Mortality After First Hospital Admission for Inflammatory Bowel Disease: A Nationwide Registry Linkage Study

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Background: The goal of this study was to determine long-term mortality and causes of death in patients after hospitalization for inflammatory bowel disease (IBD).

Methods: A cohort of patients admitted to the hospital because of IBD for the first time between 1998 and 2010 was identified by linkage of nationwide Dutch registries. Mortality risks and causes of death in Crohn's disease (CD) and ulcerative colitis (UC) patients were compared with a large random sample of individuals from the general population. Multivariable Cox regression models were used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs).

Results: In total, 23,003 patients (56.1% women; mean age, 44.8 years) were hospitalized for IBD. Patients admitted for IBD had a higher risk of death than those from the general population. Adjusted HRs for 5-year all-cause mortality were 2.42 (95% CI, 1.15–5.12) and 1.45 (95% CI, 1.26–1.66) in men and women hospitalized for CD, respectively. Corresponding HRs for UC were 1.59 (95% CI, 1.39–1.83) and 1.13 (95% CI, 0.98–1.31). Mortality among patients after hospitalization for IBD decreased between 1998–2004 and 2005–2010. Patients admitted for UC had a higher risk of all-cause mortality than those admitted for CD. Inflammatory bowel disease patients died more often from (colorectal) cancer and gastrointestinal disease and less often from cardiovascular disease relative to the general population.

Conclusions: Mortality of patients after hospitalization for IBD has decreased over time. Causes of death in CD and UC patients differ from those in the general population.

Key Words: Crohn's disease, ulcerative colitis, time trend, epidemiology

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are inflammatory bowel diseases (IBDs) with an increasing incidence and prevalence worldwide.[1] IBD causes chronic inflammation of the gastrointestinal tract and can result in serious complications, with a large impact on disability, health care utilization, and medical costs.[2–4] Mortality is an important measure of disease burden and may partly serve as an indicator of quality of care for CD and UC.

Studies on mortality in patients with IBD have reported mixed results, ranging from excess mortality in both CD and UC[5, 6] to similar life expectancies compared with the background population.[7–10] Overall, most data suggest an increased mortality risk in CD patients and no additional risk of death in UC patients.[11–15] The majority of these data derive from population-based and inception cohort studies.[5] Information regarding long-term survival and cause-specific mortality in IBD patients requiring hospitalization is, however, limited.

Approximately one-quarter of patients are admitted to the hospital within the first 2 years after diagnosis of IBD.[16] These patients are likely to have the most severe disease phenotype, with a markedly increased risk of complications and surgery. Hospital admission can therefore be considered a marker of poor disease. The aim of this study was to determine mortality and causes of death in patients after their first hospitalization for IBD in a nationwide cohort.

METHODS

Registries and Linkage Procedure

A cohort of patients admitted for IBD was constructed by linkage of 3 nationwide registries with prospective data

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collection: the Dutch Hospital Discharge Registry, the Dutch Population Registry, and the National Cause of Death Registry. A similar approach was previously used for other diseases.[17–19] Briefly, the data of these registries were linked using a unique record identification number (unique for 84% of the population). The medical and administrative data of all patients admitted to the hospital in the Netherlands are recorded in the Dutch Hospital Discharge Registry. Around 100 hospitals, including all general and university hospitals and most single specialty hospitals, participate in the registry. The registry contains information on demographics of patients (sex, date of birth) and admission data. The primary and secondary diagnoses are determined at discharge and coded using the ninth revision of the International Classification of Diseases (ICD-9).[20] The Dutch Population Registry records the information of all legally residing citizens in the Netherlands, including sex, date of birth, current address, nationality, and native country. The National Cause of Death Registry records all principal and any underlying causes of death using the 10th revision of the International Classification of Diseases (ICD-10).[21] The overall validity of the national registries and the reliability of linkage of these databases have been shown to be high.[22–25]

Study Population

Patients hospitalized for IBD were identified by selecting admissions for CD and UC from the Dutch Hospital Discharge Registry between January 1, 1998, and December 31, 2010, using the corresponding ICD-9 codes for the primary discharge diagnosis. Detailed information on these codes is provided in the Supplementary Data. The validity of using ICD-9 codes for identifying patients with IBD has previously been demonstrated to be high.[26] Those with a hospital admission for the same condition in the previous 3 years were excluded to ensure that the admissions for IBD were onset admissions. Linkage of the collected cases with the other registries resulted in a cohort of 23,003 unique patients with a first hospitalization for IBD within the study period.

