoma, proctocolectomy with ileostomy

[e] Increase in OR per year

knowledge, the largest study investigating if postoperative mortality has improved over the past decade, and which factors are associated with 90-day mortality. It is a major strength of this study that it is nationwide and population-based using a high-quality database with a completeness of 95–99% of all patients treated for colorectal cancer in Denmark. Data are collected prospectively, eliminating the risk of recall bias. Follow-up is almost complete (97%) and validity is high on primary outcome and exposure variables. All clinical data have an almost complete coverage with missing values on tumor localization or

Table 3 Subgroup analysis of volume, operative approach, and surgical specialization in all patients operated acutely for colorectal cancer (SEMS excluded). Analysis of patients with complete data

	No. of patients (%)		Unadjusted analysis 90-day mortality			Adjusted analysis 90-day mortality		
			OR	95% CI	*p* (Chisq)	OR	95% CI	*p* (Chisq)
Total	4354							
Surgical specialization[a]								
Yes	2501	(57)	1	Ref	< 0.0001	1	Ref	0.0683
No	1709	(39)	1.32	(1.15–1.51)		1.16	(0.99–1.35)	
Missing	144	(3)						
Operative approach[b]								
Minimal invasive	453	(10)	1	Ref	0.0001	1	Ref	0.0008
Open	3897	(90)	1.64	(1.27–2.11)		1.66	(1.23–2.23)	
Missing	4	(0)						
Hospital volume[c]								
< 150	982	(23)	1.01	(0.83–1.22)	0.5856	0.84	(0.67–1.06)	0.1703
150–220	1086	(25)	1.07	(0.89–1.30)		0.79	(0.62–0.99)	
220–280	1121	(26)	0.94	(0.78–1.14)		0.81	(0.65–1.01)	
> 280	1098	(25)	1	Ref		1	Ref	
Missing	67	(2)						
30-day mortality	797	(18)						
90-day mortality	1211	(28)						

[a] Adjusted for year of surgery, sex, age, Charlson comorbidity index, tumor localization, UICC stage, and primary procedure

[b] Adjusted for year of surgery, sex, age, Charlson comorbidity index, tumor localization, UICC stage, primary procedure, and surgical specialization

[c] Adjusted for year of surgery, sex, age, Charlson comorbidity index, tumor localization, UICC stage, primary procedure, surgical specialization, and operative approach

stage in only 532 patients (9%) and the validity on all variables included in the model is considered very high [9, 10].

The European Society of Gastrointestinal Endoscopy recommends SEMS as an alternative to emergency surgery only in patients at high operative risk, e.g., ASA ≥ III and/or age > 70 years, and not as standard treatment in left-sided obstructive tumors [21]. In England, 24% of the all patients with colorectal cancer from 2006 to 2013 presented as an emergency [22]. The relative 90-day survival was 65% after acute diagnosed colorectal cancer. In the English national guidelines, it is recommended to use SEMS in left-sided colorectal cancers with complete or nearly complete bowel obstruction [23]. However, guidelines are not clear in defining the indication for emergency surgery versus SEMS [23]. In Sweden, handling of acute colorectal cancer patients is more precise [24]. Treatment with SEMS is not recommended in patients with potential curable resection unless surgical intervention is considered a high risk. They argue that the risk of stent-related perforation increases the risk of postoperative mortality and of tumor spread. If curative surgery cannot be guaranteed, it is recommended to perform diverting stoma and no resection [24].

In the subgroup analysis based on 4354 patients undergoing surgical resection, there was a tendency to decreased 90-day mortality with low hospital volume of yearly surgical colorectal cancer procedures. This result deviate from both previous Danish and American studies on acute colorectal cancer surgery [18, 25], and a meta-analysis with both acute and elective surgical mode [26]. In a Danish study from 2011, 4.3% of the variation in 30-day postoperative mortality after acute colorectal cancer surgery was explained by the hospital volume level [18]. They did not adjust for operative approach or specialization of the surgeon [18]. This could explain differences in the results from the same population. In the American study, they evaluated the load of operation for the individual surgeon with the maximum level of > 10 annually resections [25]. In a Danish context, ten resections per year are low for a specialized surgeon. Furthermore, it is plausible that some severe cases have been removed to more specialized, high-volume departments for surgical intervention. In our data, we cannot adjust for this type of confounding by indication due to lack of clinical data.

We saw a positive effect on minimal invasive surgery versus open. Again, this could be a real effect due to reduced stress response in minimal invasive surgery [27, 28]. Alternatively, the result is caused by confounding by indication, if the more complex tumors, e.g., local advanced tumors were operated with an open approach, and the less complicated tumors where

Table 4 Characteristics of patients treated with stent or diverting stoma as bridge to surgery with curative intent or compromised resection, and as palliative procedure

	Bridge to surgery		Palliative surgery	
	No. of patients	(%)	No. of patients	(%)
Total	854		1777	
Year for surgery				
2005	19	(2)	111	(6)
2006	57	(7)	128	(7)
2007	62	(7)	161	(9)
2008	64	(7)	181	(10)
2009	74	(9)	155	(9)
2010	98	(11)	161	(9)
2011	97	(11)	181	(10)
2012	79	(9)	185	(10)
2013	93	(11)	172	(10)
2014	108	(13)	171	(10)
2015	103	(12)	171	(10)
Sex				
Men	460	(54)	935	(53)
Women	394	(46)	842	(47)
Age				
Mean (SD)	69	(± 11)	73	(± 12)
CCI				
0	544	(64)	855	(48)
1	159	(19)	286	(16)
2	76	(9)	188	(11)
≥ 3	75	(9)	448	(25)
Stage				
I	23	(3)	9	(1)
II	321	(38)	91	(5)
III	324	(38)	95	(5)
IV	156	(18)	1259	(71)
Missing	30	(4)	323	(18)
Tumor localization				
Right colon[a]	33	(4)	218	(12)
Transverse colon	71	(8)	130	(7)
Left colon[b]	643	(75)	935	(53)
Rectum	107	(13)	421	(24)
Missing	0		73	(4)
Primary procedure				
Stent	758	(89)	1035	(58)
Diverting stoma	96	(11)	742	(42)
Time to elective resection				
Median, days (5–95% percentile)	21	(9–127)	–	–
30-day mortality				
Yes	5	(1)	368	(21)
90-day mortality				
Yes	20	(2)	674	(38)

[a] Includes the cecum, ascending colon, and hepatic flexure

[b] Includes the splenic flexure, descending colon, and sigmoid colon

operated with minimal invasive surgery. However, we cannot explore this further in the current data.

In conclusion, the 90-day postoperative mortality after acute colorectal cancer surgery, including SEMS, has improved significantly in Denmark from 2005 to 2015. However, postoperative mortality remains high at 24% in 2015 and further studies should investigate how the perioperative period could be optimized to improve survival even more.

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A nationwide cohort study of the impact of education, income and social isolation on survival after acute colorectal cancer surgery.

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Abstract

Background Acute colorectal cancer surgery is associated with a high postoperative mortality. The aim of this observational study was to examine the association between socioeconomic position with the likelihood of undergoing acute versus elective colorectal cancer surgery and subsequently 1-year survival among patients treated with acute surgery.
Method All patients who had undergone a surgical procedure according to the Danish Colorectal Cancer (DCCG.dk) database or registered with stent or diverting stoma in the National Patient Register from 2007 to 2015 were included. Socioeconomic position was measured by highest attained education, income, urbanicity, and cohabitation status obtained from administrative registries.
Results In total, 35 661 patients were included whereof 5 310 (15%) had an acute surgery. Short and medium education (patients < 65 years), (OR = 1.58, 95% CI: 1.32-1.91 and OR = 1.34, 95% CI: 1.15-1.55, respectively), low income (OR = 1.12, 95% CI: 1.01-1.24), and living alone (OR = 1.35, 95% CI: 1.26-1.46) were associated with acute surgery. Overall, 41% died within one year postoperatively. Short education (HR = 1.18, 95% CI: 1.03-1.36), low income (HR = 1.16, 95% CI: 1.01-1.34), and living alone (HR = 1.25, 95% CI: 1.13-1.38) was associated with reduced 1-year survival after acute surgery.
Conclusion Low socioeconomic position was associated with an increased likelihood of undergoing acute colorectal cancer surgery and subsequently reduced 1-year survival after acute surgery. Lifestyle, comorbidity, and clinical factors did not explain the social gradient in survival. Attention to socioeconomic position in acute presentation of colorectal cancer is needed.

Introduction

Low socioeconomic position is associated with poor short-term and long-term survival after elective colorectal cancer surgery [1-3]. These socioeconomic inequalities in survival after colorectal cancer are observed even in countries with free health care services, such as the Scandinavian countries [1-3]. Socioeconomic position is an indicator of various social and economic factors that influence the position held in society on individual and area/group level [4]. Socioeconomic factors can have an impact on different health related exposures, both positive and negative, and on available economic resources that are important for a healthy lifestyle [4].

Patients, who present acutely with colorectal cancer with e.g. obstruction, perforation of the bowel, or bleeding, are at higher risk of poor outcome postoperatively and in the long term [5, 6]. It is crucial to identify risk factors for acute surgery in order to improve early detection of the disease, improve the perioperative care and initiate necessary rehabilitation.

The aim of this study was to investigate if the level of education, income, urbanicity, and cohabitation, as measures of different aspects of socioeconomic position, was associated with a greater likelihood of undergoing acute rather than elective colorectal cancer surgery. A further aim was to investigate whether the same socioeconomic factors were associated with 1-year survival after acute colorectal cancer surgery.

Methods

Study design and setting

In this nationwide, historical cohort study there were two primary study hypotheses. It was firstly investigated if socioeconomic position was associated with the likelihood of acute colorectal cancer surgery (first primary outcome) and with all-cause 1-year survival after acute colorectal cancer surgery (second primary outcome). All-cause survival included the complete 1-year survival after surgery and no patients were excluded or censored. Four socioeconomic factors were selected to cover different aspects of the influence on health. The primary factor being a knowledge-related asset (education), the secondary factor was economic resources reflecting the affordability of healthy lifestyle (income), the third factor was geographic aspects and structural support (urbanicity), and the last factor was social support (cohabitation) [4].

