Short-term prognosis after colorectal surgery: The impact of liver disease and serum albumin

PhD dissertation

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Preface

I clearly remember my first time in Denmark. I arrived March 5th 2008 and spent three months working on my bachelor thesis. It was my first experience with research and, definitely, ignited my interest in hepatology. Many events occurred since then but with no doubt, nothing would have happened if professor Bianchi had not been persuaded by my repeated plea to go abroad, and professor Vilstrup had not graciously accepted to host an Italian student at the Department V for a research project.

The enthusiasm at the end of the three months was the reason for my return to Denmark in January 2010, looking for a research position. That was when I first met professor Henrik Toft Sørensen. I left our first meeting feeling that he might be the mentor I was looking for and I was right! His endless knowledge, meticulous attention to detail, and his ability to keep sight of the overall project, continuously stimulated me to improve my work and explain my research decisions. I am most grateful to him for that. Special gratitude is owed to Rune for providing invaluable advice, criticism, and, most of all, for his friendship. Writing this thesis would have been impossible without considerable assistance from the highly skilled statisticians at KEA that helped me to choose appropriate statistical methods.

A special thanks to Anil because his Indian peace and happiness taught me how to enjoy every day and survive the hard time of writing my thesis. My gratitude to Claus and Henrik N. for helping me "kick-start" each day with our daily espresso on arrival at KEA. I would also like to thank the always available administrative staff at KEA, the PhD Association for all the productive meetings aimed to improve PhD education, Aarhus University for financial support, and the Mount Tabor community for the valuable time spent together. Furthermore, a special gratitude to all the patients that contributed with their information to the project.

Finally, I would like to thank my parents and sister for their unconditional support and my wonderful wife Marica for her constant presence at my side and unfailing fight for our dreams.

In conclusion, this dissertation was possible thanks to many people. I have therefore decided to use the term "we" in the thesis to highlight that I have not been alone in this endeavor.

The dissertation is based on the following three papers:

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II. Montomoli J, Erichsen R, Strate LL, Pedersen L, Nilsson T, Sørensen HT. Coexisting liver disease is associated with increased mortality after diverticular disease surgery. *Submitted.*

III. Montomoli J, Erichsen R, Antonsen S, Nilsson T, Sørensen HT. Impact of preoperative serum albumin on 30-day mortality, reoperation, and acute kidney injury following surgery for colorectal cancer: a population-based cohort study. *In manuscript.*

List of abbreviations

AKI	Acute kidney injury
BCG	Bromocresol green
CCI	Charlson Comorbidity Index
CI	Confidence interval
CPR number	Civil Personal Registration number
CRC	Colorectal cancer
CRP	C-reactive protein
CRS	Civil Registration System
CTP classification	Child-Turcotte-Pugh classification
DD	Diverticular disease
DCR	Danish Cancer Registry
DNRP	Danish National Registry of Patients
GI	Gastrointestinal
ICD	International Classification of Diseases
HSA	Human serum albumin
HR	Hazard ratio
INR	International normalized ratio
KDIGO	Kidney Disease: Improving Global Outcomes
LABKA	Laboratory information system database
MELD	Model for end-stage liver disease
NOMESCO	Nordic Medico Statistical Committee
OR	Odds ratio
PPV	Positive predictive value
TNM system	Tumor Node Metastasis system

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1. Introduction

This PhD thesis examines selected aspects of postoperative prognosis for Danish patients undergoing colorectal surgery and is based on three clinical epidemiological studies.

In the period 2006-2012, the number of yearly admissions for gastrointestinal (GI) diseases in Denmark has increased from less than 140,000 to more than 160,000.[1] In 2012, GI diseases were responsible for more than 54,000 hospitalizations and more than 400,000 hospital bed-days among the Danish population.[1] In the US, colorectal cancer (CRC) was the leading GI cause of mortality, and diverticular disease (DD) was the most frequent inpatient primary GI discharge diagnosis in 2009.[2] Accordingly, CRC and DD are among the most prevalent conditions leading to colorectal surgery.[3-5]

CRC is the third most common cancer worldwide[6] and 4,463 new CRC cases were diagnosed in Denmark in 2012 at a median age of 71 years.[7] Similarly to many other countries, age-standardized incidence of CRC has increased in the last 20 years in Denmark.[8] Nonetheless, CRC incidence has been stable for the period 2008-2012.[7] Among possible treatments in CRC patients, surgical excision of the primary tumor is the only curative approach. The overall five-year survival after CRC diagnosis among Danish patients is approximately 40-50%.[9]

True prevalence of diverticulosis (*i.e.*, the merely presence of colonic diverticula) is not well established since it is most often asymptomatic and therefore remains undetected unless incidentally diagnosed.[10] Existing data from cross-sectional studies suggest diverticulosis being very common in western populations with a prevalence of approximately 10% in people aged over 45 years and about 65% among people aged over 70 years.[11] When diverticulosis becomes symptomatic and consequently clinically significant it is defined as DD.[10] The rate of hospitalization for DD has been increasing markedly in recent decades in western countries,[2,12] accompanied by an increasing rate of surgical procedures performed on patients with complicated DD.[13] In-hospital mortality among patients admitted with DD is below 1%[2] unless patients develop severe complications or have coexisting conditions affecting prognosis (*e.g.*, advanced age, comorbidity).[12,14]

With the aging of the population, prognostic impact of comorbidity in patients undergoing colorectal surgery is becoming an increasing problem.[15] Among specific comorbidities, advanced liver disease has been reported markedly associated with poor prognosis following major surgery.[16,17] Moreover, patients with liver cirrhosis and fatty liver disease are at 50% increased risk of developing CRC compared to the general population.[18,19] Similarly, DD was found to be four times more prevalent among patients with non-alcoholic fatty liver disease than in patients with other chronic liver diseases suggesting common risk factors.[20] Consequently, patients with liver disease may be even at increased risk of colorectal surgery during their life compared to the general population. However, the impact of liver disease on prognosis after colorectal surgery has not been examined by existing literature in patients with CRC and DD, separately, and properly adjusting for potential confounding.

Among chronic non-cirrhotic liver diseases, fatty liver disease is a common condition and is likely to become the most common hepatic disease worldwide.[21] Unlike in other western countries, infectious hepatitis is not frequent in Denmark and therefore alcoholism is the most common risk factor for chronic liver disease.[22,23] Chronic liver disease often remains asymptomatic until complications become clinically manifested and decompensation occurs.[24] Virtually any liver disease can progress to fibrosis, leading to liver cirrhosis[25] which is a life-threatening disorder with an incidence rate of approximately 190 cases/1,000,000 persons per year in Denmark.[26] Liver cirrhosis and other chronic liver diseases are estimated to be the 12th leading cause of death in the US, with about 27,500 deaths annually.[27] Among patients diagnosed with liver cirrhosis, risk of mortality for all causes of death in the 12 years after diagnosis is approximately 11-fold higher than in the general population.[23] Five-year mortality in patients diagnosed with alcoholic liver cirrhosis ranges from 58% to 85% according to the development of complications.[28]

Impaired liver function is likely to affect human serum albumin (HSA) synthesis and distribution leading to HSA decrease in blood concentration.[29] Furthermore, decrement in HSA may also depend on other conditions (*e.g.*, advanced age, malnutrition, malignancy, infection, etc.).[29] Irrespective of the specific disorder that determines its concentration, HSA is able to predict prognosis in different settings including patients admitted to internal medical wards, cancer patients, and surgical patients.[30-32] Moreover, decrement in HSA has been associated with

increased risk of acute kidney injury (AKI)[33,34] that is a postoperative complication related with poor prognosis following colorectal surgery.[35,36] However, prognostic impact of HSA in patients undergoing CRC surgery has not been investigated in a population-based setting.

Therefore, we examined the impact of liver disease on short-term prognosis following CRC (study I) and DD surgery (study II). Moreover, in order to identify possible pathophysiological mechanisms associated with increased mortality among patients undergoing CRC surgery, we investigated the impact of preoperative HSA on mortality, reoperation and AKI within 30 days after surgery (study III).

2. Background

This chapter introduces some important issues related with studying prognosis and provides the background information on colorectal surgery, liver disease, and HSA relevant for the three studies in the dissertation, including a review of the relevant literature followed by a discussion of the limitations of the existing literature.

2.1 Prognosis

The three studies in this dissertation all focus on prognosis. In medicine, the term prognosis commonly refers to the expected course of an illness.[37] In this dissertation, we are interested in investigating if specific conditions such as liver disease and low preoperative HSA affect the prognosis, in which way, and to which extent. Moreover, prognosis is commonly related to specific outcomes (*e.g.*, death, cancer recurrence, kidney failure, etc.) and is reported as the probability or risk of developing that condition over a specific period. Factors that contribute to the occurrence of an outcome after the disease occurred are referred to as prognostic factors.[38] In this dissertation, the term exposure was also used synonymously to describe prognostic factor and we defined as the exposed cohort those individuals who have experienced a putative causal condition (*i.e.*, liver disease or low HSA levels) and as the unexposed, or comparison, cohort those that have not.[39]

2.1.1 Studying prognosis and causality in surgical patients

Our aim in this dissertation is to study prognosis by investigating whether an outcome can be attributed to a particular condition such as liver disease or decrease in preoperative HSA levels. Therefore, we hypothesized a causal association between exposure and outcome and this classifies our studies as etiological studies.[37] When etiological studies are carried out in an observational setting, confounding usually plays an important role because the exposure is not assigned randomly by the researcher.[40] Although the role of confounding in etiological observational studies will be analyzed more accurately in the discussion of the dissertation, it is relevant to spend a few words on confounding in this paragraph since it may bias the estimated association between a prognostic factor and an outcome. In observational studies, restriction and matching can be used during study design phase to control for confounding while confounding is

mainly handled by stratification, standardization, and multivariable models during the statistical analysis. Whereas stratification and standardization are relatively simple, the creation of a regression model able to control for potential confounders is not a straightforward process and may lead to residual confounding or even introduce further bias (*e.g.*, overadjustment bias).[41] In general, possible confounding factors should be selected *a priori* and not after evaluating whether they are unequally distributed between exposed and non-exposed individuals, or by their effect on changing the estimate in a regression analysis.[42]

Studying the impact of an exposure on postoperative prognosis can be particularly challenging due to the coincidence of several factors that may affect the prognosis, such as complexity of surgical procedures, surgeon- and patients-related factors, and anesthesiologic care.[43,44] Another peculiarity of studying prognosis after surgery that hampers comparability among studies is determined by various criteria that have been used to calculate postoperative complications, including 30-day, 90-day, and in-hospital mortality or morbidity, or specific combinations.[45-47] The difference may stem from limitations of available follow-up information, from different understanding of postoperative outcome, or from variations in the impact of a prognostic factor on an outcome according to the invasiveness of specific surgical procedures.[45] In studies on cancer prognosis, for instance, the term "postoperative mortality" has also been used to identify mean survival after surgery.[48] Last, since most deaths related to surgery are likely to be concentrated in a definable period shortly after operation, postoperative mortality can also be classified in consecutive periods (*e.g.*, 0-30 days, 31-60 days, 61-90 days, etc.) to aid in understanding the length of the association between exposure and outcome.[45] However, the increase of follow-up time also raises the probability that complications pertain to conditions not strictly related with surgery (*e.g.*, disease progression, recurrence, or newly diagnosed conditions). In this dissertation, we specified the time period to which the outcome is referred to both regarding our and cited studies. The adjective "postoperative" is used in case follow-up is not specified or simply with the meaning of "after surgery". Moreover, when we use the term "short-term prognosis", we refer to what happens within 90 days after surgery. Conversely, "long-term prognosis" refers to whatever occurs beyond 90 days. Other challenging issues in prognostic surgical studies that may be relevant for our studies, such as the introduction and development of new techniques, changes in the selection of patients undergoing surgery within the period of interest, or surgical approaches

that are likely to be different in patients with and without liver disease, will be mentioned in the following sections of interest.

2.1.2 Measuring the impact of prognostic factors in surgical patients

Identifying prognostic factors and quantifying the size of their impact on surgical outcomes is useful for clinicians and patients to improve prognosis by eliminating or reducing the influence of the most relevant conditions. Also, knowledge about such factors improves the understanding of the postoperative course and may clarify clinical requirements during the perioperative period. Additionally, the decision-making process would markedly benefit from more accurate information balancing the risks and benefits of surgery. Last, evidence on prognosis is important to policy makers because it can help make changes in the organization of the healthcare system, such as the improvement in the CRC diagnosis and treatment strategy that took place in the last decade.[49]

The impact of prognostic factors on outcome may be classified as absolute or relative effect measures.[50] Relative estimates (*i.e.*, odds ratio (OR), risk ratio, or hazard ratio (HR)) represent the main focus of etiological studies since they describe the relative risk of an outcome in presence of a potential causal factor compared to the risk in its absence.[50] Differently, absolute effect measures (*i.e.*, risk difference) may be more useful to quantify the effective burden of the outcome associated with the exposure in the study population.[51] Although mostly focusing on relative estimates describing the impact of prognostic factors on the postoperative complications, our studies also report absolute estimates of occurrence that can be used to extrapolate absolute effect measures. Finally, prognostic implications of liver disease and preoperative HSA may differ within subgroups of patients undergoing colorectal surgery even after selecting patients with the specific disease leading to surgery (*i.e.*, CRC or DD). For instance, among patients with a specific characteristic (*e.g.*, older age, male, etc.), the impact of liver disease on postoperative mortality may be higher than among patients without such characteristic (*e.g.*, younger age, female, etc.). In this case, such difference is referred to as “effect measure modification”. It is important to remember that the presence, direction, and size of effect measure modification may be dependent on the type of measure chosen in the study (*i.e.*, ratio or difference measure).[50] Using a

multiplicative model, we examined if the prognostic impact of liver disease and HSA in patients undergoing colorectal surgery is influenced by *e.g.* age, gender, and comorbidity level.

2.2 Colorectal surgery

Colorectal surgery is a sub-specialization of general surgery, which is a broad surgical specialty including procedures involving the alimentary tract, other abdominal contents, breast, neck, skin, soft tissue, and the vascular system (excluding heart and intracranial vessels).[52] Colorectal surgery comprises all surgical procedures performed to repair damage to the colon, rectum, and anus caused by disease of the lower digestive tract.[53] There are a variety of procedures that can be used to treat intestinal disorders and most of these repairs involve resection (removing all or part of the colon or rectum) and anastomosis (attaching the cut ends of the intestine together).[53] Colorectal surgery also involves the creation of an ostomy, which is a procedure that brings a portion of the intestine through the abdominal wall, creating an opening, or stoma, to carry feces out of the body to a pouch.[53] Colectomy has been reported to be the most prevalent intervention among 36 procedure groups including mainly neck, inguinal, pelvic, breast, and abdominal sites (procedures for varicosities and hemorrhoids were not included) representing 10% of the total procedures and being associated with 24% of postoperative complications within 30 days after surgery.[54] Moreover, among general surgery, colectomy is the procedure that contributes the most to 30-day mortality, overall morbidity, and excess length of hospital stay.[54]

Prevalence of CRC as indication for colorectal surgery varies from approximately 35% among non-elective surgery to more than 70% among patients undergoing elective surgery.[3-5,55-59] Conversely, DD prevalence among all indications for colorectal surgery is lower among elective procedures than among non-elective, varying from 8.5% in patients electively admitted to more than 30% among patients non-electively admitted.[3-5,55,56,58,59]

During the past decades, new techniques (*e.g.*, laparoscopy) and strategies combining new analgesic drugs, minimally invasive surgery, early mobilization, and early initiation of oral nutrition (*e.g.*, fast-track surgery) have been introduced or implemented with the goal of reducing surgical stress, enhancing postoperative recovery, and improving efficacy of the treatment.[60-62] In

Denmark, the absolute number of laparoscopic colonic resections performed nationwide increased from 26 in 2000 to 1,075 in 2010.[62] Fast-track colorectal surgery was first reported in Denmark in the mid-1990s, and in a recent review, fast-track protocol care was associated with decreased complication rates (risk ratio: 0.69; 95% confidence interval (CI): 0.51-0.93).[63] Nevertheless, we appear to be failing to accurately identify patients who are more likely to develop postoperative complications[43,64] and, consequently, an undesirable portion of patients undergoing colorectal surgery still suffer from mortality and other complications.[60,65]

Overall in-hospital mortality following colorectal surgery is reported to be below 5%.[3,66] However, it may vary from less than 1% among patients undergoing elective surgery to 15% among patients undergoing emergency surgery.[3] Besides emergency surgery, other surgery-related factors are related with increased mortality. An American population-based study reported that patients undergoing left, transverse, or total colectomy had an increased risk of in-hospital mortality ranging from 1.31 (95% CI: 1.26-1.46) to 2.88 (95% CI: 2.75-3.02) compared to patients undergoing right colectomy.[3] On the contrary, sigmoidectomy and proctectomy were associated with a decreased risk. Similarly, mortality risk associated with laparoscopy was lower than for open surgery.[3] However, it is likely that the different risk may be partially explained by the disease leading to surgery since the type of procedure performed may vary among patients with CRC and DD. Indeed, while CRC can be localized in all the large intestines, although with different frequency,[67] DD affects almost uniquely the sigmoid.[68]

Approximately 20-25% of patients undergoing colorectal surgery develop at least one surgical complication[67,69] and between 5-10% undergo unplanned reoperation.[59,70,71] Moreover, reoperation after colorectal surgery has been reported to be a predictor of one-year mortality.[59]

For the reasons mentioned above, our study populations are restricted to patients with the same disease leading to surgery and we investigated short-term prognosis separately in patients undergoing colorectal surgery for CRC (study I and study III) and DD (study II). This also allowed us to classify procedures as was most convenient according to the indication for surgery. Moreover, in study II and study III, we investigated reoperation rates besides 30-day mortality.

2.2.1 Prognosis following colorectal cancer surgery

In Denmark, the overall 30-day mortality rate following CRC surgery for the period 2006-2008 was approximately 10%.[72] For years, it has been well-known that Denmark and England had a poorer outcome of CRC, particularly within comparable populations and similar health care structures.[73-75] However, improvements in diagnostic and treatment strategy in the last decade were reflected from recent data that showed an overall 30-day mortality after CRC surgery for 2012 of 4.6%.[67] Approximately two-thirds of cancers are localized in the colon and one-third in the rectum[72,76,77] with overall 30-day mortality slightly higher in patients undergoing colon cancer surgery (5-11%) than among patients undergoing rectal cancer surgery (4-7%).[72,76,77]

Currently, the cornerstone of CRC prognosis is accurate staging of the tumor and establishing whether the tumor has spread.[67] In localized CRC, surgery is usually applied as the only treatment, whereas it is combined with adjuvant or palliative chemotherapy in non-localized CRC.[67] For rectal cancer patients, a combination of chemotherapy and radiation is used for selected patients prior to surgery. Surgery is usually performed with curative intent in localized and regional spread CRC, but also sometimes in metastatic patients to whom resection of, for example, liver metastases may be offered.[78] Therefore, types of procedures performed to treat CRC may be classified according to the intent of eradicating the primary tumor or not, as also done in study I and study III.[79]

Besides cancer stage, there is increasing recognition that other patient-related factors, such as age and comorbidity, have a substantial adverse effect on CRC prognosis.[76,77,80-85] In particular, the impact of comorbid conditions on CRC prognosis is higher on in-hospital mortality than on five-year mortality after first hospital admission for CRC.[86] Moreover, a recent English study reported that 30-day mortality following CRC surgery increases from 13.1% among patients with Charlson Comorbidity Index (CCI) equal to 1 to 24.2% among patients with CCI equal to or above 3, compared to 5.4% among patients with CCI equal to 0.[76] This corresponds to adjusted ORs ranging from 2.05 (95% CI: 1.94-2.18) for patients with CCI equal to 1 to 4.38 (95% CI: 3.98-4.82) for patients with CCI above or equal to 3, compared to patients with CCI equal to 0.[76] In the same study, 30-day mortality in patients with metastatic cancer (Dukes' stage D) was 9.9% with the corresponding risk of 30-day mortality being 2.50 (95% CI: 2.24-2.78) times higher than in patients

with localized CRC (Dukes, stage A) among which 30-day mortality was 4.2%. Both estimates were mutually adjusted for several potential confounders including cancer stage and CCI. Hence, previous findings suggest that among patients undergoing CRC surgery the comorbidity burden may have a higher impact on short-term mortality than cancer stage.

Another important determinant of postoperative outcome is urgency of CRC surgery. Based on Danish data from the annual CRC report for 2012, overall 30-day mortality after elective and non-elective (*i.e.*, acute or emergency) surgery was 2.8% and 17.0%, respectively.[67] A recent study using the same database reported promising data showing that 30-day mortality after elective CRC surgery has decreased from 7.3% in 2001-2002 to 2.5% in 2011.[87] Similarly, it was reported that 30-day mortality after non-elective surgery decreased from approximately 25 % in 2001 to 17% in 2012.[67]

To summarize, this knowledge shows that a broad variation exists in 30-day mortality following CRC surgery and suggests that comorbidities may have high impact. However, the impact of specific comorbidities on 30-day postoperative prognosis is not clear. Therefore, we conducted study I to examine if and to which extent liver disease increases 30-day mortality following CRC surgery.

2.2.2 Prognosis following diverticular disease surgery

Since the 1970s, the treatment algorithms for DD gradually changed increasing the application of non-operative management.[88] Consequently, non-elective operations for acute DD are now less common while rates of elective surgery for DD have continued to increase, especially in patients younger than 65 years.[89] Nowadays, surgery is often indicated in patients with complicated DD with perforation or fistulas who failed non-operative measures.[90] The role of elective surgery in the prevention of complicated DD is unclear and generally the decision to perform surgery is made on a case by case basis.[91,92]

These changes in selection of DD patients for surgery may partially explain the variability of in-hospital and 30-day mortality following DD surgery reported from previous studies.[12,93-102] Among patients undergoing elective DD surgery, in-hospital and 30-day mortality ranges from 0.4% to 4.7%[12,93-95,98,99,103] while it varies from 6.4% to 16.7% among those undergoing non-elective DD surgery.[12,93,96,99,100,104] Moreover, in-hospital mortality was reported to be greater than 30-day

mortality in two studies investigating patients undergoing elective and non-elective DD surgery, respectively.[103,104] This suggests that prognostic factors for complications might have an impact on mortality beyond 30 days after DD surgery. To our best knowledge, no studies investigated 30-day or in-hospital mortality after DD surgery in Denmark.

The prognostic impact of type of surgery is controversial.[88] Resection with primary anastomosis has been showed to be associated with a lower postoperative mortality than Hartmann's procedure (*i.e.*, resection with ostomy formation) in the emergency setting.[88,105,106] However, the retrospective nature of the majority of the studies included in systematic reviews allows for a considerable degree of confounding by indication since most severe patients are more likely to receive ostomy placement.[88,92,105] For this reason, we also examined the prognostic impact of liver disease in patients with and without ostomy placement in study II.

Aging of population is an important issue that comes along with two relevant prognostic factors for patients undergoing DD surgery. First, older age has been shown to increase risk of in-hospital and 30-day mortality both after elective and non-elective DD surgery.[93,98,100] Among patients aged 65-69 years and among those older than 85 years, in-hospital mortality increased from 0.56% to 6.5% after elective surgery and from 4% to 15% after non-elective surgery. [93] Second, comorbid conditions are more common in older patients and have also been reported to be associated with increased risk of in-hospital and 30-day mortality and other complications in patients admitted with DD.[12,14,93,98,103,104,107] However, knowledge about the impact of individual comorbidities on postoperative mortality is sparse.[98] An American study investigating patients undergoing elective DD surgery reported congestive heart failure to be associated with 3.5 (95% CI: 2.6-4.6) times increased risk for in-hospital mortality.[98] In the same study, chronic pulmonary obstructive disease was not associated with mortality but with pulmonary and wound complications.

Therefore, in order to better understand the impact of individual comorbidities on prognosis following DD surgery, we examined if liver disease is associated with increased risk of short-term postoperative mortality up to 90 days divided in three consecutive periods of equal duration. Moreover, to our knowledge, study II is the first to report on prognosis following DD surgery in Denmark.

2.3 Surgical prognosis in patients with liver disease (study I and study II)

It has been estimated that as much as 10% of patients with advanced liver disease require a surgical procedure other than liver transplantation in the final two years of their life[108] and these patients are at particular risk of developing complications when undergoing anesthesia and surgery.[16,17,109,110] The magnitude of operative risk seems to depend on several factors including the etiology and severity of the liver disease, the nature of the surgical procedure, and the type of anesthesia used.[16,17,111]

The Child-Turcotte-Pugh (CTP) classification system and the model for end-stage liver disease (MELD) score have been widely used to estimate disease severity and predict survival after non-transplant surgery in patients with liver cirrhosis.[112-115] In a recent study investigating 194 patients with liver cirrhosis undergoing abdominal surgery, the 30-day mortality increased from 6.3% in patients with low risk according to the CTP classification (CTP class A) to 53.2% in patients classified at high risk (CTP class C). In the same study, 30-day mortality classified according to the MELD score ranged from 5.8% in patients with MELD score 6-9 to 81.8% in patients with MELD score 80-90.[113]

In patients with chronic hepatitis, the surgical risk is considered low in presence of well-preserved hepatic function and higher when patients manifest clinical decompensation.[16,116] However, data on the postoperative prognosis in patients with non-cirrhotic liver disease are scarce and evidence comes mainly from old studies.[117-123] Expert recommendations suggest to postpone surgery in presence of acute hepatitis, when possible.

Colorectal surgery is overall associated with high morbidity and mortality rates, and, as such, is generally considered particularly high risk surgery for patients with liver cirrhosis or decompensated hepatitis.[124,125] However, patients with liver disease undergoing colorectal surgery may differ according to the disease leading to surgery. Consequently, short-term prognosis and impact of liver disease may be different. Indeed, since surgery is the only curable treatment for CRC, it is performed unless a different coexisting life-threatening condition or poor patient systemic status is present. On the contrary, DD is in general a benign disease and non-operative treatment is effective in most of the cases. Therefore, especially among patients with comorbidities at markedly increased risk of postoperative complications, a wait and see approach

is likely to be preferred until DD surgery may not be further postponed. Consequently, CRC surgery is performed in an elective setting the majority of the cases, allowing for optimization of patient medical and surgical status, complete oncological staging, and a decrease need for stoma and multi-staged operations.[126] Differently, DD surgery is often performed in case of acute perforated diverticulitis and in a non-electively setting.[92] Moreover, since comorbidity interacts with CRC to increased mortality following CRC diagnosis, especially in the first year, the impact of liver disease on 30-day mortality may differ among CRC patients and DD patients undergoing colorectal surgery.[80]

Therefore, we investigated the impact of liver disease on 30-day mortality in patients undergoing colorectal surgery for either CRC or DD, overall and in different medical/demographic subgroups.

2.3.1 Existing literature on liver disease and colorectal surgery

We searched the existing literature for all original studies or meta-analyses investigating the impact of liver disease on postoperative complications after colorectal surgery. The strategy was to include all studies within this area regardless of the specific condition leading to surgery (*i.e.*, CRC, DD, inflammatory bowel disease, etc.). Studies with the primary aim to include liver disease as covariates rather than to investigate the impact of liver disease on postoperative mortality were not included. Studies not available in English, Danish, Italian, French, or Spanish were excluded.

We used the following query to search MEDLINE (last search June 10, 2014):

"Humans"[MeSH] AND ("Liver Diseases"[MeSH Terms] OR "Liver Cirrhosis"[MeSH Terms]) AND ("colorectal surgery" OR colectomy[TIAB] OR "Colonic Diseases/surgery"[Mesh] OR "Rectal Diseases/surgery"[Mesh]) AND ("postoperative complications"[MeSH Terms] OR "Mortality"[MeSH Terms])

This query resulted in 712 publications. After reading the titles, four studies were excluded because of language restriction[127-130] and 19 studies were found to be of relevance. Among these, 13 studies were selected for full article review after abstract review.[131-143] However, only the abstract was available for one publication.[140] All the 13 studies were found relevant.

Furthermore, to perform a more comprehensive search of possible publications not found searching in MEDLINE,[144] we also searched EMBASE with the following query:

('colorectal surgery'/exp AND 'liver disease'/exp)

This query resulted in 652 hits. Of the 46 selected after title revision, five were previously identified in MEDLINE and 15 were included for abstract review but none were relevant.

Finally, we reviewed the reference lists of the publications that had been identified for full article review, and one additional publication in French was considered of relevance.[145] However, neither the abstract nor the full text was available for consultation. Therefore, we ended up with a total of 13 relevant studies (Table 2.1).

In summary, ten studies investigated postoperative complication in small groups of patients with liver disease without a comparison group undergoing colorectal surgery. Among those, five studies included only patients with primary sclerosing cholangitis and inflammatory bowel disease,[138,140-143] three studies included patients with liver cirrhosis undergoing surgery mainly or exclusively for CRC,[132,136,137] one study was restricted to curable CRC patients with portal hypertension,[131] and one study described the prognosis in patients with liver disease undergoing laparoscopy.[139] The remaining three studies were population-based and included comparison cohorts of patients without liver disease undergoing colorectal surgery. Impact of liver disease on postoperative prognosis was investigated among patients with chronic liver disease (disregarding presence of cirrhosis) in one study[133] and among patients with liver cirrhosis (categorized as having or not having portal hypertension) in two studies.[134,135] Of the latter two studies, one was limited to patients undergoing elective surgery of the colon[135] while the other included patients undergoing both elective and non-elective surgery of colon and rectum.[134]

Previous studies investigating prognosis in liver disease patients undergoing colorectal surgery report overall postoperative morbidity and mortality ranged from 23% to 83% and 6% to 27%, respectively.[131-143] Two single-center based cohort studies focused on mortality after CRC surgery reported that the overall 30-day mortality was 13% and 8%.[131,137] One study reported a reoperation rate of 11.8% among 17 patients (14 with CRC) with liver cirrhosis undergoing laparoscopic colectomy.[139] The impact of chronic liver disease on overall postoperative mortality

was reported by one study and corresponded to 6.51 (95% CI: 5.86-7.26). Two studies investigated the impact of liver cirrhosis on postoperative mortality.[134,135] Compared to patients without liver cirrhosis, adjusted ORs for mortality following elective colorectal surgery were 2.4 (95% CI: 2.1-2.8) and 3.7 (95% CI: 2.6-5.2) in patients with liver cirrhosis without portal hypertension and 5.88 (95% CI: 4.90-7.06) and 14.3 (95% CI: 9.7-21.0) in patients with liver cirrhosis and portal hypertension.[134,135] The impact of liver cirrhosis on mortality in patients undergoing non-elective surgery was only reported by Nguyen *et al.* and corresponded to 3.91 (95% CI: 3.12-4.90) in patients with liver cirrhosis without portal hypertension and 11.3 (95% CI: 8.46-15.1) in patients with complicated liver cirrhosis.[134]

Table 2.1. Studies on postoperative complications in patients with liver disease after colorectal surgery.

Author/ year	Study design / Study Period / Country	Study population and exposure	Aim/Outcome of interest	Absolute estimates	Relative estimates (95% CI)	Comments
Madbouly / 2013[131]	Single-center cohort study / 2008-2011/ Egypt	63 patients with PH and liver disease undergoing curative CRC surgery. Liver disease was present in 84% of patients.	30-day postoperative complications	Postoperative complications occurred in 23 (36.5%) patients and 5 (8%) patients died within 30 days.	NA	Patients with severe liver disease (Child-Pugh C), malnutrition and high surgical risk were excluded. Indication for surgery was colon cancer in 57% of patients and rectal cancer in 43% of patients.
Lian / 2012[138]	Single-center cohort study / 1989-2009 / OH USA	23 patients with cirrhosis secondary to primary sclerosing cholangitis undergoing colectomy surgery for inflammatory bowel disease	Postoperative complications	Postoperative complications occurred in 19 (82.6%) patients and 2 (8.7%) patients died.	NA	2 patients had cancer and 13 dysplasia.
Ghaferi / 2010[133]	Cohort study / 2005-2007/ MI USA	ACS-NSQIP database, 29,362 patients without chronic liver disease and 1,565 patients with chronic liver disease undergoing colorectal surgery	30-day postoperative complications	Complications occurred in 25.1% of patients without liver disease and in 50.4% of patients with liver disease. Postoperative mortality occurred in 3.2% vs 21.5% of patients without and with liver disease, respectively. Mortality after elective surgery was 1.8% vs 13.5%. Mortality after acute surgery was 12.0% vs 28.0%	Relative risks for postoperative complications and mortality among patients with LC without and with PH compared to patients without liver disease were 2.01 (1.91-2.11) and 6.53 (5.86-7.26), respectively.	Chronic liver disease was defined as any of the following characteristics: ascites, esophageal varices, or total bilirubin > 2 mg/dL. Cancer was indication for surgery in 47.4% of patients without liver disease and in 27.8% of patients with liver disease Relative estimates were not adjusted for patient characteristics.
Csikesz / 2009[135]	Cohort study / 1998-2005 / MA USA	NIS database, 894,211 without LC, 4,764 with LC (without PH), and 1,341 with LC and PH undergoing elective colectomy	In-hospital mortality	In-hospital mortality was 1% among patients without LC, 6% among those with cirrhosis and 17% among patients with cirrhosis and PH	Adjusted ORs for mortality were 3.7 (2.6-5.2) for patient with LC and 14.3 (9.7-21.0) for patients with LC plus PH compared to patients without LC.	Adjusted for age, gender, primary health insurance carrier, other comorbidities, and ethnicity. Absolute mortality was extrapolated from a graph. Proctolectomy was included among surgical procedures

Table 2.1. Studies on postoperative complications in patients with liver disease after colorectal surgery.

Author/ year	Study design / Study Period / Country	Study population and exposure	Aim/Outcome of interest	Absolute estimates	Relative estimates (95% CI)	Comments
Nguyen/ 2009[134]	Cohort study / 1998-2005 / Canada	NIS database, 499,541 without LC, 2,909 with LC (without PH), and 1,133 with LC and PH undergoing colorectal surgery	In-hospital mortality overall and stratified by elective and acute	Overall mortality: - patient without LC: 5% - patients with LC: 18% Mortality elective vs acute: - without LC: 1.8% vs 9.1% - with LC: 7.2% vs 20.9% - with LC + PH: 18.6% vs 35.8%	Adjusted OR (elective vs acute) - without LC: 1.00 - with LC: 2.40 (2.07-2.79) vs 3.91 (3.12-4.90) - with LC + PH: 5.88 (4.90-7.06) vs 11.3 (8.46–15.1)	Adjusted for hospital volume, total colectomy, age, gender, ethnicity, primary health insurance carrier, CCI, calendar year, region, hospital characteristics.
Meunier /2008[132]	Single-center cohort study / 1993-2006 / France	41 patients with LC undergoing 43 colorectal surgeries	In-hospital complications after surgery	Complications occurred in 33 (80.5%) and 11 (26.8%) patients died.	NA	91% of patients had alcohol-related cirrhosis. Indication for surgery: 85% cancer, 7% DD
Martinez/ 2004[139]	Single-center cohort study / 1993-2003 / Spain	17 (14 with CRC) patients with LC undergoing laparoscopy colectomy	30-day complications	Conversion to open surgery occurred in 5 (29%) patients. Postoperative complications occurred in 5 (29%) patients and 2 (11.8%) required reoperation. No postoperative deaths.	NA	29% of patients had alcohol-related cirrhosis, 36% viral-related cirrhosis. 71% of patients had Child-Pugh A and 29% Child-Pugh B.
Gervaz/ 2003[137]	Single-center cohort study / 1976-2001 / CA USA	72 patients with LC undergoing CRC surgery	30-day mortality	9 (13%) patients died within 30 days after surgery. Mortality rates in patients with child-Pugh A, B, and C were 6%, 13%, and 28%, respectively.	NA	49% of patients had alcohol-related cirrhosis, 9% biliary cirrhosis, and 25% cryptogenic.
Kartheuser/ 1996[140]	Single-center cohort study / 1970-1990 / MN USA	72 patients with primary sclerosing cholangitis and ulcerative colitis undergoing proctocolectomy	Postoperative prognosis	Overall postoperative complications occurred in 17 patients (23.6%)	NA	Only the abstract was available.
Post/ 1994[142]	Single-center cohort study / 1972-1990 / OH USA	24 patients with primary sclerosing cholangitis and inflammatory bowel disease undergoing colectomy	In-hospital complications	Postoperative complications occurred in 6 (25.0%) patients and 3 (12.5%) patients died (all with cirrhosis).	NA	8 patients had cirrhosis while 24 had hepatitis.

Table 2.1. Studies on postoperative complications in patients with liver disease after colorectal surgery.

Author/ year	Study design / Study Period / Country	Study population and exposure	Aim/Outcome of interest	Absolute estimates	Relative estimates (95% CI)	Comments
Kartheuser/ 1993[141]	Single-center cohort study / 1981-1990 / MN USA	40 patients with primary sclerosing cholangitis and ulcerative colitis undergoing proctocolectomy	30-day complications	General complications occurred in 9 (22.5%) patients and none died.	NA	
Metcalf/ 1987[136]	Single-center / 1970-1984 /	54 patients with LC undergoing colorectal surgery	In-hospital postoperative complications	Postoperative complications occurred in 26 (48%) patients and in-hospital mortality in 13 (24%) patients	NA	Indication for surgery was CRC in 48% of patients and DD in 7% of patients. Alcohol was the etiology of cirrhosis in 29% of patients.
Peck/ 1985[143]	Four center-based cohort studies / 1970-1984 / OR USA	19 patients with primary sclerosing cholangitis and ulcerative colitis undergoing proctocolectomy	Postoperative risk of abdominal wall varices development	5 (26.3%) patients developed abdominal wall varices after surgery.	NA	

Abbreviations: Charlson comorbidity index (CCI), colorectal cancer (CRC), diverticular disease (DD), liver cirrhosis (LC), not available (NA), odds ratio (OR), portal hypertension (PH).

