ORIGINAL CONTRIBUTION

The Impact of Comorbidity on Survival of Danish Colorectal Cancer Patients from 1995 to 2006 – A Population-Based Cohort Study

Lene H. Iversen, M.D., Ph.D.[1,2,3] • Mette Nørgaard, M.D., Ph.D.[1]
Jacob Jacobsen, M.Sc.[1] • Søren Laurberg, M.D., D.M.Sc.[2,3]
Henrik T. Sørensen, M.D., Ph.D., D.M.Sc.[1]

1 Department of Clinical Epidemiology, Aarhus University Hospital, Åarhus N, Denmark
2 Department of Surgery P, Aarhus University Hospital, Aarhus, Denmark
3 Scientific Research Group of Danish Colorectal Cancer Group, Aarhus University Hospital, Aarhus, Denmark

PURPOSE: The impact of comorbidity on the outcome of colorectal cancer is poorly understood. We examined the prevalence of comorbidity and its impact on survival among Danish colorectal cancer patients.

METHODS: The hospital discharge registries in northern Denmark were used to identify 13,190 patients diagnosed with colorectal cancer between 1995 and 2006, and to assess their comorbidity using the Charlson Comorbidity Index. We obtained product limit estimates of 1-year and 5-year crude survival based on three levels of comorbidity. To quantify the impact of comorbidity on mortality, we used Cox's proportional hazards regression analysis to compute the mortality rate ratio.

RESULTS: One-third of the patients had recorded comorbid conditions. Patients with moderate and severe comorbidity (Charlson scores 1–2 and score 3+) had considerably higher 1-year and 5-year mortality rates compared to patients without comorbidity. For colon cancer patients, 1-year estimates in 2004 to 2006 were mortality rate ratio$_{1\text{-}2}$ = 1.2 (95 percent confidence interval, 1.0–1.5) and mortality rate ratio$_{3+}$ = 1.8 (95 percent confidence interval, 1.4–2.3). For rectal cancer patients with severe comorbidity, the negative impact on survival increased over time.

CONCLUSIONS: Comorbidity was a strong negative prognostic factor for survival among colorectal cancer patients.

KEY WORDS: Colorectal neoplasms; Registries; Survival; Epidemiology; Denmark.

Colorectal cancer (CRC) is a common malignancy and its incidence increases sharply with age in industrialized countries.[1] The presence of diseases occurring concomitantly with CRC, such as hypertension, chronic obstructive pulmonary disease, heart disease, and diabetes, also increases with age.[2] As the population ages, more CRC patients with such comorbidities will require medical services.

Comorbidity has demonstrated a negative effect on CRC survival.[3–11] However, most studies were based on CRC patients diagnosed eight to fifteen years ago,[3,4,9,10] when both treatment modalities and comorbidity patterns may have been quite different. Other limitations of previous studies include recruitment of patients from a single institution[5–7] and inclusion of only patients older than 67 years.[9,10] As well, data on comorbidity were often procured just for two years prior to the CRC diagnosis.[9,10]

We conducted a population-based study to investigate the impact of comorbidity on survival among CRC patients diagnosed from 1995 through 2006 in northern Denmark. Our specific aims were to examine (1) the prevalence of comorbidity among CRC patients as a whole and those undergoing surgery, (2) the impact of comorbidity on short-term and long-term survival, and

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Address of correspondence: Dr. Lene H. Iversen, Department of Surgery P, Aarhus University Hospital THG, Tage-Hansens Gade 2, DK-8000 Aarhus, Denmark. E-mail: lene.h.iversen@dadlnet.dk

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(3) changes in the effects of comorbidity on survival among CRC patients during the study period.

MATERIAL AND METHODS

Study Population

We conducted the study in the four northern Danish counties of North Jutland, Ringkjøbing, Viborg, and Aarhus with a population of nearly 1.6 million persons, *i.e.*, almost 30 percent of the Danish population. Health care is free and tax supported. We identified all patients with a first-time discharge diagnosis of CRC documented in one of the four county hospital discharges from January 1, 1995 to December 31, 2006.