This is a register-based study linking data from the Danish Colorectal Cancer Group (DCCG.dk) database and various Danish registries using the personal identification number (CPR) that incorporates information on date of birth and sex which is provided to all Danish citizens and people with a Danish residence permit [7, 8]. All primary care and hospital care expenses, including diagnostics, treatment, and rehabilitation, are free-of-charge in Denmark financed by a tax-based system. In this study, colorectal cancer surgery was performed in 17 public hospitals in Denmark, which included all hospitals performing the procedure in the study period. No private facilities treating colorectal cancer exist in Denmark. The study is reported according to the STROBE checklist and the extended RECORD checklist [9, 10]. All analyses were planned a priori and the study protocol was available at clinicaltrial.org before initiation of the study (NCT number: NCT03581890) [11].

Data sources

The DCCG.dk database is a nationwide clinical database established in 2001 registering all incident cases of colorectal cancer in Denmark fulfilling the database criteria, with a >95 per cent patient coverage [12]. Patients are registered in the database if they are diagnosed and/or treated for colorectal cancer at any Danish surgical department [12]. Data on patients undergoing a surgical procedure are collected prospectively by the surgical departments and documented through a web-based platform. In the perioperative period, patient-related and surgical-related data are registered. Pathological disease characteristics, such as T- and N-category, are registered postoperatively by a pathologist. In the database, only patients with primary adenocarcinoma, mucinous adenocarcinoma, signet ring cell carcinoma, medullary carcinoma, or undifferentiated carcinoma are included. Additionally, metachronous colorectal cancers are not registered [12].

The National Patient Register is a nationwide register established in 1977 with data regarding all patient contact to Danish hospitals [13]. The register is considered the most comprehensive of its kind [13] and includes data on diagnosis according to the ICD-10 (1994 up to today), time and date of admission and priority of the admission registered at the end of each hospital contact etc.

Data on socioeconomic factors were obtained from nationwide administrative registers updated annually by Statistics Denmark by linking the personal identification number to different institutions [14]. The Danish education registries include information on all educational programs in the country of which some data are dating back as far as 1910 [15]. Data on education is collected by the Danish Ministry of Education and is generated from the educational institutions. Data on disposable income were collected from registries on personal labour marked affiliation which contain information on employment status on all people registered on the Danish labour marked [16]. Address and family status were obtained from the Danish Civil Registration System established in 1968 with continuous information on all people living in Denmark with a CPR number [7].

Participants

Patients were included in this study if they had undergone colorectal cancer surgery from January 1st 2007 to December 31st 2015 and were registered with a colorectal cancer diagnosis in the DCCG.dk database within this period. In the analysis on likelihood of acute colorectal cancer surgery, all patients were included in the analysis. In the analysis on 1-year postoperative survival, only patients who had acute surgery were included. Acute surgery was defined as the patient being registered by the operating surgeon in the DCCG.dk database with an acute procedure or registered in the NPR with a diverting stoma or insertion of a self-expanding metallic stent (SEMS) in colon or rectum within 72 hours after an acute admission at any department. ICD-10 codes were used to identify the procedures; diverting stoma (KJFF10, KJFF11, KJFF20, KJFF21, KJFF23, KJFF24, KJFF26, KJFF27, KJFF30, and KJFF31) and SEMS in colon or rectum (KJFA68 and KJGA58A). Vital status was registered in the Danish Civil Registration Register [7] and information on 1-year survival was linked to the DCCG.dk database in January 2017. Hence, all patients had 1-year follow-up unless they had migrated or disappeared. Patients were excluded if they had missing data on surgical priority (acute or elective), income up to three years before surgery, or cohabitation the year before surgery, if they migrated or disappeared within one year after acute surgery or registered with a surgical procedure dated after time of death.

Socioeconomic indicators

The highest obtained level of education was retracted from the Danish education registries [15]. The level of education was obtained by 1st of October the year before surgery. If information on educational level was missing, the level obtained up to three years before surgery was included, thus assuming that few patients would change educational level considering that colorectal cancer generally occurs at a relatively high age. Education was categorized into three standardized categories: short (seven or nine years mandatory primary school for persons born before and after 1 January 1958, respectively), medium (ten to twelve years of schooling corresponding to upper secondary school and vocational education) and long (more than twelve years of education, higher education). This corresponds to the International Standard Classification of Education (ISCED-2011) codes; short (ISCED codes 1–2, ≤ 9 years), medium (ISCED 3–4, 10–12 years), and long (ISCED 5–8, >12 years) [17]. Disposable income level was obtained from the registries on personal labour marked affiliation in the year before surgery. A patient with missing value on income the year before surgery was registered with the income up to three years before surgery. Income was grouped into quintiles taking the annual average age and sex-adjusted income in Denmark into account. Urbanicity is a variable based on geographical resources in the area of the patients' home address such as number of inhabitants, distance to a main road etc. [18] This variable reflects structural support from the health care system and is categorized into city, town, rural, or peripheral rural areas. Cohabitation status was defined as living with a partner (married or cohabiting) or living without a partner (single, widowed or divorced) and reflects emotional and instrumental support. Urbanicity and cohabitation status were obtained from the Danish Civil Registration System at the beginning of the year of surgery for each patient.

Covariates

Sex, age and year of surgery were considered confounders. Data on confounders and the potential mediators were obtained from the DCCG.dk database. These include comorbidity (Charlson Comorbidity Index (CCI score 0, 1, 2, and 3+)), smoking (never smoked, former smoker (not smoked for at least 8 weeks) or current smoker), weekly alcohol consumption (0, 1-14, 15-21 or over 21 units per week), Body Mass Index (BMI <18.9, 18.5-25, 25-30, >30), the Union for International Cancer Control stage (UICC stage I-IV), and localization of the tumour (right colon, transverse colon, left colon or rectum).

Statistical methods

The association between socioeconomic position and acute versus elective colorectal cancer surgery was analysed using a logistic regression model. There were no missing data on acute versus elective surgery. Missing data on highest education level, BMI, alcohol, smoking, stage, and localization were handled with multiple imputation using the fully conditional specification method. Ten imputed datasets were generated with all variables included in the multiple imputation, including the primary outcome, acute surgery. The model was adjusted for the confounders; age, sex, and year of surgery and in a second model the potential mediators; CCI score, BMI, smoking, alcohol, tumour localization, and UICC stage. Age was the only continuous variable. Linearity was tested by inserting a squared term in the model finding age to be non-linear. Thus, in the model, age was included as a linear spline with cut points at the tertiles. Interactions between education, comorbidity, and age, respectively, were tested. There was an interaction between education and age, which was included in the results.

Among the patients who had acute surgery, the association between socioeconomic position and 1-year survival was investigated with cox-proportional hazards regression models with time since surgery as the underlying timescale. There were no missing data on 1-year survival. Missing data on highest attained level of education, BMI, alcohol, smoking, stage, and localization were handled with multiple imputation using the fully conditional specification method. Ten imputed datasets were generated with all variables included in the multiple imputation, including the primary outcome, 1-year survival. The model was adjusted for the confounders; age, sex, and year of surgery and in a second model the potential mediators; CCI score, BMI, smoking, alcohol, tumour localization, and UICC stage. All variables in the model and 1-year survival were included in the imputation.

Survival by education level was illustrated with Kaplan-Meier curves after multiple imputation.

In an additional analysis of patients who underwent acute surgery, it was tested whether there was a difference in survival already 90 days postoperatively with a cox proportional hazards regression model adjusted for age, sex, year of surgery, CCI score, BMI, smoking, alcohol, tumour localization, and UICC stage.

All results were presented with the corresponding 95 per cent confidence interval (CI). Analyses were performed using SAS software, version 9.3. This study was reported to the Danish Data Protection Agency with registration number 2015-41-3726. Under Danish law, registration with the Danish Ethical Committee was not required.

Results

Participant characteristics

In the study period, 35 801 patients were eligible for inclusion and 140 patients were excluded due to at least one exclusion criteria (*Figure 1*). Only one patient was excluded due to migration within one year after acute surgery. In total, 35 661 patients operated for colorectal cancer were included in the study whereof 30 351 (85 per cent) underwent elective surgery and 5 310 (15 per cent) underwent acute surgery. In total, 41 per cent died within the first year after acute surgery. The Kaplan Meier plot illustrates that the unadjusted 1-year survival after acute surgery is lower among the patients with a short education (*Figure 2*). This survival difference between short versus medium and long education increases gradually with calendar time.

The proportion of acutely operated patients was 17 per cent among patients with a short education and 13 per cent among patients with a long education (*Table 1*). Overall, more patients with a short education smoked (17 per cent), had comorbidities (45 per cent), and a BMI above 30 (16 per cent) (*Table 1*). However, extensive alcohol intake of more than 21 units per week was more common among patients with a long education (7 per cent) (*Table 1*). UICC stage III and IV were distributed equally by education in all patients (*Table 1*); however, among patients who had acute surgery, there was a higher proportion of stage IV disease among patients with a long education (49 per cent) (*Table 2*). The majority of the acutely operated patients were extracted from the DCCG.dk database (73 per cent), while the remaining 27 per cent were included from the NPR.

Educational level was missing for 4 per cent of patients, with the majority (66 per cent) being more than 75 years old. The variables smoking and alcohol had the highest proportion of missing data with 17 per cent missing in both the variables (*Table 1*). Among patients who had acute surgery, information on BMI, smoking, and alcohol was missing in 26 per cent, 33 per cent and 32 per cent, respectively (*Table 2*).