2.3.2 Limitations of the existing literature

Existing literature lacks studies that investigate the impact of liver disease on short-term mortality in patients undergoing colorectal surgery for CRC or DD, respectively, and properly adjusting for potential confounding. Lack of comparison cohorts of patients without liver disease prevented from estimate the prognostic impact of liver disease on 30-day or in-hospital mortality in most of the previous studies. Of the three studies including a comparison group, two did not report prevalence of surgical indication[134,135] and one only reported CRC prevalence being double among patients without liver disease than in patients with liver disease.[133] Therefore, since none of the previous studies controlled for the specific indication for surgery, estimates on impact of liver disease on in-hospital or 30-day mortality may be biased by the different distribution of CRC or DD among patients with liver disease and patients without liver disease. Moreover, comparability among the existing literature is hampered by differences in liver disease definition and in surgical procedure selection. In the two studies investigating impact of liver cirrhosis, the comparison cohorts of patients without liver cirrhosis are likely to contain patients with non-cirrhotic liver disease and, therefore, impact of liver cirrhosis may have been underestimated. [134,135] In the study investigating patients with chronic liver disease, the authors did not adjust the estimate for patient-related prognostic factors such as comorbidity.[133] Although the authors claimed that their choice would have prevented from mitigating the impact of liver disease controlling for potential intermediate steps, it might have led to biased estimates. Finally, prognosis following colorectal surgery in patients with non-cirrhotic liver disease considered separately was not reported by any study.

Therefore, we examined the impact of liver disease in patients undergoing CRC or DD surgery in a population-based setting with a comparison cohort of patients without liver disease overall and in subgroups of patients.

2.4 Human serum albumin and its association with prognosis

HSA is synthesized in the liver (10-15 g/day) and released into the intravascular space.[146] Its half-life in healthy individuals is 12-19 days.[147] Reference serum values range from 35 to 50 g/L and HSA below 35 g/L is usually defined as hypoalbuminemia. The decrease in HSA may be due to reduced availability of amino acids, impaired synthesis, increased losses, intensified catabolism, or alteration in distribution.[29]

HSA is the most abundant plasma protein in the circulatory compartment (60%-65% of the total) and is responsible for 75% of the plasma oncotic pressure. For this property, its use in clinical practice has been mainly aimed at promoting plasma volume expansion since World War II.[148] However, during the past decade a better understanding of HSA structure and function has led to the concept that HSA has multifunctional properties ranging from provision of oncotic pressure, immune regulation, and endothelial stabilization to being a molecule that works in the intracellular compartment modifying several key pathophysiological mechanisms.[147] Moreover, many of the physiological functions of HSA depend on its capacity to bind an extraordinary diverse range of endogenous and exogenous molecules, to increase their solubility in plasma, to transport them to specific tissues and organs, or to dispose of them if they are toxic.[149,150]

HSA concentration may be affected by liver disease not only by decreasing its synthesis but mediated by chronic inflammation that is usually present in patients with liver hepatitis and cirrhosis.[151] Moreover, many other conditions associated with increased risk of postoperative complications also lead to decrement in HSA concentration such as malnutrition, cancer, and comorbid conditions including diabetes, infection, and heart and renal failure.[29,30,76,152,153]

The association between the decrease in HSA concentration and mortality rates has been examined both among healthy and hospitalized individuals.[30-32,154,155] In a British prospective study, Phillips *et al.* followed a total of 7,736 healthy men aged 40-59 years over nine years. They found that each 2.55 g/L decrement in HSA levels in a range from 35 to 57 g/L was associated with an increased overall, cancer-related, and cardiovascular-related mortality from 27% to 37% even after adjustment for age, social class, town of residence, cigarette smoking, serum total cholesterol, systolic blood pressure, serum total calcium, and forced expiratory volume in one second.[154] Among hospitalized patients, HSA below 35 g/L was reported in approximately 45% of

patients admitted in internal medicine wards in Israel and in Italy and was most commonly associated with anemia, malignancies, elderly age, renal and liver dysfunctions, and infections.[31,152] A large meta-analysis published in 2003 including 90 cohort studies for a total of 291,433 hospitalized patients showed that for each 10 g/L decline in HSA the pooled ORs were 1.89 (95% CI: 1.59-2.24) for morbidity (reported in 18 of the 90 studies) and 2.37 (95% CI: 2.10-2.68) for mortality (53 studies).[156] The prognostic role of HSA was also extensively reported among cancer patients. Approximately 60 studies investigating the impact of pretreatment HSA below 35 g/L (compared to HSA above 35 g/L) on cancer survival were summarized in a review.[30] Out of 29 studies investigating survival in GI cancer patients, two studies reported adjusted relative risks of 1.49 and 1.98 but with broad CIs including the unity[48,157] and only one study did not show an association in multivariate analysis (relative risk = 0.99; 95% CI: 0.50-1.98).[158] However, the authors adjusted the model for complete response to chemoradiotherapy that was found strongly predicted by low HSA concentration in another analysis in the same study. Therefore, the finding of no association may be caused by improper adjustment.

Although decrement in HSA has been reported to be strongly associated with increased mortality and morbidity, a criticism that is often raised regarding causality between the two is that clinical trials provided contradictory results about prognosis following HSA administration, especially among critically ill patients.[159-163] However, such argument is not sufficient to prove no causality but at most to indicate that prognosis is not affected by HSA administration. Indeed, HSA is only administrated acutely and when patient conditions are already worsened and this may partially prevent the effect of HSA on prognosis. In addition, oxidation of cysteine in position 34 is known to impair binding capacity of HSA and a previous study has reported a markedly higher percentage of oxidized forms of albumin in commercial preparation.[164] Similarly, commercial albumin solutions have also been reported to promote immunosuppression in vitro due to factors produced during preparation.[165] Last, HSA replacement has been shown beneficial in specific clinical conditions and is strongly supported by solid scientific evidence.[147,166]

In summary, previous studies provided findings supporting a causal association between decrement in HSA concentration and increased mortality demonstrating temporal correlation, dose-response relation, reproducibility, strength of association, and biological plausibility. Our

study III aims to extend the actual knowledge on prognostic role of HSA investigating its impact on 30-day mortality following CRC surgery.

2.5 Preoperative human serum albumin and surgical prognosis (study III)

Preoperative HSA has been reported to predict both short-term and long-term postoperative survival in patients undergoing surgery.[32,167-169] In a meta-analysis, risk of postoperative mortality and morbidity following non-cardiac surgery associated to a 10 g/L decrease in HSA was estimated to be 2.80 (95% CI: 2.18-3.58) and 1.73 (95% CI: 1.67-179), respectively.[156] In particular, two of the previous studies showed that decrement in HSA over the normal interval is associated with increased in-hospital mortality after non-cardiac surgery.[168,169] Moreover, patients undergoing surgery are likely to have systemic inflammation that is also a condition strongly associated with decrease of HSA concentration.[29] Previous studies reported that HSA below 35 g/L is often associated with levels of C-reactive protein (CRP) above 10 mg/L and patients with both the conditions at a markedly higher risk of long-term postoperative mortality than patients with elevated CRP but HSA within the normal interval.[170-174] Finally, AKI is a major factor of morbidity and mortality among postoperative medical complications in colon and rectal surgery,[35,36] and in a recent study investigating prognosis in patients undergoing esophageal cancer surgery reported preoperative HSA below 35 g/L to be a prognostic factor for postoperative AKI.[34] However, the impact of HSA on risk of AKI in CRC surgery has not been investigated.

Based on the recent studies on HSA functions, the decrease in HSA may be one of the pathophysiological pathways responsible for the increase of postoperative risk. Indeed, low HSA increases the risk of organ hypo-perfusion due to decrease of the intravascular oncotic pressure, raises susceptibility to infection and high inflammatory response as a result of reduction in its immunomodulatory and antioxidant properties.[147] Since prevalence of preoperative HSA below the normal interval of 35-50 g/L in patients undergoing CRC surgery was reported to vary from 10% to 57%[48,170-173,175-187] it may be relevant to examine the impact of its decrement, below and within the reference interval, on mortality, reoperation, and AKI rates in the 30 days following CRC surgery (study III). Moreover, we investigated if the impact of preoperative HSA differs within subgroups of CRC patients and in patients with different level of CRP.

2.5.1 Existing literature on albumin and colorectal cancer surgery

We searched the existing literature for original studies or meta-analyses investigating the impact of HSA on postoperative complications after CRC surgery. The strategy was to include all studies within this area regardless of preoperative cancer stage, patients' age, or type of admission (elective or non-elective). Studies with the primary aim to include HSA as covariates were not considered relevant. Studies not available in English, Danish, Italian, French, or Spanish were excluded.

We used the following query to search MEDLINE (last search June 12, 2014):

"Humans"[MeSH] AND albumin AND (colorectal cancer OR "Colorectal Neoplasms"[Mesh]) AND ("colorectal surgery" OR colectomy[TIAB] OR "Colonic Diseases/surgery"[Mesh] OR "Rectal Diseases/surgery"[Mesh]) AND ("postoperative complications"[MeSH Terms] OR "Mortality"[MeSH Terms] OR "Survival"[MeSH] or mortality OR survival)

This query resulted in 170 publications. After title review, 34 publications were selected for abstract review. Among these 34 publications, 21 were selected for full article review and 14 were relevant.[48,175,180-184,186-192]

Next, we extended our research using the following query:

colorectal surgery AND albumin[TIAB]

This query resulted in 265 hits, of which 13 were selected for abstract review, and three were found relevant.[185,193,194]

Furthermore, to perform a more comprehensive search of possible publications not found in MEDLINE, we also searched EMBASE with the following query:

'albumin'/exp AND 'cancer surgery'/exp AND 'large intestine tumor'/exp

This query resulted in 64 publications, of which we reviewed 11 abstracts. One was found to be relevant.[195]

Finally, we were aware of a relevant study that was not identified through the literature search.[196]

Therefore, we ended up with a total of 19 relevant studies (Table 2.2). Among studies selected after title revision, none were excluded because of language restriction in both the MEDLINE and EMBASE searches.

In summary, all studies reported preoperative HSA concentration and its association with CRC prognosis. However, only nine of the 19 studies stated among their aims the intention to investigate short-term mortality after CRC surgery:[180-183,188,190-192,195] five were actually able to report 30-day mortality in patients with HSA above and below 35 g/L[182,183,188,190,195] while the other four reported the association among HSA and other postoperative complications.[180,181,191,192] One recent study reported preoperative HSA as predictor of length of stay.[193] The remaining nine studies investigated the association between HSA and overall survival following CRC surgery.[48,175,184-187,189,194,196] Among the 19 studies, only two categorized patients in more than two groups according to preoperative HSA suggesting that even variation of HSA within the normal interval could be associated with different prognosis.[194,196] Both those studies only investigated long-term prognosis.

Previous studies investigating short-term prognosis in patients undergoing CRC surgery reported increased risk of postoperative complications among patients with HSA below 35 g/L.[180-184,188,190,193,195] Thirty-day mortality reported in patients with HSA below 35 g/L ranged from 2% to 28% while varied from 0.6% to 4.6% in patients with HSA above 35 g/L.[182,183,188,190,195] Among previous studies, only one Turkish study investigating 660 patients undergoing CRC surgery did not report increased mortality among patients with low HSA.[190] Relative estimates on the association between HSA and 30-day mortality were only estimated by Lai *et al.* who reported an increased risk of 2.15 (95% CI: 1.70-2.73) for 30-day mortality adjusting for potential confounding among patients with HSA below 35 g/L undergoing potentially curative elective CRC surgery, compared to patients with HSA above 35 g/L.[182]

Table 2.2. Studies of the impact of serum albumin on colorectal cancer prognosis.

Author/year	Study Period / study design / country	Study population and exposure	Aim/Outcome of interest	Absolute estimates	Relative estimates	Comments
Gohil/2014[193]	2010-2011 / single-center cohort study / UK	196 patients with preoperative HSA undergoing CRC surgery.	To investigate serum albumin impact on length of stay.	NA	Serum albumin > 34.5 g/L was associated with an adjusted OR for length of stay of 0.47 (95% CI: 0.24-0.92)	27 patients did not have sufficient data, therefore were excluded. 14% of patients underwent acute surgery.
Azab/2013[194]	2005-2011 / single-center cohort study / NY US	534 patients undergoing CRC surgery stratified in three groups according to preoperative HSA tertiles (≤ 31 g/L, 32-37 g/L, and > 37 g/L)	4-year cancer-related mortality after CRC surgery	4-year mortality: - HSA > 37 g/L: 5% - HSA 32-37 g/L: 26% - HSA ≤ 31 g/L: 38% A subanalysis included 234 patients with HSA > 35g/L (categorized in tertiles) showed 4-year mortality of 3%, 4%, and 15% in the three tertiles from the highest HSA to the smallest, respectively.	Compared to patients with HSA ≤ 31 g/L, adjusted HR was 0.73 (95% CI: 0.47-1.14) for patients with HSA 32-37 g/L and 0.22 (95% CI: 0.11-0.46) for patients with HSA >37g/L	Patients with liver disease, immunosuppressive therapy, chronic inflammatory disease, infection, bowel obstruction, and receiving preoperative chemotherapy were excluded.
Chandrasinghe/ 2013[195]	1996-2010 / single-center cohort study / Sri Lanka	181 (80%) patients with HSA > 35g/L and 45 (20%) patients with preoperative HSA < 35 g/L undergoing rectal cancer surgery with curative intent	30-day mortality and postoperative complications following rectal cancer surgery	30-day mortality was 1% and 2% in patients with HSA above and below 35 g/L (RD: 1%, 95% CI: -3-5), respectively. Postoperative complication rates were 12% and 23% (RD: 9%; 95% CI: -2-23).	NA	Patients with liver or kidney failure were excluded.
Ionescu/2013[183]	2011-2012 / single-center cohort study / Romania	75 (30%) patients with preoperative HSA < 35 g/L and 177 (70%) with HSA ≥ 35 g/L undergoing elective CRC surgery	30-day mortality and postoperative fistulas occurrence after surgery	30-day mortality was 0.6% (n=1) among patients with HSA ≥ 35 g/L and 6.7% (n=5) in patients with HSA < 35 g/L (p-= 0.01). Fistulas formation occurred in 2.3% (n=4) and 13.3% (N=10) of patients with HSA below and above 35 g/L, respectively.	Compared with HSA ≥ 35 g/L, adjusted ORs for risk of fistulas were 6.65 (95% CI 2.01-21.96) among patient with HSA < 35 g/L and 24.75 (95% CI: 6.75-90.67) among patients with HSA < 25 g/L	Only patients where anastomosis has been practiced were included.
Kye/2013[191]	2004-2011 / single-center cohort study / Sud Korea	102 patients with HSA ≥ 35 g/L and 12 patients with HSA < 35 g/L (all aged 65 or older) undergoing ileostomy following rectal cancer surgery	Postoperative mortality and diverting stoma formation related-complications	No postoperative mortality. Stoma formation-related complications occurred in 22.5% (n=23) of patients with HSA ≥ 35 g/L and 8.3% (n=1) of patients with HSA < 35 g/L.	NA	Complications included acute renal failure, adhesive ileus, parastomal hernia, stoma perforation, and prolapse.

Table 2.2. Studies of the impact of serum albumin on colorectal cancer prognosis.

Author/year	Study Period / study design / country	Study population and exposure	Aim/Outcome of interest	Absolute estimates	Relative estimates	Comments
Fujii/2012[175]	2007-2009 / single-center cohort study / Japan	143 (91%) patients with preoperative HSA ≥ 35 g/L and 15 (10%) with HSA < 35 g/L undergoing CRC surgery	Overall postoperative CRC recurrence	Recurrence occurred in 8.4% of patients with HSA ≥ 35 g/L and in 33.3% of patients with HSA < 35 g/L (p = 0.002).	NA	Patients with recurrent tumors, neoadjuvant chemo- or radio-therapy, undergoing emergency surgery, and with preoperative signs of infection or other inflammatory conditions were excluded
Khan/2011[192]	1999-2008 / single-center cohort study / Pakistan	250 patients undergoing CRC surgery	30-day morbidity and mortality following CRC surgery.	30-day mortality was 1.6% (n=4). Postoperative complications occurred in 34.8% (n=87) patients.	HSA < 35 g/L was associated with a crude OR for complications of 3.11 (95% CI: 1.18-8.15) compared to HSA ≥ 35 g/L	HSA measurement was missing for 53 (60.9%) patients with complications and 98 (60.1%) patients without complications.
Lai/2011[182]	1995-2008 / single-center cohort study / Taiwan	3,039 (81%) patients with HSA ≥ 35 g/L and 693 (18%) patients with HSA < 35 g/L undergoing potentially curative elective CRC surgery	30-day mortality and complications following CRC surgery.	Mortality rates were 0.56% (n=17) in patients with HSA ≥ 35 g/L and 4.0% (n=28) among patients with HSA < 35 g/L. Corresponding complication rates were 9.4% (n=287) and 21.5% (n=149).	Adjusted HRs for mortality and morbidity among patients with HSA < 35 g/L compared to patients with HSA ≥ 35 g/L were 3.86 (95% CI: 1.94-7.68) and 2.15 (95% CI: 1.70-2.73), respectively.	117 patients were not included in the study because without preoperative HSA.
Özoğul/2010[190]	2002-2007 / single-center cohort study / Turkey	582 (88 %) patients with HSA ≥ 35 g/L and 78 (12%) patients with HSA < 35 g/L undergoing CRC surgery	30-day mortality following surgery.	30-day mortality was 2.7% in patients with HSA ≥ 35 g/L and 2.6% in patients with HSA < 35 g/L.	NA	
Sun/2009[184]	1996-2006 / single-center cohort study / China	392 (29%) patients with preoperative HSA < 35g/L and 975 (71%) patients with HSA ≥ 35 g/L	Cancer-specific long-term survival following CRC surgery.	Survival at 60 months after surgery was approximately 65% among patients with serum albumin ≥ 35 g/L and 55% among patients with serum albumin < 35 g/L	HSA < 35 g/L showed adjusted HR for mortality of 1.45 (95% CI: 1.09-1.92) compared with patients with HSA ≥ 35 g/L.	23 patients who died within 30 days after CRC surgery were not included in the study. Absolute estimates are extrapolated from Figure 1 in the original paper.

Table 2.2. Studies of the impact of serum albumin on colorectal cancer prognosis.

Author/year	Study Period / study design / country	Study population and exposure	Aim/Outcome of interest	Absolute estimates	Relative estimates	Comments
Lohsiriwat/2008 [181]	2003-2006 / single-center cohort study / Thailand	188 (77%) patients with HSA ≥ 35 g/L and 56 (23%) patients with HSA < 35 g/L undergoing rectal cancer surgery	30-day mortality and other complications following surgery.	Overall 30-day mortality and morbidity was 1.2% (n = 3) and 25% (n = 44). Among patients with HSA < 35 g/L complications rates was 38% compared to 21% among patients with HSA ≥ 35 g/L	HSA < 35 g/L was associated with an adjusted OR for postoperative complications of 2.22 (95% CI: 1.17-4.23)	Patients with pelvic exenteration, operations for recurrences, or acute complicated conditions (e.g. colonic obstruction) were not included in the study.
Crozier/2007[189]	1999-2004 / single-center cohort study / UK	155 (91%) patients with HSA ≥ 35g/L and 16 (9%) with HSA < 35 g/L undergoing potentially curative CRC surgery.	Overall postoperative survival	NA	Adjusted HR for overall survival in patients with HSA < 35 g/L was 1.88 (95% CI: 0.85-4.17) compared to patients with HSA ≥ 35 g/L	180 patients were included in the study but 9 did not have HSA measurement.
Ishizuka/2007[48]	2001-2006 / single-center cohort study / Japan	215 (68%) patients with HSA ≥ 35 g/L and 100 (32%) patients with HSA < 35 g/L undergoing CRC surgery	Overall long-term survival following CRC surgery	Mean survival was 19.9 (95%CI: 17.9-22.0) months and 13.0 (95% CI: 10.5-15.6) months in patients with HSA ≥ 35 g/L and in those with HSA < 35 g/L, respectively.	Adjusted OR for patients with HSA < 35 g/L was 1.98 (95% CI: 0.92-4.30).	Patients who died within 30 days and those who died of noncancer-related cause after surgery were not included.
Lohsiriwat/2007 [180]	2004-2005 / single-center cohort study / Thailand	40 (43%) patients with HSA ≥ 35 g/L and 48 (57%) patients with HSA < 35 g/L undergoing elective curative right-side colon cancer surgery	30-day mortality and other postoperative complications.	No 30-day mortality occurred. Other postoperative complications occurred in 29% (n=14) of patients with HSA < 35 g/L and in none of the patients with HSA ≥ 35 g/L (p = 0.001)	NA	Patients with liver cirrhosis and complicated conditions (*e.g.*, colonic obstruction or perforation) were not included in the study.
Boonpipattanapong/2006[185]	1998-2002 / single-center cohort study / Thailand	38 (22%) patients with HSA < 35g/L and 132 (78%) with HSA ≥ 35 g/L undergoing CRC surgery	5-year survival after CRC surgery	5-year survival was 48% and 59% among patients with HSA < 35g/L and among those with HSA ≥ 35 g/L, respectively	NA	212 patients were not included because previously treated for CRC elsewhere.
Cengiz/2006[186]	1994-2003 / single-center cohort study / Turkey	66 (67%) patients with HSA > 35 g/L and 33 (33%) patients with HSA ≤ 35 g/L undergoing CRC surgery	Overall postoperative survival.	Mean overall survival was 77 and 28 months among patients with HSA ≤ 35 g/L and those with HSA > 35 g/L, respectively (p < 0.001).	Serum albumin ≤ 35 g/L was associated with a HR of 2.8 (95% CI: 1.37-5.67) compared to patients with serum albumin > 35 g/L	Patients died within 30 days were not included in the study.

Table 2.2. Studies of the impact of serum albumin on colorectal cancer prognosis.

Author/year	Study Period / study design / country	Study population and exposure	Aim/Outcome of interest	Absolute estimates	Relative estimates	Comments
Dixon/2003[187]	1991-1999 / single-center cohort study / CA US	59 (65%) patients with HSA ≥ 27 g/L and 32 (35%) patients with HSA < 27 g/L diagnosed with stage IV CRC	Overall mortality after CRC diagnosis	Median HSA was 25 g/L (IQR: 22-30) among patients that survived less than 120 days and 31 g/L (IQR: 26-35) among patients that survived more than 120 days (p = 0.002).	NA	Patients previously diagnosed with any cancer or treated for CRC were not included. 79 patients underwent CRC surgery.
Heys/1998[196]	1972-1985 / single-center cohort study / UK	431 patients with CRC and pre-treatment HSA were followed from the initial presentation	Long-term survival after CRC surgery	5-year survival: - HSA > 45 g/L: 78% - HSA 35-44 g/L: 50% - HSA 25-34 g/L: 35% - HSA < 25 g/L: 15%	Adjusted HR for mortality corresponding with an increase of 1 g/L of HSA was 0.95 (95% CI: 0.93-0.98). HR restricted to patients with localized CRC was 0.95 (95% CI: 0.91-0.97)	Type of treatment was not specified. Survival rates were extrapolated from Figure 3 of the original paper.
Hickman/1980 [188]	1959-1978 / single-center cohort study / CA US	65 (78%) patients with HSA ≥ 35 g/L and 18 (22%) patients with HSA < 35 g/L undergoing CRC surgery	30-day mortality after surgery.	30-day mortality was 4.6% among patients with HSA ≥ 35 g/L and 28% among patients with HSA < 35 g/L	NA	

Abbreviations: colorectal cancer (CRC), hazard ratio (HR), human serum albumin (HSA), confidence interval (CI), gastrointestinal (GI), interquartile range (IQR), not available (NA), odds ration (OR), person-years at risk (PYR), risk difference (RD).

2.5.2 Limitations of the existing literature

The existing literature is limited by a lack of studies able to examine the impact of HSA on short-term prognosis in a population-based setting including all patients undergoing CRC surgery. None of the previous studies were able to properly control for potential confounding because of lack of information and small sample size. Moreover, the study size prevented from exploring if the association between HSA and postoperative mortality varied in patients with different age, comorbidity burden, cancer stage, and cancer site. Furthermore, all previous studies were single-center based and generalizability of their findings may be limited. Therefore, accurate data on postoperative short-term mortality in patients with HSA concentration below and within normal interval undergoing CRC surgery are needed to better understand the prognostic effect of HSA overall and among patients with different baseline preoperative risk of postoperative death.

3. Aims of the dissertation

The literature review revealed that, although patients with liver disease are at increased risk of dying after colorectal surgery, the impact of liver disease on mortality following colorectal surgery has not been investigated in patients undergoing surgery for CRC or DD, separately. None of these studies examined if the impact of liver disease varied within subgroups of patients undergoing colorectal surgery with, *e.g.*, different comorbidity level and age. Moreover, the impact of non-cirrhotic liver disease on postoperative prognosis following colorectal surgery is essentially unknown.

Similarly, although existing literature has shown that HSA below 35 g/L is associated with increased cancer-specific and overall long-term mortality in patients with CRC compared to those with HSA above 35 g/L, its impact on short-term prognosis following CRC surgery has only been investigated in single-center studies. Moreover, the existing literature did not clarify if the prognostic impact of HSA on mortality is concentration-dependent since almost all studies identified two groups according to a cut-off point that usually corresponded with the lower bound of HSA reference interval. Last, it is also unclear if differences in preoperative HSA concentration still have an impact on 30-day prognosis over the reference interval.

To address these gaps in the existing evidence, we conducted three studies with the following aims:

Study I: To investigate 30-day mortality in patients with liver disease undergoing CRC surgery from 1996 through 2009 compared to a population-based cohort without liver disease, in a nationwide population-based setting.

Study II: To investigate 30-day mortality and reoperation in patients with liver disease undergoing colorectal surgery for DD from 1977 through 2011 compared to patients without liver disease, in a nationwide population-based setting.

Study III: To investigate impact of preoperative HSA concentration on mortality, reoperation, and AKI within 30 days following colorectal surgery because of CRC from 1997 through 2011, in a population-based setting.

4. Methods

4.1 Setting

Study I and study II were conducted within the entire Danish population of approximately 5.5 million people.[197] Study III included only patients from Northern and Central Denmark (former counties of North Jutland, Aarhus, Ringkjøbing, and Viborg, with approximately 2.2 million inhabitants). In Denmark, tax-funded health care is provided equally to all citizens. Essentially, all types of surgery for CRC and DD are managed by public hospitals.

4.2 Data sources

4.2.1 The Civil Registration System (studies I-III)

The Civil Registration System (CRS) assigns a unique 10-digit civil personal registration number (CPR number) to each Danish citizen at birth and to residents upon immigration. This identifier facilitates unambiguous individual-level linkage of nationwide registries. The CRS has recorded information on vital status (dead or alive), date of death, and residence since 1968 and is updated daily.[198]

4.2.2 The Danish National Registry of Patients (studies I-III)

The Danish National Registry of Patients (DNRP) has tracked all non-psychiatric hospitalizations since 1977.[199,200] Since 1995, the DNRP has included data from outpatient clinic visits, emergency room visits, and psychiatric units as well. The recording is mandatory and the data are used for administrative purposes and to monitor health care, including costs. For each hospital contact, the DNRP records CPR number, dates of admission and discharge, surgical and diagnostic procedures, and up to 20 discharge diagnoses (coded by physicians according to the 8th revision of the International Classification of Diseases (ICD) until the end of 1993, and according to the ICD-10 thereafter). According to Danish guidelines, the primary diagnosis represents the main reason for the admission. From 1977 to 1995, surgical procedures were coded according to the Danish classification of surgical procedures. Since 1996, they have been coded according to the NOMESCO (Nordic Medico Statistical Committee) classification of surgical procedures.[201] Since 1996, the exact date of surgery was included in the DNRP.

4.2.3 The Danish Cancer Registry (study l and study III)

The Danish Cancer Registry (DCR) has recorded all incident malignant neoplasms in Denmark since 1943 and is based on notifications from hospital departments, specialists, and autopsy reports.[202,203] The data include CPR number, date of cancer diagnosis, cancer type/site, and cancer stage at time of diagnosis. In 2004, several administrative changes occurred: (i) reporting to the DCR became electronic, and via the DNRP; (ii) the date of diagnosis was defined as the date of the first cancer-related admission instead of the first month of hospitalization; and (iii) the classification system changed from the ICD-7 to the ICD-10.[204] In addition, the recording of cancer stage was changed from the Dukes' system to the Tumor Node Metastasis (TNM) system.

4.2.4 The laboratory information system database (study III)

The laboratory information system database (LABKA) contains laboratory tests from inpatient stays, outpatient clinic visits, and visits to general practitioners.[205] All tests analyzed at hospital laboratories are immediately entered into these systems. Therefore, these systems hold laboratory test results from virtually all tests performed (except tests for which analyses are usually performed at the offices of private specialists and general practitioners as point-of-care tests, such as hemoglobin, and blood glucose).

Data from these laboratories were transferred to the LABKA since 1990, but data were first considered complete for North Jutland since 1997 and in the Central Denmark Region since 2000. Data include patient's CPR number, date of the test, test name, test code (nomenclature, properties, and units in laboratory medicine codes and/or local Danish laboratory codes), and unit.[205]

Blood test before CRC surgery

To our knowledge, Denmark does not have specific recommendations on routine preoperative blood tests in patients undergoing CRC surgery except for hemoglobin to examine for anemia.[206,207] However, the following tests are usually the minimal samples analyzed preoperatively: hemoglobin, blood type and Rh, glycaemia, Na^+, K^+, serum creatinine and HSA. Some departments also include basic phosphatase, transaminases (ASAT/ALAT), bilirubin, and CEA (personal communication) in routine blood testing.

Plasma albumin measurement in the LABKA

The assay used for HSA measurement varied between laboratories and also within laboratories during our study period while reference intervals did not change among laboratories. To our knowledge, standardization among laboratories was not implemented during the study period. HSA measurements reported as µmol/L were converted into g/L (1 g/L = 15.05 µmol/L). In order to investigate major differences during the study period, we searched the entire database for all HSA measurements among patients undergoing CRC surgery and stratified those by sample year. An increase in average HSA was observed from 2004 onwards while corresponding standard deviations remained constant (Table 4.1). HSA measurements originally reported in g/L are recorded as integer in the dataset. Therefore, estimates for results obtained after conversion from µmol/L into g/L were rounded to the nearest integer.

Table 4.1. Mean and standard deviation of serum albumin measurements stratified by year

Sample year	No. of samples	Mean (g/L)	Standard deviation
1997	641	33.4	7.0
1998	1,013	33.0	7.3
1999	1,094	33.4	7.3
2000	3,208	32.4	7.7
2001	3,588	33.1	6.9
2002	3,617	32.7	7.1
2003	3,444	33.0	7.2
2004	3,961	34.2	7.2
2005	6,500	34.7	7.1
2006	6,937	35.5	7.4
2007	4,522	36.7	6.7
2008	4,888	37.2	6.8
2009	5,631	38.1	6.2
2010	5,242	38.1	6.2
2011	3,617	36.2	6.8

4.3 Study design

All three studies were designed as population-based cohort studies utilizing information from the Danish data sources mentioned above (i.e. historical cohort studies).

4.4 Study populations

Study l included patients recorded in both the DCR and the DNRP with incident CRC that underwent a first time colorectal surgery for this indication between January 1, 1996 and January 1, 2010.

Study ll included all patients diagnosed with DD in the DNRP, who underwent colorectal surgery for this indication for the first time between January 1, 1977 and January 1, 2012. We excluded patients who were given a primary or secondary diagnosis of CRC during the same hospitalization (n = 394). Moreover, for each patient we also summarized the number of inpatient hospital admissions due to DD before the admission for DD surgery as none, 1-2, and 3+ admissions.

In study lll, we included patients diagnosed in both the DCR and the DNRP with incident CRC who underwent colorectal surgery for this indication for the first time in Northern and Central Denmark between January 1, 1997 and January 1, 2012. The study area was chosen based on the availability of laboratory data to classify patients according to preoperative HSA concentration. We also required patients included in the study to be resident in Northern and Central Denmark at the time of CRC surgery. Moreover, we included a county in the study only if more than 90% of patients undergoing surgery in that county during a specific year were registered in the LABKA (Table 4.2). Hence, the study population was further restricted to patients that had CRC surgery in North Jutland since 1997, in Aarhus since 2000, in Viborg since 2005, and in Ringkjøbing since 2006. This requirement ensured availability of data on recent HSA from the LABKA for identification.

As the indication for surgery is not coded in the DNRP we defined CRC or DD surgery in all the three studies as a procedure involving colorectal surgery performed during a hospitalization where CRC or (complicated or uncomplicated) DD, respectively, were listed as a diagnosis in the DNRP.

Table 4.2. Percentages of colorectal cancer (CRC) patients registered in the laboratory database by year of CRC surgery and county where surgery was performed. A cut-off of 90% was used to identify the study population (years and counties included in the study are indicated in bold).

Year of CRC surgery	Percentage of patients registered in the laboratory database			
	North Jutland	Ringkjøbing	Viborg	Aarhus
1996	43.5	2.9	6.4	76.2
1997	**97.3**	8.5	8.3	77.4
1998	**100**	10.5	6.7	80.7
1999	**100**	5.9	10.0	81.8
2000	**100**	10.6	15.2	**98.2**
2001	**100**	6.9	15.3	**100**
2002	**100**	13.3	14.4	**100**
2003	**100**	19.8	16.5	**99.3**
2004	**99.7**	6.5	42.1	**99.7**
2005	**100**	2.8	**93.3**	**99.7**
2006	**100**	**94.0**	**96.1**	**99.3**
2007	**99.4**	**100**	**93.7**	**99.4**
2008	**99.7**	**100**	**96.9**	**99.4**
2009	**99.7**	**100**	**100**	**98.8**
2010	**100**	**100**	**92.7**	**100**
2011	**99.7**	**100**	**97.8**	**100**

4.5 Main prognostic factors

In study I and II, the prognostic factor was liver disease. Patients diagnosed with liver disease before or during the relevant admission for colorectal surgery were identified using the DNRP and categorized as patients with non-cirrhotic liver disease and patients with liver cirrhosis.[208] Non-cirrhotic liver disease included all liver disease diagnoses except cirrhosis, *e.g.*, viral hepatitis, alcoholic hepatitis, non-alcoholic fatty liver disease, and primary biliary cirrhosis. Patients without any liver disease diagnosis were included in the unexposed cohort.

The prognostic factor in study III was a preoperative concentration of HSA below or equal to 40 g/L. The HSA measurement used was the closest to the day of CRC surgery. Only measurements one to 30 days prior to surgery date were used. Moreover, since we wanted to investigate if the effect of HSA on postoperative complications gradually increases with the decrease of its concentration, we further classified patients into the following cohorts: ≤ 25 g/L (severe hypoalbumineamia), > 25 g/L and ≤ 30 g/L (moderate hypoalbuminemia), > 30 g/L and ≤ 35 g/L (mild hypoalbuminemia), > 35 g/L and ≤ 40 g/L (low normal albuminemia). Patients with preoperative HSA above 40 g/L were considered as comparison cohort.

4.6 Outcomes

4.6.1 Mortality

Thirty-day mortality after colorectal surgery was the primary outcome in all three studies. In study II, we further collected information about 31-60 and 61-90-day mortality. The date of death was identified in the CRS.

4.6.2 Reoperation

In study II and III, we included reoperations within 30 days following DD surgery as secondary outcome. Information about reoperation was collected using the DNRP.

4.6.3 Acute Kidney Injury

In study III, we used the LABKA to collect creatinine levels in the first 30 days after CRC surgery to classify patients with postoperative AKI. AKI was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines as: (1) increase in serum creatinine equal or greater than 0.3 mg/dl (26.5 µmol/l) within 48 hours; or (2) increase in serum creatinine equal or greater than 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days.[209] We did not have information about urinary volume.

4.7 Potential confounding factors

We used the CRS to obtain information on age, gender, and (in study II and III) marital status. From the DNRP, we included information on type of admission, classified as elective or non-elective to describe the acuteness of patient presentation, and year and type of surgery. In study I and III, CRC surgery was categorized according to the intention of eradicating the primary tumor as “radical resection” and “non-eradicative procedures”. “Radical resection” included surgeries such as partial and total resections of the colon and/or rectum while “non-eradicative procedures” included colostomy, stent placement, or excision of a very small part of the colon. “Radical resection” was further divided into laparoscopic and open surgery. In study II, we classified DD surgery into two groups: surgery that required stoma creation and surgery without stoma.

We estimated patients’ comorbidity burden using the CCI that includes 19 diseases, each assigned a weight between one and six.[210] The sum of the individual scores represents a measure of a

patient's level of comorbidity. We modified the original index according to the ICD-8 and ICD-10 diagnosis codes used in the DNRP.[211] From the index score, we excluded mild and severe liver disease (study I and II), CRC and CRC metastases (study I and III), and secondary liver cancers (study I). We classified patients as having a low comorbidity level (score = 0), a moderate comorbidity level (score = 1-2), or a high comorbidity level (score ≥ 3). In addition, we collected information on previous hospital diagnoses of alcohol abuse and/or alcohol-related diseases regardless of liver disease.

In study I and III, we used the DCR to obtain information on CRC cancer site (colon or rectum) and stage (Table 4.3).

Table 4.3. CRC stage categories.

CRC stage	Dukes	TNM ≥2004
Localized	A,B	T1-4,x N0 M0 T1-2 N0 Mx T1 Nx M0,x
Non-localized:		
- Regional	C	T1-4,x N1-3 M0
- Metastatisized/Distant	D	T1-4,x N0-3,x M1
Unknown		T0,a,is T2-4,x Nx M0,x T3-4,x N0 Mx T1-4,x N1-2 Mx

Moreover, in study III we used the LABKA to collect information on other preoperative blood tests from one-30 days prior to surgery such as hemoglobin, creatinine, CRP, etc. Using values of creatinine, total bilirubin, and international normalized ratio (INR) we computed the preoperative MELD that was recently reported being an independent predictor of mortality in patients with and without liver disease undergoing colorectal surgery.[212]

4.8 Statistical analysis

In all three studies, we followed patients from the date of colorectal surgery until death, emigration, or end of study, whichever came first. In study II, for those patients that underwent

DD surgery before 1996, date of surgery was defined as the date of the relevant hospital admission because the procedure date was not recorded in the DNRP.

Analyses were performed using the statistical software package Stata 12.0 (StataCorp LP, College Station, TX, USA) and SAS 9.2 (SAS Institute INC., Cary, NC, USA). All three studies were approved by the Danish Data Protection Agency, record number 2006-41-6707 (study I and II) and 2009-41-3866 (Study III). The use of data obtained from Danish registries is generally available to researchers and their use does not require informed consent. Relevant codes used in each study are provided in the Addition file 1 (paper I) and Appendix (paper II and III).

4.8.1 Characteristics of patients undergoing colorectal surgery

In all three studies, we calculated the frequency of patients with demographic, type of admission, type of surgery, and comorbidity characteristics. In study I and II, we described cancer stage and site, and only in study I we described the prevalence of esophageal and gastric varices among patients with and without liver disease. In study II, we described the number of hospital admissions for DD prior to surgery. In study III, we also described the characteristics of patients with missing preoperative HSA.