Data Sources

Hospital discharge registries, established in 1977, are used by all Danish counties to collect data on hospitalizations. For the four northern counties, data from health care databases are merged into a research database managed by Aarhus University Hospital and updated daily. Discharge data in the database include the personal identification number (a unique 10-digit identifier assigned, since 1968, to all Danish residents by the Central Office of Civil Registration[12] dates of hospital admission and discharge, surgical procedure(s) performed, and up to 20 discharge diagnoses provided by physicians. High validity of the data from the discharge registries has been demonstrated.[13,14] The discharge registries do not include valid data on tumor stage. However, according to the national Danish Colorectal Cancer Group (DCCG) database[15] the stage distribution among CRC patients who underwent surgery in 2005, was Stage I: 10 percent, Stage II: 35 percent, Stage III: 29 percent, and Stage IV: 19 percent. The stage distribution has been stable since the DCCG database was established in 2001.

Discharge diagnoses were classified according to the International Classification of Diseases (ICD), 8th revision until the end of 1993 and 10th revision thereafter.[16] ICD-10 codes used for CRC were C18-C21. CRC patients who underwent surgery were identified using the following codes, consistent with the Nordic Classification of Surgical Procedures (NCSP)[17:] KJFA68, KJFA83-84, KJFA96-97, KJFB20-97, KJFC00-51, KJFF10-13, KJFF20-31, KJFH00-33, KJFH96, KJFW96-98, KJGA32-52, KJGA73-96, KJGA98, KJGB00-50, KJGB96-97, and KJGW96-98. The NCSP codes became available on January 1, 1996. For patients who did not undergo an operation included in these procedure codes, we extracted all KJxxxx section codes to ascertain the occurrence of other significant gastrointestinal operations.

Comorbidity

To quantify comorbidity, we computed a Charlson Comorbidity Index score[18] for each patient based on discharge diagnoses documented in all Danish hospital discharge registries in the 10 years preceding the hospital admission for CRC. The Charlson Comorbidity Index was developed in the 1980s in a cohort of 559 medical patients and tested for its ability to predict risk of death from comorbid disease in a second cohort of 685 patients during a 10-year follow-up period.[18] The Index includes 19 disease categories, each of which are weighted from 1 to 6 according to its relative risk for death within one year and then added to form a total score. During the last two decades the Index has been adapted for use with hospital discharge data in ICD-based databases and has been a widely used, valid, and reliable tool to assess the impact of comorbidities on mortality in many different cancer groups.[19–25]

Cancer diagnosis within 60 days before the CRC diagnosis was excluded from the calculations, in order to eliminate possible nonspecific cancer diagnoses related to the CRC diagnosis. Charlson Comorbidity Index scores were categorized into three groups: no (score 0), moderate (score 1–2), and severe (score 3+) morbidity.

Mortality

Denmark's Civil Registration system contains information on vital status (dead or alive), date of death, and residence. The unique 10-digit personal identification number allows linkage among registries. All study patients were followed from the date of hospital admission with a CRC diagnosis until death, emigration, or December 31, 2006, whichever came first.

Change in Diagnostic Techniques and Treatment Modalities During the 1995–2006 Period

Since 1995, colonoscopy and flexible sigmoidoscopy have replaced barium enema and rigid proctoscopy as diagnostic tools. Since 2001, patients with rectal cancer have been evaluated preoperatively with an MR scan of the pelvis, and a multidisciplinary team has developed their treatment plans. Colon cancer patients younger than 76 years with regional lymph node metastases have been offered adjuvant chemotherapy since 1997.[26] For rectal cancer patients, the surgical total mesorectal excision (TME) technique[27] has been available since 1996 and adjuvant radiotherapy since 2001.[28] For tumors located in the rectosigmoid colon, the TME technique has allowed more accurate differentiation between rectal cancer (defined as an adenocarcinoma located within 15 cm from the anal verge) and colon cancer over time, with a relative decrease in the rectal cancer incidence. Self-expanding metallic stents (SEMS) were introduced in the early 2000s for emergent decompression of the bowel in selected patients, who later may undergo an elective procedure. Some patients presenting with late-stage disease are treated only with SEMS. Besides improvements in general surgical techniques and perioperative care, the

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number of hospitals treating CRC patients decreased from 16 to 10 in the four counties between 2001 to 2004.[15]