Risk of acute versus elective surgery

There was an interaction between education and age in the model. Short and medium educational levels were associated with an increased risk of having acute colorectal cancer compared to a long education among patients younger than 65 years when adjusting for age, sex, year of surgery, comorbidity, BMI, smoking, alcohol, UICC stage, and tumour localization (Odds Ratio (OR) of 1.58 (95 per cent CI: 1.32-1.91) and 1.34 (95 per cent CI: 1.15-1.55), respectively, *Figure 1*). No association between education and the OR of acute surgery was observed for other age groups. Adjusting for potential mediating factors resulted in only slight changes of the effect estimates. Low income was associated with an increased risk of acute surgery, only significant in the second income quintile with an OR of 1.07 (95 per cent CI: 0.97-1.20) in the lowest and 1.12 (95 per cent CI: 1.01-1.24) in the second lowest income quintile group when adjusting for the same covariates and for education. There was no association between urbanicity and acute surgery in the adjusted model. Living alone was associated with an OR for acute surgery of 1.35 (95 per cent CI: 1.26-1.46) compared with patients living with a partner in the full-adjusted model (*Figure 1*). The association between confounders/mediators and the risk of acute colorectal cancer surgery is found in the supplementary Table 1a.

One-year survival after acute colorectal cancer surgery

Short educational level was associated with poor 1-year survival after acute colorectal cancer surgery with a Hazard Ratio (HR) of 1.18 (95 per cent CI: 1.03-1.36) when adjusted for age, sex, year of surgery, comorbidity, BMI, smoking, alcohol, UICC stage, and tumour localization *(Figure 2)*. Additionally, low income was associated with a reduced 1-year survival after adjustment. The HR was 1.16 (95 per cent CI 1.01-1.34) in the lowest income quintile and 1.17 (95 per cent CI 1.02-1.35) in the second lowest income quintile. Urbanicity did not have any association with one-year survival after full adjustment. Living alone was associated with poor survival with an adjusted HR of 1.25 (95 per cent CI 1.13-1.38) *(Figure 2)*. The association between confounders/mediators and 1-year survival after acute colorectal cancer surgery is found in the supplementary Table 1b.

Survival 90 days postoperatively

In acutely operated patients, short education was associated with 90-day postoperative survival in the fully adjusted model, albeit failing to reach statistical significance (adjusted HR =1.14, 95 per cent CI 0.99-1.32).

Discussion

In this study, poor 1-year survival among patients who had acute colorectal cancer surgery was significantly associated with shorter education, low income, and living alone. In patients <65 years of age, education was a risk factor for acute versus elective surgery. In all age groups, low income and living alone were also associated with acute surgery.

Among patients who had acute surgery, there was not sufficient information about the clinical condition such as sepsis or tumour perforation at the time of surgery, which could affect postoperative survival [19, 20]. Lack of these data could introduce residual confounding or mediation in the present results and potentially lead to overestimating the effect of socioeconomic position on 1-year survival.

It is a limitation in this study that four per cent of the included participants had missing data on the main exposure; education, especially among the elderly patients. Missing data in the lifestyle factors BMI, smoking, and alcohol were also pronounced in patients undergoing acute surgery. Missing data were handled with multiple imputation and in the process of imputation, all variables and the primary outcome were included. Multiple imputation is the preferred way to handle missing data and allows uncertainty about the missing data [21].

A major strength of this study is that it is based on a clinical database with a completeness proportion of 95-99 per cent of all patients with colorectal cancer in Denmark. With a nationwide population and very few exclusion criteria, the risk of selection bias is minimal. Furthermore, all data in the study were collected prospectively into the registries, independently of the study hypothesis, minimizing the risk of recall bias.

Despite many structural changes in the treatment of colorectal cancer within the last 10 years in Denmark and a health care system free-of-charge [22, 23] there are still differences in the risk of acute surgery and in survival one year after acute surgery according to socioeconomic position. Ten years ago, a Danish nationwide study showed that long education and living in an owned house compared with a rented house, improved 30-day survival after elective colorectal cancer surgery [1]. Identifying patients via screening could reduce the proportion of acutely operated patients. A British study from 2017 found a 40 per cent reduction in acutely operated patients after introduction of colorectal cancer screening from 23 per cent to 15 per cent ($p<0.001$) [24]. Participation in a colorectal cancer screening programme also has a socioeconomic gradient. Three recent studies showed that participation in screening increases with level of education, with income, and in patients living with a partner [25-27]. Low socioeconomic position is also associated with the likelihood of submitting a stool sample ineligible for analysis [28]. Taken together, the present results and previous findings indicate that different approaches in screening and treatment of patients with low socioeconomic position might need to be considered in future studies. A French randomized trial from 2017 with 16 250 participants aimed to improve participation of colorectal screening by introducing a navigator programme. A specially trained social worker contacted the non-participant individuals by phone, mail or home visits [29]. The overall participation rate improved 3 per cent from 24 per cent to 21 per cent ($p = 0.003$) with a higher increase in the individuals livening in affluent areas (4 per cent increase) compared with deprived areas, 3 per cent increase [29]. This implies that navigation might be a strategy to improve participation in all groups but with a relatively small effect of a navigator, the intervention strategy should be improved.

In the present results, the risk estimate for a short education level on survival after acute surgery hardly changes when adjusting for UICC stage, comorbidity, and lifestyle factors. Thus, these potential mediating factors do not seem to explain the social gradient in survival after acutely treated colorectal cancer. One Dutch study from 2014 with 6 736 colorectal cancer patients found that age, comorbidity, and acute surgery explained the educational differences in postoperative 30-day mortality in patients with colon, but not in patients with rectal cancer [30]. A British study from 2006 with 7 290 operated colorectal cancer patients similarly showed that differences in postoperative 30-day mortality were explained by emergency surgery, stage of disease, and comorbidity [31]. In the full model, socioeconomic position was no longer associated with postoperative mortality [31]. No previous studies have specifically investigated the association between socioeconomic position and 1-year survival after acute presentation of colorectal cancer. A Danish nationwide study with data from 2001 to 2004 including 8 763 patients operated for colorectal cancer (85 per cent treated with elective procedures) showed improved long-term and overall survival in patients with a high education level in adjusted analysis [2]. However, in contrast to the present study, the association between educational level and survival was, to a high extent, mediated by lifestyle and particularly comorbidity [2] indicating that drivers of socioeconomic position on health outcomes may be different according to disease trajectory.

The results of this study may be generalized to other countries with a universal health care coverage across all social groups. The estimated effect of socioeconomic position is probably stronger in countries where access to timely and optimal healthcare is yet another barrier for patients with low socioeconomic position [32]. An American study from 2014 with 83 330 patients showed an increased risk of emergency diagnosis of colorectal cancer in African-Americans living in poor neighbourhoods [33].

The main findings in the present study were that short education, low income, and living alone were associated with a greater likelihood of acute colorectal cancer surgery compared with elective and with a decreased 1-year survival after acute colorectal cancer surgery in Denmark, a country with free and equal access to health care services. The social gradient did not seem to be mediated by lifestyle, comorbidity, or disease characteristics in this population and warrants further investigations in order to improve treatment possibilities and survival in patients with colorectal cancer and low socioeconomic position. An increased focus on perioperative optimization, rehabilitation, and surveillance within at least one year after acute surgery could be beneficial in this high-risk patient group in order to improve survival.

Disclosure

The authors declare no conflict of interest.

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Table 1. Descriptive characteristics of 35 661 persons treated with surgery for colorectal cancer in Denmark, 2007-2015.

	Highest attained education									
	Short		**Medium**		**Long**		**Missing**		**Total**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	(%)
	10 751	**(30)**	**16 804**	**(47)**	**6 720**	**(19)**	**1 386**	**(4)**	**35 661**	
Surgical mode										
Acute	1 791	(17)	2 302	(14)	847	(13)	370	(27)	5 310	(15)
Elective	8 960	(83)	14 502	(86)	5 873	(87)	1 016	(73)	30 351	(85)
Sex										
Men	4 981	(46)	9 622	(57)	3 890	(58)	629	(45)	19 122	(54)
Women	5 770	(54)	7 182	(43)	2 830	(42)	757	(55)	16 539	(46)
Age										
Median age (5%-95% range)									71 (50-87)	
<65	1 955	(18)	6 208	(37)	2 937	(44)	207	(15)	11 307	(32)
65-70	1 686	(16)	3 218	(19)	1 255	(19)	122	(9)	6 281	(18)
71-75	2 289	(21)	3 080	(18)	1 126	(17)	139	(10)	6 634	(19)
>75	4 821	(45)	4 298	(26)	1 402	(21)	918	(66)	11 439	(32)
CCI										
0	5 984	(56)	10 379	(62)	4 502	(67)	671	(48)	21 536	(60)
1	2 138	(20)	2 848	(17)	1 006	(15)	338	(24)	6 330	(18)
2	1 247	(12)	1 797	(11)	591	(9)	174	(13)	3 809	(11)
≥3	1 382	(13)	1 780	(11)	621	(9)	203	(15)	3 986	(11)
BMI										
<18.5	379	(4)	446	(3)	172	(3)	78	(6)	1 075	(3)
18.5-25	3 841	(36)	6 517	(39)	3 052	(45)	551	(40)	13 961	(39)
25-30	3 171	(29)	5 350	(32)	2 048	(30)	291	(21)	10 860	(30)
>30	1 677	(16)	2 535	(15)	718	(11)	116	(8)	5 046	(14)
Missing	1 683	(16)	1 956	(12)	730	(11)	350	(25)	4 719	(13)
Smoking										
Never smoked	3 229	(30)	5 221	(31)	2 379	(35)	433	(31)	11 262	(32)
Former smoker	3 565	(33)	5 895	(35)	2 433	(36)	373	(27)	12 266	(34)
Smoker	1 854	(17)	3 038	(18)	895	(13)	177	(13)	5 964	(17)
Missing	2 103	(20)	2 650	(16)	1 013	(15)	403	(29)	6 169	(17)
Alcohol (units/week)										
0	3 155	(29)	3 249	(19)	1 111	(17)	422	(30)	7 937	(22)
1-14	4 803	(45)	8 832	(53)	3 566	(53)	458	(33)	17 659	(50)
15-21	358	(3)	1 187	(7)	595	(9)	51	(4)	2 191	(6)
>21	337	(3)	1 029	(6)	498	(7)	62	(4)	1 926	(5)
Missing	2 098	(20)	2 507	(15)	950	(14)	393	(28)	5 948	(17)