4.8.2 Cumulative incidence proportions (absolute risks)

In all three studies, we assessed 30-day mortality (1 - survival) and 95% CIs using the Kaplan-Meier method, which accounts for censoring, and plotted the cumulative mortality curves.[45] In study II, we also computed 31-60 and 61-90-day mortality. In study II and III, rates for reoperation (study II and III) and AKI (study III) occurred within 30 days following colorectal surgery were computed treating death as a competing risk.[213]

4.8.3 Cox proportional hazard regression analyses (relative risks)

We used a Cox regression model in all three studies to compute HRs with 95% CIs as a measure of the relative risk. We used multivariate Cox regression to control for potential confounding. The assumptions of proportional hazards were for all models checked graphically using log(-log(survival probability)) and found to be appropriate.

In study I and II, we used Cox regression to compute HRs for 30-day mortality among patients who had non-cirrhotic or cirrhotic liver disease with that among patients without liver disease.

Moreover, in study II we computed HRs for 31 to 61 and 61 to 90 day mortality. In study I, we controlled for gender, age, type of admission, type of surgery, cancer stage, comorbidity level, and non-hepatic alcohol-related disease. In study II, Cox regression model was mutually adjusted for gender, age (both as a continuous and a categorical variable), type of admission, type of surgery, comorbidity level, non-hepatic alcohol-related disease, and marital status.

In study III, we used Cox regression to compare 30-day mortality among patients with preoperative HSA below or equal to 40 g/L to patients with HSA above 40 g/L. Moreover, we used Cox regression to compute HRs for AKI comparing patients with different concentration of HSA. In order to control for potential confounding factors, we fully adjusted for gender, age (both as a continuous and a categorical variable), type of admission, operation year, county, cancer site, cancer stage (excluding patients with stage "unknown"), comorbidity level, alcohol-related disease, liver disease, marital status, hemoglobin, Na^+, K^+, creatinine (number of observations with complete data = 8,033). In order to bridge limitations related with categorization of HSA, we used fractional polynomial Cox regression analysis (assuming HR equal to one for HSA equal to 40 g/L) to graphically describe adjusted HRs for 30-day mortality associated with preoperative HSA (as continuous variable).[214] We also used fractional polynomials to assess adjusted HRs for AKI and reoperation.

4.8.4 Stratified analysis

All three studies included estimate of HRs for 30-day mortality stratified by covariates. These analyses are also referred to as sub-group analyses or sub-analyses and their aim was to evaluate whether the impact of the liver disease or HSA on 30-day mortality differed by subgroup (*i.e.*, effect-measure modification). In study I, we stratified by age, gender, CRC site and stage, type of admission, type of surgery, comorbidity level, and alcohol-related disease. In study II, we stratified by age, gender, type of admission, type and period of surgery, comorbidity level, alcohol-related disease, marital status, and number of previous admission for DD. In study III, we stratified by age, gender, type of admission, CRC site and stage, type and period of surgery, comorbidity level, marital status, comorbidity level, CRP (≤ 10 mg/L, > 10 mg/L and ≤ 20 mg/L, > 20 mg/L and ≤ 50 mg/L, and > 50 mg/L), and MELD (< 10 and ≥ 10). We also performed fractional polynomial analyses for HSA stratified by CRP levels.

4.8.5 Sensitivity analysis

In study III, we excluded patients without preoperative HSA from the main analysis. Moreover, patients with missing data about covariates included in the adjusted model were also excluded in the computation of the adjusted HRs. Therefore, our estimates in the main analysis may have introduced selection bias if the association between preoperative HSA and the outcome was different for patients excluded compared to those who participated in the study.[215] We therefore conducted a sensitivity analysis to examine the potential influence of excluding these patients using multiple imputation. Missing data for type of admission, CRC stage, HSA, and other laboratory measurements were imputed deterministically using the "ICE" command with 20 cycles or regression switching.[215] It was assumed that the data were "missing at random" meaning that the chance of information being missing does not depend on the value of the information itself.[215] Adjusted HRs and 95% CIs for 30-day mortality in each patient cohort compared to HSA above 40 g/L were assessed using the imputed dataset.

5. Results

5.1 Study I

5.1.1 Characteristics

A total of 369 (0.9%) patients with non-cirrhotic liver disease, 158 (0.4%) patients with liver cirrhosis, and 39,313 (98.7%) patients without liver disease underwent CRC surgery in Denmark during the study period. Median age at CRC surgery was 69 years among patients with non-cirrhotic liver disease, 67 years among patients with liver cirrhosis, and 72 years among patients without liver disease. Among patients with liver cirrhosis, 67% were male while the prevalence of males among patients with non-cirrhotic liver disease and among those without liver disease was approximately 50%. Patients with liver disease were more likely to be non-electively admitted, to undergo non-resectional surgery, and to have comorbid conditions including alcohol-related disease than patients without liver disease (Table 5.1).

Table 5.1. Characteristics of patients with and without liver diseases undergoing colorectal cancer surgery in Denmark, 1996-2009.

	No liver disease n = 39,313 (%)	Non-cirrhotic liver disease n = 369 (%)	Liver cirrhosis n = 158 (%)
Gender			
- Male	20,097 (51.1)	188 (50.9)	105 (66.5)
- Female	19,216 (48.9)	181 (49.1)	53 (33.5)
Age (years)			
- 0-59	7,046 (17.9)	75 (20.3)	39 (24.7)
- 60-69	10,083 (25.7)	116 (31.5)	55 (34.8)
- 70-79	13,169 (33.5)	113 (30.6)	50 (31.6)
- 80+	9,015 (22.9)	65 (17.6)	14 (8.9)
Type of admission			
- Non-elective	12,633 (32.1)	137 (37.1)	59 (37.3)
- Elective	26,602 (67.7)	231 (62.6)	99 (62.7)
- Missing	78 (0.2)	1 (0.3)	0 (0)
Cancer site:			
- Colon	25,905 (65.9)	264 (71.5)	100 (63.3)
- Both colon and rectum	72 (0.2)	1 (0.3)	0
- Rectum	13,336 (33.9)	104 (28.2)	58 (36.7)
Cancer stage:			
- Localized	17,044 (43.4)	163 (44.2)	65 (41.1)
- Non-localized	18,863 (48.0)	182 (49.3)	76 (48.1)
- Unknown	3,406 (8.6)	24 (6.5)	17 (10.8)
Type of surgery			
- Laparoscopic radical resection	3,483 (8.9)	35 (9.5)	10 (6.3)
- Open radical resection	31,278 (79.5)	293 (79.4)	122 (77.2)
- Non-resectional procedures	4,552 (11.6)	41 (11.1)	26 (16.5)
Comorbidity level			
- Low	24,301 (61.8)	167 (45.3)	60 (38.0)
- Moderate	11,573 (29.4)	145 (39.3)	65 (41.1)
- High	3,439 (8.8)	57 (15.4)	33 (20.9)
Alcohol-related disease present†	582 (1.5)	46 (12.5)	54 (34.2)

5.1.2 Thirty-day mortality

Thirty-day mortality was 13.3% in patients with non-cirrhotic liver disease and 24.1% among patients with liver cirrhosis, compared to 8.7% in patients without liver disease (Table 5.2 and Figure 5.1). This corresponded to adjusted HRs of 1.49 (95% CI: 1.12-1.98) for patients with non-cirrhotic liver disease and 2.59 (95% CI: 1.86-3.61) for patients with liver cirrhosis, compared with patients without liver disease.

Figure 5.1. Crude 30-day mortality curves for patients undergoing colorectal cancer surgery without liver disease, with non-cirrhotic liver disease, and with liver cirrhosis.

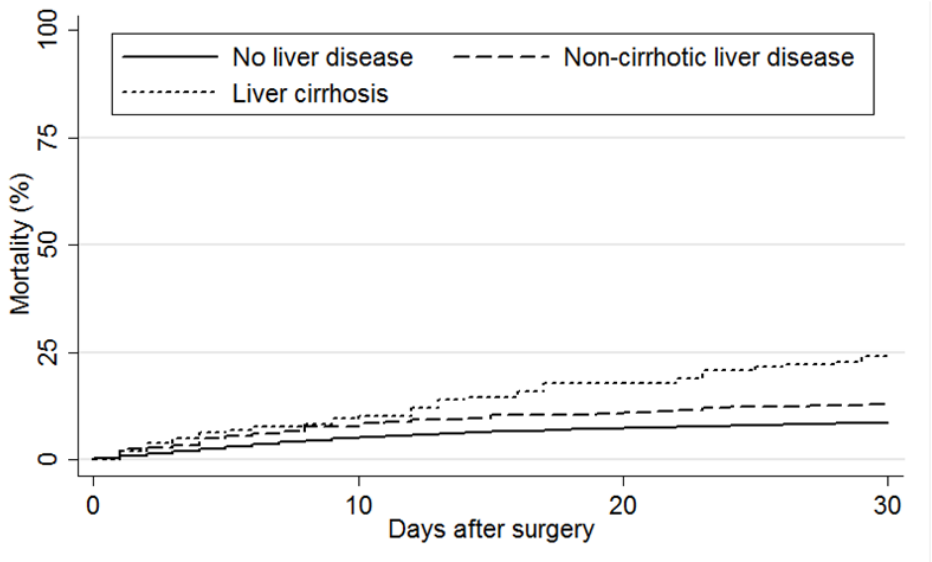


Table 5.2. Thirty-day mortality and corresponding hazard ratios (HRs) with 95% confidence intervals (CIs) after colorectal cancer surgery in patients with and without liver disease.

	No. of patients	No. of deaths	30-day mortality % (95% CI)	HR (95% CI) Crude	HR (95% CI) Adjusted*
Colorectal cancer:					
- No liver disease	39,313	3,432	8.7 (8.4-9.0)	1.00	1.00
- Non-cirrhotic liver disease	369	49	13.3 (9.8-17.8)	1.56 (1.18-2.07)	1.49 (1.12-1.98)
- Liver cirrhosis	158	38	24.1 (16.7-33.9)	2.93 (2.13-4.03)	2.59 (1.86-3.61)
Colon cancer:					
- No liver disease	25,905	2,569	9.9 (9.5-10.3)	1.00	1.00
- Non-cirrhotic liver disease	264	38	14.4 (10.2-20.1)	1.50 (1.09-2.06)	1.45 (1.05-2.00)
- Liver cirrhosis	100	27	27.0 (17.3-40.6)	2.90 (1.99-4.24)	2.50 (1.68-3.70)
Rectal cancer:					
- No liver disease	13,336	857	6.4 (6.0-6.9)	1.00	1.00
- Non-cirrhotic liver disease	104	11	10.6 (5.6-19.3)	1.68 (0.93-3.04)	1.66 (0.91-3.02)
- Liver cirrhosis	58	11	19.0 (9.8-34.8)	3.14 (1.73-5.68)	2.84 (1.52-5.30)
Non-elective surgery: ¥					
- No liver disease	12,633	2,064	16.3 (15.6-17.1)	1.00	1.00
- Non-cirrhotic liver disease	137	33	24.1 (16.3-34.7)	1.56 (1.10-2.20)	1.57 (1.11-2.22)
- Liver cirrhosis	59	21	35.6 (20.9-56.2)	2.38 (1.55-2.67)	2.48 (1.59-3.88)
Elective surgery: ¥					
- No liver disease	26,602	1,363	5.1 (4.9-5.4)	1.00	1.00
- Non-cirrhotic liver disease	231	16	6.9 (4.2-11.4)	1.36 (0.83-2.23)	1.39 (0.85-2.28)
- Liver cirrhosis	99	17	17.2 (10.2-28.1)	3.49 (2.16-5.63)	2.79 (1.70-4.57)

* Mutually adjusted for gender, age, type of admission, cancer stage, type of surgery, comorbidity level, and alcohol-related disease.

¥ Information on type of admission is missing for some patients therefore the sum of patients undergoing non-elective and elective surgery is not equal to the total number of patients included in the study.

5.1.3 Stratified analysis

Thirty-day mortality was higher in patients undergoing colon cancer surgery or non-electively admitted than in patients undergoing rectal cancer surgery or electively admitted in all cohorts. Still, consistent with the overall results, patients with non-cirrhotic liver disease and patients with liver cirrhosis had higher mortality than patients without liver disease and the impact of liver disease did not differ substantially among patients with different type of admission or cancer site (Table 5.2). Moreover, the impact of liver disease on mortality was similar between genders, within subgroups of patients with low and moderate comorbidity levels, and among patients with different CRC stage (Table 5.3). Nonetheless, the impact of liver disease was limited in patients with a high comorbidity level for both non-cirrhotic liver disease (HR = 1.17; 95% CI: 0.62-2.19) and liver cirrhosis (HR = 1.47; 95% CI: 0.68-3.15). Among patients aged 60 years or younger the impact of non-cirrhotic liver disease was particularly high corresponding with a HR of 2.71 (95% CI: 1.25-5.89). Similarly, among patients without alcohol-related disease, non-cirrhotic liver disease was associated with 2.61-fold (95% CI: 1.43-4.76) increased risk of mortality. Inversely, the impact of liver cirrhosis was higher among patients with alcohol-related cirrhosis (HR = 3.37; 95% CI: 2.30-4.92) than among those without that condition. In addition, the increased risk of 30-day mortality among patients with liver cirrhosis decreased from 3.53 (95% CI: 1.53-8.13) among patients younger than 60 years to 1.14 (95% CI: 0.36-3.59) among patients more than 80 years old. Finally, liver cirrhosis had little impact on postoperative mortality in patients undergoing non-resectional procedures (HR = 1.74; 95% CI: 0.82-3.67).

Table 5.3. Mortality hazard ratios (HRs) with 95% confidence intervals (CIs) for 30-day mortality after colorectal cancer surgery in subgroups of patients with liver disease.

Subgroups	No liver disease	Non-cirrhotic liver disease Adjusted* HR (95% CI)	Liver cirrhosis Adjusted* HR (95% CI)
Gender:			
- Male	1.00	1.37 (0.88-2.13)	2.21 (1.20-4.01)
- Female	1.00	1.56 (1.08-2.26)	2.82 (1.90-4.20)
Age (years):			
- 0-59	1.00	2.71 (1.25-5.89)	3.53 (1.53-8.13)
- 60-69	1.00	1.56 (0.83-2.95)	3.61 (2.00-6.52)
- 70-79	1.00	1.10 (0.65-1.87)	2.37 (1.40-4.02)
- 80+	1.00	1.61 (1.01-2.56)	1.14 (0.36-3.59)
Cancer stage:			
- Localized	1.00	1.16 (0.65-2.06)	3.49 (2.06-5.93)
- Non-localized	1.00	1.71 (1.20-2.43)	2.42 (1.49-3.94)
- Stage unknown	1.00	1.41 (0.58-3.42)	2.24 (0.91-5.50)
Type of surgery:			
- Laparoscopic radical resection	1.00	Not Applicable	6.82 (1.48-31.45)
- Open radical resection	1.00	1.41 (0.99-1.98)	3.01 (2.05-4.40)
- Non-resectional procedures	1.00	1.91 (1.14-3.20)	1.74 (0.82-3.67)
Comorbidity level:			
- Low	1.00	1.62 (0.97-2.70)	3.41 (1.97-5.91)
- Moderate	1.00	1.60 (1.07-2.41)	3.14 (1.91-5.16)
- High	1.00	1.17 (0.62-2.19)	1.47 (0.68-3.15)
Alcohol-related disease:			
- No	1.00	1.30 (0.94-1.81)	3.37 (2.30-4.92)
- Yes	1.00	2.61 (1.43-4.76)	1.67 (0.88-3.10)

* Mutually adjusted for gender, age, type of admission, cancer stage, type of surgery, comorbidity level, and alcohol-related disease.

5.2 Study II

5.2.1 Characteristics

We identified 233 (1.6%) patients with non-cirrhotic liver disease, 91 (0.6%) patients with liver cirrhosis, and 14,084 (97.8%) patients without liver disease who underwent DD surgery. Median age at DD surgery was 64 years among patients with non-cirrhotic liver disease, 60 years among those with liver cirrhosis, and 67 years among patients without liver disease. Patients with liver disease, especially those with liver cirrhosis, were more likely to be male, to have never married, to have a stoma placed during surgery, and to have comorbid conditions, including alcohol-related disease than patients without liver disease (Table 5.4).

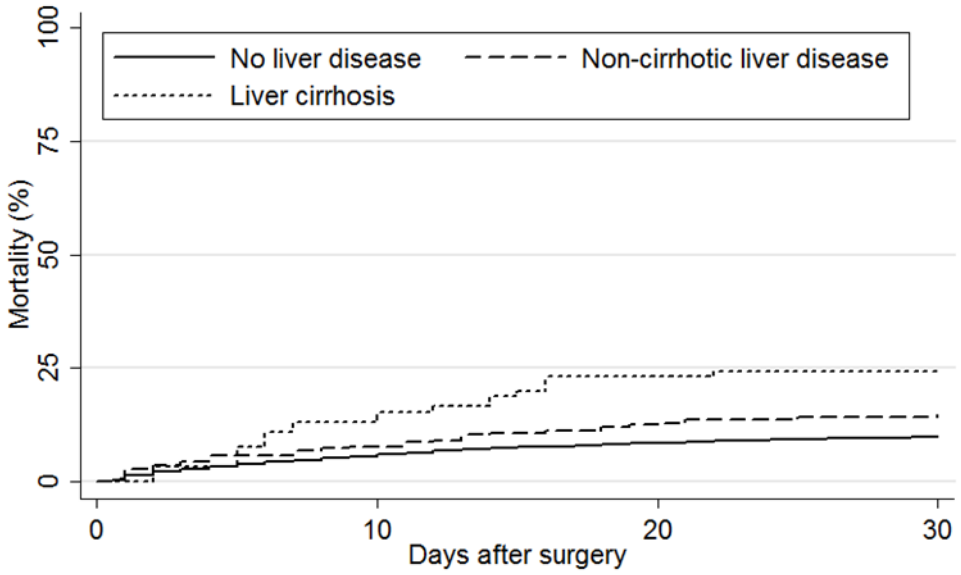
Table 5.4. Characteristics of patients with and without liver disease undergoing surgery for diverticular disease in Denmark, 1977-2011.

	No liver disease n = 14,084 (%)	Non-cirrhotic liver disease n = 233 (%)	Liver cirrhosis n = 91 (%)
Gender			
- Male	5,966 (42.4)	106 (45.5)	53 (58.2)
- Female	8,118 (57.6)	127 (54.5)	38 (41.8)
Age (years)			
- 0-59	4,489 (32.9)	85 (36.5)	45 (49.5)
- 60-69	3,636 (25.8)	67 (28.7)	21 (23.1)
- 70+	5,959 (42.3)	81 (34.8)	25 (27.5)
Period of surgery			
- 1977-1993	6,597 (46.8)	76 (32.6)	38 (41.8)
- 1994-2011	7,487 (53.2)	157 (67.4)	53 (58.2)
Type of admission			
- Non-elective	8,828 (62.7)	146 (62.7)	62 (68.1)
- Elective	5,220 (37.1)	86 (36.9)	29 (31.9)
- Missing	36 (0.3)	1 (0.4)	0
Type of surgery			
- Surgery without stoma	8,756 (62.2)	127 (54.5%)	47 (51.6)
- Surgery with stoma	5,328 (37.8)	106 (45.5%)	44 (48.4)
Comorbidity level			
- Low	9,209 (65.4)	121 (51.9)	39 (42.9)
- Moderate	3,790 (26.9)	79 (33.9)	39 (42.9)
- High	1,085 (7.7)	33 (14.2)	13 (14.3)
Alcohol-related disease present	367 (2.6)	45 (19.3)	39 (42.9)
Marital status			
- Married	7,641 (54.3)	134 (57.5)	39 (42.9)
- Never married	1,142 (8.1)	25 (10.7)	17 (18.7)
- Other	5,301 (37.6)	74 (31.8)	35 (38.4)
Previous admissions for diverticular disease			
- None	9,467 (67.2)	138 (59.2)	65 (71.4)
- 1 or 2 admissions	3,512 (24.9)	73 (31.3)	19 (20.9)
- More than 2	1,105 (7.8%)	22 (9.4)	7 (7.7)

5.2.2 Postoperative mortality

Thirty-day mortality was 14.6% in patients with non-cirrhotic liver disease and 24.2% in patients with liver cirrhosis, compared with 9.9% in patients without liver disease (Table 5.5 and Figure 5.2). This corresponded to adjusted HRs of 1.64 (95% CI: 1.16-2.31) for patients with non-cirrhotic liver disease and 2.70 (95% CI: 1.73-4.22) for patients with liver cirrhosis, compared with patients without liver disease (Table 5.5).

Figure 5.2. Crude 30-day survival curves for patients undergoing diverticular disease surgery without liver disease, with non-cirrhotic liver disease, and with liver cirrhosis.



Among patients surviving 30 days after DD surgery, mortality in the following 30 days was 3.0% among those with non-cirrhotic liver disease, 7.3% among those with liver cirrhosis, compared with 2.5% among patients without liver disease. Among patients surviving the first 60 days, mortality in the third month was between 1% and 2% in all three cohorts. Although the estimates were imprecise, the impact of liver disease on mortality was increased up to 60 days after DD surgery corresponding with a HR of 1.58 (95% CI: 0.69-3.54) for patients with non-cirrhotic liver disease and 5.19 (95% CI:1.96-13.72) for patients with liver cirrhosis (Supplementary Table 2 of paper II).

Table 5.5. Thirty-day mortality and corresponding hazard ratios (HRs) with 95% confidence intervals (CIs) in patients with and without liver disease undergoing diverticular disease surgery.

	No. of patients	No. of deaths	30-day mortality % (95% CI)	HR (95% CI) Crude	HR (95% CI) Adjusted*
Diverticular disease surgery:					
- No liver disease	14,084	1,400	9.9 (9.5-10.5)	1.00	1.00
- Non-cirrhotic liver disease	233	34	14.6 (10.7-19.8)	1.50 (1.07-2.11)	1.64 (1.16-2.31)
- Liver cirrhosis	91	22	24.2 (16.6-34.4)	2.62 (1.72-3.99)	2.70 (1.73-4.22)
1977-1993:					
- No liver disease	6,597	556	8.4 (7.8-9.1)	1.00	1.00
- Non-cirrhotic liver disease	76	8	10.5 (5.4-20.0)	1.27 (0.63-2.54)	1.48 (0.73-3.00)
- Liver cirrhosis	38	8	21.1 (11.1-37.7)	2.67 (1.33-5.36)	3.25 (1.53-6.89)
1994-2011:					
- No liver disease	7,487	844	11.3 (11.0-12.0)	1.00	1.00
- Non-cirrhotic liver disease	157	26	16.6 (11.6-23.4)	1.50 (1.02-2.22)	1.69 (1.13-2.51)
- Liver cirrhosis	53	14	26.4 (16.6-40.5)	2.52 (1.49-4.28)	2.42 (1.39-4.21)
Non-elective surgery: ¥					
- No liver disease	8,828	1,279	14.5 (13.8-15.3)	1.00	1.00
- Non-cirrhotic liver disease	146	32	21.9 (16.0-29.5)	1.57 (1.11-2.24)	1.72 (1.20-2.45)
- Liver cirrhosis	62	21	33.9 (23.6-47.1)	2.59 (1.69-3.99)	2.68 (1.70-4.24)
Elective surgery: ¥					
- No liver disease	5,220	120	2.3 (1.9-2.7)	1.00	1.00
- Non-cirrhotic liver disease	86	2	2.3 (0.6-9.0)	1.01 (0.25-4.09)	0.83 (0.20-3.39)
- Liver cirrhosis	29	1	3.5 (0.5-22.1)	1.50 (0.21-10.73)	2.27 (0.30-17.14)

* Mutually adjusted for gender, age (both as a continuous and a categorical variable), type of admission, type of surgery, comorbidity level, alcohol-related disease, and marital status.

¥ Information on type of admission is missing for some patients therefore the sum of patients undergoing non-elective and elective surgery is not equal to the number of all patients included in the study.

5.2.3 Reoperation rates

Reoperation rates within the first 30 days after DD surgery did not greatly differ among study cohorts. Among patients with non-cirrhotic liver disease, 10.7% (95% CI: 7.2%-15.1%) underwent reoperation and among those with liver cirrhosis 7.7% (95% CI: 3.4%-14.3%) underwent reoperation, compared to 8.3% (95% CI: 7.8%-8.7%) among patients without liver disease.

5.2.4 Stratified analyses

As expected, in each cohort 30-day mortality was markedly higher among DD patients with a non-elective admission than among those electively admitted (Table 5.5). Thirty-day mortality stratified by calendar period of DD surgery was higher for the period 1994-2011 than for the period 1977-1993 (Table 5.5). The impact of liver disease remained substantially increased in the different subgroups of patients although the low number of deaths among liver disease patients in each

stratum resulted in imprecise estimates (Table 5.6). Notably, in patients with liver cirrhosis, the risk of mortality is particularly increased among those younger than 60 years, among those undergoing surgery without stoma creation, among those with low comorbidity, among those without alcohol-related disease or never married (Table 5.6).

Table 5.6. Mortality hazard ratios (HRs) with 95% confidence intervals (CIs) for 30-day mortality after diverticular disease surgery in subgroups of patients with liver disease.

	No liver disease	Non-cirrhotic liver disease Adjusted* HR (95%CI)	Liver cirrhosis Adjusted* HR (95%CI)
Gender:			
- Male	1.00	2.01 (1.22-3.31)	3.07 (1.55-6.05)
- Female	1.00	1.40 (0.86-2.27)	2.50 (1.38-4.54)
Age (years):			
- 0-59	1.00	1.42 (0.51-3.96)	4.66 (2.10-10.37)
- 60-69	1.00	2.89 (1.59-5.26)	1.96 (0.70-5.48)
- 70+	1.00	1.34 (0.84-2.15)	2.43 (1.26-4.67)
Type of surgery:			
- Surgery without stoma	1.00	1.66 (0.84-3.28)	3.34 (1.58-7.07)
- Surgery with stoma	1.00	1.64 (1.10-2.45)	2.38 (1.37-4.16)
Comorbidity level:			
- Low	1.00	1.54 (0.77-3.07)	4.41 (1.97-9.84)
- Moderate	1.00	1.92 (1.14-3.23)	2.42 (1.22-4.83)
- High	1.00	1.40 (0.74-2.65)	2.18 (0.92-5.18)
Alcohol-related disease:			
- Yes	1.00	0.51 (0.16-1.64)	1.18 (0.50-2.79)
- No	1.00	1.91 (1.34-2.74)	4.11 (2.50-6.76)
Marital status:			
- Married	1.00	1.88 (1.20-2.94)	2.31 (0.91-5.86)
- Never married	1.00	1.79 (0.65-4.94)	4.05 (1.79-9.16)
- Other	1.00	1.22 (0.64-2.31)	2.36 (1.21-4.60)
Previous admissions for diverticular disease			
- None	1.00	1.67 (1.11-2.53)	3.59 (2.25-5.73)
- 1 or 2 admissions	1.00	2.62 (1.27-5.42)	0.43 (0.06-3.30)
- More than 2	1.00	0.95 (0.23-4.00)	2.06 (0.27-15.53)

* Mutually adjusted for gender, age (both as a continuous and a categorical variable), type of admission, type of surgery, comorbidity level, alcohol-related disease, and marital status.

5.3 Study III

5.3.1 Characteristics

We identified 10,347 patients undergoing first-time CRC surgery in the study period (Table 5.7, Table 5.8, and Figure 5.3). Of those, 9,339 (90.3%) had at least one measurement of HSA in the thirty days before surgery and 9,669 (82.0%) in the week before surgery. Among patients with preoperative HSA, the prevalence of HSA below 35 g/L was 26.4% (n = 2,464). The prevalence of women, old patients, and colon cancers increased according with the decrease in HSA. Moreover, patients with HSA below 40 g/L were more likely to be non-electively admitted, to have metastasized CRC, to undergo non-resectional surgery, and to have comorbid conditions than patients with HSA greater than 40 g/L. Information on other preoperative blood tests and MELD score for each patient cohort is reported in Table 5.8. Characteristics of patients with missing preoperative HSA (n = 1,008) are reported in Table 5.7, 5.8, and in Supplementary Table 3 (paper III).

Figure 5.3. Flow chart of patient selection.

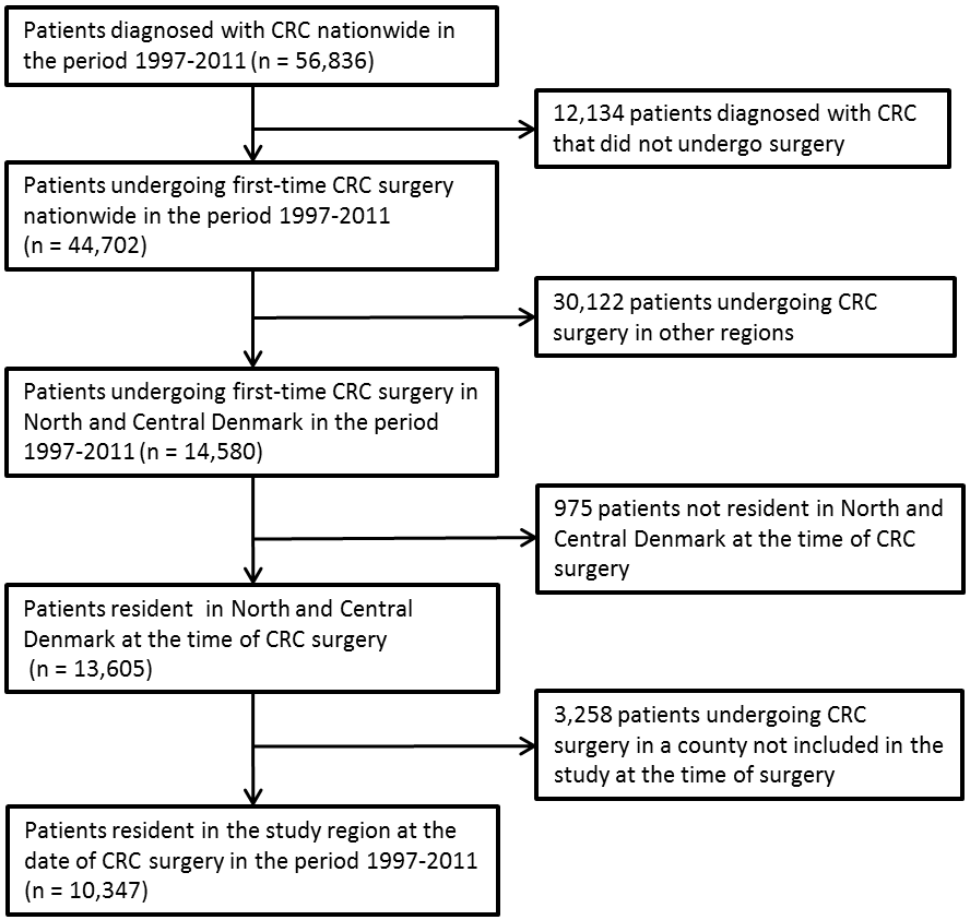


Table 5.7 Characteristics of patients undergoing surgery for colorectal cancer surgery.

	Serum albumin concentration					
	Hypoalbuminemia			Normal albuminemia		Missing albumin
	Severe ≤ 25 g/L n = 401 (%)	Moderate 26-30 g/L n = 784 (%)	Mild 31-35 g/L n = 1,742 (%)	Low 36-40 g/L n = 3,065 (%)	High > 40 g/L n = 3,347 (%)	n = 1,008 (%)
Gender:						
- Male	143 (35.7)	371 (47.3)	844 (48.5)	1,660 (54.2)	1,910 (57.1)	514 (51.0)
- Female	258 (64.3)	413 (52.7)	898 (51.5)	1,405 (45.8)	1,437 (42.9)	494 (49.0)
Median age (IQR):	76 (68-82)	76 (68-82)	75 (65-81)	71 (63-78)	67 (59-74)	71 (61-79)
Age (%):						
- <60 years	48 (12.0)	64 (8.2)	234 (13.4)	549 (17.9)	857 (25.6)	210 (20.8)
- 60-69 years	60 (15.0)	170 (21.7)	380 (21.8)	824 (26.9)	1,122 (33.5)	237 (23.5)
- 70-79 years	154 (38.4)	280 (35.7)	605 (34.7)	1,064 (34.7)	990 (29.6)	317 (31.4)
- >=80 years	139 (34.7)	270 (34.4)	523 (30.0)	628 (20.5)	378 (11.3)	244 (24.2)
Type of admission:						
- Elective	122 (30.4)	348 (44.4)	1,128 (64.8)	2,544 (83.0)	3,118 (93.2)	534 (53.0)
- Non-elective	279 (69.6)	435 (55.5)	612 (35.1)	516 (16.8)	227 (6.8)	465 (46.1)
- Missing	0	1 (0.1)	2 (0.1)	5 (0.2)	2 (<0.1)	9 (0.9)
Cancer site:						
- Colon	302 (75.3)	599 (76.4)	1,212 (69.6)	1,856 (60.6)	1,689 (50.5)	779 (77.3)
- Rectum	99 (24.7)	185 (23.6)	530 (30.4)	1,209 (39.4)	1,658 (49.5)	229 (22.7)
Cancer stage:						
- Localized	124 (30.9)	251 (32.0)	671 (38.5)	1,287 (42.0)	1,517 (45.3)	385 (38.2)
- Regional	98 (24.4)	205 (26.2)	460 (26.4)	841 (27.4)	1,051 (31.4)	299 (29.7)
- Metastasized	119 (29.7)	215 (27.4)	365 (21.0)	527 (17.2)	340 (10.2)	206 (20.4)
- Unknown	60 (15.0)	113 (14.4)	246 (14.1)	410 (13.4)	439 (13.1)	118 (11.7)
Type of surgery:						
- Open radical resection	266 (66.3)	579 (73.9)	1,369 (78.6)	2,470 (80.6)	2,546 (76.1)	721 (71.5)
- Laparoscopic radical resection	4 (1.0)	7 (0.9)	65 (3.7)	271 (8.8)	541 (16.2)	121 (12.0)
- Non-eradicative procedures	131 (32.7)	198 (25.3)	308 (17.7)	324 (10.6)	260 (7.8)	166 (16.5)
Comorbidity:						
- Low	207 (51.6)	377 (48.1)	932 (53.5)	1,763 (57.5)	2,159 (64.5)	656 (65.1)
- Moderate	134 (33.4)	278 (35.5)	587 (33.7)	964 (31.5)	918 (27.4)	268 (26.6)
- High	60 (15.0)	129 (16.5)	223 (12.8)	338 (11.0)	270 (8.1)	84 (8.3)
Alcohol-related disease:						
- No	386 (96.3)	764 (97.4)	1,707 (98.0)	3,017 (98.4)	3,290 (98.3)	988 (98.0)
- Yes	15 (3.7)	20 (2.6)	35 (2.0)	48 (1.6)	57 (1.7)	20 (2.0)
Marital status:						
- Married	172 (42.9)	359 (45.8)	855 (49.1)	1,731 (56.5)	2,139 (63.9)	516 (51.2)
- Never married	40 (10.0)	55 (7.0)	137 (7.9)	218 (7.1)	214 (6.4)	82 (8.1)
- Other	189 (47.1)	370 (47.2)	750 (43.1)	1,116 (36.4)	994 (29.7)	410 (40.7)

Abbreviations: interquartile range (IQR)

Table 5.8. Preoperative blood measurements in patients undergoing surgery for colorectal cancer surgery.

	Serum albumin concentration					
	Hypoalbuminemia			Normal albuminemia		Missing albumin
	Severe	Moderate	Mild	Low	High	
	≤ 25 g/L	26-30 g/L	31-35 g/L	36-40 g/L	> 40 g/L	
	n = 401	n = 784	n = 1,742	n = 3,065	n = 3,347	n = 1,008
Albumin, g/L						
- Mean (SD)	22.0 (3.0)	28.4 (1.4)	33.3 (1.4)	38.1 (1.4)	43.4 (2.1)	-
- Median (IQR)	23 (21-24)	29 (27-30)	34 (32-35)	38 (37-39)	43 (42-45)	-
Hemoglobin, mmol/L						
- Median (IQR)	6.6 (6.1-7.6)	6.9 (6.3-7.6)	7.3 (6.5-8.0)	7.9 (7.1-8.7)	8.5 (7.8-9.1)	8.0 (7.1-8.8)
- Missing, n (%)	0	2 (0.3)	3 (0.2)	10 (0.3)	8 (0.2)	553 (54.9)
Na^+, mmol/L:						
- Median (IQR)	137 (134-139)	137 (135-140)	139 (137-141)	140 (138-142)	140 (139-142)	140 (137-141)
- Missing, n (%)	0	2 (0.3)	2 (0.1)	3 (0.1)	2 (0.1)	572 (56.8)
K^+, mmol/L:						
- Median (IQR)	3.8 (3.4-4.2)	3.9 (3.5-4.3)	4.0 (3.7-4.3)	4.1 (3.8-4.3)	4.1 (3.8-4.3)	4.0 (3.7-4.3)
- Missing, n (%)	0	3 (0.4)	2 (0.1)	3 (0.1)	1 (<0.1)	569 (56.5)
Leukocytes, 10^9/L:						
- Median (IQR)	11.2 (8.5-15.1)	10.0 (7.8-13.2)	8.8 (6.9-11.2)	8.0 (6.5-9.9)	7.4 (6.1-9.0)	9.1 (6.9-11.8)
- Missing n (%)	28 (7.0)	82 (10.5)	359 (20.6)	846 (27.6)	945 (28.2)	752 (74.6)
Creatinine, µmol/L:						
- Median (IQR)	68 (55-85)	74 (61-93)	78 (66-93)	79 (68-95)	77 (67-90)	78 (67-91)
- Missing, n (%)	0	1 (0.1)	0	5 (0.2)	1 (<0.1)	556 (55.2)
CRP, mg/L:						
- Median (IQR)	85 (41-146)	51 (24-102)	26 (10-62)	10 (10-26)	10 (8-10)	19 (10-55)
- Missing n (%)	40 (10.0)	121 (15.4)	460 (26.4)	1,019 (33.3)	1,054 (31.5)	812 (80.6)
Platelet, 10^9/L:						
- Median (IQR)	411 (309-537)	392 (300-514)	353 (278-455)	316 (250-398)	290 (242-353)	324 (253-417)
- Missing, n (%)	80 (20.0)	197 (25.1)	537 (30.8)	1,027 (33.5)	1,065 (31.8)	818 (81.2)
INR:						
- Median (IQR)	1.2 (1.1-1.3)	1.1 (1.0-1.2)	1.0 (1.0-1.1)	1.0 (1.0-1.1)	1.0 (0.9-1.1)	1.1 (1.0-1.2)
- Missing, n (%)	121 (30.2)	276 (35.2)	682 (39.2)	1,162 (37.9)	1,123 (33.6)	845 (83.8)
Bilirubin, µmol/L:						
- Median (IQR)	9 (6-13)	8 (6-13)	8 (5-11)	8 (6-11)	8 (6-11)	10 (7-12)
- Missing, n (%)	72 (18.0)	214 (27.3)	625 (35.9)	1,130 (36.9)	1,036 (31.0)	821 (81.5)
ALAT, U/L:						
- Median (IQR)	17 (11-28)	17 (12-28)	17 (12-25)	17 (13-25)	20 (15-27)	18 (13-28)
- Missing, n (%)	135 (33.7)	324 (41.33)	812 (46.6)	1,410 (46.0)	1,204 (36.0)	815 (80.9)
MELD:						
- < 10, n (%)	177 (44.1)	331 (42.2)	720 (41.3)	1,308 (42.7)	1,742 (52.1)	100 (9.9)
- ≥ 10, n (%)	76 (19.0)	97 (12.4)	120 (6.9)	200 (6.5)	127 (3.8)	20 (2.0)
- Missing, n (%)	148 (36.9)	356 (45.4)	902 (51.8)	1,557 (50.8)	1,478 (44.16)	888 (88.1)

Abbreviations: interquartile range (IQR), C-reactive protein (CRP), International Normalized Ratio (INR), model for end-stage liver disease (MELD)

5.3.2 Postoperative mortality

Overall 30-day mortality was 2.0% in patients with HSA above 40 g/L and increased from 4.9% in patients with HSA 36-40 g/L to 26.9% in patients with HSA equal to or below 25 g/L (Table 5.9 and Figure 5.4). Corresponding adjusted HRs increasing from 1.75 (95% CI: 1.25-2.46) among patients with HSA 36-40 g/L to 7.59 (95% CI: 4.95-11.64) among patients with HSA equal to or below 25 g/L, compared to patients with HSA above 40.0 g/L (Table 5.9). Age and admission type were largely responsible for the change in estimates by adjustment. The strong concentration-response pattern of HSA impact on 30-day mortality was also showed by the fractional polynomials analysis (Figure 5.5A).