Statistical Analysis

This study encompassed four time periods: 1995–1997, 1998–2000, 2001–2003, and 2004–2006. For each period, we computed the prevalence of comorbidity among CRC patients and the proportion undergoing surgery (data not available in 1995) in each Charlson comorbidity group. The inclusion period ended on June 30, 2006 for colon cancer patients and on March 31, 2006 for rectal cancer patients because of the time interval required between diagnosis and surgery to capture diagnostic evaluations such as CT-scans/US of the liver, in addition to MR scans of the pelvis in rectal cancer patients and preoperative radiotherapy in selected cases. To ascertain possible changes in treatment policies over time, we computed for each comorbidity group in each time period the proportion of patients undergoing a resection (NCSP codes: KJFB20-97, KJFH00-33, KJFH96, KJGB00-50 and KJGB96-97), a diversion only/local procedure (KJFA68, KJFA83-84, KJFA96-97, KJFC00-51, KJFF10-13, KJFF 20-31, KJFW96-98, KJGA32-52, KJGA73-96, KJGA98, KJGW96-98) and no surgical treatment.

For each comorbidity group and time period, we obtained product limit estimates of 1-year and 5-year crude survival using the Kaplan- Meier method. The calculation of 30-day mortality was based on the date of surgery. To compare 1-year and 5-year mortality rates among the comorbidity groups in the four periods, we computed 1-year and 5-year hazard ratios as a measure of the mortality rate ratio (MRR) using Cox proportional hazards regression analysis. Charlson Comorbidity Index score 0 served as the reference group. We adjusted for age and gender. We also calculated MRR by comorbidity group separately for patients who underwent a resection. Similarly, we computed and compared 30-day, 1-year, and 5-year mortality rates over time, adjusting for age, gender, and comorbidity score using the period 1995 to 1997 as the reference period.

All estimates are presented with an associated 95 percent confidence interval (CI). Analyses were performed separately for patients with colon and rectal cancer. Statistical analyses were performed with SAS® software (version 9.13, SAS Institute, Cary, NC).

RESULTS

Colon Cancer

A total of 7,970 patients were diagnosed with colon cancer between 1995 and 2006. The number of patients in the three comorbidity groups, their age and sex distribution, and rate of three different surgical treatment options (resection, diversion/local procedure or no surgery) in the four time periods are shown in Table 1. During the study period, the prevalence of patients with no comorbidity, *i.e.*, Charlson score 0, decreased from 69 percent to 57 percent (Table 1). The median age for each comorbidity group did not change during the study period. Among patients with comorbidity, treatment policy changed over time. The resection rate increased in patients with Charlson

TABLE 1. Characteristics of patients with colon cancer from 1995 through 2006

	Year of diagnosis				
Characteristics, n (%)	*1995–1997*	*1998–2000*	*2001–2003*	*2004–2006*	*Total*
Charlson score 0	1254 (69)	1275 (64)	1214 (61)	1244 (57)	4987 (63)
Charlson score 1–2	444 (24)	546 (28)	612 (31)	689 (32)	2291 (29)
Charlson score 3+	118 (6)	156 (8)	180 (9)	238 (11)	692 (9)
Male ratio, %	45	46	48	48	47
Female ratio, %	55	54	52	52	53
Median age, y (range)					
Charlson score 0	71 (20–96)	71 (21–100)	70 (15–96)	70 (19–97)	71 (15–100)
Charlson score 1–2	75 (15–95)	75 (31–95)	75 (45–97)	76 (23–97)	75 (15–97)
Charlson score 3+	74 (43–93)	73 (34–99)	75 (40–93)	76 (33–93)	75 (33–99)
Treatment[a]					
Resection rate, %					
Charlson score 0	82.5	84.4	85.0	82.7	83.8
Charlson score 1–2	72.0	79.4	78.7	78.2	77.7
Charlson score 3+	56.9	60.8	63.3	67.6	63.2
Diversion/local procedure rate, %					
Charlson score 0	5.9	5.1	3.7	4.5	4.7
Charlson score 1–2	5.6	7.1	5.3	5.0	5.8
Charlson score 3+	5.8	10.8	2.7	1.9	4.9
No surgery, %					
Charlson score 0	11.4	10.3	11.2	12.6	11.3
Charlson score 1–2	22.3	13.3	15.8	16.6	16.4
Charlson score 3+	37.2	28.2	33.8	30.3	31.7

[a]Data not available for 1995. Inclusion period ended June 30, 2006.