Income										
1st quintile	2 788	(26)	3 286	(20)	569	(8)	320	(23)	6 963	(20)
2nd quintile	2 909	(27)	3 707	(22)	677	(10)	307	(22)	7 600	(21)
3rd quintile	2 012	(19)	3 771	(22)	1 310	(19)	250	(18)	7 343	(21)
4th quintile	1 177	(11)	3 354	(20)	2 325	(35)	271	(20)	7 127	(20)
5th quintile	1 865	(17)	2 686	(16)	1 839	(27)	238	(17)	6 628	(19)
Urbanicity										
City	3 280	(31)	7 393	(44)	3 511	(52)	672	(48)	14 856	(42)
Town	3 983	(37)	4 919	(29)	1 674	(25)	365	(26)	10 941	(31)
Rural	1 866	(17)	2 889	(17)	1 007	(15)	186	(13)	5 948	(17)
Peripheral	1 622	(15)	1 603	(10)	5 28	(8)	163	(12)	3 916	(11)
Cohabitation										
Living with a partner	5 840	(54)	11 406	(68)	4 760	(71)	509	(37)	22 515	(63)
Living alone	4 911	(46)	5 398	(32)	1 960	(29)	877	(63)	13 146	(37)
UICC Stage										
I	1 636	(15)	2 919	(17)	1 257	(19)	149	(11)	5 961	(17)
II	3 545	(33)	5 247	(31)	1 958	(29)	466	(34)	11 216	(31)
III	2 791	(26)	4 412	(26)	1 819	(27)	353	(25)	9 375	(26)
IV	1 882	(18)	2 790	(17)	1 169	(17)	244	(18)	6 085	(17)
Missing	897	(8)	1 436	(9)	517	(8)	174	(13)	3 024	(8)
Tumor localization										
Right colon	3 171	(29)	4 391	(26)	1 683	(25)	423	(31)	9 668	(27)
Transverse colon	645	(6)	872	(5)	311	(5)	126	(9)	1 954	(5)
Left colon	3 567	(33)	5 876	(35)	2 522	(38)	495	(36)	12 460	(35)
Rectum	3 344	(31)	5 626	(33)	2 180	(32)	338	(24)	11 488	(32)
Missing	24	(0)	39	(0)	24	(0)	4	(0)	91	(0)
Year of surgery										
2007-2010	4 350	(40)	5 799	(35)	2 257	(34)	805	(58)	13 211	(37)
2011-2013	3 190	(30)	5 027	(30)	1 946	(29)	316	(23)	10 479	(29)
2014-2016	3 211	(30)	5 978	(36)	2 517	(37)	265	(19)	11 971	(34)

CCI, Charlson Comorbidity Index score; BMI, body mass index; UICC, Union for International Cancer Control

Table 2. Descriptive characteristics by education of 5 310 persons undergoing acute surgery for colorectal cancer, Denmark, 2007-2015.

	Highest attained education									
	Short		**Medium**		**Long**		**Missing**		**Total**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
	1 791	**(34)**	**2 302**	**(43)**	**847**	**(16)**	**370**	**(7)**	**5 310**	
1-year mortality										
Yes	807	(45)	828	(36)	300	(35)	225	(61)	2 160	(41)
90-day mortality										
Yes	486	(27)	446	(19)	165	(19)	156	(42)	1 253	(24)
Sex										
Men	759	(42)	1 210	(53)	480	(57)	146	(39)	2 595	(49)
Women	1 032	(58)	1 092	(47)	367	(43)	224	(61)	2 715	(51)
Age										
Median age (5%-95% range)									73	(50-90)
<65	312	(17)	798	(35)	321	(38)	36	(10)	1 467	(28)
65-70	227	(13)	417	(18)	140	(17)	19	(5)	803	(15)
71-75	283	(16)	367	(16)	131	(15)	17	(5)	798	(15)
>75	969	(54)	720	(31)	255	(30)	298	(81)	2 242	(42)
CCI										
0	846	(47)	1 284	(56)	483	(57)	144	(39)	2 757	(52)
1	353	(20)	394	(17)	125	(15)	91	(25)	963	(18)
2	229	(13)	229	(10)	81	(10)	51	(14)	590	(11)
≥3	363	(20)	395	(17)	158	(19)	84	(23)	1 000	(19)
BMI										
<18.5	100	(6)	101	(4)	28	(3)	23	(6)	252	(5)
18.5-25	634	(35)	926	(40)	388	(46)	131	(35)	2 079	(39)
25-30	367	(20)	514	(22)	197	(23)	53	(14)	1 131	(21)
>30	168	(9)	210	(9)	54	(6)	15	(4)	447	(8)
Missing	522	(29)	551	(24)	180	(21)	148	(40)	1 401	(26)
Smoking										
Never smoked	439	(25)	587	(25)	268	(32)	103	(28)	1 397	(26)
Former smoker	409	(23)	554	(24)	217	(26)	56	(15)	1 236	(23)
Smoker	311	(17)	486	(21)	118	(14)	36	(10)	951	(18)
Missing	632	(35)	675	(29)	244	(29)	175	(47)	1 726	(33)
Alcohol (units/week)										
0	489	(27)	484	(21)	176	(21)	101	(27)	1 250	(24)
1-14	590	(33)	915	(40)	363	(43)	85	(23)	1 953	(37)
15-21	38	(2)	119	(5)	36	(4)	6	(2)	199	(4)
>21	46	(3)	121	(5)	48	(6)	8	(2)	223	(4)
Missing	628	(35)	663	(29)	224	(26)	170	(46)	1 685	(32)

Income										
1st quintile	480	(27)	455	(20)	72	(9)	94	(25)	1 101	(21)
2nd quintile	481	(27)	554	(24)	88	(10)	93	(25)	1 216	23)
3rd quintile	356	(20)	504	(22)	184	(22)	67	(18)	1 111	(21)
4th quintile	172	(10)	429	(19)	301	(36)	64	(17)	966	(18)
5th quintile	302	(17)	360	(16)	202	(24)	52	(14)	916	(17)
Urbanicity										
City	589	(33)	1061	(46)	457	(54)	177	(48)	2 284	(43)
Town	636	(36)	637	(28)	200	(24)	98	(26)	1 571	(30)
Rural	315	(18)	379	(16)	123	(15)	49	(13)	866	(16)
Peripheral	251	(14)	225	(10)	67	(8)	46	(12)	589	(11)
Cohabitation										
Living with a partner	801	(45)	1376	(60)	524	(62)	98	(26)	2 799	(53)
Living alone	990	(55)	926	(40)	323	(38)	272	(74)	2 511	(47)
UICC Stage										
I	27	(2)	38	(2)	15	(2)	8	(2)	88	(2)
II	449	(25)	564	(25)	169	(20)	86	(23)	1 268	(24)
III	438	(24)	552	(24)	193	(23)	82	(22)	1 265	(24)
IV	714	(40)	997	(43)	412	(49)	119	(32)	2 242	(42)
Missing	163	(9)	151	(7)	58	(7)	75	(20)	447	(8)
Tumor localization										
Right colon	572	(32)	684	(30)	267	(32)	108	(29)	1 631	(31)
Transverse colon	161	(9)	197	(9)	65	(8)	49	(13)	472	(9)
Left colon	826	(46)	1 124	(49)	413	(49)	175	(47)	2 538	(48)
Rectum	215	(12)	260	(11)	81	(10)	34	(9)	590	(11)
Missing	17	(1)	37	(2)	21	(2)	4	(1)	79	(1)
Year of surgery										
2007-2010	782	(44)	881	(38)	312	(37)	225	(61)	2 200	(41)
2011-2013	574	(32)	815	(35)	291	(34)	90	(24)	1 770	(33)
2014-2016	435	(24)	606	(26)	244	(29)	55	(15)	1 340	(25)

CCI, Charlson Comorbidity Index score; BMI, body mass index; UICC, Union for International Cancer Control

Figure 1. Flow chart of the study population of persons who were treated with surgery for colorectal cancer in Denmark, 2007-2015