5.3.3 Reoperation and acute kidney injury

Reoperation rates within the first 30 days after CRC surgery were approximately 10% in all study cohorts (Table 5 in paper III). AKI rates within the 30 days after CRC surgery gradually increased from 19.5% among patients with HSA above 40 g/L to 29.2% among patients with HSA below or equal to 25 g/L. Compared to patients with HSA above 40g/L, adjusted HRs for reoperation and AKI in patients with HSA equal to or below 25 g/L were 2.09 (95% CI: 1.41-3.08) and 1.64 (95% CI: 1.28-2.11), respectively (Figure 5.5, panel C and D; Table 5 of paper III).

5.3.4 Stratified analyses

Stratified analyses showed that decreasing levels of HSA were associated with an increase of 30-day mortality also in subgroups of patients (Table 5.10). The same pattern was observed in patients with different levels of CRP or with MELD score above or below 10. Consistent with the overall results, the stratified adjusted HRs showed that the impact of HSA on 30-day mortality increased with the decrement in the HSA concentration although the estimates were imprecise (Table 5.10). Decrement in HSA was associated with increased risk of 30-day mortality also among patients with different CRP levels (Table 5.10 and Figure 5.5B). However, 95% CIs often included the unit.

Figure 5.4. Crude 30-day mortality curves for patients undergoing surgery for colorectal cancer according to preoperative serum albumin concentration.

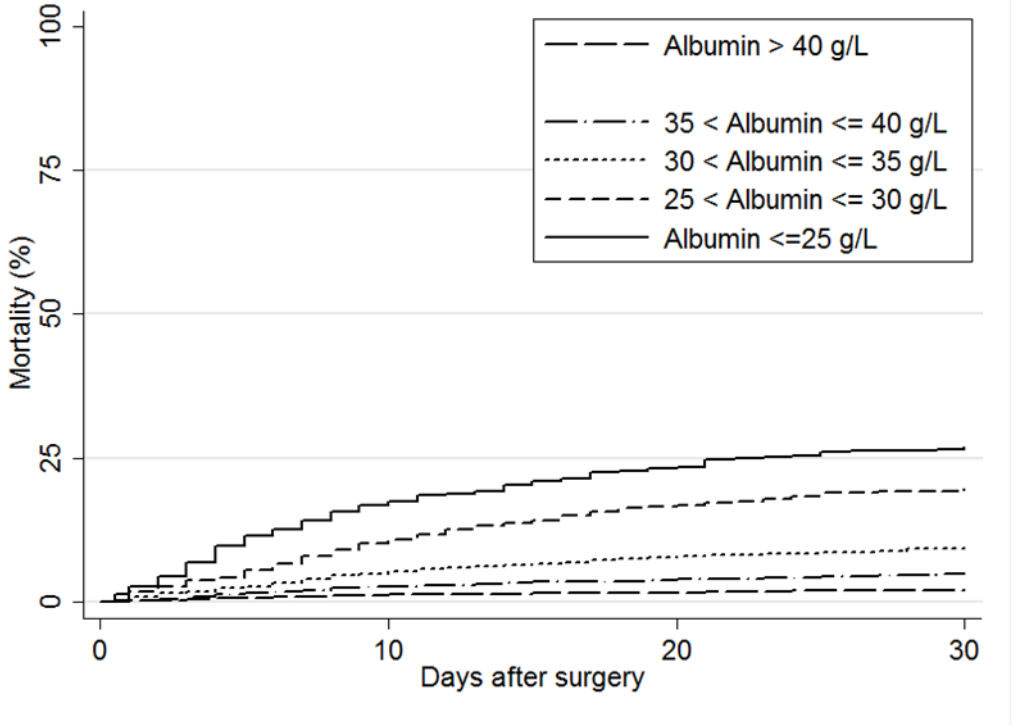


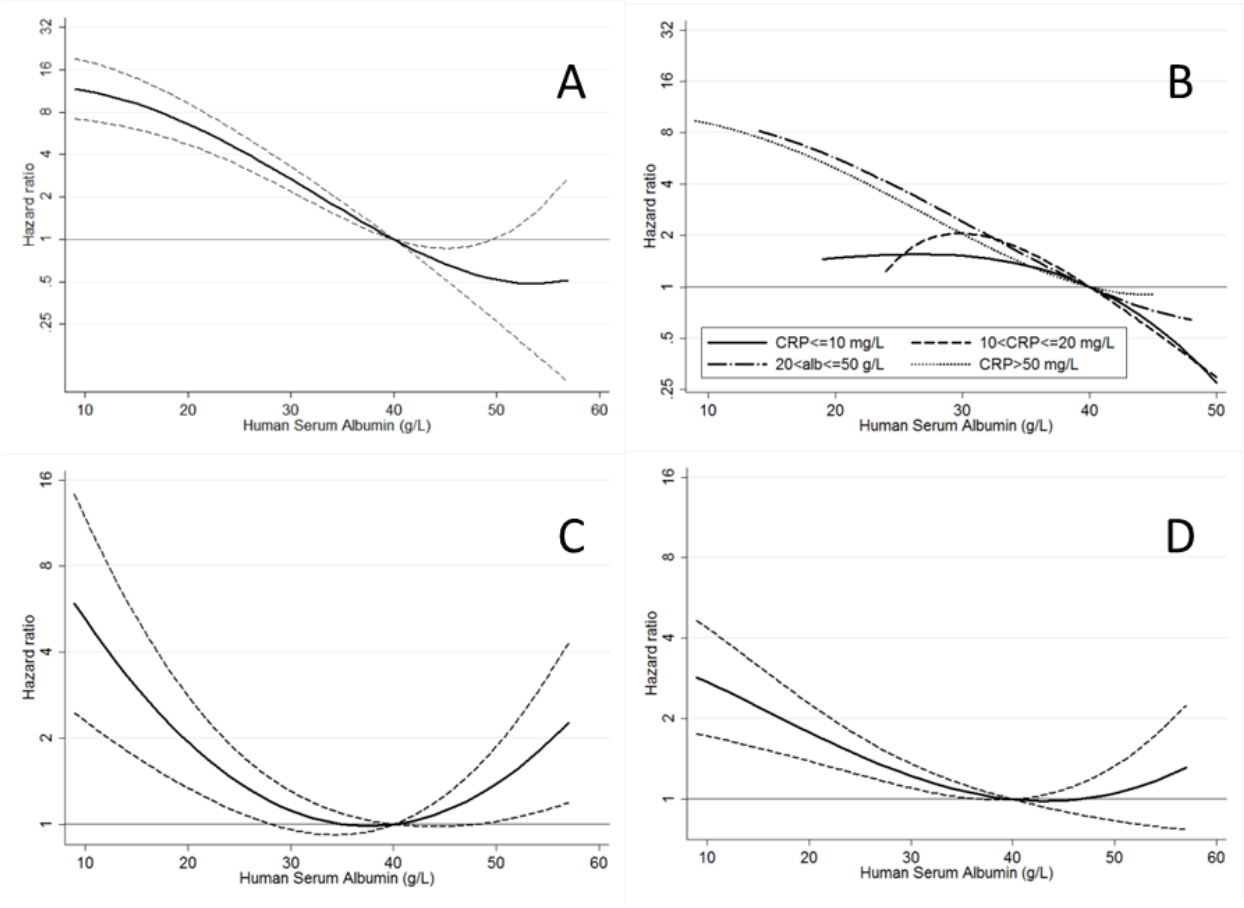
Table 5.9. Thirty-day mortality and corresponding hazard ratios (HRs) with 95% confidence intervals (CIs) in patients with different preoperative serum albumin concentration undergoing surgery because of colorectal cancer.

	No. of patients	No. of deaths	30-day mortality %* (95% CI)	HR (95% CI) Crude	HR (95% CI) Adjusted‡
Colorectal cancer surgery					
- Albumin ≤ 25 g/L	401	108	26.9 (22.9-31.6)	15.89 (11.69-21.59)	7.59 (4.95-11.64)
- Albumin 26-30 g/L	784	154	19.6 (17.0-22.6)	10.91 (8.18-14.56)	5.19 (3.53-7.63)
- Albumin 31-35 g/L	1,742	163	9.4 (8.1-10.8)	4.92 (3.70-6.56)	2.58 (1.80-3.69)
- Albumin 36-40 g/L	3,065	149	4.9 (4.2-5.7)	2.50 (1.87-3.34)	1.75 (1.25-2.45)
- Albumin > 40 g/L	3,347	66	2.0 (1.6-2.5)	1.00	1.00

*Calculated using the Kaplan-Meier method.

‡ Mutually adjusted for gender, age (both as a continuous and a categorical variable), type of admission, operation year, county, cancer site, cancer stage (excluded patients with stage "unknown"), comorbidity level, alcohol-related disease, liver disease, marital status, hemoglobin, Na^+, K^+, creatinine (number of observations with complete data = 8,033).

Figure 5.5. Adjusted hazard ratios associated with preoperative HSA concentration for 30-day mortality, overall (A) and stratified by C-reactive protein (CRP) levels (B), reoperation (C), and acute kidney injury (D). Adjusted HRs in panel A, C, and D are provided with 95% confidence interval (dash lines).



5.3.5 Sensitivity analysis

The impact of preoperative HSA concentration on 30-day mortality was similar after imputation of missing HSA measurements before CRC surgery. The adjusted 30-day HRs were 7.50 (95% CI: 5.10-11.03) for HSA below 25 g/L, 4.99 (95% CI: 3.51-7.10) for HSA 26-30 g/L, 2.76 (95% CI: 2.00-3.79) for HSA 31-35 g/L, and 1.78 (95% CI: 1.32-2.40) for HSA 36-40 g/L, compared to HSA above 40 g/L.

Table 5.10. Thirty-day mortality and corresponding adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) in subgroups of patients with different preoperative serum albumin concentration undergoing surgery because of colorectal cancer.

	Serum albumin concentration									
	≤ 25 g/L		26-30 g/L		31-35 g/L		36-40 g/L		> 40 g/L	
	30-day mortality* % (n)	Adjusted HR‡ (95% CI)	30-day mortality* % (n)	Adjusted HR‡ (95% CI)	30-day mortality* % (n)	Adjusted HR‡ (95% CI)	30-day mortality* % (n)	Adjusted HR‡ (95% CI)	30-day mortality* % (n)	Reference group
Gender:										
- Male	30.1% (43)	8.23 (4.49-15.09)	24.5% (91)	5.79 (3.45-9.71)	10.3% (87)	2.68 (1.65-4.35)	5.2% (86)	1.73 (1.11-2.71)	1.9% (37)	1.00
- Female	25.2% (65)	6.79 (3.65-12.63)	15.3% (63)	4.28 (2.39-7.65)	8.5% (76)	2.29 (1.39-3.92)	4.5% (63)	1.64 (0.99-2.72)	2.0% (29)	1.00
Age (years):										
- <60 years	12.5% (6)	7.39 (1.32-41.22)	14.1% (9)	11.84 (2.65-52.97)	3.9% (9)	2.18 (0.51-9.35)	1.8% (10)	2.29 (0.69-7.61)	0.6% (5)	1.00
- 60-69 years	15.0% (9)	6.63 (2.13-20.61)	15.3% (26)	4.75 (1.77-12.76)	5.5% (21)	2.55 (1.03-6.31)	2.1% (17)	1.34 (0.57-3.15)	1.1% (12)	1.00
- 70-79 years	27.9% (43)	8.76 (4.40-17.44)	19.3% (54)	5.23 (2.79-9.77)	7.6% (46	2.12 (1.19-3.80)	4.6% (49)	1.41 (0.83-2.40)	2.7% (27)	1.00
- >=80 years	36.0% (50)	7.09 (3.50-14.36)	24.1% (65)	4.57 (2.40-8.68)	16.6% (87))	2.66 (1.46-4.85)	11.6% (73)	2.17 (1.22-3.86)	5.8% (22)	1.00
Type of admission:										
- Non-elective	28.0% (78)	7.78 (3.17-19.12)	21.2%	5.36 (2.23-12.88)	11.9%	2.68 (1.12-6.44)	9.7%	2.32 (0.97-5.55)	4.0%	1.00
- Elective	24.6% (30)	8.08 (4.45-14.67)	17.8%	5.31 (3.27-8.62)	8.0%	2.56 (1.68-3.90)	3.9%	1.52 (1.04-2.21)	1.8%	1.00
Cancer site:										
- Colon	29.8% (90)	6.68 (4.01-11.14)	18.4% (110)	3.96 (2.47-6.34)	9.2% (112)	2.05 (1.32-3.20)	5.2% (96)	1.43 (0.94-2.19)	2.4% (41)	1.00
- Rectum	18.2% (18)	8.90 (3.77-21.05)	23.8% (44)	10.76 (5.40-21.44)	9.6% (51)	3.83 (2.06-7.12)	4.4% (53)	2.52 (1.44-4.41)	1.5% (25)	1.00
Cancer stage:										
- Localized	17.7% (22)	4.22 (2.14-8.36)	16.7% (42)	4.02 (2.25-7.19)	7.2% (48)	2.08 (1.24-3.46)	4.8% (62)	1.74 (1.10-2.73)	2.1% (32)	1.00
- Regional	25.5% (25)	11.01 (4.44-27.33)	15.1% (31)	5.88 (2.65-13.07)	7.8% (36)	3.90 (1.88-8.11)	3.7% (31)	2.11 (1.05-4.25)	1.2% (13)	1.00
- Metastasized	38.7% (46)	10.61 (4.72-23.88)	27.9% (60)	6.58 (3.05-14.18)	11.8% (43)	2.64 (1.25-5.58)	5.7% (30)	1.53 (0.74-3.19)	2.9% (10)	1.00
Year of surgery:										
- 1997-2005	29.8% (78)	4.40 (2.52-7.67)	20.4% (95)	3.03 (1.82-5.05)	8.2% (82)	1.39 (0.85-2.28)	4.5% (68)	1.05 (0.66-1.68)	3.1% (28)	1.00
- 2006-2011	21.6% (30)	10.11 (5.17-19.79)	18.5% (59)	8.49 (4.84-14.92)	11.0% (81)	4.90 (2.94-8.15)	5.2% (81)	2.81 (1.76-4.49)	1.6% (38)	1.00
Type of surgery:										
- Open radical resection	24.8% (66)	5.32 (3.26-8.68)	16.2% (94)	3.43 (2.21-5.30)	8.6% (118)	2.03 (1.37-3.01)	4.9% (120)	1.52 (1.06-2.18)	2.2% (57)	1.00
- Laparoscopic radical resection	0%	-	14.3% (1)	-	7.7% (5)	9.13 (1.32-63.34)	3.3% (9)	3.19 (0.74-13.78)	0.7% (4)	1,00
- Non-eradicative procedures	32.1% (42)	44.40 (9.48-207.97)	29.8% (59)	30.81 (6.91-41.59)	13.0% (40)	9.35 (2.10-41.59)	6.2% (20)	4.43 (0.98-20.05)	1.9% (5)	1,00

Table 5.10. Thirty-day mortality and corresponding adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) in subgroups of patients with different preoperative serum albumin concentration undergoing surgery because of colorectal cancer.

	Serum albumin concentration									
	≤ 25 g/L		26-30 g/L		31-35 g/L		36-40 g/L		> 40 g/L	
	30-day mortality* % (n)	Adjusted HR‡ (95% CI)	30-day mortality* % (n)	Adjusted HR‡ (95% CI)	30-day mortality* % (n)	Adjusted HR‡ (95% CI)	30-day mortality* % (n)	Adjusted HR‡ (95% CI)	30-day mortality* % (n)	Reference group
Comorbidity:										
- Low	23.7% (49)	7.87 (4.05-15.26)	15.9% (60)	5.39 (2.96-9.82)	6.6% (61)	1.91 (1.08-3.37)	2.8% (49)	1.22 (0.72-2.06)	1.3% (28)	1.00
- Moderate	29.9% (40)	9.36 (4.65-18.83)	23.0% (64)	6.68 (3.59-12.45)	10.9% (64)	3.31 (1.86-5.86)	6.6% (64)	2.10 (1.24-3.58)	2.9% (27)	1.00
- High	31.7% (19)	6.91 (2.45-19.53)	23.3% (30)	4.77 (1.91-11.94)	17.0% (38)	3.55 (1.51-8.34)	10.7% (36)	2.84 (1.25-6.43)	4.1% (11)	1.00
Marital status:										
- Married	27.3% (47)	11.09 (5.95-20.66)	20.1% (72)	6.70 (3.83-11.74)	8.3% (71)	3.52 (2.11-5.89)	3.7% (64)	1.72 (1.06-2.79)	1.5% (31)	1.00
- Never married	25.0% (10)	10.50 (1.72-64.07)	27.3% (15)	5.58 (1.05-29.76)	8.0% (11)	1.26 (0.27-5.87)	6.0% (13)	2.29 (0.59-8.79)	2.3% (5)	1.00
- Other	27.0% (51)	5.75 (3.03-10.92)	18.1% (67)	4.15 (2.32-7.41)	10.8% (81)	2.23 (1.30-3.81)	6.5% (72)	1.76 (1.06-2.91)	3.0% (30)	1.00
C-reactive protein:§										
- ≤ 10.0 mg/L	14.3% (2)	5.33 (1.06-26.83)	9.5% (7)	1.81 (0.57-5.76)	6.2% (20)	1.88 (0.88-4.00)	4.1% (41)	1.48 (0.82-2.67)	1.6% (29)	1.00
- 10.1-20.0 mg/L	13.8% (4)	4.31 (0.87-21.32)	9.7% (7)	1.91 (0.53-6.85)	12.2% (27)	3.09 (1.21-7.86)	6.7% (27)	1.93 (0.83-4.50)	3.6% (11)	1.00
- 20.1-50.0 mg/L	23.6% (17)	7.47 (2.22-25.08)	21.0% (38)	7.26 (2.40-22.00)	9.6% (33)	3.38 (1.18-9.70)	5.6% (22)	1.88 (0.67-5.31)	2.7% (5)	1.00
- > 50.0 mg/L	29.3% (72)	4.19 (0.97-18.12)	26.5% (89)	3.63 (0.86-15.35)	13.4% (53)	1.36 (0.32-5.85)	10.6% (26)	1.44 (0.33-6.25)	8.1% (3)	1.00
MELD:¥										
- <10	23.2% (41)	7.06 (3.61-13.80)	18.1% (60)	5.20 (2.87-9.42)	9.2% (66)	2.74 (1.60-4.71)	4.5% (59)	1.63 (0.99-2.69)	1.9% (33)	1.00
- ≥ 10	43.4% (33)	9.22 (3.27-25.97)	43.4% (42)	8.62 (3.17-23.42)	19.2% (23)	2.75 (1.03-7.32)	15.5% (31)	2.36 (0.94-5.92)	6.3% (8)	1.00

*Calculated using the Kaplan-Meier method.

‡ Mutually adjusted for gender, age (both as a continuous and a categorical variable), type of admission, operation year (calendar year), county, cancer site, cancer stage (excluded patients with stage "unknown"), comorbidity level, alcohol-related disease, liver disease, marital status, hemoglobin, Na^+, K^+, creatinine (number of observations with complete data = 8,033).

§ Patients with preoperative C-reactive protein measurement = 6,841.

¥ Patients with preoperative MELD = 5,018.

6. Discussion

6.1 Main conclusions

In summary, we found that liver disease increased postoperative mortality after CRC and DD surgery (study I and II). Impact of liver disease on 30-day mortality was similar in both patients undergoing CRC and DD surgery, corresponding to approximately 1.5 among patients with non-cirrhotic liver disease and 2.5 among patients with liver cirrhosis compared with patients without liver disease. However, findings stratified by type of admission suggested that 30-day mortality in patients electively admitted is markedly higher among those undergoing CRC surgery than among patients undergoing DD surgery, both in patients with and without liver disease. The same difference was not found among patients undergoing non-elective surgery.

In study III, we found that HSA below 35 g/L was present in approximately 30% of patients undergoing first-time surgery for CRC. Thirty-day mortality after CRC surgery increased according with the decrease of preoperative HSA levels. In particular, we found that also a decrease in HSA within the reference interval was associated with an increased risk for mortality compared to patients with HSA above 40 g/L. Moreover, our results suggested that low preoperative HSA is associated with increased mortality both among patients at high and low prior risk. Our findings also showed that HSA below 30 g/L may increase risk of postoperative reoperation and AKI.

6.2 Methodological considerations

In all three studies of this dissertation, we examined causal associations between potential prognostic factors and outcomes. Before conclude any found association as a causal association we should question about the precision and validity of our estimates.[216]

By precise estimates, we refer to estimates with little random error (or play of chance) that we evaluated statistically by 95% CIs and presented in the result section. The size of our study cohorts, together with the relative large number of outcomes, yielded statistical precise estimates with relatively narrow CIs in the main analyses; therefore chance played a minimal role on our overall estimates. Nonetheless, in some stratified analyses, our results were prone to imprecision

and therefore more sensitive to chance. However, statistically imprecise estimates among exposed patients in those subgroups cannot be used to exclude any association (type II error).

Validity of the estimates refers to the absence of systematic errors or biases and it mostly corresponds with the ability of the measurement to describe the real association between the exposure and the outcome apart from random variation. In the following paragraphs, we identified and discussed possible sources of systematic errors that are usually defined as biases and classified into three general categories: selection bias, information bias, and confounding. While selection bias and information bias stem from the study design and can only be prevented during this phase, confounding can be handled both during the study design and during the statistical analysis.[41,217,218]

6.2.1 Selection bias

Selection bias could have mainly stemmed from procedures used to select subjects.[40] Selection bias would have determined a distortion of estimates of effect in case the association between a prognostic factor and 30-day mortality is different among included patients in comparison to patients not included.

All three studies in this dissertation were conducted in well-defined populations with uniform access to health care, using high-quality administrative and medical database. In addition, we had complete follow-up ensured by the Danish CRS as previously described.[198] These features minimized the risk of selection bias. Nonetheless, the criteria used to define CRC and DD surgery could have led us to not include patients undergoing surgery for those conditions and/or to include patients with colorectal surgery performed for other reasons. However, any improper inclusion or exclusion is unlikely to be associated with liver disease or HSA.

Moreover, within the different study periods, study I and II included nearly all patients undergoing colorectal surgery for CRC or DD, respectively, in Denmark.

In study lll, exclusion of patients without preoperative HSA measurement (n = 1,008) might have introduced selection bias. However, more than 50% of patients with missing HSA were also missing other routine blood tests such as hemoglobin, serum creatinine, K^+, and Na^+ suggesting that preoperative blood tests for these patients were not performed in a laboratory included in

the database. Moreover, estimates obtained using multiple imputation support the results from the complete series analysis. Last, we have no reasons to believe that the associations observed among study participants would be different among non-participants.

6.2.2 Information bias

We can have introduced information bias by obtaining erroneous information about liver disease, preoperative HSA concentration, and/or outcomes.[40] Both prognostic factors and outcomes were included in the studies as categories, and information error could have led to misclassification of patients into incorrect categories.

Liver disease

In study I and II, liver disease misclassification could have derived from incorrect coding of non-cirrhotic liver disease and liver cirrhosis. A previous validation study reported the positive predictive value (PPV) for liver cirrhosis diagnosis to be as high as 85%.[219] We expect high PPV also for patients with non-cirrhotic liver disease.[220] However, whereas patients with liver cirrhosis are likely to be diagnosed during preoperative examination or intraoperatively and therefore correctly categorized, patients with non-cirrhotic liver disease, especially among those with mild liver diseases, may remain undiagnosed. Consequently, completeness (i.e. sensitivity) among patients with non-cirrhotic liver disease might be lower than in patients with liver cirrhosis and we might have included patients with liver disease in the comparison cohort. Moreover, we cannot exclude that patients with liver cirrhosis where misclassified with non-cirrhotic liver disease and vice versa. In these circumstances, the impact on HRs is not predictable although it is more likely that we underestimated the effect of the category at highest risk, which is liver cirrhosis.[216]

Human serum albumin

In study III, patients with HSA below or equal to 40 g/L were considered exposed and different types of information bias could have arisen. Differences among and within laboratories could have led to classified patients with the same "real" HSA concentration in different groups. Unfortunately, it is difficult to examine the extent of this kind of misclassification since no standardization took place among and within laboratories during the study period. Since HSA was categorized in intervals of 5 g/L except for concentrations above 40 g/L and below 25 g/L, this type of misclassification is more likely to have affected patients with HSA between these two cut-off

points. Another type of information bias could have happened in patients with high inflammatory status. Indeed, a previous study reported in vitro and among hemodialysis patients that oxidative stress may impair HSA quantification by BCG (bromocresol green colorimetric method) estimating lower HSA concentration than the actual level.[221] This method has been used and is still used in some laboratories (*e.g.*, at Aarhus University Hospital) in the study region (personal communication with the Department of Clinical Biochemistry in Aarhus). Therefore, we could have categorized patients with high oxidative stress among patients with lower HSA than their actual concentration. This hypothesis may partially explain the finding that the interquartile range of CRP is 8-10 mg/L among patients with HSA above 40 g/L. However, no studies reported the degree of underestimation in HSA measurement according to CRP levels, therefore, we can only conclude that the impact of HSA concentration on study outcomes might have been underestimated.

Death

Postoperative mortality was the primary outcome in all three studies. Since the information on death was obtained from the CRS (described in section 4.2.1), which contains complete information on and the exact date of death, misclassification is unlikely.

Reoperations

In study II and III, misclassification of reoperations is difficult to estimate. We expect codes for reoperation having high PPV. However, sensitivity could be low since patients undergoing reoperation due to complications could have been coded with an operation code instead of one of the specific codes for reoperation. If so, we expected misclassification to be independent of the exposure, therefore it is more likely to have biased our estimates toward the null.

AKI

In study III, we assessed the risk of AKI as defined by change in plasma creatinine according to the creatinine criteria in the KDIGO classification.[209] Unfortunately, it is difficult to examine the extent of any misclassification because no gold standard exists. Moreover, renal tubular secretion of creatinine is increased in patients with low HSA leading to lower creatinine levels and, therefore, to overestimation of kidney function.[222] Hence, we may have underestimated the risk of postoperative AKI in patients with low HSA.

6.2.3 Confounding

Confounding can be defined as a distortion of the estimated impact of liver disease and HSA on postoperative complications. This distortion is caused by differences in patients with liver disease or with HSA below or equal to 40 g/L compared to patients without liver disease or with HSA above 40 g/L, respectively. It is therefore important to highlight that the concept of confounding is hypothesis specific. Hence, a potential confounder can be identified only in relation with the examined prognostic factor and the outcome. To fulfill the classical definition of a confounder, a variable should have the following characteristics: 1) be an independent cause of the outcome (or a proxy/marker for the cause); 2) be differently distributed across exposure categories; and 3) not be on the causal pathway between exposure and outcome.[216]

In all three studies, we dealt with well-known potential confounding such as age, gender, comorbidity level, and alcohol-related disease by adjustment and stratification. Moreover, we both adjusted and stratified by two more covariates relevant for our surgical settings: type of surgery and type of admission. We therefore were able to control for some relevant confounding factors. However, further confounding issues related to the specific hypothesis examined in each study may have biased our estimates.

Among patients undergoing CRC surgery, cancer stage and comorbidity are among the prognostic factors with the highest impact on short-term prognosis as described in the Background section. Moreover, patients with liver disease may have different risks of developing metastases (*e.g.*, liver metastases) than patients without liver disease. Similarly, they may differ from type and severity of comorbidity. In study I, although we controlled by cancer stage and comorbidity level, residual confounding may have biased our estimates. Moreover, unmeasured confounding such as smoking and medication use that are likely to be more frequent among patients with liver disease may have also biased our estimates. Despite these limitations and based on strength of association in study I, it is unlikely that these factors explain our results completely.

In study II, the main limitation was a lack of detailed information about patients with/without perforated DD, sepsis, or peritonitis prevented us from adjusting for severity of the DD. The finding of relatively low mortality after elective DD surgery in patients with liver disease may be partially explained by accurate selection of those patients with the lowest risk, especially among

patients with liver cirrhosis. However, patients with liver disease are well-known to be at increased risk of infection.[223] Therefore, liver disease may also increase risk of developing severe complicated DD. In this case, development of DD complication would have been an intermediate step; therefore, adjusting for DD severity would have been incorrect.

In study III, we investigated the impact of a pathophysiological mechanism on postoperative complications. Therefore, in order to eliminate all potential confounding we should have controlled for all other possible pathophysiological mechanisms and it would have been impossible even in an experimental setting. However, type of admission and age were responsible for almost the entire variation between crude and adjusted HRs suggesting that these two factors were also acting as surrogates of other confounders. Moreover, we also included in the fully adjusted model other laboratory tests (*i.e.*, hemoglobin, Na^+, K^+, and creatinine) as marker of undetected comorbidities and we stratified each cohort for CRP levels and MELD score. Although HSA is affected by other unmeasured or only partially measured conditions (*e.g.*, malnutrition, infection, alcohol consumption, and cancer stage) that may increase risk of postoperative complications through none albumin-related pathways, the strength of association and the "dose-response" pattern of HR are barely explained only by confounding.

6.3 In light of the existing literature

6.3.1 Study I and II

Thus, study I and II extend existing literature on 30-day mortality in patients with liver disease undergoing colorectal surgery using population-based samples and, furthermore, particularly by evaluating the impact of liver disease in subgroups of patients. Moreover, to our knowledge, our studies were the first to investigate 30-day mortality separately in patients with non-cirrhotic liver disease undergoing colorectal surgery. We confirmed that mortality among patients with liver disease, especially among those with liver cirrhosis, is higher than in patients without liver disease.[133-135] However, although overall absolute 30-day mortality was similar in the two studies, CRC patients undergoing elective surgery with and without liver disease had markedly higher mortality than DD patients. In both studies, the risk for 30-day mortality was approximately 1.5-fold and 2.5-fold higher in patients with non-cirrhotic liver disease and in patients with liver

cirrhosis, respectively, than in patients without liver disease. Compared to previous studies, our adjusted estimates tended to be similar to patients with liver cirrhosis without portal hypertension but markedly lower than among patients with liver cirrhosis and portal hypertension.[133-135] Aside from the fact that we were not able to categorize patients with and without portal hypertension, the difference may be partially explained by a higher mortality in the comparison cohorts in our studies than in the former ones. Moreover, earlier studies did not take into account the disease leading to surgery. No previous studies investigated prognosis after DD surgery in liver disease patients and no Danish studies investigated 30-day mortality after DD surgery in the general population. However, an English population-based study reported an overall 30-day mortality of 10.1% similar to our finding in patients without liver disease.[12] The reported postoperative 30-day mortality after elective and non-elective DD surgery was 2.1% and 15.9%, respectively. Finally, we were able to show that liver disease had an impact on mortality up to 60 days after DD surgery.

6.3.2 Study III

To our knowledge, our study was the first population-based study investigating the impact of preoperative HSA levels on 30-day mortality among patients undergoing CRC surgery. Our findings are supported by previous single-center studies investigating short-term prognosis in patients undergoing CRC surgery that reported an increased risk for postoperative complications among patients with HSA below 35 g/L compared to patients with HSA above 35 g/L.[181,183,188,192,195] Among previous studies, only one provided relative estimates reporting an increased risk of 2.15 (95% CI: 1.70-2.73) for 30-day mortality adjusting for potential confounding among patients with HSA below 35 g/L compared to HSA above 35 g/L.[182]

Furthermore, we showed that HSA increased the risk of 30-day mortality not exclusively when its concentration was below 35 g/L but that its impact on prognosis is strongly associated with its concentration and the risk of 30-day mortality gradually increased with the decrease of HSA even within the normal interval. To our knowledge, only two studies included HSA as a continuous or categorical variable to investigate if the impact of HSA on four- and five-year mortality after CRC surgery increased with the decrement in its concentration.[194,196]

In accordance with our findings of increased risk of reoperation and postoperative AKI in patients with low HSA, one study reported six-fold increased risk of anastomotic leakage in patients

undergoing CRC surgery with HSA below 35 g/L compared to HSA equal to or above 35 g/L[183] and a previous meta-analysis reported an increased risk for AKI of 2.06 (95% CI: 1.42-2.99) associated with 10 g/L decrement in HSA among patients who had undergone surgery or had been admitted to an intensive care unit.[33]

Finally, our results stratified by CRP suggested that decrement in HSA may still have a prognostic impact among patients with similar levels of CRP. More than 60 studies in the last decades have investigated the prognosis of cancer patients using the Glasgow prognostic score, an inflammation-based prognostic score that categorizes patients according to HSA below or above 35 g/L and CRP below or above 10 mg/L assigning a score that ranges from 0 to 2.[224] Those studies showed that the Glasgow prognostic score is able to predict long-term prognosis in cancer patients. Our results suggested that although the Glasgow prognostic score may help to identify patients undergoing CRC surgery at high risk of death, postoperative mortality among those patients may vary from approximately 10% to 30%.

7. Conclusions

The aim of this dissertation was to examine the impact of liver disease and HSA on short-term prognosis among Danish patients undergoing colorectal surgery. This goal has been reached; both non-cirrhotic liver disease and liver cirrhosis have been shown to have an impact on 30-day mortality in patients undergoing colorectal surgery for CRC (study I) or DD (study II). Moreover, a decrement in preoperative HSA was associated with a concentration-dependent increased risk of mortality, reoperation, and AKI in the 30 days following CRC surgery (study III).

8. Perspective

The investigations presented in this dissertation will contribute to better understanding the prognosis in patients undergoing colorectal surgery. Moreover, it will provide a foundation for further studies aiming to modify prognosis in patients undergoing CRC and DD surgery developing new strategies and improving pre- and intra-operative care. First, future investigations should attempt to estimate the prognostic impact of liver disease according to disease severity. The Danish pathology registry and coverage extension of the LABKA may markedly contribute to this aim. Moreover, nationwide laboratory data or chart review, will allow to estimate 30-day mortality risk in patients with severity of liver function based on well-known prognostic scores (*i.e.*, MELD or CTP) or based on the prevalence of liver disease complications. Second, we showed that also patients with non-cirrhotic liver diseases are at increased risk of 30-day mortality after colorectal surgery. However, besides differences related to liver disease severity, postoperative prognosis may markedly vary among patients with different etiology of liver disease. Therefore, the prognostic impact of liver disease with similar severity but differing by etiology should be investigated by future studies. Particularly, based on the rapid increase of the non-alcoholic fatty liver disease prevalence in the westernized countries, investigations on its impact on prognosis in patients undergoing colorectal surgery may help to understand surgical risks related with that condition. Third, non-elective surgery is associated with the most important burden of mortality both among patients with liver disease and among those without. Therefore, studies aimed to compare prognosis following different approaches (*e.g.*, minimal invasive surgical care or new medical protocols) in patients acutely admitted should be undertaken. Moreover, our findings suggested that liver disease is associated with a markedly high absolute mortality in both CRC patients undergoing elective and non-elective surgery. Differently, absolute mortality following elective DD surgery in patients with liver disease is relatively low. Future studies investigating risk factors for developing complicated DD in patients with liver disease will help to identify those patients that may benefit from elective DD surgery. Fourth, the findings of study III highlight the possible role of HSA as a pathophysiological mechanism of liver disease and other chronic and acute diseases associated with poor postoperative prognosis. Moreover, HSA is a multifunctional protein and its function depends on the total HSA amount but also on its functional capacity. Therefore, HSA concentration does not provide sufficient information regarding the actual

functional state although we showed that decrement in HSA is markedly associated with worse prognosis. Further studies should aim to investigate the *effective albumin concentration*[147] on large scale, combining methods used for HSA quantification with techniques able to provide information about HSA structure (*e.g.*, spectrometry) and its function. We believe the development of methodologies able to estimate accurately the *effective concentration* of HSA would extend the possibility of observational and experimental studies to investigate the actual impact of HSA on prognosis in a much more accurate way.

This dissertation may also have implications on clinical practice and healthcare strategies. For example, our findings from study I and study II underscore the importance of improving perioperative care in patients with liver disease. Moreover, considering that in Denmark the majority of liver diseases are secondary to alcohol consumption, actions oriented towards prevention of liver disease development should be strongly undertaken. Finally, our findings from study III may suggest that preoperative HSA administration could improve 30-day mortality. However, as mentioned in section 2.4, existing evidence shows contradictory results. Therefore, further investigations are necessary to examine the properties of HSA in commercial solutions and to better select patients with impaired *effective albumin concentration* before drawing deceptive conclusions on the potential benefit of HSA administration.