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score 1–2 (72 percent *vs.* 78 percent) and Charlson score 3+ (57 percent *vs.* 68 percent). The proportion of patients undergoing no surgery declined for patients with Charlson score 1–2 (22 percent *vs.* 17 percent) and Charlson score 3+ (37 percent *vs.* 30 percent), as well as the proportion who had diversion only/local procedure and Charlson score 3+ (6 percent *vs.* 2 percent).

From the selected procedure codes, 1,037 patients did not have an operation identified. Among those, 407 had another gastrointestinal operation included in the KJxxxx section (Appendix 1).

Overall Survival and Mortality by Level of Comorbidity

Overall 1-year and 5-year survival decreased with increasing Charlson score in all four time periods (Table 2). Five-year survival for patients with severe comorbidity (Charlson score 3+) was less than half of that among patients with no comorbidity (Table 2). After adjusting for age and gender, 1-year and 5-year MRR increased to at least 1.2 for patients with Charlson score 1–2 and to at least 1.7 for patients with Charlson score 3+ (Table 2). Restricting the analyses to patients who underwent a resection yielded nearly the same 1-year and 5-year MRR (data not shown).

Changes in the Effects of Comorbidity on Survival Over Time

One-year and 5-year MRR for patients with Charlson scores 1–2 and 3+ did not change between 1995 and 2006, except from a minor increase in 2001–2003 (Table 2). Results for patients with severe comorbidity should be interpreted with caution because of low patient numbers.

Rectal Cancer

During the study period, 5,220 patients were diagnosed with rectal cancer. The prevalence of rectal cancer patients with no comorbidity declined from 71 percent to 63 percent between the 1995 to 1997 and 2001 to 2006 periods (Table 3). The median age of patients without comorbidity concurrently decreased from 70 years to 66 years. During the study period, the treatment policy changed for patients with comorbidity (Table 3). For patients with Charlson score 1–2, the resection rate increased from 59 percent in 1996 to 1997 to 71 percent in 2001 to 2003, but decreased again to 61 percent in 2004 to 2006. For patients with Charlson score 3+, the resection rate was stable, but more patients had no surgery than diverson only/local procedure. The number of rectal cancer patients who did not undergo surgery, according to the selected procedure codes, was 798. Among these, 306 underwent another gastrointestinal operation (Appendix 1).

Overall Survival and Mortality by Level of Comorbidity

Overall 1-year and 5-year survival decreased with increasing Charlson score in all four time periods (Table 4). Five-year survival for patients with severe comorbidity was almost half of that for patients with no comorbidity (Table 4). After adjustment for age and gender, 1-year and 5-year MRR for patients with Charlson score 1–2 were at least 1.4 (Table 4). For patients with severe comorbidity, 1-year and 5-year MRR ranged from 1.9 to

TABLE 2. Overall survival and adjusted relative mortality rates of patients with colon cancer from 1995 through 2006

	Year of diagnosis			
	1995–1997	*1998–2000*	*2001–2003*	*2004–2006*
30-day mortality, % (95% CI)[a]				
Resection	8 (6–9)[b]	8 (7–10)	9 (8–11)	7 (5–8)
Diversion/local procedure	36 (27–49)[b]	27 (20–36)	36 (27–47)	28 (21–38)
1-year overall survival,% (95% CI)				
Charlson score 0	69 (66–71)	70 (68–73)	75 (72–77)	75 (73–78)
Charlson score 1–2	60 (55–64)	62 (58–66)	63 (59–66)	69 (65–72)
Charlson score 3+	53 (43–61)	51 (43–59)	44 (37–51)	58 (51–65)
5-year overall survival (95% CI)				
Charlson score 0	42 (39–45)	43 (40–46)		
Charlson score 1–2	32 (27–36)	31 (27–35)		
Charlson score 3+	18 (12–25)	20 (14–26)		
1-year relative mortality rate[c] (95% CI)				
Charlson score 0	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Charlson score 1–2	1.3 (1.1–1.5)	1.2 (1.0–1.4)	1.5 (1.2–1.8)	1.2 (1.0–1.5)
Charlson score 3+	1.7 (1.3–2.3)	1.9 (1.5–2.4)	2.5 (2.0–3.2)	1.8 (1.4–2.3)
5-year relative mortality rate[c] (95% CI)				
Charlson score 0	1 (reference)	1 (reference)		
Charlson score 1–2	1.3 (1.1–1.4)	1.3 (1.1–1.4)		
Charlson score 3+	1.9 (1.5–2.3)	1.8 (1.5–2.2)		