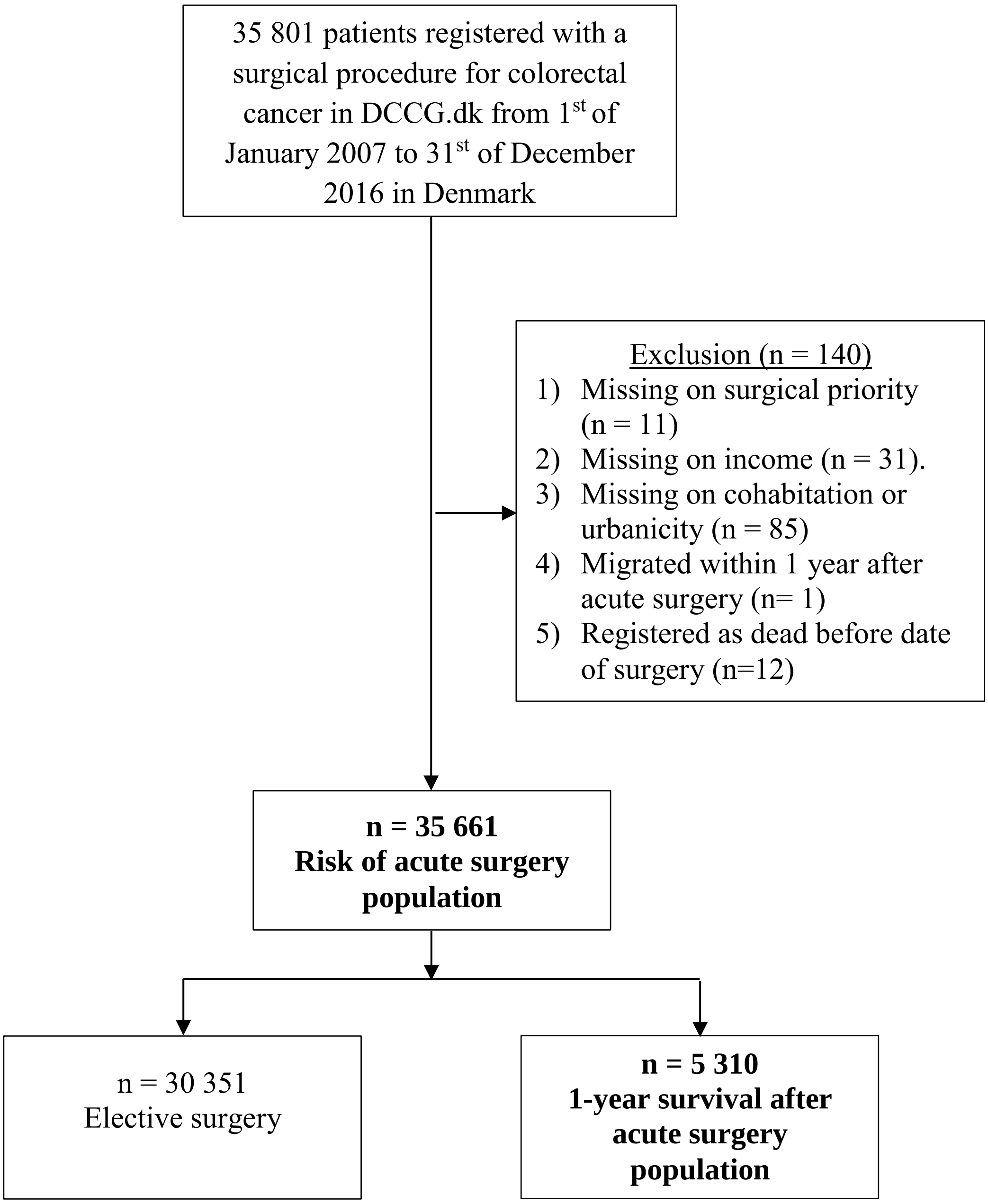
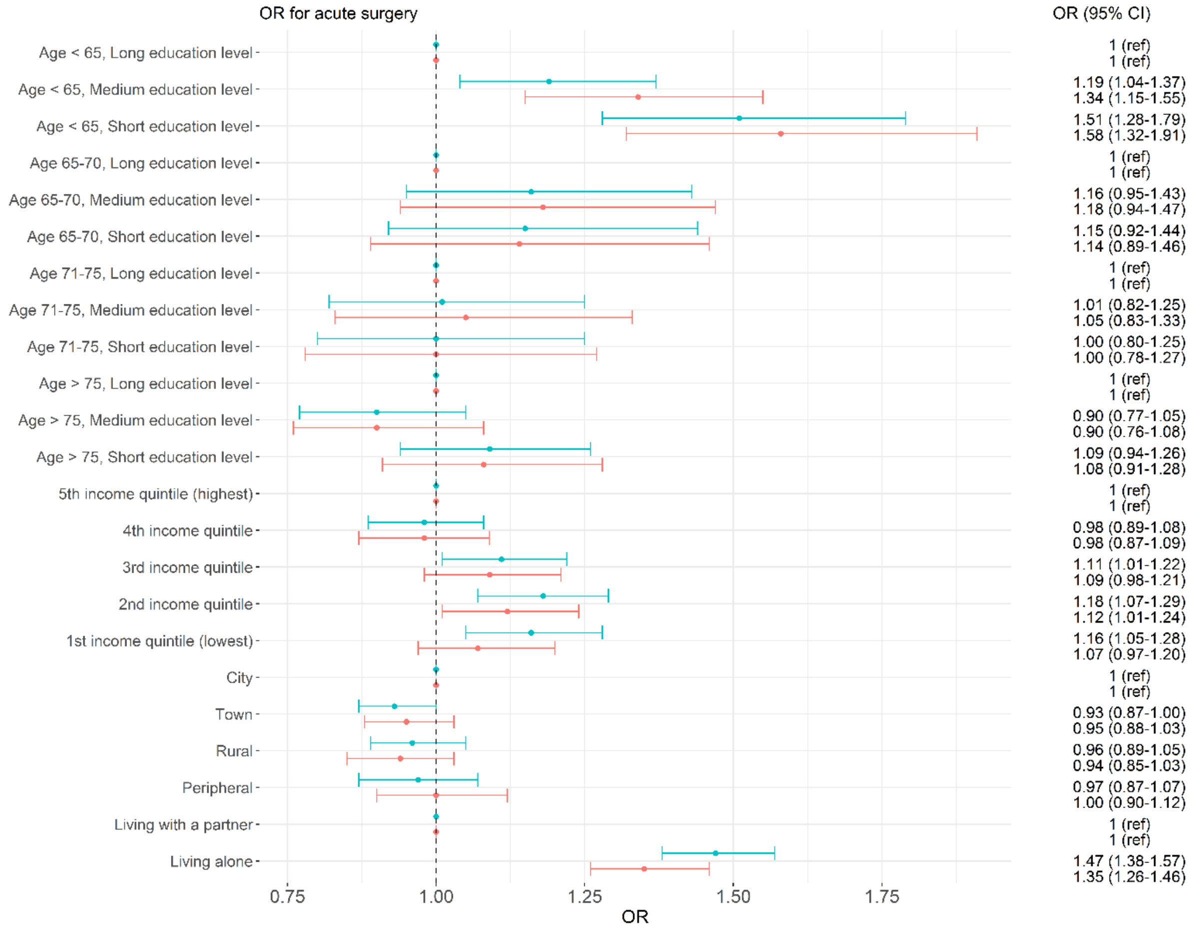
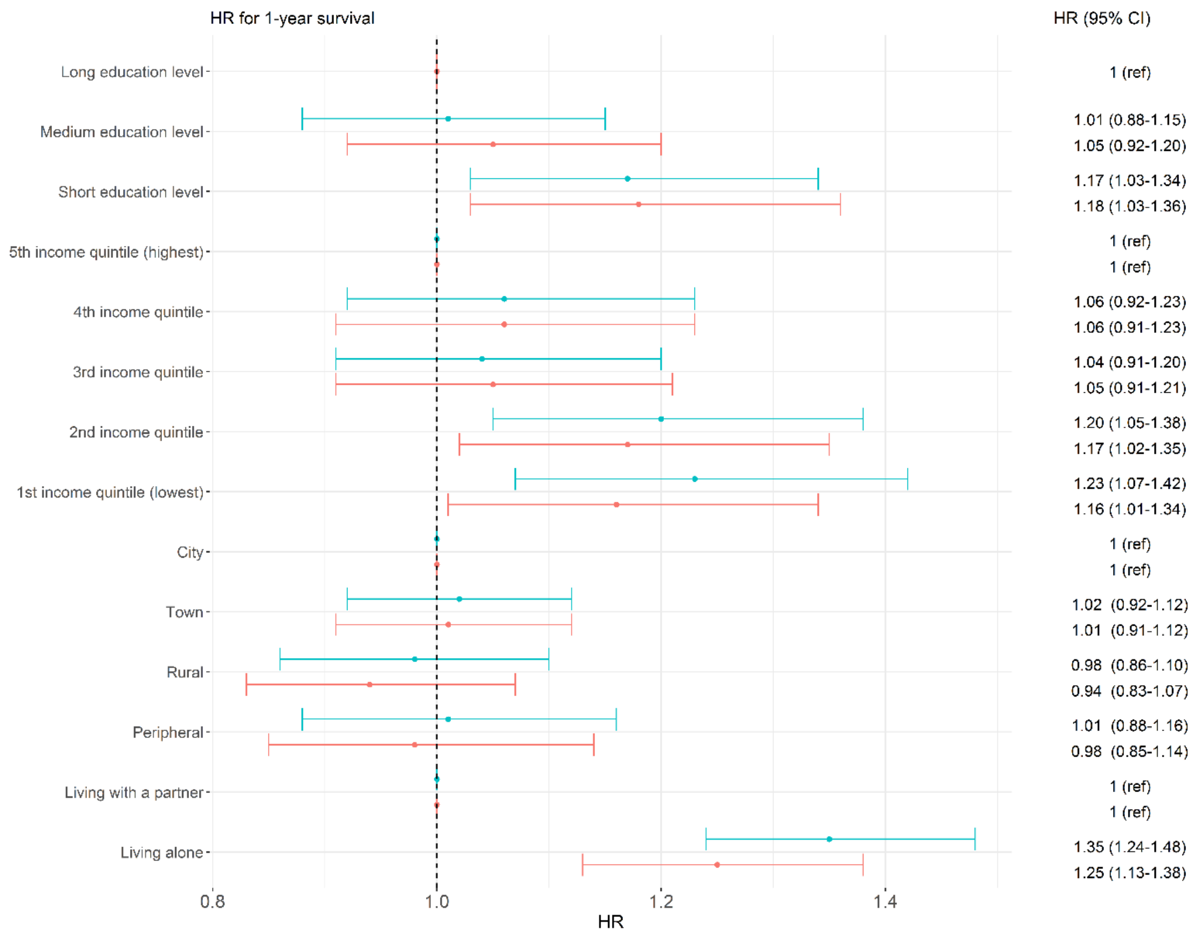


Figure 2. Age-, sex- and year-adjusted and multivariate adjusted odds ratios (ORs) with corresponding 95% confidence intervals (CI) for acute surgery in 35 661 persons operated for colorectal cancer, Denmark, 2007-2015.