9. Summary

Colorectal surgery particularly related to colorectal cancer (CRC) and diverticular disease (DD) is among the most frequent surgical procedures. Colectomy has been reported to be associated with 24% of postoperative complications within 30 days after surgery.

Liver cirrhosis is a life-threatening disorder and together with other chronic liver diseases it is estimated to be the 12th most common cause of death in the US. The prevalence of chronic non-cirrhotic liver diseases appears to be increasing especially based on the spread of some of the risk factors such as obesity and diabetes.

Albumin is the main circulating protein in healthy individuals and it is produced exclusively in the liver. A decrease of its concentration has been shown to be associated with liver disease and also other conditions (*e.g.*, cancer, infection, and malnutrition) that increase the risk of postoperative complications. Therefore, decrement in albumin concentration may be a pathophysiological mechanism that leads to increased 30-day mortality after colorectal surgery.

This dissertation was written on the basis of three clinical epidemiological studies: two nationwide cohort studies and one population-based cohort study in Northern and Central Denmark. We used the unique civil registration number to link data from Danish population-based administrative and medical registries, facilitating complete study populations, accurate history of preadmission comorbidity, and adjustment for other important confounding factors.

The aims of this thesis were to examine the impact of liver disease on 30-day mortality following colorectal surgery for CRC (study I) and DD (study II), overall and in different demographic/medical subgroups; and to examine the impact of preoperative serum albumin concentration on mortality, reoperation, and acute kidney injury (AKI) within 30 days following CRC surgery (study III).

Study l included 39,840 patients undergoing CRC surgery during 1996-2009. Of those, 369 (0.9%) had non-cirrhotic liver disease and 158 (0.4%) had liver cirrhosis. Thirty-day mortality was 13.3% in patients with non-cirrhotic liver disease and 24.1% in patients with liver cirrhosis, compared to 8.7% in patients without liver disease.

Study ll included 14,408 patients undergoing DD surgery in Denmark during 1977-2011. Of those, 233 (1.6%) had non-cirrhotic liver disease and 91 (0.6 %) had liver cirrhosis. Thirty-day mortality was 9.9% in patients without liver disease and 14.6% in patients with non-cirrhotic liver disease, and 24.2% among patients with liver cirrhosis. Liver disease had an impact on mortality up to 60 days after DD surgery.

The impact of liver disease on 30-day mortality was similar in both patients undergoing CRC (study I) and DD (study II) surgery, corresponding to approximately 1.5 among patients with non-cirrhotic liver disease and 2.5 among patients with liver cirrhosis compared with patients without liver disease.

Study lll included 9,339 patients with preoperative serum albumin measurement undergoing colorectal surgery for CRC in Northern and Central Denmark during 1997-2011. Of those, 26.4% (n = 2,464) of patients had serum albumin below 35 g/L. The overall 30-day mortality gradually increased from 2.0% in patients with serum albumin above 40 g/L to 26.9% in patients with serum albumin equal to or below 25 g/L. Corresponding adjusted HRs increased from 1.75 (95% CI: 1.25-2.45) among patients with serum albumin between 35-40 g/L to 7.59 (95% CI: 4.95-11.64) among patients with serum albumin equal to or below 25 g/L, compared to patients with serum albumin above 45 g/L. Low preoperative HSA also increased reoperation and AKI rates, although to a lesser extent.

The most important methodological considerations are related to the observational study design and the use of medical database. Therefore, selection, information, and confounding bias might influence our findings; the latter two types are the most likely. However, we find it implausible that the effects of these biases alone fully explain our observations.

10. Dansk resume

Kolorektalkirurgi, relateret til kolorektalkræft (CRC) og divertikulitis (DD), er blandt de hyppigste kirurgiske indgreb. Man har registreret kolektomi til at være associeret med 24 % af de postoperative komplikationer der opstår inden for 30 dage efter operation.

Levercirrose (skrumpelever) er en livstruende sygdom og estimeres sammen med andre kroniske leversygdomme til at være den 12. hyppigste dødsårsag i USA. Prævalensen af kronisk non-cirrotisk leversygdom ser ud til at være stigende specielt på grund af udbredelsen af risikofaktorer såsom overvægt og diabetes (sukkersyge).

Albumin er det hyppigste cirkulerende protein i kroppen hos raske individer og produceres udelukkende i leveren. Et fald i koncentrationen af albumin har vist sig at være associeret med leversygdom og andre sygdomme (bl.a. kræft, infektion og fejlernæring) som øger risikoen for postoperative komplikationer. Det er derfor muligt, at et fald i albuminkoncentrationen er den patofysiologiske mekanisme som fører til øget 30-dages mortalitet (dødelighed) efter kolorektalkræftkirurgi.

Denne afhandling er baseret på tre kliniske epidemiologiske studier: to landsdækkende kohortestudier og et populationsbaseret kohortestudie begrænset til Region Nordjylland og Region Midtjylland. Vi anvendte CPR-numre til at koble data fra danske populationsbaserede administrative og medicinske registre for at muliggøre komplette studiepopulationer, korrekt information om komorbiditeter og justering for andre vigtige confoundere.

Formålet med denne afhandling var at undersøge betydningen af leversygdom for 30-dages mortaliteten efter kolorektalkirurgi for CRC (studie I) og DD (studie II) overordnet og i forskellige demografiske/medicinske undergrupper. Derudover var formålet at undersøge betydningen af præoperativ serumalbuminkoncentration for mortalitet, reoperation og akut nyresvigt (AKI) inden for 30 dage efter CRC kirurgi (studie III).

Studie I inkluderede 39.840 patienter opereret for CRC i løbet af 1996-2009. Af disse havde 369 (0,9 %) non-cirrotisk leversygdom og 158 (0,4 %) levercirrose. 30-dages mortaliteten var 13,3 % hos patienter med non-cirrotisk leversygdom og 8,7 % hos patienter med levercirrose.

Studie II inkluderede 14.408 patienter opereret for DD i Danmark i løbet af 1977-2011. Af disse havde 233 (1,6 %) non-cirrotisk leversygdom og 91 (0,6 %) havde leversygdom. 30-dages mortaliteten var 9,9 % hos patienter uden leversygdom, 14,6 % hos patienter med non-cirrotisk leversygdom og 24,2 % blandt patienter med levercirrose. Leversygdom havde en betydning for mortaliteten i op til 60 dage efter DD kirurgi.

Betydningen af leversygdom for 30-dages mortaliteten var ens for patienter opereret for CRC (studie I) og divertikulitis (studie II), nemlig omkring halvandegang højere blandt patienter med non-cirrotisk leversygdom og 2,5-gange højere blandt patienter med levercirrose sammenlignet med patienter uden leversygdom.

Studie III inkluderede 9.339 patienter opereret for CRC i Region Nordjylland og Region Midtjylland i perioden 1997-2011 som havde præoperative serumalbuminmålinger. Af disse havde 26,4 % (n = 2.464) af patienterne serumalbumin under 35g/L. Den overordnede 30-dages mortalitet steg gradvist fra 2,0 % hos patienter med serumalbumin over 40 g/L til 26,9 % hos patienter med serumalbumin under eller lig med 25 g/L. De justerede hazard ratios steg tilsvarende fra 1,75 (95 % CI: 1,25-2,45) blandt patienter med serumalbumin 35-40 g/L til 7.59 (95 % CI: 4,95-11,64) hos patienter med serumalbumin under 25 g/L, sammenlignet med patienter med serumalbumin over 45g/L. Ligeledes steg den kumulerede incidens af AKI og reoperationer hos patienter med lavt præoperativt serumalbumin, dog i mindre grad.

De vigtigste metodologiske overvejelser er relateret til det observationelle studiedesign og brugen af medicinske databaser. Derfor har selektion, information og confounding bias muligvis påvirket vore fund. Det mest sandsynlige er de to sidstnævnte. Vi finder det dog ikke plausibelt, at effekten af disse bias alene kan forklare vores observationer.

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Paper I

BMC Gastroenterology

RESEARCH ARTICLE Open Access

Liver disease and 30-day mortality after colorectal cancer surgery: a Danish population-based cohort study

Jonathan Montomoli*, Rune Erichsen, Christian Fynbo Christiansen, Sinna Pilgaard Ulrichsen, Lars Pedersen, Tove Nilsson and Henrik Toft Sørensen

Abstract

Background: Colorectal cancer (CRC) is common, with surgery as the main curative treatment. The prevalence of chronic liver disease has increased, but knowledge is limited on postoperative mortality in patients with liver disease who undergo CRC surgery. Hence, we examined 30-day mortality after CRC surgery in patients with liver disease compared to those without liver disease.

Methods: We used medical databases to conduct a nationwide cohort study of all patients undergoing CRC surgery in Denmark from 1996 through 2009. We further identified patients diagnosed with any liver disease before CRC surgery and categorized them into two cohorts: patients with non-cirrhotic liver disease and patients with liver cirrhosis. Patients without liver disease were defined as the comparison cohort. Using the Kaplan-Meier method, we computed 30-day mortality after CRC surgery in each cohort. We used a Cox regression model to compute hazard ratios as measures of the relative risk (RR) of death, controlling for potential confounders including comorbidities. In order to examine the impact of liver disease in different subgroups, we stratified patients by gender, age, cancer stage, cancer site, timing of admission, type of surgery, comorbidity level, and non-hepatic alcohol-related disease.

Results: Overall, 39,840 patients underwent CRC surgery: 369 (0.9%) had non-cirrhotic liver disease and 158 (0.4%) had liver cirrhosis. Thirty-day mortality after CRC surgery was 8.7% in patients without liver disease and 13.3% in patients with non-cirrhotic liver disease (adjusted RR of 1.49 95% confidence interval (CI): 1.12-1.98). Among patients with liver cirrhosis, mortality was 24.1%, corresponding to an adjusted RR of 2.59 (95% CI: 1.86-3.61). The negative impact of liver disease on postoperative mortality was found in all subgroups.

Conclusions: Pre-existing liver disease was associated with a markedly increased 30-day mortality following CRC surgery.

Keywords: Liver disease, Colorectal neoplasms, Surgery, Mortality, Epidemiology

Background

Prevalence of liver diseases is increasing worldwide, and fatty liver and liver cirrhosis are known risk factors for colorectal cancer (CRC) [1,2]. Among the available treatments for CRC, surgical excision of the primary tumor remains the only curative approach [3] and liver disease patients who have CRC surgery may be at increased risk of postoperative complications and death, related to effects of anesthesia, bleeding during surgery, infections, and subsequent multi-organ failure [4].

However, only a few studies have addressed the association between liver disease and mortality following colorectal surgery [5-10], and only one focused on mortality after CRC surgery [5]. Former studies reported in-hospital and 30-day mortalities in liver disease patients ranging from 6% to 41% after colorectal surgery, compared with 1% to 5% in patients without liver disease. The majority of former studies has been based on data from referral centers [5,8,9] and did not include patients with non-cirrhotic liver disease [5,7-10]. Moreover, they

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have been hampered by small study populations [5,8,9], lack of information on comorbidity and surgery [5,8], lack of comparison cohorts of patients without liver disease undergoing same type of surgery [5,8,9], and restriction to in-hospital mortality [7,9,10]. The comorbidity data in former studies were limited by incomplete information as only diagnoses recorded within a short period before surgery were available [6,7,9,10].

Accurate data on mortality in patients with liver disease undergoing CRC surgery are needed to better understand the prognostic effect of liver disease in CRC patients. Such results also may help to optimize perioperative care.

We therefore conducted a nationwide cohort study investigating 30-day mortality after CRC surgery in patients with liver disease compared to those without liver disease.

Methods

This cohort study was conducted within the entire Danish population which accumulates to 6.8 million people in the study period from January 1, 1996 through December 31, 2009. The National Health Service provides tax-funded medical care, including CRC surgery, for all Danish residents. Since 1968, a unique civil registration number (CPR number) has been assigned to all Danish residents at birth or upon immigration [11]. The CPR number allows accurate record linkage at an individual level among all Danish registries. The study was approved by the Danish Data Protection Agency. According to Danish law, the study did not require approval from the health research ethics committee system.

Study cohort

We included all patients with a diagnosis of CRC who underwent first-time CRC surgery during the study period. Patients with a CRC diagnosis (see Additional file 1 for diagnosis codes) were identified using the Danish Cancer Registry (DCR), which contains records of all incident cases of malignant neoplasms in Denmark since 1943 [12]. Data recorded for each individual include method of cancer verification, cancer stage, and place of residence on the date of cancer diagnosis. Tumors registered after January 1, 1978 have been reclassified according to the *International Classification of Diseases, 10th revision* (ICD-10).

We used the CPR number to link CRC patients identified in the DCR to the Danish National Registry of Patients (DNRP) to obtain information about comorbidities and surgery. The DNRP includes information on all non-psychiatric hospitalizations since 1977 and on outpatient contacts since 1995 [13]. Diagnoses have been recorded according to the ICD-8 until 1993 and according to the ICD-10 thereafter. Each record includes the dates of hospital admission and discharge, up to 20 discharge diagnoses, the type of admission (acute or elective), and information about surgery, including type and date of surgical procedure. Since 1996, surgical procedures have been coded according to the NOMESCO (Nordic Medico-Statistical Committee) Classification of Surgical Procedures [14]. We therefore chose 1996 as the beginning of our study period.

As the indication for surgery is not coded in the DNRP, we defined CRC surgery as a procedure involving colorectal surgery performed during a hospitalization where CRC was listed as a diagnosis in the DNRP (see Additional file 1 for codes). We categorized CRC surgery into groups according to type of the first recorded procedure. "Radical resection" included surgeries with the intention of eradicating the primary tumor, such as partial and total resections of the colon and/or rectum. This group was further divided into laparoscopic and open surgery. "Non-resectional procedures" included colostomy, stent placement, or excision of a very small part of the colon (see Additional file 1 for codes). For each patient we reported the timing of the admission as elective or acute using the information about type of the hospitalization in the DNRP.

We classified CRCs with local spread at the time of first diagnosis as "localized" and those with regional and/or distant metastases as "non-localized" (see Additional file 1 for codes).

Liver disease

We used the DNRP to identify patients with a diagnosis of liver disease (see Additional file 1 for diagnosis codes) before the CRC surgery date. Liver disease patients were divided into two different cohorts: patients with non-cirrhotic liver disease and patients with liver cirrhosis [15]. Non-cirrhotic liver disease included all liver disease diagnoses except liver cirrhosis, *eg*, viral hepatitis, alcoholic hepatitis, non-alcoholic fatty liver disease, or primary biliary cirrhosis. Patients with no history of liver disease prior to CRC surgery were defined as the comparison cohort.

Comorbidity

We used the DNRP to compute Charlson Comorbidity Index scores to quantify the burden of comorbidity [16]. The Charlson Comorbidity Index includes 19 diseases, each assigned a score between one and six. The sum of the individual scores represents a measure of a patient's level of comorbidity. We identified the diseases in the Charlson Comorbidity Index using ICD-8 and ICD-10 diagnosis codes [17], excluding mild and severe liver disease, CRC, CRC metastases, secondary liver cancers, and hepatocellular carcinoma. We classified patients as having a low (score = 0), a moderate (score = 1-2), or a high

comorbidity level (score ≥ 3). In addition, we obtained information on hospital diagnoses of non-hepatic alcohol-related disease, defined as alcohol abuse or alcohol-related diseases disregarding alcoholic liver disease [18], and presence of gastric or esophageal varices (see Additional file 1 for relevant codes).

Mortality data

We followed all CRC patients from the date of CRC surgery until death, emigration, or 30 days, whichever came first. Date of death or emigration was obtained from the Civil Registration System, which tracks the vital status and residence of all Danish residents and is updated daily [19].

Statistical analyses

The Kaplan-Meier method was used to compute 30-day mortality after CRC surgery in each patient cohort overall and to consider colon and rectal cancer separately. Moreover, we stratified 30-day mortality in each cohort by period of CRC surgery (1996-2002 or 2003-2009) and timing of admission (acute or elective). We used a Cox regression model to compute hazard ratios as a measure of the relative risk (RR) of death and 95% confidence intervals (CIs), comparing 30-day mortality after surgery among CRC patients in each liver disease cohort to that of the comparison cohort of CRC patients without liver disease. In the first analysis, we controlled for gender, age, timing of admission, type of surgery, cancer stage, comorbidity level, and non-hepatic alcohol-related disease. The proportional hazard assumption was checked graphically and found appropriate.

Next, to examine the impact of liver disease on 30-day mortality after CRC surgery in subgroups within each cohort, we stratified the analysis by gender, age category (0-59, 60-69, 70-79, and 80+ years), comorbidity level (low, moderate, and high), cancer site (colon, rectum, or both), stage (localized, non-localized or stage unknown), timing of admission (acute or elective), type of surgery (open radical resection, laparoscopic radical resection, or non-resectional procedure), and non-hepatic alcohol-related disease (yes or no).

Results

Descriptive data

We identified 39,840 CRC patients undergoing CRC surgery. Of these, 369 (0.9%) had non-cirrhotic liver disease and 158 (0.4%) had liver cirrhosis. Median age at CRC surgery was 72 years among patients without liver disease, 69 years among patients with non-cirrhotic liver disease, and 67 years among those with liver cirrhosis. Among non-cirrhotic liver disease patients, 60 (16.3%) had alcoholic hepatitis, 49 (13.3%) had viral hepatitis, 34 (9.2%) had non-alcoholic fatty liver disease, 4 (1.1%) had primary biliary cirrhosis, and 222 (60.2%) had other non-cirrhotic liver diseases.

Of patients with non-cirrhotic liver disease and liver cirrhosis 37% had acute admission, compared to 32% in the comparison cohort of patients without liver disease (Table 1). CRC patients with liver disease, especially those with liver cirrhosis, were more likely to have comorbid conditions, including non-hepatic alcohol-related disease, than patients without liver disease (Table 1). The higher comorbidity level in patients with liver disease persisted when stratified by cancer stage. For instance, among patients with non-localized CRC, a high level of comorbidity was found in 4.0% of the patients without liver disease, in 8.7% of those with non-cirrhotic liver disease, and in 12.0% of those with liver cirrhosis (see Additional file 2). Furthermore, type of surgery differed, with non-resectional procedures performed in less than 12% of patients with non-cirrhotic liver disease or without liver disease and in approximately 17% of cirrhotic patients (Table 1).

Postoperative mortality

Thirty-day mortality was 13.3% in patients with non-cirrhotic liver disease and 24.1% among patients with liver cirrhosis, compared to 8.7% in patients without liver disease (Table 2). Moreover, survival among patients with non-cirrhotic liver disease seems to differ from that among patients with liver cirrhosis beyond the first week after CRC surgery (Figure 1). Compared with the cohort of CRC patients without liver disease, the adjusted RR was 1.49 (95% CI: 1.12-1.98) for non-cirrhotic liver disease and 2.59 (95% CI: 1.86-3.61) for patients with liver cirrhosis (Table 2). There was no substantial difference in the impact of liver disease on mortality in the 1996-2002 period and the 2003-2009 period (data not shown). Notably, the 30-day mortality among patients with acute admission was as high as 16.3% for those without liver disease, but increased to 24.1% among patients with non-cirrhotic liver disease and 35.6% among those with liver cirrhosis. Corresponding results for CRC patients electively admitted were 5.1% for patients without liver disease, 6.9% for those with non-cirrhotic liver disease, and 17.2% for CRC patients with liver cirrhosis (see Additional file 3).

Thirty-day mortality was higher after colon cancer surgery than after rectal cancer surgery in all cohorts. Still, both colon and rectal cancer patients with liver disease had higher mortality than patients without liver disease (Table 2).

Table 3 shows adjusted RRs of 30-day mortality after CRC surgery for patients with liver disease stratified into subgroups. The impact of liver disease on 30-day mortality after surgery in CRC patients did not differ substantially between genders or within subgroups of patients with low

Table 1 Characteristics of patients with and without liver diseases undergoing colorectal cancer surgery in Denmark, 1996-2009

Subgroups	No liver disease N (%)	Non-cirrhotic liver disease N (%)	Liver cirrhosis N (%)
Gender:			
- Male	20,097 (51.1%)	188 (50.1%)	105 (66.5%)
- Female	19,216 (48.9%)	181 (49.1%)	53 (33.5%)
Age (years):			
- 0-59	7,046 (17.9%)	75 (20.3%)	39 (24.7%)
- 60-69	10,083 (25.7%)	116 (31.5%)	55 (34.8%)
- 70-79	13,169 (33.5%)	113 (30.6%)	50 (31.6%)
- 80+	9,015 (22.9%)	65 (17.6%)	14 (8.9%)
Cancer site:			
- Colon	25,905 (65.9%)	264 (71.5%)	100 (63.3%)
- Both colon and rectum	72 (0.2%)	1 (0.3%)	0 (0.0%)
- Rectum	13,336 (33.9%)	104 (28.2%)	58 (36.7%)
Timing of admission:			
- Acute	12,633 (32.1%)	137 (37.1%)	59 (37.3%)
- Elective	26,602 (67.7%)	231 (62.6%)	99 (62.7%)
- Missing	78 (0.2%)	1 (0.3%)	0 (0%)
Cancer stage:			
- Localized	17,044 (43.4%)	163 (44.2%)	65 (41.1%)
- Non-localized	18,863 (48.0%)	182 (49.3%)	76 (48.1%)
- Stage unknown	3,406 (8.6%)	24 (6.5%)	17 (10.8%)
Surgery:			
- Laparoscopic radical resection	3,483 (8.9%)	35 (9.5%)	10 (6.3%)
- Open radical resection	31,278 (79.5%)	293 (79.4%)	122 (77.2%)
- Non-resectional procedures	4,552 (11.6%)	41 (11.1%)	26 (16.5%)
Comorbidity level:			
- Low	24,301 (61.8%)	167 (45.3%)	60 (38.0%)
- Moderate	11,573 (29.4%)	145 (39.3%)	65 (41.1%)
- High	3,439 (8.8%)	57 (15.4%)	33 (20.9%)
Non-hepatic alcohol-related disease[†]	582 (1.5%)	46 (12.5%)	54 (34.2%)
Gastric and esophageal varices	19 (0.1%)	2 (0.5%)	29 (18.4%)
Distribution of the diseases included in the modified Charlson Comorbidity Index:			
Myocardial infarction	2,282 (5.8%)	15 (4.1%)	10 (6.3%)
Congestive heart failure	1,918 (4.9%)	21 (5.7%)	7 (4.4%)
Peripheral vascular disease	1,622 (4.1)	27 (7.3%)	13 (8.2%)
Cerebrovascular disease	3,348 (8.5%)	46 (12.5%)	15 (9.5%)
Dementia	359 (0.9%)	7 (1.9%)	3 (1.9%)
Chronic pulmonary disease	2,864 (7.3%)	54 (14.6%)	19 (12.0%)
Connective tissue disease	1,064 (2.7%)	25 (6.8%)	5 (3.2%)
Ulcer disease	2,121 (5.4%)	34 (9.2%)	30 (19.0%)
Uncomplicated type 1 and 2 diabetes	2,173 (5.5%)	42 (11.4%)	29 (18.4%)
Hemiplegia	71 (0.2%)	2 (0.5%)	0
Moderate to severe renal disease	568 (1.4%)	11 (3.0%)	9 (5.7%)
Diabetes with end organ damage	922 (2.4%)	20 (5.4%)	16 (10.1%)

Table 1 Characteristics of patients with and without liver diseases undergoing colorectal cancer surgery in Denmark, 1996-2009 *(Continued)*

Any tumor*	3,594 (9.1%)	39 (10.6%)	15 (9.5%)
Leukemia	101 (0.3%)	1 (0.3%)	1 (0.6%)
Lymphoma	214 (0.5%)	2 (0.5%)	3 (1.9%)
Metastatic solid tumor§	433 (1.1%)	8 (2.2%)	2 (1.3%)
AIDS	7 (<0.1%)	1 (0.3%)	0 (0.0%)

* Colorectal cancer and hepatocellular carcinoma were excluded.
† Including both diagnoses of alcohol abuse and non-hepatic alcohol-related diseases.
§ Colorectal cancer metastases and secondary liver cancers were excluded.

and moderate comorbidity levels, different CRC stage, and elective or acute admission. Nevertheless, for patients with non-cirrhotic liver disease who underwent CRC surgery at an age of 60 years or younger, the RR was particularly high (adjusted RR = 2.71; 95% CI: 1.25-5.89). In patients with non-hepatic alcohol-related disease, the impact of liver disease on mortality was less pronounced for non-cirrhotic liver disease patients (adjusted RR = 1.30; 95% CI: 0.94-1.81) than for those with liver cirrhosis (adjusted RR = 3.37; 95% CI: 2.30-4.92). In addition, the impact of liver cirrhosis appeared more pronounced among patients less than 80 years old as in older patients whereas liver cirrhosis had little impact on patients undergoing non-resectional procedures (adjusted RR = 1.74; 95% CI: 0.82-3.67). Finally, the impact of liver disease was limited in patients with a high comorbidity level for both non-cirrhotic liver disease (adjusted RR = 1.17; 95% CI: 0.62-2.19) and liver cirrhosis (adjusted RR = 1.47; 95% CI: 0.68-3.15).

Discussion

We found that patients with non-cirrhotic liver disease or liver cirrhosis had a substantially higher postoperative 30-day mortality after colon and rectal cancer surgery than patients without liver disease. The association between non-cirrhotic liver disease and postoperative mortality appeared most pronounced among patients aged 60 years or younger. The impact of liver disease on mortality is evident among patients with low and moderate comorbidity levels, different CRC stage, and different timing of admission (acute vs. elective). However, among

Table 2 Relative risk (RR) and 30-day mortality after colorectal cancer surgery in patients with and without liver disease

Cancer site	Patients	Deaths within 30 days	30-day mortality %*	RR (95% CI)	
		N	(95% CI)	Crude	Adjusted
Colorectal cancer§					
- No liver disease	39,313	3,432	8.7 (8.4-9.0)	1.00	1.00
- Non-cirrhotic liver disease	369	49	13.3 (9.8-17.8)	1.56 (1.18-2.07)	1.49 (1.12-1.98)
- Liver cirrhosis	158	38	24.1 (16.7-33.9)	2.93 (2.13-4.03)	2.59 (1.86-3.61)
Colon cancer					
- No liver disease	25,905	2,569	9.9 (9.5-10.3)	1.00	1.00
- Non-cirrhotic liver disease	264	38	14.4 (10.2-20.1)	1.50 (1.09-2.06)	1.45 (1.05-2.00)
- Liver cirrhosis	100	27	27.0 (17.3-40.6)	2.90 (1.99-4.24)	2.50 (1.68-3.70)
Rectal cancer					
- No liver disease	13,336	857	6.4 (6.0-6.9)	1.00	1.00
- Non-cirrhotic liver disease	104	11	10.6 (5.6-19.3)	1.68 (0.93-3.04)	1.66 (0.91-3.02)
- Liver cirrhosis	58	11	19.0 (9.8-34.8)	3.14 (1.73-5.68)	2.84 (1.52-5.30)

RR, relative risk; CI, confidence interval.
* Calculated using the Kaplan-Meier method.
§ Overall colorectal cancers patients including patients with both colon and rectal cancers.

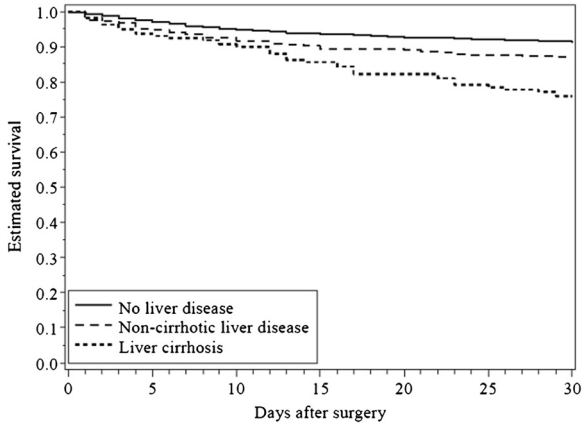

Figure 1 Crude 30-day survival curves for patients undergoing colorectal cancer surgery without liver disease, with non-cirrhotic liver disease, and with liver cirrhosis.

patients with a high level of comorbidity, we found a less pronounced impact of liver disease on mortality.

Thus, our data extend former research on postoperative mortality in patients with liver disease and CRC by using a population-based sample and, furthermore, particularly by evaluating the influence of other comorbidities and CRC stage and site. Only one cohort study based on data from a single US hospital in 2003 focused on mortality after CRC surgery in 72 patients with liver cirrhosis [5]. Of these, 49% had alcohol-related liver cirrhosis and the 30-day mortality after CRC surgery was 13%. Among patients with the most severe cirrhotic disease, identified as Child-Pugh class C, the postoperative mortality was 28% [5]. However, RRs could not be estimated because the study did not include a comparison cohort of patients without liver disease.

Table 3 Relative risk of 30-day mortality after colorectal cancer surgery in subgroups of patients with liver disease

Subgroups	Patients N	No liver disease (reference cohort)	Non-cirrhotic liver disease Adjusted* RR (95%CI)	Liver cirrhosis Adjusted* RR (95%CI)
Gender:				
- Male	20,390	1.00 (ref)	1.37 (0.88-2.13)	2.21 (1.20-4.01)
- Female	19,450	1.00 (ref)	1.56 (1.08-2.26)	2.82 (1.90-4.20)
Age at colorectal surgery (years):				
- 0-59	7,160	1.00 (ref)	2.71 (1.25-5.89)	3.53 (1.53-8.13)
- 60-69	10,254	1.00 (ref)	1.56 (0.83-2.95)	3.61 (2.00-6.52)
- 70-79	13,332	1.00 (ref)	1.10 (0.65-1.87)	2.37 (1.40-4.02)
- 80+	9,094	1.00 (ref)	1.61 (1.01-2.56)	1.14 (0.36-3.59)
Timing of admission:				
- Acute	12,829	1.00 (ref)	1.57 (1.11-2.22)	2.48 (1.59-3.88)
- Elective	26,932	1.00 (ref)	1.39 (0.85-2.28)	2.79 (1.70-4.57)
Cancer stage:				
- Localized	17,272	1.00 (ref)	1.16 (0.65-2.06)	3.49 (2.06-5.93)
- Non-localized	19,121	1.00 (ref)	1.71 (1.20-2.43)	2.42 (1.49-3.94)
- Stage unknown	3,447	1.00 (ref)	1.41 (0.58-3.42)	2.24 (0.91-5.50)
Surgery:				
- Laparoscopic radical resection	3,528	1.00 (ref)	NA	6.82 (1.48-31.45)
- Open radical resection	31,693	1.00 (ref)	1.41 (0.99-1.98)	3.01 (2.05-4.40)
- Non-resectional procedures	4,619	1.00 (ref)	1.91 (1.14-3.20)	1.74 (0.82-3.67)
Comorbidity level:				
- Low	24,528	1.00 (ref)	1.62 (0.97-2.70)	3.41 (1.97-5.91)
- Moderate	11,783	1.00 (ref)	1.60 (1.07-2.41)	3.14 (1.91-5.16)
- High	3,529	1.00 (ref)	1.17 (0.62-2.19)	1.47 (0.68-3.15)
Non-hepatic alcohol-related disease†:				
- Yes	682	1.00 (ref)	1.30 (0.94-1.81)	3.37 (2.30-4.92)
- No	39,158	1.00 (ref)	2.61 (1.43-4.76)	1.67 (0.88-3.10)

RR, Relative Risk; CI, Confidence Interval; NA, Not Applicable.
* Mutually adjusted for gender, age, timing of admission, cancer stage, surgery, comorbidity level, and non-hepatic alcohol-related disease.
† Including both diagnoses of alcohol abuse and non-hepatic alcohol-related diseases.

Other previous studies included patients undergoing colorectal surgery for non-CRC indications and did thus not estimate the impact of liver disease on postoperative mortality related to CRC alone.

Recently, Meunier *et al*. reported a 26% in-hospital mortality among 41 patients with liver cirrhosis undergoing colorectal surgery [9]. Of these patients, 39 had an alcoholic etiology and 35 received surgery for CRC. The results are supported by our finding showing that alcoholic liver cirrhosis represents an additional negative prognostic factor for patients undergoing CRC surgery [20,21].

Nguyen *et al.* reported a 29% in-hospital mortality after colorectal surgery among patients with liver cirrhosis complicated by portal hypertension and 14% in patients with compensated liver cirrhosis [10]. After stratification by acuity of presentation (elective vs. nonelective), in-hospital mortality was 1.8% vs. 9.1% among patients without liver cirrhosis, 7.2% vs. 20.9% among those with liver cirrhosis without portal hypertension, and 18.6% vs. 35.8% among those with liver cirrhosis with portal hypertension. Consequently, the impact of liver cirrhosis on mortality was higher among patients with elective admission (adjusted odds ratio = 3.91; 95% CI: 3.12-4.90) than in patients who had nonelective admission (adjusted odds ratio = 2.40; 95% CI: 2.07-2.79) [10]. Our results confirmed higher mortality among patients acutely admitted compared with those with an elective admission, especially among patients with liver cirrhosis. Yet, we did not show any major difference in adjusted RR between acute vs. elective admission. Finally, Ghaferi *et al*. analyzed 30-day mortality after colorectal surgery in about 1,500 patients with chronic liver disease, including both non-cirrhotic and cirrhotic diseases, and compared it to postoperative mortality in a group of 30,000 patients without liver disease. Patients with chronic liver disease had a postoperative mortality of 21.5% compared to an overall mortality of 3.2% in the control group [6]. Again, these results confirm that mortality among patients with liver disease – particularly those with complicated liver cirrhosis – is higher than in patients without liver disease. Unfortunately, none of the previous studies included non-cirrhotic liver disease as an individual group, and our results thus remain the only source of evidence.

The increased postoperative mortality in patients with liver cirrhosis may have several explanations. Liver cirrhosis is a complex disease involving different organ systems, increasing the risk of postoperative complications, and decreasing the patient's recuperative capacity [4]. Previous studies have identified hepatic coagulopathy as a risk factor for postoperative mortality in patients with chronic liver disease undergoing surgery [22-24], as well as ascites, hepatic encephalopathy, elevated creatinine levels, and other manifestations of portal hypertension [25]. Furthermore, liver disease is known to modify the effect of various drugs, attenuate immune function, and consequently increase the risk of infection and eventually mortality [4,26,27]. Finally, although liver disease, especially liver cirrhosis, has negative systemic effects, other diseases coexisting with liver disease may also contribute to increased postoperative mortality as suggested by the less pronounced impact of liver disease in patients with severe comorbidity.

The validity of our findings depends on several factors. We used population-based registries with complete follow-up. We had complete data on surgical procedures and on hospital diagnoses, which minimized selection and referral bias. Both the DCR data on cancer [12] and the DNRP [13] data on liver diseases, surgical procedures and comorbidity [17] are of high quality. Nonetheless, we cannot rule out that our results were affected by undiagnosed liver diseases, but this would have caused us to underestimate the RRs of postoperative mortality. Moreover, we included patients with both acute and chronic non-cirrhotic liver disease, such as viral hepatitis, in the non-cirrhotic liver disease cohort. Hence, it is likely that some patients had completely recovered from an acute liver disease by the time of surgery. We may therefore have underestimated the impact of non-cirrhotic liver disease on mortality.

Conclusion

Our data show that patients with liver disease, especially liver cirrhosis, have markedly increased mortality after CRC surgery compared to patients without liver disease. Perioperative management of patients with liver disease should thus be carefully planned in order to minimize complications and death.

Additional files

Additional file 1: Codes used in the analysis.

Additional file 2: Descriptive table on distribution of comorbidity depending on cancer stage in patients with no liver disease, non-cirrhotic liver disease, and liver cirrhosis.

Additional file 3: Relative risk (RR) and 30-day mortality after acute and elective colorectal cancer surgery in patients without liver disease, in those with non-cirrhotic liver disease, and in those with liver cirrhosis.

Abbreviations

CI: Confident Interval; CPR number: Unique Civil Registration Number; CRC: Colorectal Cancer; DCR: Danish Cancer Registry; DNRP: Danish National Registry of Patients; ICD: International Classification of Diseases; NOMESCO: Nordic Medico-Statistical Committee; RR: Relative Risk.

Competing interests

The authors disclose no competing interests.

Authors' contributions

JM: study concept and design, data interpretation, and manuscript preparation; RE, CFC: study concept and design, data interpretation, and manuscript review; SPU, LP: acquisition of data, and statistical analysis; TN, HTS: study design, critical analysis of the data, manuscript review, and study supervision. All the authors have approved the final draft submitted.

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Additional file 1

ICD codes, NOMESCO codes, and cancer stage codes used in the analysis, are shown.

The Danish Cancer Registry

Colorectal Cancer: ICD-8: 153-154; ICD-10: C18, C19, C20

Colorectal cancer stage classification:

- Localized:
    - Dukes: A,B
    - TNM*: T0,1-4,x N0 M0; T0,1-2 N0 Mx; T0,1 Nx M0,x
- Non-localized:
    - Dukes: C,D
    - TNM*: T0,1-4,x N1-3 M0-1,x; T0,1-4,x N0 M1; T0,1-4,x Nx M1
- Unknown
    - TNM*: T2-4,x Nx M0,x; T2-4,x N0 Mx

* Colorectal cancers were classified according to TNM from 2004 on.