[a]Inclusion period ended June 30, 2006.
[b]Data not available for 1995.
[c]Adjusted for age, gender, time, and treatment policy.

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TABLE 3. Characteristics of patients with rectal cancer from 1995 through 2006

	Year of diagnosis				
Characteristic n (%)	*1995–1997*	*1998–2000*	*2001–2003*	*2004–2006*	*Total*
Charlson score 0	943 (71)	878 (68)	884 (67)	798 (63)	3503 (67)
Charlson score 1–2	329 (25)	329 (25)	342 (26)	351 (28)	1351 (26)
Charlson score 3+	64 (5)	90 (7)	99 (7)	113 (9)	366 (7)
Male ratio, %	54	54	57	59	56
Female ratio, %	46	46	43	41	44
Median age, y (range)					
Charlson score 0	70 (20–95)	69 (18–96)	68 (31–98)	66 (30–95)	68 (18–98)
Charlson score 1–2	74 (39–95)	74 (28–94)	73 (41–100)	73 (32–96)	74 (28–100)
Charlson score 3+	75 (27–97)	75 (38–94)	74 (49–93)	74 (39–96)	75 (27–97)
Treatment[a]					
Resection rate, %					
Charlson score 0	72.6	76.3	74.7	70.6	73.9
Charlson score 1–2	59.3	69.9	71.3	61.0	66.3
Charlson score 3+	51.1	60.0	48.4	51.6	52.9
Diversion/local procedure rate, %					
Charlson score 0	11.1	10.0	9.7	10.6	10.2
Charlson score 1–2	17.7	11.5	14.0	16.4	14.5
Charlson score 3+	18.6	14.4	14.1	10.9	13.9
No surgery, %					
Charlson score 0	16.1	13.6	15.4	18.7	15.7
Charlson score 1–2	22.9	18.5	14.6	22.5	19.0
Charlson score 3+	30.2	25.5	37.3	37.3	33.1

[a]Data not available for 1995. Inclusion period ended March 31, 2006.

3.2. Nearly the same MRR were found for the group of patients who had a resection (data not shown).

Changes in the Effects of Comorbidity on Survival Over Time

Disparities in 1-year and 5-year survival between rectal cancer patients with Charlson score 1–2 and patients with no comorbidity showed only small increases during the study period as a whole (Table 4). However, for patients with Charlson score 3+, the 1-year MRR increased from 2.2 in 1995–1997 to 3.2 in 2004 to 2006, while the 5-year MRR remained stable at 1.9 both in 1995–1997 and in 1998 to 2000. The number of rectal cancer patients with Charlson score 3+ was low.

TABLE 4. Overall survival and adjusted relative mortality rates of patients with rectal cancer from 1995 through 2006

	Year of diagnosis			
	1995–1997	*1998–2000*	*2001–2003*	*2004–2006*
30-day mortality, % (95% CI)[a]				
Resection	4 (3–6)[b]	6 (4–7)	6 (4–7)	6 (5–8)
Diversion/local procedure	11 (6–18)[b]	13 (9–20)	14 (10–21)	13 (9–19)
1-year overall survival, % (95% CI)				
Charlson score 0	75 (72–78)	78 (75–81)	81 (78–84)	83 (80–86)
Charlson score 1–2	65 (60–70)	67 (61–71)	69 (64–74)	71 (66–76)
Charlson score 3+	50 (37–61)	54 (44–64)	47 (37–57)	50 (39–59)
5-year overall survival, % (95% CI)				
Charlson score 0	43 (40–46)	46 (42–49)		
Charlson score 1–2	30 (25–35)	28 (24–33)		
Charlson score 3+	19 (10–29)	21 (13–30)		
1-year relative mortality rate,[c] % (95% CI)				
Charlson score 0	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Charlson score 1–2	1.4 (1.1–1.8)	1.5 (1.2–1.9)	1.6 (1.3–2.1)	1.5 (1.1–2.0)
Charlson score 3+	2.2 (1.5–3.2)	2.3 (1.7–3.3)	3.1 (2.3–4.2)	3.2 (2.3–4.4)
5-year relative mortality rate,[c] % (95% CI)				
Charlson score 0	1 (reference)	1 (reference)		
Charlson score 1–2	1.4 (1.2–1.6)	1.5 (1.2–1.7)		
Charlson score 3+	1.9 (1.4–2.5)	1.9 (1.5–2.4)		