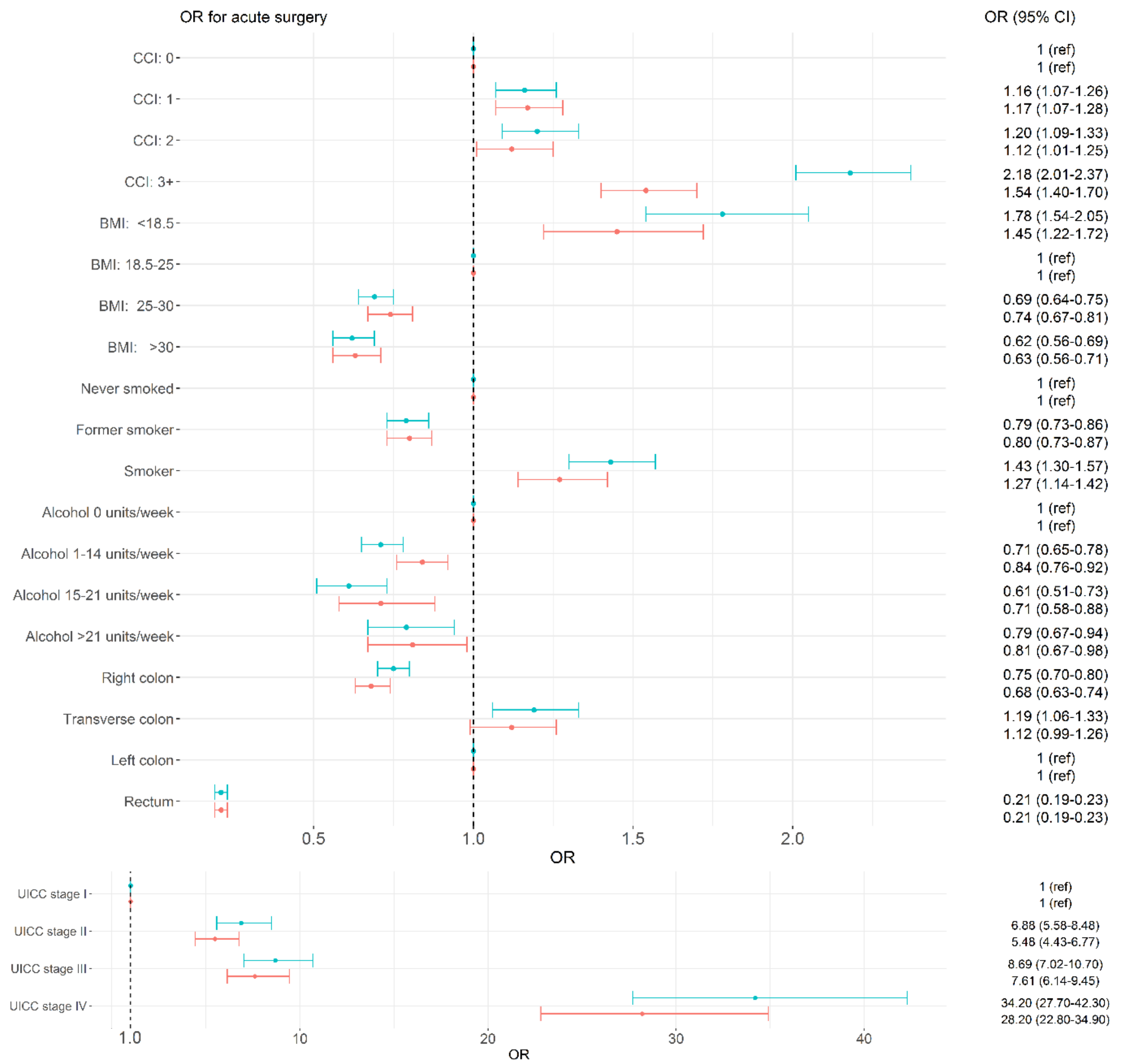
Blue line: adjusted for sex, age and year of surgery.
Red line: Adjusted for sex, age, year of surgery, Charlson Comorbidity Index score, BMI, smoking, drinking, UICC stage, and localization. Income additionally adjusted for education. Urbanicity additionally adjusted for education and income. Cohabitation additionally adjusted for education, income and urbanicity.

Figure 3. Age-, sex- and year adjusted and multivariate adjusted hazard ratios (HRs) with corresponding 95% confidence intervals (CI) for 1-year mortality among 5 310 persons treated with acute surgery for colorectal cancer in Denmark, 2007-2015



Blue line: adjusted for sex, age and year of surgery.
Red line: Adjusted for sex, age, year of surgery, Charlson Comorbidity Index score, BMI, smoking, drinking, UICC stage, and localization. Income additionally adjusted for education. Urbanicity additionally adjusted for education and income. Cohabitation additionally adjusted for education, income and urbanicity.

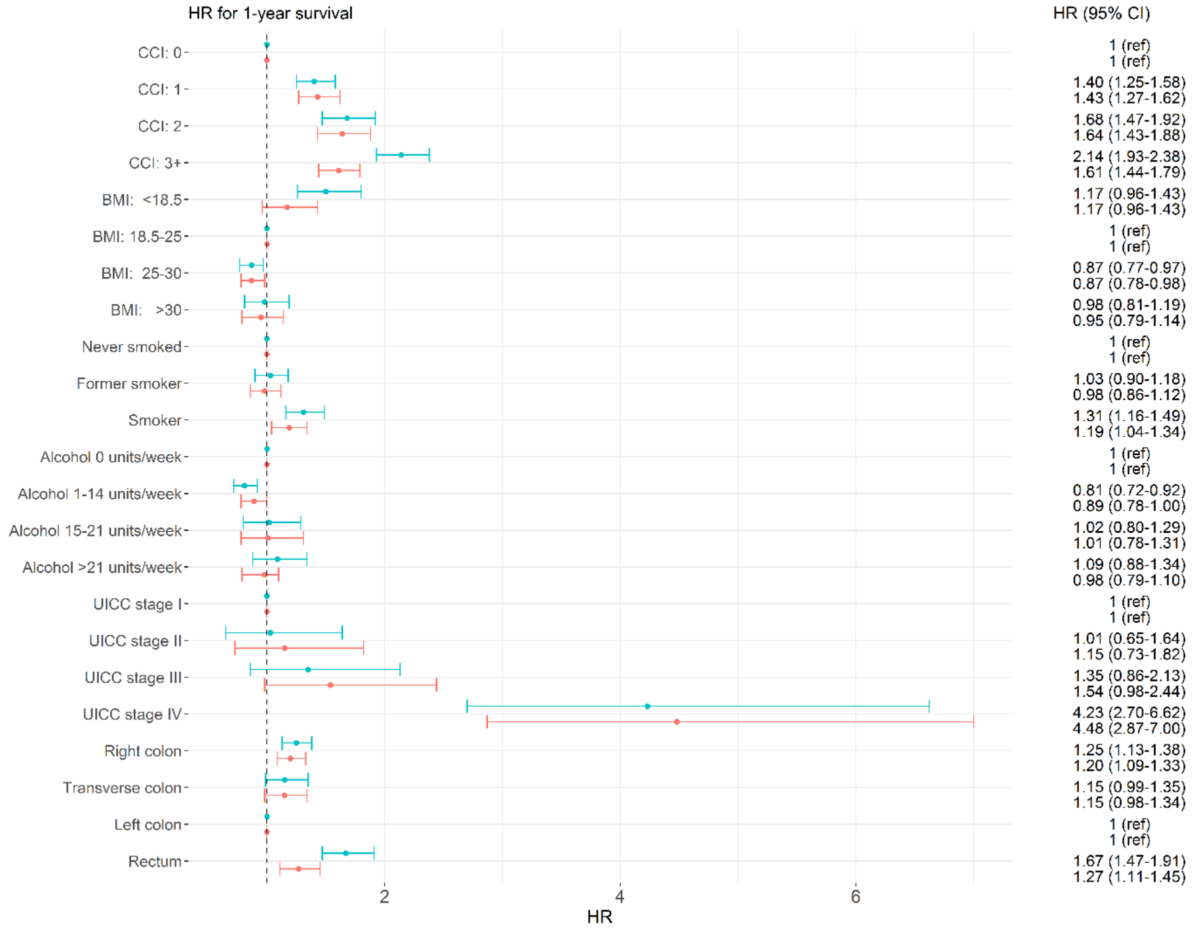
Figure S1. Age-, sex- and year-adjusted and multivariate adjusted odds ratios (ORs) with corresponding 95% confidence intervals (CI) for acute surgery in 35 661 persons operated for colorectal cancer, Denmark, 2007-2015.



Blue line: adjusted for sex, age and year of surgery.

Red line: Adjusted for sex, age, year of surgery, Charlson Comorbidity Index score, BMI, smoking, drinking, UICC stage, and localization. Income additionally adjusted for education. Urbanicity additionally adjusted for education and income. Cohabitation additionally adjusted for education, income and urbanicity.

Figure S2. Age-, sex- and year adjusted and multivariate adjusted hazard ratios (HRs) with corresponding 95% confidence intervals (CI) for 1-year mortality among 5 310 persons treated with acute surgery for colorectal cancer in Denmark, 2007-2015



Blue line: adjusted for sex, age and year of surgery.
Red line: Adjusted for sex, age, year of surgery, Charlson Comorbidity Index score, BMI, smoking, drinking, UICC stage, and localization. Income additionally adjusted for education. Urbanicity additionally adjusted for education and income. Cohabitation additionally adjusted for education, income and urbanicity.

Prediction of the postoperative 90-day mortality after acute colorectal cancer surgery, model development and validation.

Authors

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Abstract

Background Acute colon cancer surgery is associated with a 90-day postoperative mortality of 21%. The aim of this study was to develop and externally validate a model to predict the risk of 90-day mortality after acute colon cancer surgery.

Methods The model was developed by data from all patients undergoing acute colorectal cancer surgery in 2014 and registered in the Danish Colorectal Cancer Group (DCCG.dk) database. The model was externally validated in patients undergoing the same surgery in 2015. The primary outcome was 90-day mortality and the tested predictor variables were age, sex, performance status, BMI, smoking, alcohol, education level, cohabitation, tumour localization, and primary procedure. Missing data were handled with multiple imputation. Selection of included variables was done with backwards selection according to smallest Akaike information criterion (AIC). Bootstrapping was used to shrink the model. Discrimination was evaluated with a Receiver Operated Characteristic (ROC) curve, calibration with a calibration slope, and the overall accuracy of the model was assessed with a Brier score.

Results 535 patients were included in the development of the model and 554 patients in the model validation. The 90-day mortality was 18% in 2014 and 20% in 2015. Age, performance status, alcohol, smoking, and primary procedure were the final variables included in the model. Accuracy and discrimination were acceptable in the internal validation with a Brier score of 0.12 and an area under the curve (AUC) of 0.80. Calibration was not well fitted with a calibration slope of 1.0 and an intercept of 1.0 in the internal validation. External validation shows a good accuracy (Brier score = 0.16), an acceptable discrimination (AUC = 0.72), and a poor calibration with a calibration slope of 1.0 and an intercept of 1.0.