The Danish National Registry of Patients

Hospital diagnoses were as follows:

- *Colorectal surgery (NOMESCO codes):*
    - Open radical resection: JGB00, JGB10,JGB20, JGB30, JGB40, JGB50, JGB60, JGB96, JFB20, JFB30, JFB 33, JFB40, JFB43, JFB46, JFB50, JFB60, JFB63, JFB96, JFH00, JFH10, JFH20, JFH30, JFH33, JFH40, JFH96, JGA00, JGA70
    - Laparoscopic radical resection: JGB01, JGB11, JGB31, JGB97, JFB21, JFB31, JFB34, JFB41, JFB44, JFB47, JFB51, JFB61, JFB64, JFB97, JFH01, JFH11

    - Non-eradicative procedures: JGA32-58, JGA73-98, JGW, JFA68, JFA83-84, JFA96-97, JFC, JFF10-13, JFF20-31, JFW
- *Liver cirrhosis*: ICD-8: 571.09, 571.92, 571.99; ICD-10: K70.3, K71.7, K74.5, K74.6
- *Non-cirrhotic liver disease* → ICD-8: 570.00–573.09 (excluding 571.09, 571.92, 571.99), 070.01-070.09; ICD-10: K70.0- K70.9 (excluding K70.3) R74.0, K71.0–K77.8 (excluding K71.7, K74.5, K74.6), B15–B19
- *Disease included in the adjusted Charlson Comorbidity Index:*
    - Myocardial infarction: ICD-8: 410; ICD-10: I21, I22, I23
    - Congestive heart failure: ICD-8: 427.09, 427.10, 427.11, 427.19, 428.99, 782.49; ICD-10: I50, I11.0, I13.0, I13.2
    - Peripheral vascular disease: ICD-8: 440, 441, 442, 443, 444, 445; ICD-10: I70, I71, I72, I73, I74, I77
    - Cerebrovascular disease: ICD-8: 430-438; ICD-10: I60-I69, G45, G46
    - Dementia: ICD-8: 290.09-290.19, 293.09; ICD-10: F00-F03, F05.1, G30
    - Chronic pulmonary disease: ICD-8: 490-493, 515-518; ICD-10: J40-J47, J60-J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3
    - Connective tissue disease: ICD-8: 712, 716, 734, 446, 135.99; ICD-10: M05, M06, M08, M09, M30, M31, M32, M33, M34, M35, M36, D86
    - Ulcer disease: ICD-8: 530.91, 530.98, 531-534; ICD-10: K22.1, K25-K28
    - Uncomplicated type 1 and type 2 diabetes: ICD-8: 249.00, 249.06, 249.07, 249.09, 250.00, 250.06, 250.07, 250.09; ICD-10: E10.0, E10.1, E10.9, E11.0, E11.1, E11.9
    - Hemiplegia: ICD-8: 344; ICD-10: G81, G82
    - Moderate to severe renal disease: ICD-8: 403, 404, 580-583, 584, 590.09, 593.19, 753.10-753.19, 792; ICD-10: I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61
    - Diabetes with end-organ damage: ICD-8: 249.01-249.05, 249.08, 250.01-250.05, 250.08; ICD-10: E10.2-E10.8, E11.2-E11.8
    - Any tumor (excluding CRC): ICD-8: 140-194 (excluding 153-154, 155.09); ICD-10: C00-C75 (excluding C18-C20, C22)
    - Leukemia: ICD-8: 204-207; ICD-10: C91-C95
    - Lymphoma: ICD-8: 200-203, 275.59; ICD-10: C81-C85, C88, C90, C96

    - Metastatic solid tumor (excluding metastases from CRC): ICD-8: 195-198, 199 (excluding patients with diagnoses 197.59, 197.79, and 197.89); ICD-10: C76-C80 (excluding patients with diagnoses C78.5 and C78.7)
    - AIDS: ICD-8: 079.83; ICD-10: B21-B24
- *Non-hepatic alcohol-related disease:* ICD-8: 291-291.9, 303-303.9, 980; ICD-10: F10.2, F10.7, F10.8, I42.6, G62.1, K29.2, G72.1, G31.2, T51, Z72.1
- *Gastric and esophageal varices:* ICD-8: 456.0X; ICD-10: I85.X, I86.4

Additional file 2

Descriptive table on distribution of comorbidity depending on cancer stage in patients with no liver disease, non-cirrhotic liver disease, and liver cirrhosis.

	No liver disease N (%) **n = 39,313**	**Non-cirrhotic liver disease N (%)** **n = 369**	**Liver cirrhosis N (%)** **n = 158**
Localized:	17,044 (43.4%)	163 (44.2%)	65 (41.1%)
- Low comorbidity level	10,486 (26.7%)	75 (20.3%)	29 (18.4%)
- Moderate comorbidity level	5,109 (13.0%)	67 (18.2%)	26 (16.4%)
- High comorbidity level	1,449 (3.7%)	21 (5.7%)	10 (6.3%)
Non-localized:	18,863 (48.0%)	182 (49.3%)	76 (48.1)
- Low comorbidity level	11,993 (30.5%)	87 (23.5%)	26 (16.5%)
- Moderate comorbidity level	5,298 (13.5%)	63 (17.1%)	31 (19.6%)
- High comorbidity level	1,572 (4.0%)	32 (8.7%)	19 (12.0%)
Stage unknown:	3,406 (8.6%)	24 (6.5%)	17 (10.8%)
- Low comorbidity level	1,822 (4.6%)	5 (1.4%)	5 (3.2%)
- Moderate comorbidity level	1,166 (3.0%)	15 (4.0%)	8 (5.1%)
- High comorbidity level	418 (1.0%)	4 (1.1%)	4 (2.5%)

Additional file 3

Relative risk (RR) and 30-day mortality after acute and elective colorectal cancer surgery in patients without liver disease, in those with non-cirrhotic liver disease, and in those with liver cirrhosis.

	Patients N	Deaths within 30 days N	30-day mortality %* (95% CI)	RR (95% CI) Crude	RR (95% CI) Adjusted
Acute surgery[¥]					
- No liver disease	12,633	2064	16.3 (15.6-17.1)	1.00	1.00
- Non-cirrhotic liver disease	137	33	24.1 (16.3-34.7)	1.56 (1.10-2.20)	1.57 (1.11-2.22)
- Liver cirrhosis	59	21	35.6 (20.9-56.2)	2.38 (1.55-2.67)	2.48 (1.59-3.88)
Elective surgery[¥]					
- No liver disease	26,602	1363	5.1 (4.9-5.4)	1.00	1.00
- Non-cirrhotic liver disease	231	16	6.9 (4.2-11.4)	1.36 (0.83-2.23)	1.39 (0.85-2.28)
- Liver cirrhosis	99	17	17.2 (10.2-28.1)	3.49 (2.16-5.63)	2.79 (1.70-4.57)

* Calculated using the Kaplan-Meier method.

[¥] Information on surgery timing is missing for some patients therefore the sum of patients undergoing to acute and elective surgery is not equal to the number of all patients included in the study.

Paper II

Coexisting Liver Disease is Associated with Increased Mortality after Diverticular Disease Surgery

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ABSTRACT

Background: Coexistence of liver disease in patients undergoing surgery for diverticular disease (DD) may increase the risk of postoperative complications, but the evidence is limited.

Aim: To investigate the impact of liver disease on mortality and reoperation rates following DD surgery.

Methods: We performed a cohort study based on medical databases of all patients undergoing DD surgery in Denmark during 1977-2011, categorizing them into three cohorts according to history of liver disease: patients with non-cirrhotic liver disease, those with liver cirrhosis, and those without liver disease (comparison cohort). Using the Kaplan-Meier method, we computed mortality in each cohort for 0-30, 31-60, and 61-90 days following DD surgery. We used a Cox regression model to compute hazard ratios as measures of the relative risk (RR) of death, controlling for potential confounders, including other comorbidities. In addition, we assessed the reoperation rate within 30 days of initial surgery.

Results: Of 14 408 patients undergoing DD surgery, 233 (1.6%) had non-cirrhotic liver disease and 91 (0.6 %) had liver cirrhosis. Thirty-day mortality was 9.9% in patients without liver disease and 14.6% in patients with non-cirrhotic liver disease (adjusted RR = 1.64 (95% confidence interval (CI): 1.16-2.31)). Among patients with liver cirrhosis, mortality was 24.2% (adjusted RR = 2.70 (95% CI: 1.73-4.22)). Liver disease had an impact on mortality up to 60 days after DD surgery. The reoperation rate was approximately 10% in each cohort.

Conclusion: Pre-existing liver disease has a major impact on postoperative mortality following DD surgery.

Keywords: liver disease; diverticular disease; surgery; mortality; cohort; epidemiology

INTRODUCTION

The rate of hospitalization for diverticular disease (DD) has been increasing markedly in recent decades in Western countries [1,2], accompanied by an increasing rate of surgical procedures performed on patients with complicated DD [3]. Among benign diseases of the large intestine, DD has become the most common indication for colorectal surgery, accounting for approximately 20% of all colorectal surgery [4-6].

Generally, patients with liver disease are at high risk of postoperative complications and death [7]. This risk is related to adverse effects of anesthesia, bleeding during surgery, infections, and subsequent multi-organ failure [8]. Existing studies of patients undergoing colorectal surgery have reported in-hospital and 30-day mortality ranging from 6% to 41% in patients with liver disease, compared with 1% to 10% in patients without liver disease [9-15]. However, these studies included patients with a range of surgical indications, with colorectal cancer as the only disease [14,15] or the most common disease leading to colorectal surgery [11,12]. Three previous studies investigated only in-hospital mortality [10,12,13] and the others did not examine the impact of liver disease on mortality more than 30 days after colorectal surgery [9,11,14,15]. To our knowledge, no previous study has focused on postoperative mortality following colorectal surgery for DD in patients with and without liver disease. We therefore undertook a population-based cohort study to examine postoperative mortality and rate of reoperation after DD surgery in patients with liver disease compared to those without liver disease. We also assessed the effect of liver disease on mortality in relevant patient subgroups. Such data are needed to understand and potentially prevent postoperative mortality.

METHODS

This cohort study was conducted within the entire Danish population, which consisted of 8.2 million persons during the study period (January 1, 1977 through January 1, 2012). The National Health Service provides tax-funded medical care for all Danish residents [16]. Since 1968, a unique civil personal registration (CPR) number has been assigned to every Danish resident at birth or upon immigration [17]. The CPR number

allows accurate record linkage at the individual level among all Danish registries.

Study population

Our study cohort included all patients diagnosed with DD, who underwent colorectal surgery for this indication for the first time. Patients with a diagnosis of complicated or uncomplicated DD were identified using the Danish National Registry of Patients (DNRP), which includes information on all Danish non-psychiatric hospitalizations since 1977 and on outpatient hospital specialist clinics contacts since 1995 [18]. Diagnoses were recorded according to the *International Classification of Diseases* (ICD)*, 8th revision* (ICD-8) until 1993 and the *10th revision* (ICD-10) thereafter. Each record includes the date of hospital admission and discharge, up to 20 discharge diagnoses, type of admission (non-elective or elective), and information about type of surgical procedure. From 1977 to 1995, surgical procedures were coded according to the Danish classification of surgical procedures. Since 1996, they have been coded according to the NOMESCO (Nordic Medico-Statistical Committee) classification of surgical procedures [19]. Before 1996, date of surgery was defined as the date of the relevant hospital admission because the procedure date was not recorded in the DNRP.

We defined DD as the indication for colorectal surgery if complicated or uncomplicated DD was listed as the primary or a secondary diagnosis during the relevant hospitalization. We excluded patients who were given a primary or secondary diagnosis of colorectal cancer during the same hospitalization (n = 394).

We divided procedure types of primary surgery into two groups: surgery that required stoma creation and surgery without stoma [20]. We also classified admissions as elective or non-elective as an indication of the acuteness of patient presentation [4].

Liver disease

We used the DNRP to identify patients receiving a diagnosis of liver disease before or during the relevant admission for DD surgery and categorized them into three cohorts: patients with non-cirrhotic liver disease, those with liver cirrhosis, and those without

liver disease (comparison cohort). Non-cirrhotic liver disease included all liver disease diagnoses except cirrhosis, *e.g*., viral hepatitis, alcoholic hepatitis, non-alcoholic fatty liver disease, and primary biliary cirrhosis [14,21].

Potential confounders

We computed Charlson Comorbidity Index (CCI) scores to quantify patients' burden of comorbidity in addition to liver disease, based on diagnoses registered in the DNRP at any time prior to or during the DD surgery admission [22]. The CCI includes 19 diseases, each assigned a weight between one and six. The sum of the individual scores represents a measure of a patient's level of comorbidity. We modified the original index for use with ICD-8 and ICD-10 diagnosis codes [23] and excluded mild and severe liver disease from the index score. We classified patients as having a low comorbidity level (score = 0), a moderate comorbidity level (score = 1-2), or a high comorbidity level (score ≥ 3). In addition, because alcohol abuse has been reported to be associated with increased morbidity after colorectal surgery regardless of the presence of liver disease [24-26], we obtained information on previous hospital diagnoses of alcohol abuse and/or alcohol-related diseases. For each patient we also summarized the number of inpatient hospital admissions due to DD before the admission for DD surgery as none, 1-2, and 3+ admissions [27]. Finally, we obtained information about marital status [28] using the Civil Registration System (CRS), which tracks the vital status, marital status, and residence of all Danish citizens. The CRS is updated on a daily basis [29].

Mortality and reoperation data

We followed patients from their date of DD surgery until death, emigration, or end of study, whichever came first. Date of death or emigration was obtained from the CRS. We used the DNRP to obtain data on reoperations within 30 days following DD surgery [30].

Diagnostic and surgical codes are provided in the Appendix (Supplementary material).

Statistical analysis

Our primary outcome was postoperative mortality. For this analysis, we used the Kaplan-Meier method primarily to compute cumulative 30-day mortality in each patient cohort, but also to compute 31-60 and 61-90-day mortality with 95% confidence intervals (CIs) [31].

In addition, we evaluated 30-day mortality stratified by elective vs. non-elective hospital admissions in each patient cohort. In order to evaluate differences in the postoperative mortality risk among patients undergoing DD surgery over time, we also stratified 30-day mortality into two roughly equal periods: 1977-1993 and 1994-2011.

We used a Cox regression model controlling for potential confounding factors to compare postoperative mortality among patients undergoing DD surgery who had non-cirrhotic or cirrhotic liver disease with that among patients without liver disease. Crude and adjusted hazard ratios with 95% CIs were computed as a measure of the relative risk (RR) of death.

To examine the impact of liver disease on 30-day mortality in different demographic/medical subgroups, we estimated RRs stratified by gender, age category (0-59, 60-69, and 70+ years), calendar period of surgery, comorbidity level, type of admission, type of surgery, history of non-hepatic alcohol-related disease, marital status, and number of DD-related hospital admissions before admission for DD surgery.

We computed reoperation rates, our secondary outcome, within 30 days following surgery, treating death as a competing risk [32].

Analyses were performed using STATA version 12.0 (StataCorp LP, College Station, TX, USA). The study was approved by the Danish Data Protection Agency, record number 2006-41-6707. The use of data obtained from Danish registries is generally available to researchers and their use does not require informed consent.

RESULTS

Descriptive data

We identified 14,408 patients undergoing first-time DD surgery. Of these, 233 (1.6%) had non-cirrhotic liver disease, 91 (0.6%) had liver cirrhosis, and 14,084 (97.8%) had no liver disease. Median age at DD surgery was 67 years among patients without liver disease, 64 years among patients with non-cirrhotic liver disease, and 60 years among those with liver cirrhosis. Patients without liver disease were more likely to be female than patients with liver diseases (Table 1). Among non-cirrhotic liver disease patients, 39 (17%) had alcoholic liver disease, 19 (8.2%) had viral hepatitis, 14 (6.0%) had non-alcoholic fatty liver disease, 7 (3.0%) had primary biliary cirrhosis, and 154 (66%) had other non-cirrhotic liver diseases.

Patients with liver disease, in particular those with liver cirrhosis, were more likely to have comorbid conditions, to have never married, and to have a stoma placed during DD surgery, compared with patients without liver disease (Table 1). The distribution of individual diseases included in the CCI for each cohort is reported in Supplementary Table 1.

Postoperative mortality

Thirty-day mortality was 14.6% in patients with non-cirrhotic liver disease and 24.2% in patients with liver cirrhosis, compared with 9.9% in patients without liver disease (Table 2 and Figure 1).

Among patients surviving 30 days after DD surgery, mortality in the following 30 days was 3.0% among those with non-cirrhotic liver disease, 7.3% among those with liver cirrhosis, compared with 2.5% among patients without liver disease. Among patients surviving the first 60 days, mortality in the third month was between 1% and 2% in all three cohorts (Supplementary Table 2).

As expected, in each cohort 30-day mortality was markedly higher among DD patients with a non-elective admission than among those electively admitted (Table 2). Thirty-

day mortality stratified by calendar period of DD surgery was higher for the period 1994-2011 than for the period 1977-1993 (Table 2).

Compared with the cohort of DD patients without liver disease, the adjusted RR for 30-day mortality was 1.64 (95% CI: 1.16-2.31) for patients with non-cirrhotic liver disease and 2.70 (95% CI: 1.73-4.22) for patients with liver cirrhosis (Table 2). Liver disease increased risk of postoperative mortality up to 60 days after DD surgery, although the estimates were imprecise (Supplementary Table 2).

Table 3 shows 30-day RRs of death after DD surgery for patients with non-cirrhotic liver disease and those with liver cirrhosis, compared to those without liver disease, stratified into other demographic/medical subgroups. Liver disease was associated with an increased RR of postoperative mortality after DD surgery in all of the different subgroups, although the low number of deaths among liver disease patients in each stratum resulted in imprecise estimates. Notably, the impact of both non-cirrhotic liver disease and liver cirrhosis on 30-day mortality was markedly pronounced among patients without non-hepatic alcohol-related disease undergoing DD surgery, with RRs of 1.91 (95% CI: 1.34-2.74) and 4.11 (95% CI: 2.50-6.76), respectively.

Reoperation

Reoperation rates within the first 30 days after DD surgery did not greatly differ among study cohorts. Among patients with non-cirrhotic liver disease 10.7% (95% CI: 7.2%-15.1%) underwent reoperation and among those with liver cirrhosis 7.7% (95% CI: 3.4%-14.3%) underwent reoperation, compared to 8.3% (95% CI: 7.8%-8.7%) among patients without liver disease.

DISCUSSION

We found that postoperative mortality after DD surgery was substantially higher among patients with liver disease than among those without liver disease. Moreover, we found that liver disease had an impact on mortality up to 60 days after surgery. The impact of both non-cirrhotic liver disease and liver cirrhosis was particularly evident

among patients without non-hepatic alcohol-related disease. Despite findings for 30-day mortality, reoperation frequency after DD surgery did not differ markedly among the three cohorts.

To our best knowledge, this is the first study to investigate postoperative mortality in patients with liver disease who undergo DD surgery. Earlier studies, that investigated in-hospital or 30-day mortality among liver disease patients undergoing colorectal surgery, did not take into account the disease leading to surgery or included only patients with colorectal cancer [9-15]. Thus in a US population-based study, Nguyen *et al.* investigated in-hospital mortality after colorectal surgery for any indication, comparing 4,242 patients with liver cirrhosis to 499,541 without liver cirrhosis [13]. In-hospital mortality was 18% among patients with liver cirrhosis and 5% among those without this condition. In 2010, Ghaferi *et al*. compared 30-day mortality after colorectal surgery in patients with chronic liver disease (n = 1,565), including both non-cirrhotic and cirrhotic liver disease, with that in patients without liver disease (n = 29,362). Patients with chronic liver disease had a postoperative mortality rate of 22%, compared to 3.2% among patients without liver disease [9].

Our study corroborated high postoperative mortality in patients with liver disease, but it also showed markedly higher postoperative mortality among patients without liver disease, compared with earlier studies [9-15].

A population-based study that investigated mortality after DD surgery in England showed overall 30-day mortality to be 10.1% [2]. The reported postoperative mortality after elective and non-elective DD surgery was 2.1% and 15.9%, respectively. Our study showed similar 30-day mortality both overall and stratified by elective and non-elective surgery among patients without liver disease. These findings support our hypothesis that inclusion of patients with different diseases leading to surgery in previous studies that investigated the impact of liver disease on mortality after colorectal surgery may have affected their estimates. The higher impact of liver disease on postoperative mortality among patients without non-hepatic alcohol-related disease than among those with that condition confirmed previous studies that reported alcohol abuse to be independently associated with increased morbidity after colorectal surgery [24-26]. Finally, the finding of no difference among reoperation

rates in the three cohorts may be explained by the hesitancy to reoperate patients with liver disease, especially those with liver cirrhosis because of the serious prognosis.

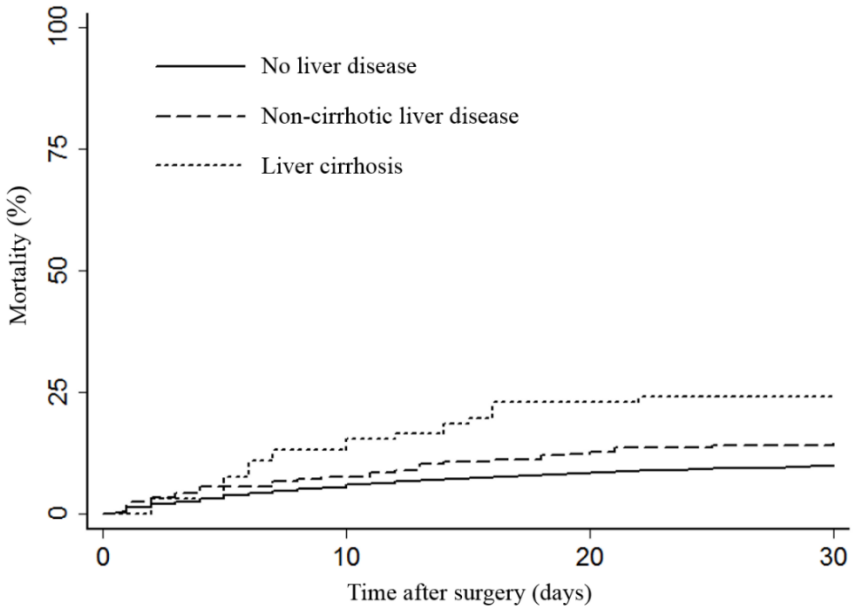
High postoperative mortality in patients with liver disease may have several explanations. Liver disease affects recuperative capacity and increases risk of death. Indeed, liver disease often induces portal hypertension, resulting in gastrointestinal manifestations such as bleeding gastroesophageal varices, hypertensive gastropathy/colopathy, ascites, and spontaneous bacterial peritonitis [13,33,34]. Moreover, advanced liver cirrhosis involves different organ systems, leading to hepatic coagulopathy, hepatic encephalopathy, renal dysfunction, malnutrition, and impaired immune function. Consequently, surgery may precipitate hepatic decompensation and thus increase risk of morbidity, postoperative complication, and mortality [7,8,35]. The evidence of markedly high absolute mortality after non-elective hospital admissions among patients with liver cirrhosis may be partially explained by the difficulty of optimizing the condition of liver disease patients before unplanned surgery. Finally, we found higher 30-day mortality among patients with and without liver disease, who underwent DD surgery after 1994 than in those undergoing the same surgery before that date. These findings may be explained partially by changes in the surgical indication for DD during the study period [27].

The validity of our risk estimates depends on several factors. We used population-based databases with complete follow-up. We had complete data on surgical procedures [36] and on hospital diagnoses [37], minimizing selection and referral biases. Data in the DNRP on liver diseases [38], surgical procedures [36], and comorbidity [23] have high positive predictive value when compared with diagnoses in medical records. Nonetheless, we cannot rule out that our results were affected by some misclassifications. For instance, some patients with mild liver diseases might not have been recorded in the DNRP due to underreporting. Conversely, some patients correctly recorded with a liver disease diagnosis might have been diagnosed with a non-cirrhotic disease instead of liver cirrhosis or vice versa. Regardless of the origin of such misclassification, the potential bias is somewhat unpredictable since patients are categorized in more than two exposure groups, but our risk estimates are most likely conservative [39]. Finally, although we adjusted for potential confounders, including comorbidities, we cannot entirely rule out some residual (*e.g.*: alcoholism, severity of

comorbidities) or unmeasured confounding (*e.g.*: smoking, malnutrition). Moreover, misclassification of the specific information about patients with/without perforated DD, sepsis, or peritonitis prevented us from adjusting for the severity of the DD [40].

In conclusion, we found that patients with liver diseases, particularly liver cirrhosis, had markedly increased postoperative mortality after DD surgery compared to patients without liver disease. At the same time, risk of reoperation did not differ substantially among patients with and without liver disease. Perioperative management and individualized risk assessment together with prolonged postoperative care may improve survival among patients with liver cirrhosis undergoing DD surgery.

Figure 1. Crude cumulative 30-day mortality curves for patients undergoing surgery for diverticular disease, according to history of liver disease.



No. at risk				
No liver disease	14 084	13 302	12 898	12 687
Non-cirrhotic liver disease	233	215	204	200
Liver cirrhosis	91	79	70	69

Table 1. Characteristics of patients with and without liver disease undergoing surgery for diverticular disease, Denmark, 1977-2011.

	No liver disease N (%) Total = 14,084	Non-cirrhotic liver disease N (%) Total = 233	Liver cirrhosis N (%) Total = 91
Gender			
- Male	5,966 (42%)	106 (46%)	53 (58%)
- Female	8,118 (58%)	127 (55%)	38 (42%)
Age (years)			
- 0-59	4,489 (32%)	85 (37%)	45 (50%)
- 60-69	3,636 (26%)	67 (29%)	21 (23%)
- 70+	5,959 (42%)	81 (35%)	25 (28%)
Period of surgery			
- 1977 to 1993	6,597 (47%)	76 (33%)	38 (42%)
- 1994 to 2011	7,487 (53%)	157 (67%)	53 (58%)
Type of admission			
- Non-elective	8,828 (63%)	146 (63%)	62 (68%)
- Elective	5,220 (37%)	86 (37%)	29 (32%)
- Missing	36 (0.3%)	1 (0.4%)	0 (0.0%)
Type of surgery			
- Surgery without stoma	8,756 (62%)	127 (55%)	47 (52%)
- Surgery with stoma	5,328 (38%)	106 (44%)	44 (48%)
Comorbidity level			
- Low	9,209 (65%)	121 (52%)	39 (43%)
- Moderate	3,790 (27%)	79 (34%)	39 (43%)
- High	1,085 (7.7%)	33 (14%)	13 (14%)
Non-hepatic alcohol-related disease present[†]	367 (2.6%)	45 (19%)	39 (43%)
Marital status:			
- Married	7,641 (54%)	134 (58%)	39 (43%)
- Never married	1,142 (8.1%)	25 (11%)	17 (19%)
- Other	5,301 (38%)	74 (32%)	35 (38%)
Previous admissions for diverticular disease			
- None	9,467 (67%)	138 (59%)	65 (71%)
- 1 or 2 admissions	3,512 (25%)	73 (31%)	19 (21%)
- More than 2	1,105 (8%)	22 (10%)	7 (8%)

[†] Including diagnoses of alcohol abuse and non-hepatic alcohol-related diseases.

Table 2. Thirty-day mortality and relative risk in patients with and without liver disease undergoing surgery for diverticular disease, overall and stratified by type of admission and period of surgery.

	No. of patients	No. of deaths	30-day mortality %*	RR (95% CI)	
	N	N	(95% CI)	Crude	Adjusted‡
Diverticular disease surgery					
No liver disease	14,084	1,400	9.9 (9.5-10.5)	1.00	1.00
Non-cirrhotic liver disease	233	34	14.6 (10.7-19.8)	1.50 (1.07-2.11)	1.64 (1.16-2.31)
Liver cirrhosis	91	22	24.2 (16.6-34.4)	2.62 (1.72-3.99)	2.70 (1.73-4.22)
Elective admission§					
No liver disease	5,220	120	2.3 (1.9-2.7)	1.00	1.00
Non-cirrhotic liver disease	86	2	2.3 (0.6-9.0)	1.01 (0.25-4.09)	0.83 (0.20-3.39)
Liver cirrhosis	29	1	3.5 (0.5-22.1)	1.50 (0.21-10.73)	2.27 (0.30-17.14)
Non-elective admission§					
No liver disease	8,828	1,279	14.5 (13.8-15.3)	1.00	1.00
Non-cirrhotic liver disease	146	32	21.9 (16.0-29.5)	1.57 (1.11-2.24)	1.72 (1.20-2.45)
Liver cirrhosis	62	21	33.9 (23.6-47.1)	2.59 (1.69-3.99)	2.68 (1.70-4.24)
1977-1993					
No liver disease	6,597	556	8.4 (7.8-9.1)	1.00	1.00
Non-cirrhotic liver disease	76	8	10.5 (5.4-20.0)	1.27 (.63-2.54)	1.48 (0.73-3.00)
Liver cirrhosis	38	8	21.1 (11.1-37.7)	2.67 (1.33-5.36)	3.25 (1.53-6.89)
1994-2011					
No liver disease	7,487	844	11.3 (11.0-12.0)	1.00	1.00
Non-cirrhotic liver disease	157	26	16.6 (11.6-23.4)	1.50 (1.02-2.22)	1.69 (1.13-2.51)
Liver cirrhosis	53	14	26.4 (16.6-40.5)	2.52 (1.49-4.28)	2.42 (1.39-4.21)

Abbreviations: relative risk (RR), confidence interval (CI)

*Calculated using the Kaplan-Meier method.

‡ Mutually adjusted for gender, age (both as a continuous and a categorical variable), type of admission, type of surgery, comorbidity level, non-hepatic alcohol-related disease, and marital status.

§Information on type of admission is missing for some patients. Therefore the sum of patients with non-elective and elective admissions is not equal to the number of all patients included in the study.

Table 3. Relative risk of 30-day postoperative mortality in subgroups of patients with liver disease compared to patients without liver disease, adjusted for potential confounding factors.

	No liver disease	Non-cirrhotic liver disease Adjusted RR‡ (95% CI)	Liver cirrhosis Adjusted RR‡ (95% CI)
Gender			
- Male	1.00	2.01 (1.22-3.31)	3.07 (1.55-6.05)
- Female	1.00	1.40 (0.86-2.27)	2.50 (1.38-4.54)
Age (years):			
- 0-59	1.00	1.42 (0.51-3.96)	4.66 (2.10-10.37)
- 60-69	1.00	2.89 (1.59-5.26)	1.96 (0.70-5.48)
- 70+	1.00	1.34 (0.84-2.15)	2.43 (1.26-4.67)
Type of surgery			
- Surgery without stoma	1.00	1.66 (0.84-3.28)	3.34 (1.58-7.07)
- Surgery with stoma	1.00	1.64 (1.10-2.45)	2.38 (1.37-4.16)
Comorbidities level			
- Low	1.00	1.54 (0.77-3.07)	4.41 (1.97-9.84)
- Moderate	1.00	1.92 (1.14-3.23)	2.42 (1.22-4.83)
- High	1.00	1.40 (0.74-2.65)	2.18 (0.92-5.18)
Non-hepatic alcohol-related disease †			
- Yes	1.00	0.51 (0.16-1.64)	1.18 (0.50-2.79)
- No	1.00	1.91 (1.34-2.74)	4.11 (2.50-6.76)
Marital status			
- Married	1.00	1.88 (1.20-2.94)	2.31 (0.91-5.86)
- Never married	1.00	1.79 (0.65-4.94)	4.05 (1.79-9.16)
- Other	1.00	1.22 (0.64-2.31)	2.36 (1.21-4.60)
Previous admissions for diverticular disease			
- None	1.00	1.67 (1.11-2.53)	3.59 (2.25-5.73)
- 1 or 2 admissions	1.00	2.62 (1.27-5.42)	0.43 (0.06-3.30)
- More than 2	1.00	0.95 (0.23-4.00)	2.06 (0.27-15.53)

Abbreviations: relative risk (RR), confidence interval (CI)

‡ Mutually adjusted for gender, age (both as a continuous and a categorical variable), type of admission, type of surgery, comorbidity level, non-hepatic alcohol-related disease, and marital status.

† Including diagnoses of alcohol abuse and non-hepatic alcohol-related diseases.

Appendix

ICD codes, NOMESCO codes, and the Danish classification of surgical procedures used in the analysis.

The Danish National Registry of Patients

Hospital diagnoses:

- *Diverticular disease:* ICD-8: 562.10, 562.11, 562.18, 562.19, 562.12; ICD-10: K57.3, K57.5, K57.9, K57.2, K57.4, K57.8
- *Colorectal cancer (codes used to exclude patients from the study cohort):* ICD-8: 153-154 ; ICD-10: C18-C20
- *Colorectal surgery:*
    - Surgery without stoma: Danish classification of surgical procedures (1977 - 1995): 43700, 43800, 43820, 43840, 43860, 43880, 44140, 44150, 44200, 44900, 44920, 44940, 44960, 44980, 45020, 45060, 45065, 45100, 45120, 45690, 46210, 46350, 46400, 46410, 46430, 46440, 46450, 46490, 46530, 46709, 47310, 47320, 47330, 47340, 47350, 47360, 47370, 43701, 43801, 43821, 44901, 44921, 44941, 44961, 44981, 45021, 45061, 45691; NOMESCO codes (since 1996): KJFA83, KJFA96, KJFB20, KJFB30, KJFB 33, KJFB40, KJFB43, KJFB46, KJFB50, KJFB96, KJFH00, KJFH30, KJFH96, KJFW96, KJFW98, KJFC00, KJFC10, KJFC20, KJFC30, KJFC40, KJFC50, KJFA84, KJFA97, KJFB21, KJFB31, KJFB34, KJFB41, KJFB44, KJFB47, KJFB51, KJFB97, KJFH01, KJFH11, KJFH31, KJFW97, KJFC01, KJFC11, KJFC21, KJFC31, KJFC41, KJFC51;
    - Surgery with stoma: Danish classification of surgical procedures: 43740, 45180 or any code included in the “surgery without stoma” classification in addition to 43741 or 43745 or 43750 or 43751 or 43759 or 45160 or 45200 or 45201 or 45210 or 45240 or 47000 or 47100 or 47110 or 47120 or 47220; NOMESCO codes: KJFB60, KJFB61, KJFB63, KJFB64, KJFH10, KJFH20, KJFH11, KJFH21, KJFH33, KJFH40 or any code

included in the “surgery without stoma” classification in addition to KJFF 13 or KJFF16 or KJFF20 or KJFF21 or KJFF23 or KJFF24 or KJFF26 or KJFF27 or KJFF30 or KJFF31 or KJFF96 or KJFF97

- *Reoperation codes:*
    - Reoperation after colorectal surgery for wound dehiscence: Danish classification of surgical procedures: 49020, 49040; NOMESCO: KJWA
    - Reoperation after colorectal surgery because of bleeding: Danish classification of surgical procedures: 48960, 48961; NOMESCO: KJWD, KJWE
    - Reoperation after colorectal surgery because of infection: Danish classification of surgical procedures: 49000, 49001; NOMESCO: KJWB, KJWC
    - Reoperation after colorectal surgery because of insufficient anastomosis: Danish classification of surgical procedures: 48980, 48981; NOMESCO: KJWF
    - Reoperation after colorectal surgery for other causes: NOMESCO: KJWW
- *Liver cirrhosis*: ICD-8: 571.09, 571.92, 571.99; ICD-10: K70.3, K71.7, K74.5, K74.6
- *Non-cirrhotic liver disease*: ICD-8: 570.00–573.09 (excluding 571.09, 571.92, and 571.99), 070.01-070.09; ICD-10: K70.0- K70.9 (excluding K70.3), R74.0, K71.0–K77.8 (excluding K71.7, K74.5, and K74.6), B15–B19
- *Disease included in the modified Charlson Comorbidity Index:*
    - Myocardial infarction: ICD-8: 410; ICD-10: I21, I22, I23
    - Congestive heart failure: ICD-8: 427.09, 427.10, 427.11, 427.19, 428.99, 782.49; ICD-10: I50, I11.0, I13.0, I13.2
    - Peripheral vascular disease: ICD-8: 440, 441, 442, 443, 444, 445; ICD-10: I70, I71, I72, I73, I74, I77
    - Cerebrovascular disease: ICD-8: 430-438; ICD-10: I60-I69, G45, G46
    - Dementia: ICD-8: 290.09-290.19, 293.09; ICD-10: F00-F03, F05.1, G30
    - Chronic pulmonary disease: ICD-8: 490-493, 515-518; ICD-10: J40-J47, J60-J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3

    - Connective tissue disease: ICD-8: 712, 716, 734, 446, 135.99; ICD-10: M05, M06, M08, M09, M30, M31, M32, M33, M34, M35, M36, D86
    - Ulcer disease: ICD-8: 530.91, 530.98, 531-534; ICD-10: K22.1, K25-K28
    - Uncomplicated type 1 and type 2 diabetes: ICD-8: 249.00, 249.06, 249.07, 249.09, 250.00, 250.06, 250.07, 250.09; ICD-10: E10.0, E10.1, E10.9, E11.0, E11.1, E11.9
    - Hemiplegia: ICD-8: 344; ICD-10: G81, G82
    - Moderate to severe renal disease: ICD-8: 403, 404, 580-583, 584, 590.09, 593.19, 753.10-753.19, 792; ICD-10: I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61
    - Diabetes with end-organ damage: ICD-8: 249.01-249.05, 249.08, 250.01-250.05, 250.08; ICD-10: E10.2-E10.8, E11.2-E11.8
    - Any tumor: ICD-8: 140-19; ICD-10: C00-C75
    - Leukemia: ICD-8: 204-207; ICD-10: C91-C95
    - Lymphoma: ICD-8: 200-203, 275.59; ICD-10: C81-C85, C88, C90, C96
    - Metastatic solid tumor: ICD-8: 195-198, 199; ICD-10: C76-C80
    - AIDS: ICD-8: 079.83; ICD-10: B21-B24
- *Non-hepatic alcohol-related disease:* ICD-8: 291-291.9, 303-303.9, 980; ICD-10: F10.2, F10.7, F10.8, I42.6, G62.1, K29.2, G72.1, G31.2, T51, Z72.1

Supplementary Table 1. Prevalence of individual diseases from the Charlson Comorbidity Index in patients with and without liver diseases undergoing surgery for diverticular disease in Denmark, 1977-2011.

	No liver disease N (%) Total = 14 084	Non-cirrhotic liver disease N (%) Total = 233	Liver cirrhosis N (%) Total = 91
Myocardial infarction	646 (4.6%)	10 (4.3%)	4 (4.4%)
Congestive heart failure	590 (4.2%)	18 (7.7%)	4 (4.4%)
Peripheral vascular disease	517 (3.7%)	15 (6.4%)	9 (9.9%)
Cerebrovascular disease	881 (6.3%)	22 (9.4%)	12 (13.2%)
Dementia	120 (0.9%)	5 (2.2%)	2 (2.2%)
Chronic pulmonary disease	1 178 (8.4%)	31 (13.3%)	18 (19.8%)
Connective tissue disease	687 (4.9%)	20 (8.6%)	4 (4.4%)
Ulcer disease	755 (5.4%)	20 (8.6%)	14 (15.4%)
Diabetes type 1 and 2	464 (3.3%)	15 (6.4%)	7 (7.7%)
Hemiplegia	32 (0.2%)	0 (0.0%)	0 (0.0%)
Moderate to severe renal disease	294 (2.1%)	12 (5.2%)	4 (4.4%)
Diabetes with end-organ damage	131 (0.9%)	6 (2.6%)	3 (3.3%)
Any tumor	1 104 (7.8%)	23 (9.9%)	8 (8.8%)
Leukemia	41 (0.3%)	1 (0.4%)	0 (0.0%)
Lymphoma	81 (0.6%)	0 (0.0%)	2 (2.2%)
Metastatic solid tumor	142 (1.0%)	3 (1.3%)	1 (1.1%)
AIDS	3 (<0.1%)	0 (0.0%)	0 (0.0%)

Supplementary Table 2. Postoperative mortality and relative risk in patients with and without liver disease within 31-60 and 61-90 days following surgery for diverticular disease.