[a]Inclusion period ended March 31, 2006.
[b]Data not available for 1995.
[c]Adjusted for age, gender, time, and treatment policy.

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DISCUSSION

In this population-based study of 13,190 CRC patients, at least one-third of patients had documented comorbid conditions. The study provides convincing evidence that the presence of comorbidity is an important prognostic factor for CRC patients. Both 1-year and 5-year survival decreased with increasing Charlson Comorbidity Index scores, with the highest impact for rectal cancers, clearly suggesting that CRC patients with comorbidities have increased mortality after CRC treatment. Patients with severe comorbidity may die with, rather than from, their CRC.

Our data extend findings from previous reports. Decreasing long-term survival among CRC patients with comorbidity was reported in recent population-based studies.[8,10,11] Gross *et al.* found that 5-year survival was 54 percent for rectal cancer patients aged 65 to 79 years with no comorbidity and 33 percent for patients with at least two comorbid conditions.[10] A recent Dutch study reported that cardiovascular disease, COPD, and diabetes showed independent prognostic effects on overall survival among colon cancer patients, while cardiovascular disease and COPD had independent prognostic effects on rectal cancer survival.[11]

Population-based studies indicate that short-term survival is also negatively influenced by comorbidity.[4,8,11] In addition, the Charlson Age-Comorbidity Index (CACI), a measure that adds an age factor to the Charlson Comorbidity Index, was a strong predictor of perioperative and cancer-related mortality in a small-scale study of 279 CRC patients.[7]

The mainstay of treatment for CRC is resection with curative intent. The influence of comorbidity on the overall resection rate has been evaluated in a few studies, which found that comorbidity had no influence on the overall resection rate.[4,8] One study did report, however, that comorbidity leads both to less frequent use of adjuvant chemotherapy in patients with Stage III colon cancer and to less frequent use of adjuvant radiotherapy in patients with rectal cancer.[8] Confounding by cancer treatment may flaw these observations, as the study did not differentiate between curative surgery and palliative surgery. In patients with severe comorbidity, surgeons may choose a palliative resection or a diversion procedure rather than a more extensive resection with curative intent. The current study lacks data on cancer staging, which may be unevenly distributed among the three comorbidity groups. However, we disaggregated surgical procedures into resections and diversion alone/local procedures, and found that the latter, independent of tumor origin, were undertaken slightly less often in patients with severe comorbidity over time. Among colon cancer patients with comorbidity, the proportion who had a resection increased during the study period, especially in those with severe comorbidity. In contrast, the proportion who did not have surgery increased among rectal cancer patients with severe comorbidity. This difference may be related to physicians' reliance on palliative treatment in cases of disseminated disease and/or severe comorbidity among rectal cancer patients. In colon cancer, resection was the preferred treatment, even in case of severe comorbidity. To minimize the influence of confounding by cancer treatment, we also examined mortality separately for the group of patients who underwent resection. Even in this specific group, which received the most homogenous and aggressive treatment, we observed increasing MRR with an increasing level of comorbidity. Thus the poorer outcome among CRC patients with comorbidity could not be caused only by suboptimal treatment.