Conclusion We developed a prediction model for 90-day mortality after acute colon cancer surgery with the variables age, performance status, alcohol, smoking, and diverting stoma. The model had an acceptable accuracy and discrimination in the external validation; however, a poor calibration.

Introduction

The annual incidence of colorectal cancer was estimated to be 1.7 million worldwide and caused around 860,000 deaths in 2018 [1, 2]. These numbers are expected to increase in the future affecting especially low and middle-income countries [3].

Acute colorectal cancer surgery is associated with a high postoperative 30-day mortality of 8%-12% [4-6]. In Denmark, the 90-day postoperative mortality was 21% in 2016 after acute colorectal cancer surgery [6]. The proportion of patients presenting with emergency presentation of colorectal cancer due to obstruction, perforation or bleeding, varies from 13%-26% [5, 7, 8]. In Denmark, around 10% of all colorectal cancer surgery is performed acutely [9].

Prognostic models to predict the postoperative mortality risk have several advantages. A prediction model can be used to improve patient and family counselling in shared decision-making. With an increasing focus on perioperative optimization after emergency surgery, it would be valuable to select the high-risk patients for a more comprehensive perioperative monitoring and treatment [10-13]. High-risk patients might also benefit from short and more spared surgery. Finally, it will be easier to compare the adjusted mortality risks between hospitals, regions and countries adjusting for case-mix. To our knowledge, no other existing model predicts preoperatively the postoperative mortality risk of acute colon cancer surgery.

The aim of this study was to develop and validate a model predicting the risk of 90-mortality after acute colon cancer surgery.

Methods

This article is reported according to the TRIPOD guidelines [14].

Source of data for development and validation

Data for development and validation were collected in the Danish Colorectal Cancer Group (DCCG.dk) database [15]. The DCCG.dk database registers the final procedure only, and information about diverting stoma or self-expanding metallic stents (SEMS) in patients getting elective surgery as the final procedure (bridge-to-surgery) was obtained from the National Patient Register (NPR) [16]. All Danish residence have a personal identification number that links information on care and healthcare services to the national registries and databases. All patients undergoing acute colon cancer surgery, according to the DCCG.dk or NPR, and registered with a diagnose in the DCCG.dk database from first of January to 31st of

December 2014 were included in the development dataset. End of follow-up was the first of April 2015. The model was externally validated in a temporal different cohort with all patients from first of January to 31st of December 2015 having the same procedure. End of follow-up was the 1st of April 2015 in the validation cohort. There were no changes in nationwide clinical guidelines concerning acute surgery in the development and validation study period.

DCCG.dk database

The DCCG.dk database is a nationwide, population-based clinical quality database with prospectively collected data [15]. The completeness proportion of all colorectal cancers was 99% in 2014-2015. The database includes all patients diagnosed with adenocarcinomas of the colon or rectum at a surgical department in Denmark. In the database, there is no registration of metachronous cancer or recurrences. In addition, the database only includes patients with tumours that histologically origin from primary adenocarcinoma, mucinous adenocarcinoma, signet ring cell carcinoma, medullary carcinoma, or undifferentiated carcinoma. Each surgical department registers prospectively clinical and pathological data into the DCCG.dk database.

The National Patient Registry

The NPR is a register established in 1977 and holds information on all admissions and outpatient visits at any hospital in Denmark [16]. The variables collected in the NPR are time and date of admission, surgical procedure and final diagnose at discharge [16].

Participants

All patients in both the development and validation cohort underwent an acute surgical procedure for colon cancer at a public surgical department in Denmark. All treatments and care were free-of-charge financed by taxes. In the development cohort, 23 hospitals throughout Denmark performed the surgical procedure, while 22 of the hospitals performed the procedure in the validation cohort.

Patients were eligible for inclusion in the development cohort if they were registered with a colorectal cancer diagnose in 2014 in DCCG.dk and a surgical procedure. Procedures included right hemicolectomy, transverse colectomy, left hemicolectomy, sigmoid colectomy, Hartmann’s procedure, other colectomy +/- stoma, diverting stoma, intestinal bypass, subtotal/total colectomy, examination under anaesthesia only, anterior resection +/- stoma, or insertion of SEMS. Patients registered in NPR in 2014 with a SEMS or diverting stoma as only procedure within 72 hours after admission were also included. Eligibility criteria were the same for the validation cohort except that the year of diagnose and surgery was 2015.

In both the development and the validation cohort, patients were excluded if they were registered with an elective surgical procedure prior to the acute procedure, if registered in the DCCG.dk with a local procedure or APE (abdominoperineal excision), if registered with a date of death prior to surgical date, or migrated or disappeared within 90 days after the acute surgical procedure.

Outcome

The primary outcome was postoperative 90-day mortality. The vital status was obtained from the Danish Civil Registration System (CRS) that holds continuously updated information on vital status on all Danish residents linked via the personal identification number assigned to all Danish residence [17].

Predictors

We aimed to develop a model to predict mortality bedside before acute colon cancer surgery. Thus, only variables known prior to surgery were eligible as candidate predictors. Two surgical professors in colorectal cancer selected a list of nine candidate predictors prior to model development based on the literature. The candidates included age, sex, WHO performance score, body mass index (BMI), smoking, alcohol, educational level, cohabitation, tumour localization, and primary procedure, *Table 1*. The surgeon registered patient-related factors during the perioperative period such as performance status, BMI, alcohol, smoking, tumour localization and surgical procedure. Age and sex were incorporated in the unique identification number.

Sample size

Based on previous annual reports from DCCG.dk, we expected the 90-day mortality after acute colorectal cancer surgery to be around 20%. According to the rule of thumb, ten events are required per candidate predictor to reduce the risk of overfitting [18]. We expected around 400-500 patients undergoing surgical resection per year and tested ten candidate predictors.

Missing data

In the DCCG.dk database, there were no missing values in age, sex, procedure performed, mortality and date of mortality. This is due to the personal identification number and the diagnose-based payment system in Denmark. Lifestyle variables had most missing values in the DCCG.dk database. We did not expect that missing values on lifestyle variables depended on the observed values and assumed missing values to be missing at random. Missing data were handled with multiple imputation.

In both the development and validation of the model, multiple imputation was performed independently with ten imputed datasets. There were missing values on performance score, BMI, smoking, alcohol, educational level, cohabitation, and tumour localization. In the imputation of the ten datasets, all candidate predictors and outcome were included (90-day mortality, age, sex, performance score, BMI, alcohol, smoking, education level, cohabitation, tumour localization, and primary procedure).

Model building

The model predicting 90-day mortality after acute colorectal cancer surgery was conducted with a logistic regression model. After multiple imputation, predictor variables were selected by backwards selection according to the minimum Akaike information criterion (AIC). One thousand bootstrapping models were generated to create a shrinkage factor, including a slope and an intercept, and incorporated in the final model to minimize the risk of overfitting [18]. Quantitative variables were tested for linearity by inserting a squared term in the model. Age and BMI were found linear. The operative risk of each patient was calculated by adding the scores of each predictor variable in the development cohort, for internal validation, and in the validation cohort for external validation.

Performance of the model was evaluated similarly in development and validation of the prediction model. Accuracy of the prediction model was tested with a Brier score [19]. Discrimination was tested with c-statistics, Receiver Operated Characteristic (ROC) curve analysis [20]. An Area Under the Curve (AUC) between 0.7 and 0.8 was regarded as “fair discrimination”, and values higher than 0.8 were regarded as “good discrimination” [21]. Calibration was tested with a calibration slope. When the slope is 1.0 and the intercept cuts zero in both axis, the calibration slope is optimal with concordance between the observed and predicted mortality risk in all risk groups.

All analysis were performed using SAS software, version 9.4.

Results

In the development cohort, we included 535 patients operated in 2014 and excluded eight patients based on one of the exclusion criteria, *Figure 1*. The mean age was 73 years, 52%

were women, 31% of the patients had a performance status ≥ 2, 7% were underweight while 10% were obese, 49% smoked now or were former smokers, 4% drank more alcohol than recommended. A medium educational level was most common (49%) and cohabitation was equally distributed with 48% living alone. The tumours were primarily located to the left side (44%), rectum cancer counted for 11%, and 70% had a surgical procedure as primary intervention. The 90-day mortality rate was 18% in the development cohort, *Table 1*.

In the validation cohort, 554 patients were included of the 568 patients eligible for inclusion. The reason for exclusion of 14 patients was mainly registration of elective surgery prior to acute surgery, *Figure 1*. With some exceptions, the demographics was almost similar. The mean age was 72 years and 51% were women. Performance status was overall better than in the development cohort with 20% having a score of ≥ 2. More patients in the development cohort were overweight and 38% had a BMI >25. Weekly alcohol intake was the same (4% drank more than recommended) and 46% smoked now or previously. Medium educational level was also the most frequent (42%) and 45% lived without a partner. Forty percent of the tumours were localized in the left colon and 9% in the rectum. Surgery was the most common primary procedure (68%). The 90-day postoperative mortality rate was 24% in the validation cohort, *Table 1*.

The developed prediction model and internal validation

The variables selected in the prediction model were age, performance status, alcohol, smoking and primary procedure, *Table 2*. In the internal validation, the accuracy was good with a Brier score of 0.12. The model had a good discrimination with an AUC of 0.80. The calibration of the model showed a good slope of 1.0. However, the intercept was 1.0 indicating suboptimal baseline risk prediction, *Table 3*.

External validation

In the temporal, external validation of the prediction model, the accuracy was good with a Brier score of 0.16. The discrimination was acceptable with an AUC of 0.72. Also in the external validation, the calibration of the model showed a good slope of 1.0 and a suboptimal intercept of 1.0 meaning that the baseline risk was estimated too high, *Table 3*.

Discussion

With this study, we present the first preoperative prediction model for 90-day mortality after acute colorectal cancer surgery. The model was developed in 535 Danish patients and the predictor variables selected were age, performance score, weekly alcohol intake, smoking status and primary surgical procedure. The internal validation showed good accuracy, good discrimination, but poor calibration due to overestimation of the background risk. In the external validation of all patients operated in 2015, the accuracy was good, the discrimination was acceptable, and the calibration was poor.