	31- to 60-day mortality			61- to 90-day mortality		
	%* (95% CI)	RR (95% CI)		%* (95% CI)	RR (95% CI)	
		Crude	Adjusted‡		Crude	Adjusted‡
Diverticular disease surgery						
No liver disease	2.5 (2.3-2.8)	1.00	1.00	1.0 (0.9-1.2)	1.00	1.00
Non-cirrhotic liver disease	3.0 (1.4-6.6)	1.20 (0.54-2.69)	1.57 (0.69-3.54)	1.0 (0.3-4.1)	1.03 (0.26-4.17)	1.01 (0.24-4.23)
Liver cirrhosis	7.3 (3.1-16.5)	2.90 (1.20-7.01)	5.19 (1.96-13.72)	1.6 (0.2-10.7)	1.58 (0.22-11.32)	1.16 (0.14-9.37)

Abbreviations: relative risk (RR), confidence interval (CI)

*Calculated using the Kaplan-Meier method.

‡ Mutually adjusted for gender, age (both as a continuous and a categorical variable), timing of admission, type of surgery, comorbidity level, non-hepatic alcohol-related disease, and marital status.

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Paper III

Impact of preoperative serum albumin on 30-day mortality, reoperation, and acute kidney injury following surgery for colorectal cancer: a population-based cohort study

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ABSTRACT

Background: Surgery is the only potentially curable treatment for colorectal cancer (CRC). Human serum albumin (HSA) below 35 g/L is a predictor of poor prognosis but its impact on 30-day prognosis among patients undergoing CRC surgery has not been investigated in a population-based setting.

Methods: We performed a cohort study including patients undergoing CRC surgery in North and Central Denmark (1997-2011). We categorized these patients according to HSA concentration measured one to 30 days prior to surgery date. We assessed mortality, reoperation, and acute kidney injury (AKI) rates within 30 days following CRC surgery and we used Cox regression model to compute hazard ratios (HRs) as measures of the relative risk, controlling for potential confounders.

Results: Of the 9,339 patients undergoing first-time CRC surgery with HSA measurement, 26.4% (2,464) had HSA below 35 g/L. Thirty-day mortality increased from 4.9% among patients with HSA 36-40 g/L to 26.9% among patients with HSA equal to or below 25 g/L, compared to 2.0% among patients with HSA above 40 g/L. The corresponding adjusted HRs increased from 1.75 (95% CI: 1.25-2.45) among patients with HSA 36-40 g/L to 7.59 (95% CI: 4.95-11.64) among patients with HSA equal to or below 25 g/L, compared with patients with HSA above 40 g/L. Low preoperative HSA also increased reoperation and AKI risk, although to a lesser extent.

Conclusion: A low preoperative HSA concentration is associated with substantial increased risk of 30-day mortality following CRC surgery and increased risk of postoperative AKI and reoperation.

Keywords: serum albumin; colorectal cancer; surgery; mortality; complications; epidemiology

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer in Europe[1] with surgery as the only curative treatment.[2] Within 30 days after CRC surgery, approximately 20% of patients develop at least one postoperative surgical complication[2], more than 5% undergo unplanned reoperation,[3, 4] and approximately 5% die.[2, 5] Among postoperative medical complications in colon and rectal surgery, acute kidney injury (AKI) is a major factor of morbidity and mortality.[6, 7] Moreover, preoperative conditions such as advanced cancer, presence of comorbidity, and old age have also been reported to increase postoperative mortality.[5, 8]

A common feature associated with previous conditions is a decrease in human serum albumin (HSA) concentration.[9, 10] HSA is the main circulating protein in healthy individuals and plays a major role in maintaining organ perfusion being responsible for 75% of the plasma oncotic pressure. Moreover, HSA is a multifunctional protein with antioxidant, immunomodulatory, and detoxification functions.[11] Therefore, a decrement in its concentration may contribute to increase the risk of mortality. Gibbs *et al.* reported that a decrease of HSA from concentrations greater than 46 g/L to less than 21 g/L was associated with a corresponding increase in 30-day mortality rates from 1% to 29% among more than 54,000 American veterans undergoing major noncardiac surgery.[12] Several studies have reported that HSA below 35 g/L is associated with poor overall survival after CRC surgery.[13-25] However, the association between preoperative HSA and 30-day mortality following CRC surgery has not been examined in a population-based setting. In addition, the existing studies that quantified the impact of low HSA on postoperative mortality and other complications were not able to properly control for potential confounding because of lack of information and small number of outcomes.[16, 18, 19, 26] Moreover, none of the previous studies examined if a decrement of preoperative HSA within the reference interval (35-50 g/L) is still associated with a corresponding increase in mortality risk in patients undergoing CRC surgery.

Systemic inflammation is well known to increase levels of acute-phase proteins such as C-reactive protein (CRP)[27] and decrease HSA concentration.[9] Moreover, survival in CRC patients with HSA below 35 g/L is even worse when associated with a concentration of CRP above 10 mg/L.[28-40] However, the impact of HSA on 30-day mortality in relation with preoperative CRP levels has not been examined.

We therefore conducted a large study within a population-based hospital setting with complete history of preadmission comorbidity to examine the impact of preoperative HSA below and within normal range on mortality, reoperation, and AKI within 30 days after CRC surgery. We further investigated the impact of HSA on 30-day mortality in subgroups of patients with different baseline preoperative risks and different CRP levels.

MATERIALS AND METHODS

Setting

We conducted this cohort study using prospectively collected data from medical registries in North and Central Denmark (former counties of North Jutland, Aarhus, Ringkjøbing, and Viborg, with approximately 2.15 million inhabitants) from 1 January 1997 to 31 December 2011. Since 1968, a unique civil personal registration (CPR) number has been assigned to every Danish resident at birth or upon immigration and allows accurate record linkage at the individual level among all Danish registries.[41]

Colorectal cancer patients

Our study cohort included patients diagnosed with CRC, who underwent colorectal surgery for this indication for the first time in North and Central Denmark during the period 1997-2011. CRC patients were identified using the Danish Cancer Registry (DCR), which contains date of diagnosis, stage, and other information of all incident cases of malignant neoplasms in Denmark since 1943.[42] Tumors registered after 1 January 1978 have been reclassified according to the *International Classification of Diseases* (ICD), *10th revision* (ICD-10). In order to identify which of these patients underwent CRC surgery, we linked them to the Danish National Registry of Patients (DNRP) which includes information on hospitalizations since 1977 and on outpatient contacts since 1995.[43] Each record includes the dates of hospital admission and discharge, up to 20 discharge diagnoses that have been recorded according to the ICD-8 until 1993 and according to the ICD-10 thereafter. The DNRP also collects type of admission (non-elective or elective) and information about surgery, including type and date of surgical procedure. Since 1996, surgical procedures have been coded according to the NOMESCO (Nordic Medico-Statistical Committee) Classification of

Surgical Procedures.[44] First-time CRC surgery was defined as the first procedure involving colorectal surgery performed during a hospitalization where CRC was listed as a diagnosis in the DNRP. CRC surgery was categorized according to the intention of eradicating the primary tumor as "radical resection" and "non-eradicative procedures". "Radical resection" included surgeries such as partial and total resections of the colon and/or rectum while "non-eradicative procedures" included colostomy, stent placement, or excision of a very small part of the colon. "Radical resection" was further divided into laparoscopic and open surgery. CRC stage was reported as "localized" if Dukes' stage A or B, "regionally spread" if Dukes' stage C, and "metastasized" if Dukes' stage D. We also collected information on type of admission, classified as elective or non-elective (*i.e.* acute or emergent) to describe the acuteness of patient presentation.[45] Using the Civil Registration System (CRS) which is updated on a daily basis and tracks the vital status, marital status, and residence of all Danish residents,[46] we restricted the study population to patients living in the study region at the time of the CRC surgery. Moreover, since counties started transferring data to the laboratory database at different times during the study period,[47] the study population was restricted to patients who had CRC surgery in North Jutland since 1997, in Aarhus since 2000, in Viborg since 2005, and in Ringkjøbing since 2006 (Supplementary Table 1). The laboratory database contains laboratory tests from inpatient stays, outpatient clinic visits, and visits to general practitioners.[47] The National Health Service provides tax-funded medical care covering surgery for all Danish residents and all types of CRC surgery were provided in the study region during the period investigated.

Preoperative serum albumin concentration

For each patient we searched the laboratory database for the preoperative measurement of HSA (rounded to the nearest integer) closest to the day of CRC surgery. Only measurements one to 30 days prior to surgery date were used. During the study period, the normal interval was 36-45 g/L for persons aged 40 to 70 years and 34-45 g/L for those older than 70 years. We categorized patients into the following cohorts: ≤ 25 g/L (severe hypoalbuminemia), > 25 g/L and ≤ 30 g/L (moderate hypoalbuminemia), > 30 g/L and ≤ 35 g/L (mild hypoalbuminemia), > 35 g/L and ≤ 40 g/L (low normal albuminemia), and > 40 g/L (high normal albuminemia).

Covariates

We quantified patients' burden of comorbidity using the Charlson Comorbidity Index (CCI) that includes 19 diseases, each assigned a score between one and six.[48] Using diagnoses registered in the DNRP, we identified the diseases in the CCI at any time prior to or during the CRC surgery admission,[49] excluding CRC and CRC metastases. We classified patients as having low (score = 0), moderate (score = 1-2), or high comorbidity level (score ≥ 3). We also identified patients with alcohol-related disease defined as alcohol abuse or alcohol-related diseases disregarding alcoholic liver disease.[50] Information about marital status was obtained using the CRS.[51]

Using the laboratory database we also collected information on other preoperative blood tests from one to 30 days prior to surgery such as hemoglobin, creatinine, CRP, *etc*. Model for End-stage Liver Disease (MELD) was recently reported being an independent predictor of mortality in patients with and without liver disease undergoing colorectal surgery.[52] Using values of creatinine, total bilirubin, and international normalized ratio (INR), we computed the preoperative MELD as previously described.[52, 53]

Postoperative mortality, reoperation and acute kidney injury

Our primary outcome was 30-day mortality. Information about date of death or emigration was obtained from the CRS. As secondary outcomes, we included reoperation and AKI occurring within 30 days following surgery. We used the DNRP to obtain data on reoperations. Creatinine levels in the first 30 days after CRC surgery were used to classify patients with postoperative AKI. AKI was defined according to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines as: (1) increase in serum creatinine equal or greater than 0.3 mg/dl (26.5 µmol/l) within 48 hours; or (2) increase in serum creatinine equal or greater than 1.5 times baseline (last preoperative creatinine measurement), which is known or presumed to have occurred within the prior seven days.[54] We did not have information about urinary volume. Diagnostic and surgical codes are provided in Appendix.

Statistical analysis

We followed patients from their exact date of CRC surgery until death, emigration, or end of study, whichever came first.

We used the Kaplan-Meier method primarily to compute cumulative 30-day mortality in each patient cohort defined using preoperative HSA.[55] We used Cox regression analysis controlling for potential confounding factors to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) as a measure of the relative risk for postoperative mortality in each patient cohort compared to patients with preoperative HSA above 40 g/L. The assumption of proportional hazards was checked graphically using log(-log(survival probability)) plots and was found appropriate.

To examine the impact of HSA on 30-day mortality in different subgroups, we stratified 30-day mortality and corresponding adjusted HRs by elective vs. non-elective hospital admissions, gender, age category (0-59, 60-69, 70-79, and 80+ years), cancer site (colon or rectum), cancer stage, type of surgery, comorbidity level, marital status, and MELD (< 10 and ≥ 10). We also stratified patients according to the year of surgery (1997-2005, 2006-2011).[56] Moreover, in order to investigate the impact of HSA in patients with similar inflammatory status we estimated 30-day mortality and corresponding HRs in each HSA cohort stratified by preoperative concentration of CRP (≤ 10 mg/L, > 10 mg/L and ≤ 20 mg/L, > 20 mg/L and ≤ 50 mg/L, and > 50 mg/L). We also estimated reoperation and AKI rates within 30 days following surgery, treating death as a competing risk.[57] We computed HRs and 95% CIs for reoperation and AKI using Cox regression analysis in each patient cohort compared to patients with preoperative HSA above 40 g/L.[58]

The categorization of HSA assumes that the impact of HSA on the outcomes is equal within the same interval and that it is discontinuous as interval boundaries are crossed.[59] In order to bridge such limitation, we used fractional polynomial Cox regression analysis to graphically describe adjusted HRs for 30-day mortality associated with preoperative HSA (as continuous variable) overall and stratified by CRP levels.[60] We also used fractional polynomials to assess adjusted HRs for reoperation and AKI. For all the fractional polynomial Cox regression analyses we assumed HRs equal to one for HSA equal to 40 g/L.

Finally, we conducted a sensitivity analysis to examine the potential influence of excluding patients with missing information on preoperative HSA and other variables. Therefore, missing data for type of admission, CRC stage (*i.e.* stage unknown), HSA and other laboratory measurements were imputed deterministically with 20 cycles or regression switching.[61] It was assumed that the data were "missing at random" meaning that the chance of information being missing does not depend on the value of the information itself. Adjusted HRs and 95% CIs for 30-

day mortality in each patient cohort compared to HSA above 40 g/L were assessed using the imputed dataset.

Analyses were performed using STATA version 12.0 (StataCorp LP, College Station, TX, USA). The study was approved by the Danish Data Protection Agency, record number 2009-41-3866. Data obtained from Danish registries are generally available to researchers and their use does not require informed consent.

RESULTS

Descriptive data

We identified 10,347 patients (median age 71, interquartile range: 62-78) undergoing first-time CRC surgery in the study period (Table 1 and Figure 1). Of those, 9,339 (90.3%) had at least one measurement of HSA in the 30 days before surgery and 9,669 (82.0%) in the week before surgery. HSA below 35 g/L was present in 26.4% (n = 2,464) of patients with preoperative HSA measurement. Patients with HSA equal to or below 40 g/L were more likely to be old, female, have comorbid conditions including alcohol-related disease, than those with HSA above 40 g/L (Table 1). Moreover, compared with patients with HSA above 40 g/L, patients with lower HSA were more likely to have metastasized cancer and primary localization in the colon. The prevalence of non-elective admission increased with the decrease of HSA. The distribution of individual diseases included in the CCI for each cohort is reported in Supplementary Table 2. Information on other preoperative blood tests and MELD score for each patient cohort is reported in Table 2. Preoperative CRP was available for 66.1% (n = 6,841) and it was markedly increased among patients with low HSA (Table 2). Information about patients with missing preoperative HSA (n = 1,008) are reported in Table 1, Table 2, and Supplementary Table 3.

Postoperative mortality

Overall 30-day mortality increased from 2.0% in patients with HSA above 40 g/L to 26.9% in patients with HSA equal to or below 25 g/L (Table 3 and Figure 2). The absolute mortality difference between the two cohorts was 25.0% (95% CI: 20.6%-29.3%).

The corresponding adjusted HRs increased from 1.75 (95% CI: 1.25-2.45) among patients with HSA 35-40 g/L to 7.59 (95% CI: 4.95-11.64) among patients with HSA equal to or below 25 g/L, compared with patients with HSA above 40 g/L. Age and admission type were largely responsible for the change in estimates by adjustment. As expected, in each cohort 30-day mortality was higher among patients admitted non-electively than among patients with an elective admission. Similarly, elderly patients had experienced higher postoperative mortality than younger patients (Table 3). However, adjusted HRs showed that a decrease in HSA was associated with a gradually increased risk of mortality regardless of type of admission or age group (Table 3).

Table 4 shows 30-day mortality and corresponding adjusted HRs for 30-day mortality after CRC surgery for patients in each cohort stratified by subgroups. In all the subgroups, postoperative mortality was lowest among patients with HSA above 40 g/L and gradually increased with decreasing HSA levels. Notably, 30-day mortality was affected even by changes within what is clinically considered the normal HSA range (35 g/L to 40 g/L as compared with >40 g/L) (Table 3 and 4). Adjusted HRs showed a markedly higher risk of mortality associated with a decrease in HSA in most of the subgroups, especially among patients with HSA below 35 g/L. However, 95% CIs tend to be imprecise and among patients stratified by CRP levels often included the unit.

The strong concentration-response relation between 30-day mortality and preoperative HSA was confirmed from the fractional polynomial analysis reporting adjusted HRs inversely associated with HSA concentration both overall and in patients with different CPR levels (Figure 3).

Reoperation and postoperative acute kidney injury

Reoperation rates within the first 30 days after CRC surgery did not greatly differ among study cohorts and did not increase with the decrease of HSA, except among patients with HSA equal to or below 25 g/L (Table 5). AKI rates within the 30 days after CRC surgery gradually increased from 19.5% among patients with HSA above 40 g/L to 29.2% among patients with HSA equal to or below 25 g/L. Notably, among patients that experienced postoperative AKI, 30-day mortality increased from 15.6% among patients with preoperative HSA above 40 g/L to 42.7% among those with

preoperative HSA equal to or below 25 g/L (data not shown). Adjusted HRs for reoperation and AKI indicated an increased risk associated with decrement of HSA below 35 g/L (Table 5 and Figure 4).

Sensitivity analysis

The impact of preoperative HSA concentration on 30-day mortality was similar after imputation of missing HSA measurements before CRC surgery. The adjusted 30-day HRs were 7.50 (95% CI: 5.10-11.03) for HSA below 25 g/L, 4.99 (95% CI: 3.51-7.10) for HSA 26-30 g/L, 2.76 (95% CI: 2.00-3.79) for HSA 31-35 g/L, and 1.78 (95% CI: 1.32-2.40) for HSA 36-40 g/L, compared to HSA above 40 g/L.

DISCUSSION

In this large cohort study conducted within a population-based hospital setting we found that 30-day mortality after CRC surgery was inversely associated with preoperative HSA concentration. In particular, we found that also a decrease in HSA within the reference interval is associated with an increased risk for mortality compared to patients with HSA above 40 g/L. Moreover, decrement in preoperative HSA was associated with increased mortality both among patients at high and low prior risk and among patients with CRP levels below and above 10 mg/L. Last, our findings suggested that decrement in HSA may have also an impact on reoperation and postoperative AKI.

Our study extends current knowledge by examining the differential impact of preoperative HSA concentration on 30-day prognosis following CRC surgery overall and in subgroups of patients in a population-based setting. In comparison with previous studies, we reported a similar prevalence of HSA below 35 g/L.[16-18, 22, 30, 62] However, former studies included CRC patients markedly different for cancer stage, acuteness of presentation, and age; therefore the prevalence of hypoalbuminemia ranged from 10% to 57%.[15-23, 28-33, 35, 36, 39] Previous studies investigating short-term prognosis in patients undergoing CRC surgery reported increased risk of postoperative complications among patients with HSA below 35 g/L.[15-19, 24, 25, 63, 64] Among previous studies, Lai *et al.* reported an increased risk of 2.15 (95% CI: 1.70-2.73) for 30-day mortality adjusting for potential confounding among patients with HSA below 35 g/L undergoing potentially curative elective CRC surgery, compared to patients with HSA above 35 g/L.[19] Our findings are supported

by previous studies and show that the impact of HSA on 30-day mortality has a concentration-response pattern and is not limited to the cut off of 35 g/L. Two previous studies were able to report that also variations in HSA concentration within the normal range had an impact on short-term mortality after gastro-intestinal elective surgery.[65, 66] However, none of the two studies reported relative estimates about the prognostic impact of HSA. Therefore, our study extended existing knowledge showing that decrement of HSA within the reference interval has an impact on postoperative mortality among patients undergoing CRC surgery. In particular, prognosis of cancer patients with low HSA and systemic inflammatory response has been explored using the Glasgow prognostic score that classifies high risk patients with both hypoalbuminemia (< 35 g/L) and CRP above 10 mg/L.[13] Our results suggested that although the Glasgow prognostic score may help to identify patients undergoing CRC surgery at high risk of death, postoperative mortality among those patients may vary from approximately 10% to 30%. Last, in accordance with our findings of increased risk of reoperation and postoperative AKI in patients with low HSA, one study reported six times increased risk of anastomotic leakage in patients undergoing CRC surgery with HSA below 35 g/L compared to HSA equal to or above 35 g/L[18] and a meta-analysis provided evidence for two times increased risk of AKI associated with 10 g/L decrement in HSA among patients undergoing surgery or admitted to an intensive care unit.[67]

Many different conditions affecting body recovering capacity may affect HSA concentration including cancer stage, old age, and systemic inflammation.[10, 68] For this reason, HSA has been used as indicator of patient severity and was found to be a good predictor of prognosis.[9] However, decrement in HSA may have a direct impact on prognosis affecting organ vascularization, hamper distribution of antibiotics, perpetuate inflammation, and promote intravascular coagulation. Indeed, during the past decade a better understanding the HSA structure and function has led to the concept that HSA has multifunctional properties ranging from provision of oncotic pressure, immune regulation, and endothelial stabilization to being a molecule that works in the intracellular compartment modifying several key pathophysiological mechanisms.[11] Our findings of increased risk of AKI and reoperation associated with decrement in HSA may partially support this hypothesis. A criticism that is often raised regarding causality between decreased HSA concentration and prognosis is that clinical trials provided contradictory results about prognosis

following HSA administration, especially among critically ill patients.[69-73] However, such argument is not sufficient to prove no causality but at most to indicate that prognosis is not affected by HSA administration. Moreover, HSA replacement has been shown beneficial in specific clinical conditions.[11, 74] Previous studies showing no benefit from HSA administration were performed in acute patients when their conditions were already worsened and this may have prevented the effect of HSA on prognosis. Moreover, the quality of administrated HSA should also be questioned based on previous studies investigating HSA in commercial solutions that reported high prevalence of oxidized forms[75] and in vitro immunosuppressive activity.[76]

The main strengths of our study include its large size, its population-based design with uniform access to health care in Denmark, comprehensive laboratory data, complete and accurate history of preadmission comorbidity,[49] and complete follow-up data. However, additional issues should be considered when interpreting our results. We do not have information on cause of death and this prevents us from investigating possible differences in the specific complication leading to death among patients with different preoperative HSA concentration. However, we showed that low HSA may increase the risk of conditions likely to be responsible for postoperative death such as AKI and complications requiring reoperation. Unmeasured or only partially measured conditions (*e.g.* malnutrition, infection, alcohol consumption, and smoking) known to affect HSA concentration may increase the risk of postoperative complications also through a not HSA-related pathway and therefore might have biased our estimates. However, the strength of association and the concentration-response pattern of HRs are unlikely explained only by residual or unmeasured confounding. Moreover, type and age were responsible for most of the variation between crude and adjusted HRs suggesting that these two factors were also acting as surrogates of other confounders Last, missing data on preoperative HSA may have biased our estimates in case the reason for observations being missing depends on the unseen observations themselves.[77] However, more than 50% of patients with missing HSA did not have any preoperative measurement suggesting that preoperative blood tests for these patients were not performed in a laboratory included in the database at the time of surgery. Moreover, we imputed missing HSA measurements using variables well known to be associated with HSA (*e.g.* age, comorbidity level, cancer stage, type of admission) and obtained estimates that were similar to those obtained from

the complete case analysis. Therefore, we believe it is strongly unlikely that missing data could have biased our findings.

In conclusion, our results showed that a decrement of preoperative HSA was associated with a concentration-dependent increased risk of mortality in the 30 days following CRC surgery even within concentrations corresponding with the actual reference interval. Furthermore, we showed that the impact of low HSA on postoperative mortality persisted among patients with different baseline preoperative risk and varying for severity of systemic inflammation. Finally, our findings suggested that decrement in HSA might increase postoperative mortality by increasing the risk of complications requiring reoperation and declining kidney function.

Figure 1. Flow chart of patient selection.

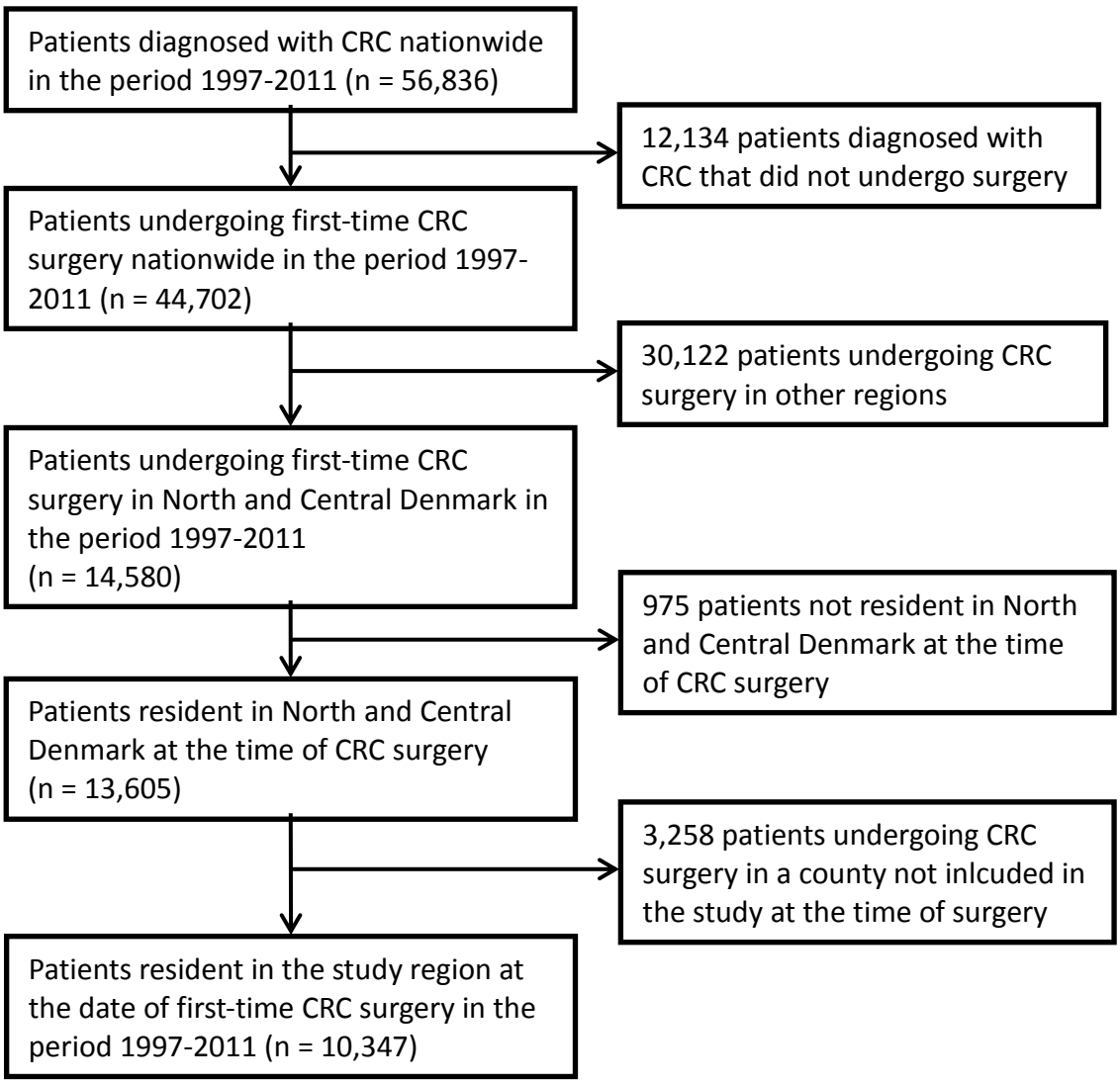


Figure 2. Crude 30-day mortality curves for patients undergoing surgery for colorectal cancer according to preoperative serum albumin concentration.

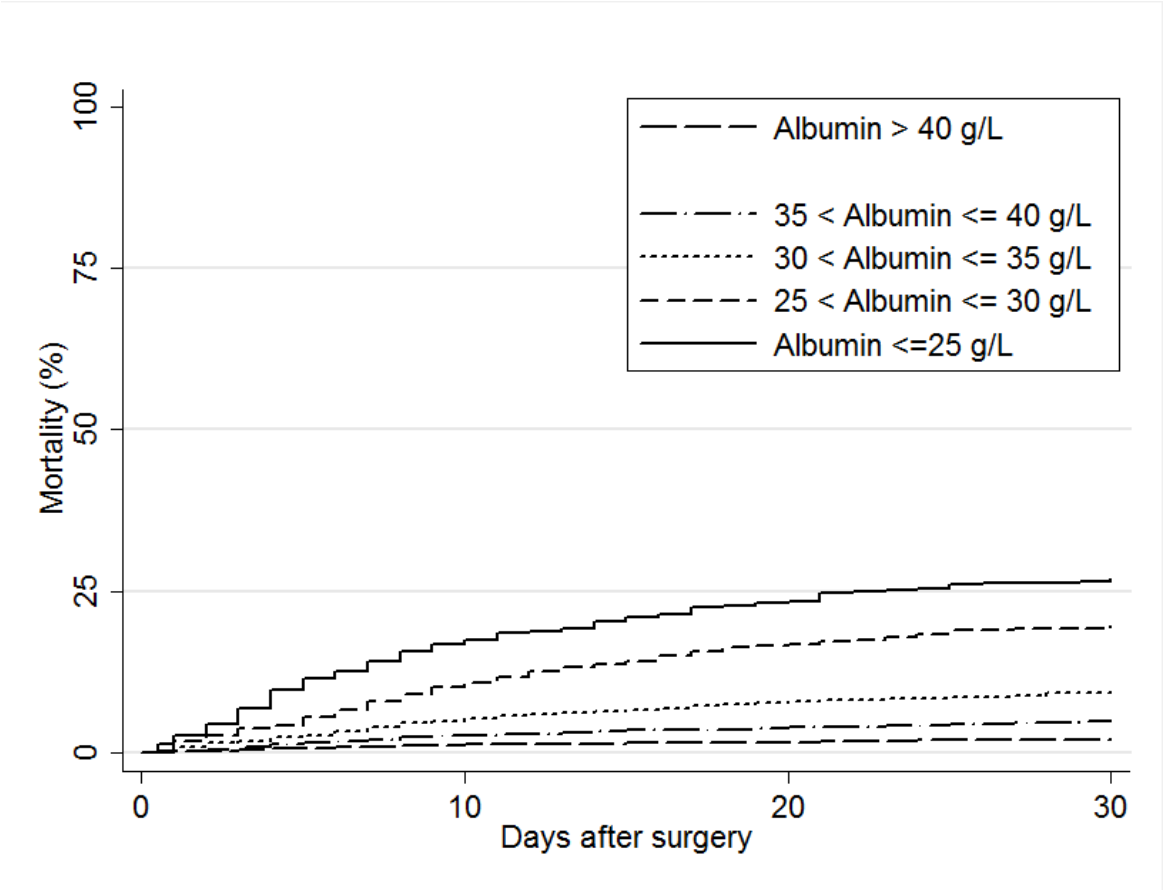


Figure 3. Adjusted hazard ratios (HRs) for 30-day mortality, overall (A) and stratified by C-reactive protein (CRP) levels (B), associated with preoperative HSA concentration. Adjusted HRs in Figure A are provided with 95% confidence interval (dashed lines).

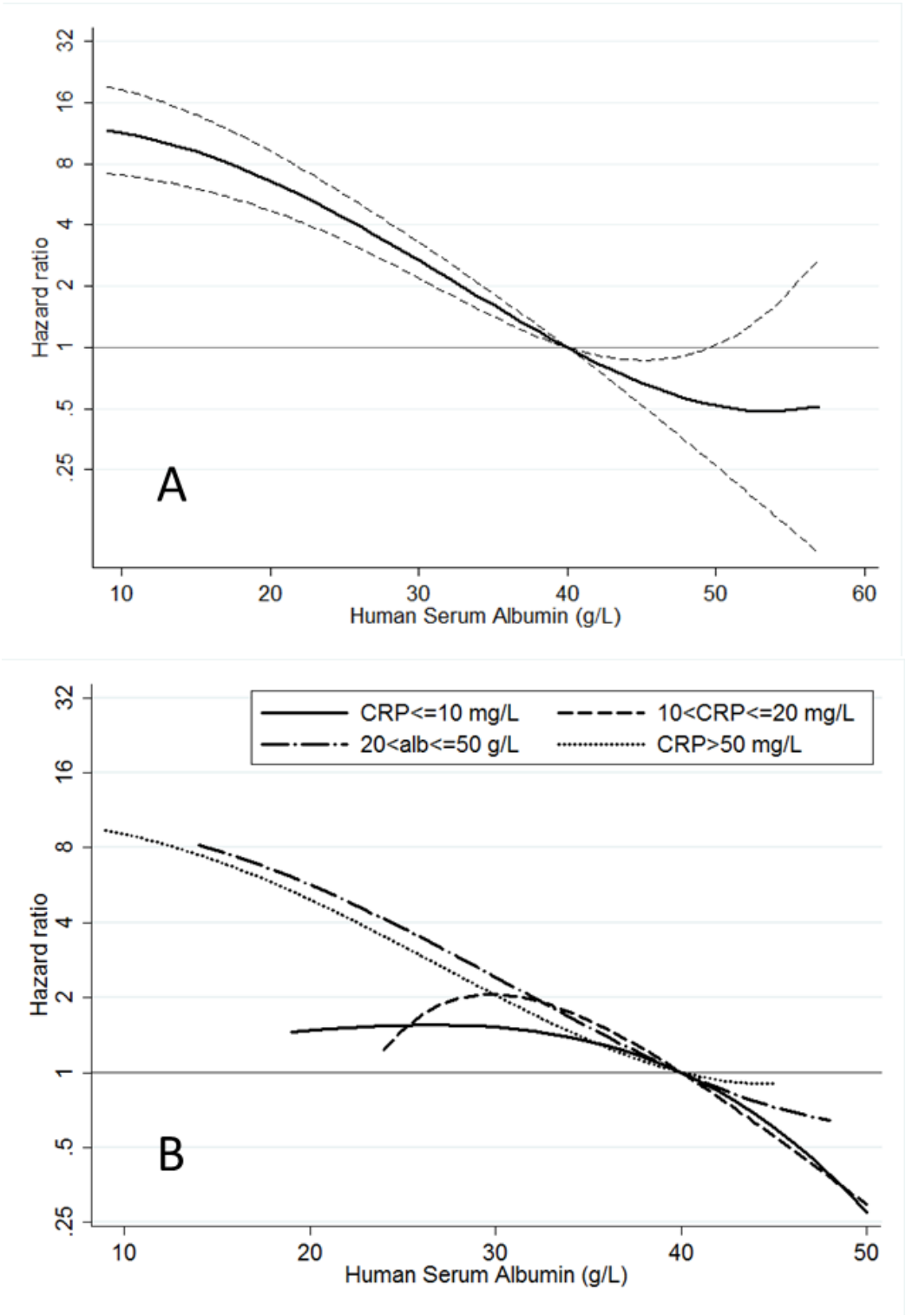
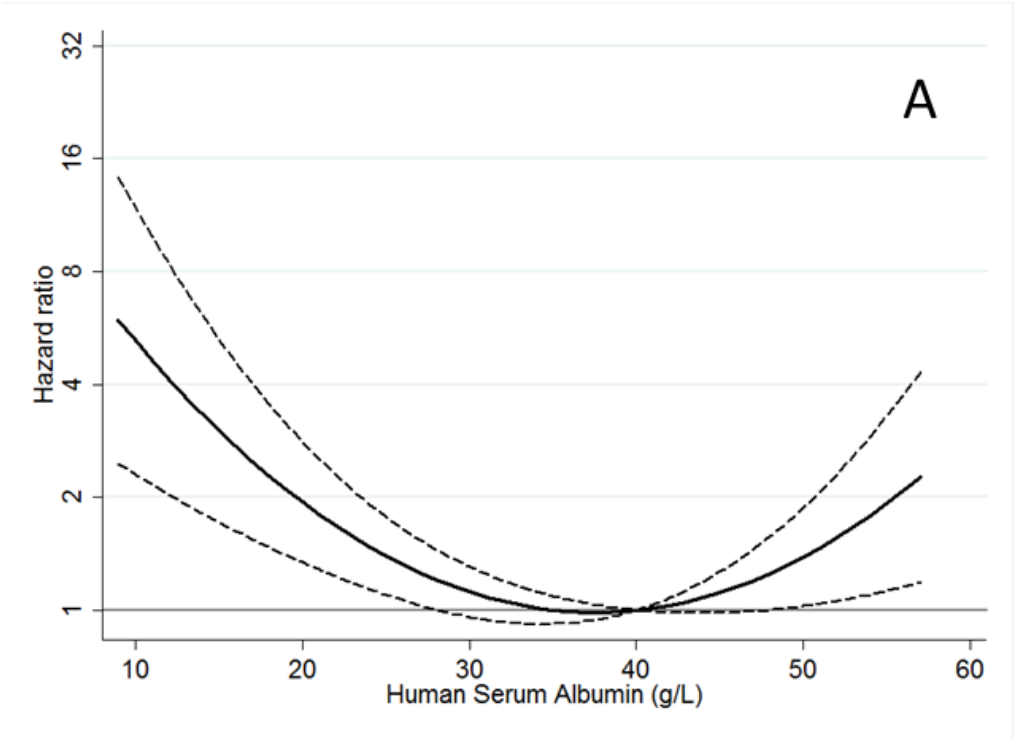


Figure 4. Adjusted hazard rations and corresponding 95% confidence intervals (dashed lines) for reoperation (Figure A) and acute kidney injury (Figure B) associated with preoperative HSA concentration.