The mechanism through which comorbid conditions affected cancer survival appear complex. Some combinations of conditions, *e.g.*, diabetes mellitus and congestive heart failure, appear to affect survival more than other combinations of conditions, *e.g.,* diabetes mellitus and chronic obstructive pulmonary disease.[10] An evaluation is needed as to why CRC patients with comorbidity have inferior survival compared to patients with no comorbid conditions. However, the low autopsy rate worldwide makes it difficult to obtain exact data on causes of death. Reasonable speculation is that pre-existing comorbidity may render CRC patients more vulnerable to fatal events in the early postoperative period, as suggested by the 1-year survival rates for patients with comorbidity compared to patients without comorbidity. Nevertheless, 30-day and 1-year survival among colon cancer patients with comorbidity improved to some extent during the study period despite an increasing proportion undergoing a resection. A comprehensive assessment of comorbidity should be incorporated into the preoperative evaluation to permit a tailored approach to perioperative care. Survival should improve if patients are treated perioperatively by a multidisciplinary team including anesthetists and internists as well as colorectal surgeons.

The strengths of our study include a large sample size and complete long-term follow-up using computerized nationwide registries; since the study was based on administrative data from the northern part of Denmark, covering about 30 percent of the Danish population. The patients were identified within the last decade and thus received up-to-date treatment. To calculate the Charlson Comorbidity Index, we retrieved discharge diagnoses from hospitalizations documented in nationwide hospital discharge registries in a 10-year period prior to the admission for CRC. Some diagnoses, like diabetes mellitus, may be missed going back only one year prior to the CRC diagnosis, as they may not be documented as discharge diagnoses in all of a patient's hospitalizations. Thus, all patients with severe comorbidity should have been captured in our study.

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Some possible limitations may influence the interpretation of our results. First, administrative discharge diagnoses are not entirely accurate,[29] so misclassification and coding errors may have occurred. Second, since diagnoses from outpatient treatments were not included in the study, some patients with minor comorbidity not requiring hospital admission, such as connective tissue disease or peptic gastrointestinal ulcers, could have been missed. Third, in 2000 the Danish health care authorities introduced a new accounting method based on Diagnosis Related Groups (DRG). The DRG system calls for more complete registration of concomitant diseases in addition to the main condition. Our finding of higher comorbidity scores over time may be caused partly by this administrative change, although the trend was noted even before 2000. Thus, patients in the three Charlson Comorbidity Index groups may not be completely comparable over time, with some "score-migration" occurring. These changes would be expected to contribute to improved comorbidity-specific survival, as we observed in patients without comorbidity and in 1-year survival in CRC patients with moderate comorbidity and colon cancer patients with severe comorbidity. Still, we did not observe improved survival in all comorbidity groups. Similar observations have been made for Danish breast cancer patients.[30]

Finally, the Charlson Comorbidity Index is not comprehensive in its adjustment for comorbidity. Patients with the same Charlson Comorbidity may have different outcomes, as conditions like congestive heart failure may be associated with higher mortality than conditions like connective tissue diseases. Other comorbidity indices have been developed for health services research with administrative data. The performance of four claims-based comorbidity indices (Elixhauser's set of 30 condition indicators, Klabunde's outpatient and inpatient indices weighted for CRC patients, Diagnostic Cost Groups, and the Adjusted Clinical Group System) has been compared in a cohort study including 5,777 Stage III colon cancer patients.[31] Although some comorbidity indices demonstrated minor advantages over others, each was fairly robust in predicting both chemotherapy receipt and noncancer death. We are unaware that the Charlson Comorbidity Index has proven to be inferior to these other indices.

CONCLUSION

In this population-based study of CRC patients diagnosed and treated with modern techniques, we observed that comorbidity was present among at least one-third of CRC patients. Comorbidity, ascertained from hospital discharge registries in the 10-year period before the CRC diagnosis, substantially impacted survival outcomes. In the 2004 to 2006 period, the 1-year MRR for colon and rectal cancer patients with severe comorbidity were almost two- and three-times higher, respectively, compared to patients without comorbidity.

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APPENDIX 1. Distribution of other operations among patients who did not have a resection or a diversion/local procedure

Procedure, n	Colon cancer	Rectal cancer
Endoscopic polypectomy	102	65
Exploratory laparotomy/ diagnostic laparoscopy	67	23
Biopsy from the peritoneum/ omentectomy/drainage of the peritoneal cavity	33	8
Dilatation of the bowel or rectum	33	19
Appendectomy	23	0
Small bowel resection	13	0
Other diagnostic procedures/minor operations (mostly endoscopic)	136	129
Incision/biopsy or local excision from the anal canal	0	62

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