A limitation in the development of this prediction model was that there could be a power issue. In prediction models, there is a rule of thumb that the degree of freedom of candidate predictor variables should be less than one for each outcome event [22]. In the development, this only gives 9 degrees of freedom. A further limitation in this study is that data were not collected prospectively which limits the possible predictor variables to those available in the DCCG.dk dataset [23]. In the present study, lack of important predictor variables can cause residual confounding and decrease the performance of the prediction model [23]. Compared with regular retrospective studies, register-based studies have a minimal risk of recall bias due to prospective collection of data, a major strength in the present study [24]. It would still be better to use data from a randomized controlled trial (RCT) due to the risk of confounding by indication in observational studies in the choice of primary surgical procedure [25]. The primary surgical procedure was included in the final prediction model. However, due to the risk of confounding by indication and no assumption of a causal relation between procedure and outcome, changing the procedure from e.g. resection to SEMS might not change the risk of 90-day mortality. Previous studies have showed that SEMS and surgical resection are equivalent treatment strategies in the risk of short-term mortality [26, 27].

It is a major strength in this study that data are retracted from a nation-wide database with a completeness proportion of 99% [15]. It reduces selection bias and improves similarities between the cohort the model was developed on and the target population it should be extrapolated to. It is a main issue in development of prediction models to choose an appropriate and representative population for the study question [23, 28]. The register-based data also enable us to follow all patients 90 days postoperatively and no patients had missing data on the outcome. We chose a clearly defined primary outcome with no risk of misclassification, important for the patients and a relevant clinical measurement. All variables were available at the time the model was intended to be used, they were similar for all patients, and they were collected independently of knowledge of the outcome [28].

The existing prediction models for postoperative mortality after colorectal cancer are not specific for acute surgery. Several know models such as the physiological and operative severity score for the enumeration of mortality (POSSUM), the Portsmouth Possum (P-POSSUM), the colorectal POSSUM (CR-POSSUM) and the prediction model from the association of Coloproctology in Great Britain and Ireland (ACPGBI) have showed good results in predicting postoperative mortality in colorectal cancer [29] [30-33]. The main problem with the known prediction model is that they are not specific for acute surgery and that they all include perioperative and postoperative variables. Knowing the operative mortality after surgery is more of academic or statistic interest; thus, it is too late to change anything in the treatment strategy. It is important to decide when in the treatment, the model is to be applied to get most clinical impact [18]. The model developed in this present study is important in the perioperative decision and treatment strategies. It is important to test the model in a clinical trial with clinical consequences of a high score, to investigate the clinical impact of the model.

In conclusion, we have developed a model that predicts 90-day mortality after colorectal cancer surgery by age, performance status, smoking status, alcohol consumption, and primary procedure. In the interval validation, the model had a good discrimination, a good accuracy and a poor calibration. In the external validation, the mode showed good accuracy, acceptable discrimination and poor calibration due to underestimation of the baseline mortality risk.

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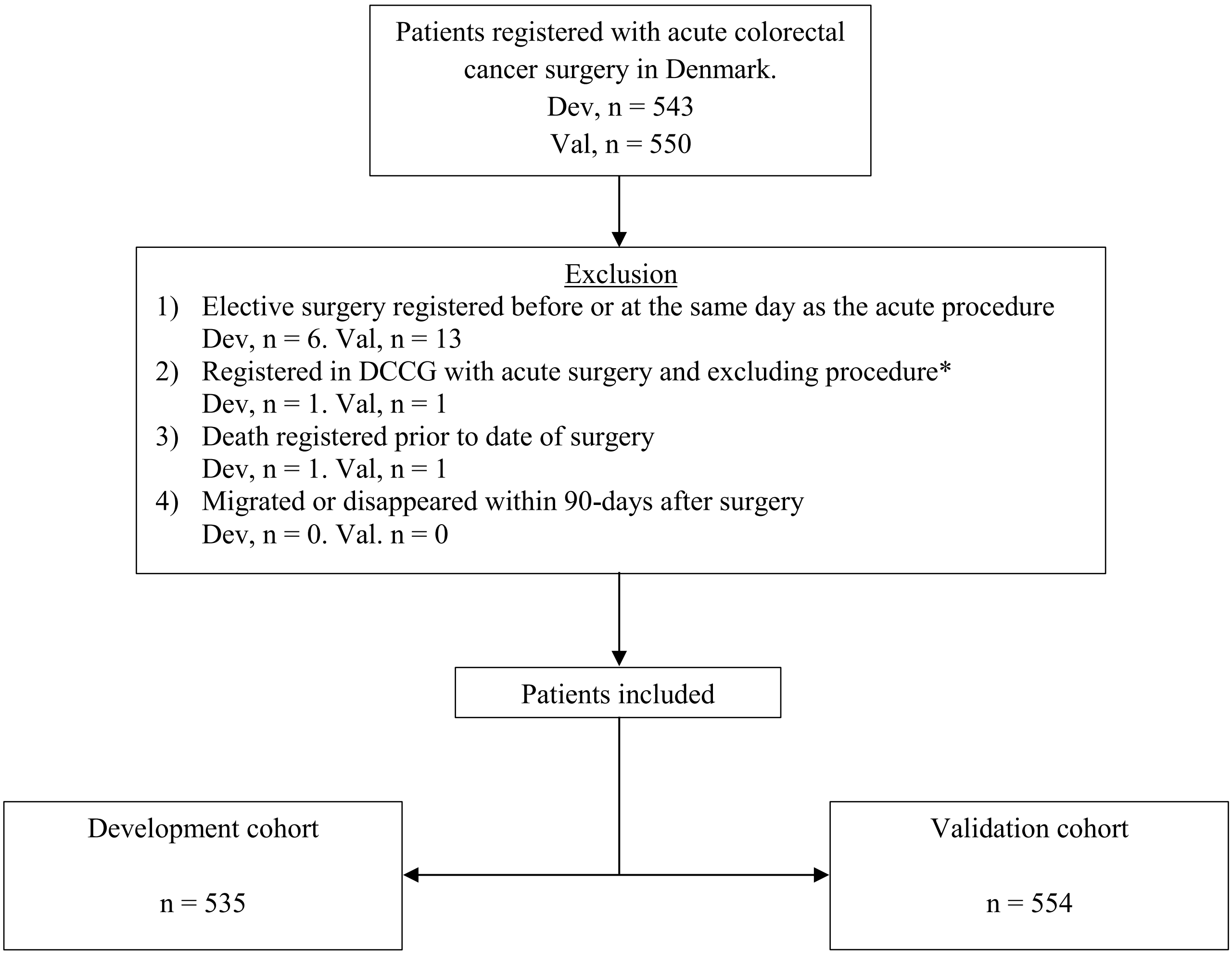
Figure 1. Flow chart of patient exclusion in the development (dev) and validation (val) cohort.



* Abdominoperineal excision of rectum, transanal endoscopic microsurgery (TEM), and other local procedures including polypectomy

Table 1. Demography of development and validation cohort

	Development cohort		Validation cohort	
	No of patients (%)		**No of patients (%)**	
Total	535		554	
90-day mortality				
Yes	94	(18)	135	(24)
Sex				
Men	255	(48)	273	(49)
Women	280	(52)	281	(51)
Age				
Mean (+/- SD)	73	(12)	72	(12)
<65-70	132	(25)	144	(26)
>70-75	82	(15)	92	(17)
>75-80	74	(14)	91	(16)
>80	247	(46)	227	(41)
Performance status				
0	184	(34)	224	(40)
1	139	(26)	169	(31)
2	99	(19)	76	(14)
3+	64	(12)	34	(6)
Missing	49	(9)	51	(9)
BMI				
< 18.5	35	(7)	30	(5)
>18,5 – 24	290	(54)	278	(50)
25 – 30	117	(22)	157	(28)
> 30	53	(10)	58	(10)
Missing	40	(7)	31	(6)
Smoking				
Smoker	122	(23)	103	(19)
Former smoker[1]	137	(26)	151	(27)
No	156	(29)	196	(35)
Missing	120	(22)	104	(19)
Alcohol				
Within recommended[2]	370	(69)	416	(75)
More than recommended	24	(4)	22	(4)
Missing	141	(26)	116	(21)
Educational level				
Long	96	(18)	109	(20)
Medium	260	(49)	234	(42)
Short	152	(28)	187	(34)
Missing	27	(5)	24	(4)

Cohabitation				
Living with a partner	275	(51)	306	(55)
Living alone	259	(48)	248	(45)
Missing	1	(0)	0	(0)
Tumour localization				
Right colon[3]	173	(32)	181	(33)
Transverse colon	42	(8)	60	(11)
Left colon[4]	236	(44)	219	(40)
Rectum	57	(11)	52	(9)
Missing	27	(5)	42	(8)
Primary Procedure				
Stent	163	(30)	175	(32)
Surgery	372	(70)	379	(68)

1. Not smoked for minimum 8 weeks. 2. Recommended is categorized as less than 14 units per week for women and less than 21 units per week for men. 3.

Table 2. Prediction Model.

	Risk group	**Score**
Age		
	<65	0.00
	>65-70	0.92
	>70-75	1.08
	>75	1.67
Performance Score		
	0	0.00
	1	1.11
	2	1.45
	3-4	2.14
Alcohol (weekly recommendation)[1]		
	Below	0.00
	Above	0.78
Smoking		
	Never smoked	0.00
	Former smoker[2]	0.45
	Smoker	0.89
Primary procedure		
	Stent	0.00
	Surgery	0.48

1. Above weekly recommendation is defined as >14 units/week for women and >21 units/week for men. 2. Not smoked for minimum weeks.
In(R/1−R) = -4.66788 + (score), where R is the risk of death

Table 3. Internal and external validation of the model

	Internal validation	Extern validation
Brier	0.12	0.16
AUC	0.80	0.72
Calibration slope (intercept)	1.0 (1.00)	1.0 (1.00)