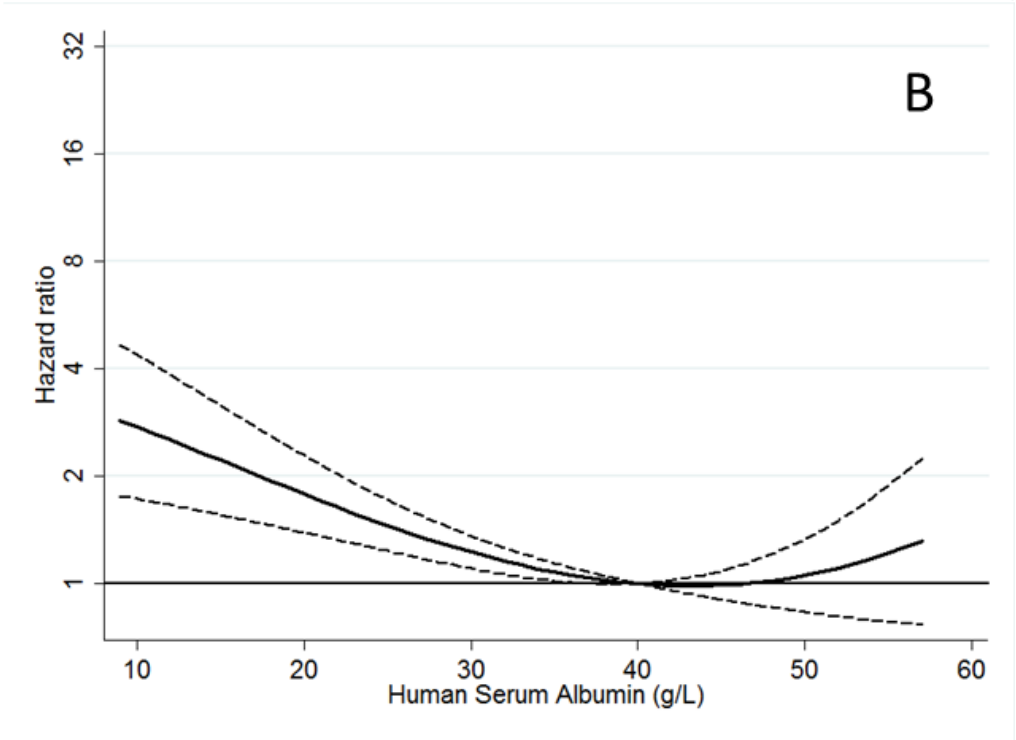


Table 1. Characteristics of patients undergoing colorectal cancer surgery.

	Serum albumin concentration					
	Hypoalbuminemia			Normal albuminemia		Missing albumin
	Severe <=25 g/L n = 401	Moderate 26-30 g/L n = 784	Mild 31-35 g/L n = 1,742	Low 36-40 g/L n = 3,065	High >40 g/L n = 3,347	n = 1,008
Gender (%):						
− Male	143 (35.7)	371 (47.3)	844 (48.5)	1,660 (54.2)	1,910 (57.1)	514 (51.0)
− Female	258 (64.3)	413 (52.7)	898 (51.6)	1,405 (45.8)	1,437 (42.9)	494 (49.0)
Median age (IQR):	76 (68-82)	76 (68-82)	75 (65-81)	71 (63-78)	67 (59-74)	71 (61-79)
Age (%):						
− <60 years	48 (12.0)	64 (8.2)	234 (13.4)	549 (17.9)	857 (25.6)	210 (20.8)
− 60-69 years	60 (15.0)	170 (21.7)	380 (21.8)	824 (26.9)	1,122 (33.5)	237 (23.5)
− 70-79 years	154 (38.4)	280 (35.7)	605 (34.7)	1,064 (34.7)	990 (29.6)	317 (31.5)
− >=80 years	139 (34.7)	270 (34.4)	523 (30.0)	628 (20.5)	378 (11.3)	244 (24.1)
Type of admission:						
− Elective	122 (30.4)	348 (44.4)	1,128 (64.8)	2,544 (83.1)	3,118 (93.2)	534 (53.5)
− Non-elective	279 (69.6)	435 (55.6)	612 (35.2)	516 (16.9)	227 (6.8)	465 (46.2)
− Missing	0	1 (0.1)	2 (0.1)	5 (0.16)	2 (0.1)	9 (0.9)
Cancer site:						
− Colon	302 (75.3)	599 (76.4)	1,212 (69.6)	1,856 (60.6)	1,689 (50.5)	779 (77.3)
− Rectum	99 (24.7)	185 (23.6)	530 (30.4)	1,209 (39.5)	1,658 (49.5)	229 (22.7)
Cancer stage:						
− Localized	124 (30.9)	251 (32.0)	671 (38.5)	1,287 (42.0)	1,517 (45.3)	385 (38.2)
− Regional	98 (24.4)	205 (26.2)	460 (26.4)	841 (27.4)	1,051 (31.4)	299 (29.7)
− Metastasized	119 (29.7)	215 (27.4)	365 (21.0)	527 (17.2)	340 (10.2)	206 (20.4)
− Unknown	60 (15.0)	113 (14.4)	246 (14.1)	410 (13.4)	439 (13.1)	118 (11.7)
Type of surgery:						
− Open radical resection	266 (66.3)	579 (73.9)	1,369 (78.6)	2,470 (80.6)	2,546 (76.1)	721 (71.5)
− Laparoscopic radical resection	4 (1.0)	7 (0.9)	65 (3.7)	271 (8.8)	541 (16.2)	121 (12.0)
− Non-eradicative procedures	131 (32.7)	198 (25.3)	308 (17.7)	324 (10.6)	260 (7.8)	166 (16.5)
Comorbidity:						
− Low	205 (51.1)	375 (47.8)	928 (53.3)	1,752 (57.2)	2,153 (64.3)	651 (64.6)
− Moderate	134 (33.4)	279 (35.6)	585 (33.6)	969 (31.6)	916 (27.4)	271 (26.9)
− High	62 (15.5)	130 (16.6)	229 (13.2)	344 (11.2)	278 (8.3)	86 (8.5)
Alcohol-related disease:						
− No	386 (96.3)	764 (97.5)	1,707 (98.0)	3,017 (98.4)	3,290 (98.3)	988 (98.0)
− Yes	15 (3.7)	20 (2.6)	35 (2.0)	48 (1.6)	57 (1.7)	20 (2.0)
Marital status:						
− Married	172 (42.9)	359 (45.8)	855 (49.1)	1,731 (56.5)	2,139 (63.9)	516 (51.2)
− Never married	40 (10.0)	55 (7.0)	137 (7.9)	218 (7.1)	214 (6.4)	82 (8.1)
− Other	189 (47.1)	370 (47.2)	750 (43.1)	1,116 (36.4)	994 (29.7)	410 (40.7)

Abbreviations: interquartile range (IQR)

Table 2. Preoperative blood measurements in patients undergoing colorectal cancer surgery.

	Serum albumin concentration					
	Hypoalbuminemia			Normal albuminemia		Missing
	Severe	Moderate	Mild	Low	High	albumin
	<=25 g/L	26-30 g/L	31-35 g/L	36-40 g/L	>40 g/L	
	n = 401	n = 784	n = 1,742	n = 3,065	n = 3,347	n = 1,008
Albumin, g/L						
− Mean (SD)	22.0 (3.0)	28.4 (1.4)	33.3 (1.4)	38.1 (1.4)	43.4 (2.1)	-
− Median (IQR)	23 (21-24)	29 (27-30)	34 (32-35)	38 (37-39)	43 (42-45)	-
Hemoglobin, mmol/L						
− Median (IQR)	6.6 (6.1-7.6)	6.9 (6.3-7.6)	7.3 (6.5-8)	7.9 (7.1-8.7)	8.5 (7.8-9.1)	8.0 (7.1-8.8)
− Missing, n (%)	0	2 (0.3)	3 (0.2)	10 (0.3)	8 (0.2)	553 (54.9)
Na^+, mmol/L:						
− Median (IQR)	137 (134-139)	137 (135-140)	139 (137-141)	140 (138-142)	140 (139-142)	140 (137-141)
− Missing, n (%)	0	2 (0.3)	2 (0.1)	3 (0.1)	2 (0.1)	572 (56.8)
K^+, mmol/L:						
− Median (IQR)	3.8 (3.4-4.2)	3.9 (3.5-4.3)	4 (3.7-4.3)	4.1 (3.8-4.3)	4.1 (3.8-4.3)	4 (3.7-4.3)
− Missing, n (%)	0	3 (0.4)	2 (0.1)	3 (0.1)	1 (<0.1)	569 (56.5)
Leukocytes, 10^9/L:						
− Median (IQR)	11.2 (8.5-15.1)	10.0 (7.8-13.2)	8.8 (6.9-11.2)	8.0 (6.5-9.9)	7.4 (6.1-9.0)	9.1 (6.9-11.8)
− Missing n (%)	28 (7.0)	82 (10.5)	359 (20.6)	846 (27.6)	945 (28.2)	752 (74.6)
Creatinine, µmol/L:						7
− Median (IQR)	68 (55-85)	74 (61-93)	78 (66-93)	79 (68-95)	77 (67-90)	8 (67-91)
− Missing, n (%)	0	1 (0.1)	0	5 (0.2)	1 (<0.1)	556 (55.2)
C-reactive protein, mg/L:						
− Median (IQR)	85 (41-146)	51 (24-102)	26 (10-62)	10 (10-26)	10 (8-10)	19 (10-55)
− Missing n (%)	40 (10.0)	121 (15.4)	460 (26.4)	1,019 (33.3)	1,054 (31.5)	812 (80.6)
Platelet, 10^9/L:						
− Median (IQR)	411 (309-537)	392 (300-514)	353 (278-455)	316 (250-398)	290 (242-353)	324 (253-417)
− Missing, n (%)	80 (20.0)	197 (25.1)	537 (30.8)	1,027 (33.5)	1,065 (31.8)	818 (81.2)
INR:						
− Median (IQR)	1.2 (1.1-1.3)	1.1 (1.0-1.2)	1.0 (1.0-1.1)	1.0 (1.0-1.1)	1.0 (0.9-1.1)	1.1 (1.0-1.2)
− Missing, n (%)	121 (30.2)	276 (35.2)	682 (39.2)	1,162 (37.9)	1,123 (33.6)	845 (83.8)
Bilirubin, µmol/L:						
− Median (IQR)	9 (6-13)	8 (6-13)	8 (5-11)	8 (6-11)	8 (6-11)	10 (7-12)
− Missing, n (%)	72 (18.0)	214 (27.3)	625 (35.9)	1,130 (36.9)	1,036 (31.0)	821 (81.5)
ALAT, U/L:						
− Median (IQR)	17 (11-28)	17 (12-28)	17 (12-25)	17 (13-25)	20 (15-27)	18 (13-28)
− Missing, n (%)	135 (33.7)	324 (41.33)	812 (46.6)	1,410 (46.0)	1,204 (36.0)	815 (80.9)
MELD:						
− < 10, n (%)	177 (44.1)	331 (42.2)	720 (41.3)	1,308 (42.7)	1,742 (52.1)	100 (9.9)
− ≥ 10, n (%)	76 (19.0)	97 (12.4)	120 (6.9)	200 (6.5)	127 (3.8)	20 (2.0)
− Missing, n (%)	148 (36.9)	356 (45.4)	902 (51.8)	1,557 (50.8)	1,478 (44.16)	888 (88.1)

Abbreviations: standard deviation (SD), interquartile range (IQR), international normalized ratio (INR), model for end-stage liver disease (MELD)

Table 3. Thirty-day mortality and corresponding hazard ratios in patients with different preoperative serum albumin concentration undergoing colorectal cancer surgery, overall and stratified by type of admission, cancer type, and period of surgery.

	No. of patients N	No. of deaths N	30-day mortality %* (95% CI)	Hazard Ratio (95% Confidence Interval (CI))	
				Crude	Adjusted‡
Colorectal cancer surgery					
Albumin ≤ 25 g/L	401	108	26.9 (22.9-31.6)	15.89 (11.69-21.59)	7.59 (4.95-11.64)
Albumin 26-30 g/L	784	154	19.6 (17.0-22.6)	10.91 (8.18-14.56)	5.19 (3.53-7.63)
Albumin 31-35 g/L	1,742	163	9.4 (8.1-10.8)	4.92 (3.70-6.56)	2.58 (1.80-3.69)
Albumin 36-40 g/L	3,065	149	4.9 (4.2-5.7)	2.50 (1.87-3.34)	1.75 (1.25-2.45)
Albumin > 40 g/L	3,347	66	2.0 (1.6-2.5)	1.00	1.00
Elective admission§					
Albumin ≤ 25 g/L	122	30	24.6 (17.9-33.2)	15.32 (9.84-23.83)	8.08 (4.45-14.67)
Albumin 26-30 g/L	348	62	17.8 (14.2-22.3)	10.57 (7.38-15.15)	5.31 (3.27-8.62)
Albumin 31-35 g/L	1,128	90	8.0 (6.5-9.7)	4.50 (3.23-6.26)	2.56 (1.68-3.90)
Albumin 36-40 g/L	2,544	99	3.9 (3.2-4.7)	2.15 (1.55-2.98)	1.52 (1.04-2.21)
Albumin > 40 g/L	3,118	57	1.8 (1.4-2.4)	1.00	1.00
Non-elective admission§					
Albumin ≤ 25 g/L	279	78	28.0 (23.1-33.6)	8.19 (4.11-16.33)	7.78 (3.17-19.12)
Albumin 26-30 g/L	435	92	21.2 (17.6-25.3)	5.83 (2.94-11.57)	5.36 (2.23-12.88)
Albumin 31-35 g/L	612	73	11.9 (9.6-14.8)	3.14 (1.57-6.28)	2.68 (1.12-6.44)
Albumin 36-40 g/L	516	50	9.7 (7.4-12.6)	2.51 (1.23-5.10)	2.32 (0.97-5.55)
Albumin > 40 g/L	227	9	4.0 (2.1-7.5)	1.00	1.00
Age 0-59 years					
Albumin ≤ 25 g/L	48	6	12.5 (5.8-25.7)	23.03 (7.03-75.46)	7.39 (1.32-41.22)
Albumin 26-30 g/L	64	9	14.1 (7.6-25.3)	25.55 (8.56-76.24)	11.84 (2.65-52.97)
Albumin 31-35 g/L	234	9	3.9 (2.0-7.3)	6.68 (2.24-19.94)	2.18 (0.51-9.35)
Albumin 36-40 g/L	549	10	1.8 (1.0-3.4)	3.15 (1.08-9.20)	2.29 (0.69-7.61)
Albumin > 40 g/L	857	5	0.6 (0.2-1.4)	1.00	1.00
Age 60-69 years					
Albumin ≤ 25 g/L	60	9	15.0 (8.1-26.8)	15.11 (6.37-35.87)	6.63 (2.13-20.61)
Albumin 26-30 g/L	170	26	15.3 (10.7-21.6)	15.39 (7.77-30.50)	4.75 (1.77-12.76)
Albumin 31-35 g/L	380	21	5.5 (3.6-8.4)	5.26 (2.59-10.69)	2.55 (1.03-6.31)
Albumin 36-40 g/L	824	17	2.1 (1.3-3.3)	1.94 (0.92-4.05)	1.34 (0.57-3.15)
Albumin > 40 g/L	1,122	12	1.1 (0.6-1.9)	1.00	1.00
Age 70-79 years					
Albumin ≤ 25 g/L	154	43	27.9 (21.5-35.7)	11.89 (7.35-19.24)	8.76 (4.40-17.44)
Albumin 26-30 g/L	280	54	19.3 (15.1-24.4)	7.71 (4.86-12.24)	5.23 (2.79-9.77)
Albumin 31-35 g/L	605	46	7.6 (5.8-10.0)	2.87 (1.78-4.61)	2.12 (1.19-3.80)
Albumin 36-40 g/L	1,064	49	4.6 (3.5-6.1)	1.70 (1.06-2.72)	1.41 (0.83-2.40)
Albumin > 40 g/L	990	27	2.7 (1.9-4.0)	1.00	1.00
Age 80+ years					
Albumin ≤ 25 g/L	139	50	36.0 (28.6-44.5)	7.54 (4.56-12.45)	7.09 (3.50-14.36)
Albumin 26-30 g/L	270	65	24.1 (19.4-29.6)	4.57 (2.82-7.40)	4.57 (2.40-8.68)
Albumin 31-35 g/L	523	87	16.6 (13.7-20.1)	3.03 (1.90-4.83)	2.66 (1.46-4.85)
Albumin 36-40 g/L	628	73	11.6 (9.4-14.4)	2.05 (1.28-3.31)	2.17 (1.22-3.86)
Albumin > 40 g/L	378	22	5.8 (3.9-8.7)	1.00	1.00

*Calculated using the Kaplan-Meier method.

‡ Mutually adjusted for gender, age (both as a continuous and a categorical variable), type of admission, operation year (calendar year), county, cancer site, cancer stage (excluded patients with stage "unknown"), comorbidity level, alcohol-related disease, liver disease, marital status, hemoglobin, Na, K, creatinine (number of observations with complete data = 8,033).

§Information on type of admission is missing for some patients. Therefore, the sum of patients with non-elective and elective admissions is not equal to the number of all patients included in the study.

Table 4. Thirty-day mortality and corresponding adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) in subgroups of patients with different preoperative serum albumin concentration undergoing colorectal cancer surgery.

	Serum albumin concentration									
	≤ 25 g/L		**26-30 g/L**		**31-35 g/L**		**36-40 g/L**		**>40 g/L**	
	30-day mortality* % (n)	Adjusted HR‡ (95% CI)	30-day mortality* % (n)	Adjusted HR‡ (95% CI)	30-day mortality* % (n)	Adjusted HR‡ (95% CI)	30-day mortality* % (n)	Adjusted HR‡ (95% CI)	30-day mortality* % (n)	Reference group
Gender:										
− Male	30.1% (43)	8.23 (4.49-15.09)	24.5% (91)	5.79 (3.45-9.71)	10.3% (87)	2.68 (1.65-4.35)	5.2% (86)	1.73 (1.11-2.71)	1.9% (37)	1.00
− Female	25.2% (65)	6.79 (3.65-12.63)	15.3% (63)	4.28 (2.39-7.65)	8.5% (76)	2.29 (1.39-3.92)	4.5% (63)	1.64 (0.99-2.72)	2.0% (29)	1.00
Cancer site:										
− Colon	29.8% (90)	6.68 (4.01-11.14)	18.4% (110)	3.96 (2.47-6.34)	9.2% (112)	2.05 (1.32-3.20)	5.2% (96)	1.43 (0.94-2.19)	2.4% (41)	1.00
− Rectum	18.2% (18)	8.90 (3.77-21.05)	23.8% (44)	10.76 (5.40-21.44)	9.6% (51)	3.83 (2.06-7.12)	4.4% (53)	2.52 (1.44-4.41)	1.5% (25)	1.00
Cancer stage:										
− Localized	17.7% (22)	4.22 (2.14-8.36)	16.7% (42)	4.02 (2.25-7.19)	7.2% (48)	2.08 (1.24-3.46)	4.8% (62)	1.74 (1.10-2.73)	2.1% (32)	1.00
− Regional	25.5% (25)	11.01 (4.44-27.33)	15.1% (31)	5.88 (2.65-13.07)	7.8% (36)	3.90 (1.88-8.11)	3.7% (31)	2.11 (1.05-4.25)	1.2% (13)	1.00
− Metastasized	38.7% (46)	10.61 (4.72-23.88)	27.9% (60)	6.58 (3.05-14.18)	11.8% (43)	2.64 (1.25-5.58)	5.7% (30)	1.53 (0.74-3.19)	2.9% (10)	1.00
Year of surgery:										
− 1997-2005	29.8% (78)	4.40 (2.52-7.67)	20.4% (95)	3.03 (1.82-5.05)	8.2% (82)	1.39 (0.85-2.28)	4.5% (68)	1.05 (0.66-1.68)	3.1% (28)	1.00
− 2006-2011	21.6% (30)	10.11 (5.17-19.79)	18.5% (59)	8.49 (4.84-14.92)	11.0% (81)	4.90 (2.94-8.15)	5.2% (81)	2.81 (1.76-4.49)	1.6% (38)	1.00
Type of surgery:										
− Open radical resection	24.8% (66)	5.32 (3.26-8.68)	16.2% (94)	3.43 (2.21-5.30)	8.6% (118)	2.03 (1.37-3.01)	4.9% (120)	1.52 (1.06-2.18)	2.2% (57)	1.00
− Laparoscopic radical resection	0%	-	14.3% (1)	-	7.7% (5)	9.13 (1.32-63.34)	3.3% (9)	3.19 (0.74-13.78)	0.7% (4)	1,00
− Non-eradicative procedures	32.1% (42)	44.40 (9.48-207.97)	29.8% (59)	30.81 (6.91-41.59)	13.0% (40)	9.35 (2.10-41.59)	6.2% (20)	4.43 (0.98-20.05)	1.9% (5)	1,00
Comorbidity:										
− Low	23.7% (49)	7.87 (4.05-15.26)	15.9% (60)	5.39 (2.96-9.82)	6.6% (61)	1.91 (1.08-3.37)	2.8% (49)	1.22 (0.72-2.06)	1.3% (28)	1.00
− Moderate	29.9% (40)	9.36 (4.65-18.83)	23.0% (64)	6.68 (3.59-12.45)	10.9% (64)	3.31 (1.86-5.86)	6.6% (64)	2.10 (1.24-3.58)	2.9% (27)	1.00
− High	31.7% (19)	6.91 (2.45-19.53)	23.3% (30)	4.77 (1.91-11.94)	17.0% (38)	3.55 (1.51-8.34)	10.7% (36)	2.84 (1.25-6.43)	4.1% (11)	1.00
Marital status:										
− Married	27.3% (47)	11.09 (5.95-20.66)	20.1% (72)	6.70 (3.83-11.74)	8.3% (71)	3.52 (2.11-5.89)	3.7% (64)	1.72 (1.06-2.79)	1.5% (31)	1.00
− Never Married	25.0% (10)	10.50 (1.72-64.07)	27.3% (15)	5.58 (1.05-29.76)	8.0% (11)	1.26 (0.27-5.87)	6.0% (13)	2.29 (0.59-8.79)	2.3% (5)	1.00
− Other	27.0% (51)	5.75 (3.03-10.92)	18.1% (67)	4.15 (2.32-7.41)	10.8% (81)	2.23 (1.30-3.81)	6.5% (72)	1.76 (1.06-2.91)	3.0% (30)	1.00

C-reactive protein:[§]										
− ≤ 10.0 mg/L	14.3% (2)	5.33 (1.06-26.83)	9.5% (7)	1.81 (0.57-5.76)	6.2% (20)	1.88 (0.88-4.00)	4.1% (41)	1.48 (0.82-2.67)	1.6% (29)	1.00
− 10.1-20.0 mg/L	13.8% (4)	4.31 (0.87-21.32)	9.7% (7)	1.91 (0.53-6.85)	12.2% (27)	3.09 (1.21-7.86)	6.7% (27)	1.93 (0.83-4.50)	3.6% (11)	1.00
− 20.1-50.0 mg/L	23.6% (17)	7.47 (2.22-25.08)	21.0% (38)	7.26 (2.40-22.00)	9.6% (33)	3.38 (1.18-9.70)	5.6% (22)	1.88 (0.67-5.31)	2.7% (5)	1.00
− > 50.0 mg/L	29.3% (72)	4.19 (0.97-18.12)	26.5% (89)	3.63 (0.86-15.35)	13.4% (53)	1.36 (0.32-5.85)	10.6% (26)	1.44 (0.33-6.25)	8.1% (3)	1.00
MELD:[¥]										
− <10	23.2% (41)	7.06 (3.61-13.80)	18.1% (60)	5.20 (2.87-9.42)	9.2% (66)	2.74 (1.60-4.71)	4.5% (59)	1.63 (0.99-2.69)	1.9% (33)	1.00
− ≥ 10	43.4% (33)	9.22 (3.27-25.97)	43.4% (42)	8.62 (3.17-23.42)	19.2% (23)	2.75 (1.03-7.32)	15.5% (31)	2.36 (0.94-5.92)	6.3% (8)	1.00

*Calculated using the Kaplan-Meier method.

[‡] Mutually adjusted for gender, age (both as a continuous and a categorical variable), type of admission, operation year (calendar year), county, cancer site, cancer stage (excluded patients with stage “unknown”), comorbidity level, alcohol-related disease, liver disease, marital status, hemoglobin, Na, K, creatinine (number of observations with complete data = 8,033).

[§] Patients with preoperative C-reactive protein measurement = 6,841.

[¥] Patients with preoperative MELD = 5,018.

Table 5. Rates and corresponding adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for reoperation and postoperative acute kidney injury in patients with different preoperative serum albumin concentration undergoing colorectal cancer surgery.

	No. of cases N	Cumulative incidence* % (95% CI)	HR (95% CI)	
			Crude	Adjusted‡
30-day reoperation				
Albumin ≤ 25 g/L	47	11.7% (8.8-15.1)	1.36 (1.00-1.84)	2.09 (1.41-3.08)
Albumin 26-30 g/L	62	7.9% (6.2-9.9)	0.85 (0.65-1.11)	1.11 (0.79-1.57)
Albumin 31-35 g/L	162	9.3% (8.0-10.7)	0.97 (0.80-1.17)	1.20 (0.95-1.53)
Albumin 36-40 g/L	270	8.8% (7.8-9.8)	0.90 (0.77-1.06)	0.99 (0.82-1.20)
Albumin > 40 g/L	328	9.8% (8.8-10.8)	1.00	1.00
30-day acute kidney injury				
Albumin ≤ 25 g/L	117	29.2% (24.8-33.7)	1.65 (1.35-2.00)	1.64 (1.28-2.11)
Albumin 26-30 g/L	216	27.6% (24.5-30.7)	1.50 (1.29-1.75)	1.35 (1.10-1.66)
Albumin 31-35 g/L	377	21.6% (19.7-23.6)	1.13 (1.00-1.28)	1.03 (0.88-1.22)
Albumin 36-40 g/L	629	20.5% (19.1-22.0)	1.06 (0.95-1.18)	1.02 (0.89-1.16)
Albumin > 40 g/L	654	19.5% (18.2-20.9)	1.00	1.00

*Cumulative incidence treating death as a competing risk.

‡ Mutually adjusted for gender, age (both as a continuous and a categorical variable), type of admission, operation year (calendar year), county, cancer site, cancer stage (excluded patients with stage “unknown”), comorbidity level, alcohol-related disease, liver disease, marital status, hemoglobin, Na, K, creatinine (number of observations with complete data = 8,033).

Appendix

The following codes were used to identify cancer information in the Danish Cancer Registry:

Colorectal Cancer:

- Colon cancer: ICD-8: 153; ICD-10: C18
- Rectal cancer: ICD-8: 154; ICD-10: C19, C20

Colorectal cancer stage classification:

- Localized:
    - Dukes: A,B
    - TNM*: T1-4,x N0 M0; T1-2 N0 Mx; T1 Nx M0,x
- Regional:
    - Dukes: C
    - TNM*: T1-4,x N1-3 M0
- Metastasized
    - Dukes: D
    - TNM*: T1-4,x N0-3,x M1
- Unknown
    - TNM*: T0,a,is; T2-4,x Nx M0,x; T3-4,x N0 Mx; T1-4,x N1-2 Mx

* Colorectal cancers were classified according to TNM from 2004 on.

The following codes were used to identify conditions in the Danish National Registry of Patients:

- *Colorectal surgery (NOMESCO codes):*
    - Open radical resection: JGB00, JGB10,JGB20, JGB30, JGB40, JGB50, JGB60, JGB96, JFB20, JFB30, JFB 33, JFB40, JFB43, JFB46, JFB50, JFB60, JFB63, JFB96, JFH00, JFH10, JFH20, JFH30, JFH33, JFH40, JFH96, JGA00, JGA70
    - Laparoscopic radical resection: JGB01, JGB11, JGB31, JGB97, JFB21, JFB31, JFB34, JFB41, JFB44, JFB47, JFB51, JFB61, JFB64, JFB97, JFH01, JFH11
    - Non-resectional procedures: JGA32-58, JGA73-98, JGW, JFA68, JFA83-84, JFA96-97, JFC, JFF10-13, JFF20-31, JFW
- *Disease included in the adjusted Charlson Comorbidity Index:*
    - Myocardial infarction: ICD-8: 410; ICD-10: I21, I22, I23
    - Congestive heart failure: ICD-8: 427.09, 427.10, 427.11, 427.19, 428.99, 782.49; ICD-10: I50, I11.0, I13.0, I13.2
    - Peripheral vascular disease: ICD-8: 440, 441, 442, 443, 444, 445; ICD-10: I70, I71, I72, I73, I74, I77
    - Cerebrovascular disease: ICD-8: 430-438; ICD-10: I60-I69, G45, G46
    - Dementia: ICD-8: 290.09-290.19, 293.09; ICD-10: F00-F03, F05.1, G30
    - Chronic pulmonary disease: ICD-8: 490-493, 515-518; ICD-10: J40-J47, J60-J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3
    - Connective tissue disease: ICD-8: 712, 716, 734, 446, 135.99; ICD-10: M05, M06, M08, M09, M30, M31, M32, M33, M34, M35, M36, D86
    - Ulcer disease: ICD-8: 530.91, 530.98, 531-534; ICD-10: K22.1, K25-K28
    - Mild liver disease: ICD-8: 571, 573.01, 573.04; ICD-10: B18, K70.0-K70.3, K70.9, K71, K73, K74, K76.0
    - Uncomplicated type 1 and type 2 diabetes: ICD-8: 249.00, 249.06, 249.07, 249.09, 250.00, 250.06, 250.07, 250.09; ICD-10: E10.0, E10.1, E10.9, E11.0, E11.1, E11.9
    - Hemiplegia: ICD-8: 344; ICD-10: G81, G82
    - Moderate to severe renal disease: ICD-8: 403, 404, 580-583, 584, 590.09, 593.19, 753.10-753.19, 792; ICD-10: I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61

- Diabetes with end-organ damage: ICD-8: 249.01-249.05, 249.08, 250.01-250.05, 250.08; ICD-10: E10.2-E10.8, E11.2-E11.8
- Any tumor (excluding CRC): ICD-8: 140-194 (excluding 153-154); ICD-10: C00-C75 (excluding C18-C20)
- Leukemia: ICD-8: 204-207; ICD-10: C91-C95
- Lymphoma: ICD-8: 200-203, 275.59; ICD-10: C81-C85, C88, C90, C96
- Moderate to severe liver disease: ICD-8: 070.00, 070.02, 070.04, 070.06, 070.08, 573.00, 456.00-456.09; ICD-10: B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85
- Metastatic solid tumor (excluding metastases from CRC): ICD-8: 195-198, 199 (excluding patients with diagnoses 197.59, 197.79); ICD-10: C76-C80 (excluding patients with diagnoses C78.5 and C78.7)
- AIDS: ICD-8: 079.83; ICD-10: B21-B24

- *Non-hepatic alcohol-related disease:* ICD-8: 291-291.9, 303-303.9, 980; ICD-10: F10.2, F10.7, F10.8, I42.6, G62.1, K29.2, G72.1, G31.2, T51, Z72.1
- *Re-operation codes:*
  - Reoperation after colorectal surgery for wound dehiscence:
    - NOMESCO: KJWA
  - Reoperation after colorectal surgery because of bleeding:
    - NOMESCO: KJWD, KJWE
  - Reoperation after colorectal surgery because of infection:
    - NOMESCO: KJWB, KJWC
  - Reoperation after colorectal surgery because of insufficient anastomosis:
    - NOMESCO: KJWF
  - Reoperation after colorectal surgery for other causes:
    - NOMESCO: KJWW

Supplementary Table 1. Percentages of colorectal cancer (CRC) patients with at least one laboratory measurement of any type coded in the laboratory database by year of CRC surgery and county where CRC surgery was performed. A cut-off of 90% was used to identify the study population (years and counties included in the study are indicated in bold).

Year of CRC surgery	Percentage of patients with laboratory measurement			
	Nordjyllands	Ringkjøbing	Viborg	Aarhus
1996	43.5	2.9	6.4	76.2
1997	**97.3**	8.5	8.3	77.4
1998	**100.0**	10.5	6.7	80.7
1999	**100.0**	5.9	10.0	81.8
2000	**100.0**	10.6	15.2	**98.2**
2001	**100.0**	6.9	15.3	**100.0**
2002	**100.0**	13.3	14.4	**100.0**
2003	**100.0**	19.8	16.5	**99.3**
2004	**99.7**	6.5	42.1	**99.7**
2005	**100.0**	2.8	**93.3**	**99.7**
2006	**100.0**	**94.0**	**96.1**	**99.3**
2007	**99.4**	**100.0**	**93.7**	**99.4**
2008	**99.7**	**100.0**	**96.9**	**99.4**
2009	**99.7**	**100.0**	**100.0**	**98.8**
2010	**100.0**	**100.0**	**92.7**	**100.0**
2011	**99.7**	**100.0**	**97.8**	**100.0**

Supplementary Table 2. Prevalence of individual disease from the Charlson Comorbidity Index (excluding liver disease) in patients undergoing surgery for colorectal cancer in North and Central Denmark, 1997-2012.

	Serum albumin concentration					
	Hypoalbuminemia			Normal albuminemia		Missing albumin
	Severe <=25 g/L n = 401	Moderate 26-30 g/L n = 784	Mild 31-35 g/L n = 1,742	Low 36-40 g/L n = 3,065	High >40 g/L n = 3,347	n = 1,008
Myocardial infarction	21 (5.2)	50 (6.4)	114 (6.5)	193 (6.3)	190 (5.7)	58 (5.8)
Congestive heart failure	29 (7.2)	46 (5.9)	119 (6.8)	146 (4.8)	110 (3.3)	50 (5.0)
Peripheral vascular disease	18 (4.5)	47 (6.0)	102 (5.9)	154 (5.0)	115 (3.4)	41 (4.1)
Cerebrovascular disease	43 (10.7)	101 (12.9)	195 (11.2)	307 (10.0)	234 (7.0)	79 (1.8)
Dementia	8 (2.0)	10 (1.3)	15 (0.9)	26 (0.9)	12 (0.4)	11 (1.1)
Chronic pulmonary disease	37 (9.2)	110 (14.0)	191 (11.0)	279 (9.1)	224 (6.7)	68 (6.8)
Connective tissue disease	15 (3.7)	21 (2.7)	54 (3.1)	88 (2.9)	92 (2.8)	23 (2.3)
Ulcer disease	37 (9.2)	57 (7.3)	114 (6.5)	199 (6.5)	155 (4.6)	48 (4.8)
Mild liver disease	6 (1.5)	11 (1.4)	16 (0.9)	20 (0.7)	15 (0.5)	10 (1.0)
Diabetes type 1 and 2	31 (7.7)	51 (6.5)	117 (6.7)	209 (6.8)	185 (5.5)	54 (5.4)
Hemiplegia	0	1 (0.1)	3 (0.2)	10 (0.3)	6 (0.2)	1 (0.1)
Moderate to severe renal disease	9 (2.2)	24 (3.1)	40 (2.3)	58 (1.9)	50 (1.5)	14 (1.4)
Diabetes with end-organ damage	15 (3.7)	25 (3.2)	53 (3.0)	83 (2.7)	66 (2.0)	14 (1.4)
Any tumor	42 (10.5)	105 (13.4)	181 (10.4)	286 (9.3)	278 (8.3)	81 (8.0)
Leukemia	1 (0.3)	2 (0.3)	2 (0.1)	9 (0.3)	9 (0.3)	4 (0.4)
Lymphoma	4 (1.0)	4 (0.5)	12 (0.7)	18 (0.6)	21 (0.6)	2 (0.2)
Moderate to severe liver disease	2 (0.5)	2 (0.3)	5 (0.3)	4 (0.1)	5 (0.2)	2 (0.2)
Metastatic solid tumor	17 (4.2)	32 (4.1)	43 (2.5)	55 (1.8)	61 (1.8)	13 (1.3)
AIDS	0	0	1 (0.1)	0	1 (<0.1)	1 (0.1)

Supplementary Table 3. Characteristics of patients undergoing colorectal cancer surgery with and without preoperative serum albumin measurement.

	Patients with albumin measurement	Patients without albumin measurement		
		Overall	With other laboratory in the 30 days before surgery	Without any laboratory test in the 30 days before surgery
	n = 9,339	n = 1,008	n = 490	n = 518
Gender (%):				
− Male	4,928 (52.8%)	514 (51.0%)	242 (49.4%)	272 (52.5%)
− Female	4,411 (47.2%)	494 (49.0%)	248 (50.6%)	246 (47.4%)
Age (%):				
− <60 yr	1,752 (18.8%)	210 (20.8%)	107 (21.8%)	103 (19.9%)
− 60-69 yr	2,556 (27.4%)	237 (23.5%)	123 (25.1%)	114 (22.0%)
− 70-79 yr	3,093 (33.1%)	317 (31.5%)	148 (30.2%)	169 (32.6%)
− >=80 yr	1,938 (20.8%)	244 (24.1%)	112 (22.9%)	132 (25.5%)
Type of admission:				
− Elective	7,260 (77.4%)	534 (53.5%)	307 (62.7%)	227 (43.8%)
− Non-elective	2,069 (22.2%)	465 (46.2%)	178 (36.3%)	287 (55.4%)
− Missing	10 (0.1%)	9 (0.9%)	5 (1.0%)	4 (0.8%)
Cancer site:				
− Colon	5,658 (60.6%)	779 (77.3%)	370 (75.5%)	409 (79.0%)
− Rectum	3,681 (39.4%)	229 (22.%)	120 (24.5%)	109 (21.0%)
Cancer stage:				
− Localized	3,850 (41.2%)	385 (38.2%)	193 (39.4%)	192 (37.1%)
− Regional	2,655 (28.4%)	299 (29.7%)	148 (30.2%)	151 (29.2%)
− Metastasized	1,566 (16.8%)	206 (20.4%)	91 (18.6%)	115 (22.2%)
− Unknown	1,268 (13.6%)	118 (11.7%)	58 (11.8%)	60 (11.6%)
Type of surgery:				
− Open radical resection	7,230 (77.4%)	721 (71.5%)	344 (70.2%)	377 (72.8%)
− Laparoscopic radical resection	888 (9.5%)	121 (12.0%)	76 (15.5%)	45 (8.7%)
− Non-eradicative procedures	1,221 (13.1%)	166 (16.5%)	70 (14.3%)	96 (18.5%)
Comorbidity:				
− Low	5,438 (58.2%)	656 (65.1%)	326 (66.5%)	330 (63.7%)
− Moderate	2,881 (30.9%)	268 (26.6%)	125 (25.5%)	143 (27.6%)
− High	1,020 (10.9%)	84 (8.3%)	39 (8.0%)	45 (8,7%)
Alcohol-related disease:				
− No	9,164 (98.1%)	988 (98.0%)	484 (98.8%)	504 (97.3%)
− Yes	175 (1.9%)	20 (2.0%)	6 (1.2%)	14 (2.7%)
Marital status:				
− Married	5,256 (56.3%)	516 (51.2%)	259 (52.9%)	257 (49.6%)
− Never married	664 (7.1%)	82 (8.1%)	40 (8.2%)	42 (8.1%)
− Other	3,419 (36.6%)	410 (40.7%)	191 (39.0%)	219 (42.3%)

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