A randomly selected group from the general Dutch population served as controls. The Dutch Population Registry was used to randomly select 500 persons of every age, up to 102 years, on the date of January 1, 2005. Thereafter, there were fewer than 500 persons per age. This resulted in a sample of 51,272 individuals.

Validity of National Hospital Discharge Registry Data

The validity of the Dutch Hospital Discharge Registry for identification of patients admitted for IBD was assessed by randomly selecting 100 hospitalizations for CD and UC in the University Medical Center Utrecht during the period 1998–2010 from the registry, using the same ICD-9 codes for the primary discharge diagnosis. The methods and results are described in the Supplementary Data. In summary, the positive predictive value of an ICD-9 code for IBD in the hospital discharge registry data for IBD being the cause of hospitalization was 89%, and the positive predictive value for having IBD was 97%. The type of IBD (CD or UC) was incorrect in 2% of cases. Admissions for IBD-unclassified were categorized as UC.

Comorbidity

Data on comorbidity were obtained from discharge summaries of the index admission or from previous hospital admissions. A modified version of the Charlson comorbidity index was used to express presence and extent of comorbidity.[27] This index is based on assigning points to 12 medical conditions and ranges from 0 to 24 points. The Charlson comorbidity index has been shown to be a valid and reliable method of assessing comorbidity.[28]

Follow-up and Outcome Measures

Date and underlying cause of death were obtained through linkage of cases to the National Cause of Death Registry using record identification numbers. Individuals were censored if they migrated out of the Netherlands or if their linkage number was not unique. One-year mortality and 5-year mortality risk were defined as risk of death within 1 and 5 years after the index date, respectively. These time intervals were chosen to evaluate mortality in the medium and long term in patients requiring hospitalization for IBD. Based on ICD-10 codes, causes of death were categorized into the following groups: cardiovascular disease, cancer, dementia, gastrointestinal diseases, lower respiratory tract infections, chronic lower respiratory diseases, genitourinary diseases, and other causes. Cancer was subdivided into different types of cancer. The specific codes are provided in the Supplementary Data. Gastrointestinal diseases include all diseases of the digestive system, ranging from the oral cavity to the intestines, liver, biliary tract, and pancreas, including noninfective enteritis and colitis.

Data Analysis

Categorical data were summarized as percentages. Normally and non–normally distributed, continuous data were summarized as means with SDs and medians with interquartile ranges (IQRs), respectively. Using Cox proportional hazard regression analyses, risks of 1-year and 5-year mortality were assessed by calculating hazard ratios (HRs) with 95% confidence intervals (CIs). The proportional hazards assumption was checked using Schoenfeld residuals. HRs were adjusted for potential confounders, including age, marital status, ethnic origin, and the Charlson comorbidity index. Risk of death in CD and UC patients was compared between those admitted during the periods 1998–2004 and 2005–2010 and compared with individuals from the general population. In addition, factors associated with mortality were determined within the cohort, including an evaluation of differences in prognosis between CD

and UC. A 2-sided *P* value of <0.05 was considered statistically significant. Data were analyzed with SPSS, version 22 (IBM Corp., Armonk, NY, USA).

Ethical Considerations

Linkage of data from the different nationwide registries was performed in agreement with privacy legislation in the Netherlands.[24] All analyses were performed in a secure environment of Statistics Netherlands using only anonymized data. The study was performed according to the regulations of research complying with Dutch law on medical research in humans. The validation of the national hospital discharge registry data by review of the medical records of a sample of patients from the University Medical Center Utrecht received exempt status from the institutional Medical Ethics Research Committee.

RESULTS

In total, 23,003 patients (56.1% women; mean age, 44.8 years) were admitted to the hospital because of IBD between 1998 and 2010 (Table 1). This included 5152 men and 7972 women hospitalized for CD and 4957 men and 4922 women hospitalized for UC. A random sample of 22,479 men and 28,793 women from the general Dutch population were selected for comparison. The median follow-up was ~5 years.

Within the cohort, mortality after hospitalization for CD decreased between the periods 1998–2004 and 2005–2010 (Table 2), although this was not significant in men. The 1-year all-cause mortality rate fell from 4.9% to 4.4% (adjusted HR, 0.81; 95% CI, 0.62–1.06) in men and from 4.1% to 3.4% (adjusted HR, 0.76; 95% CI, 0.59–0.96) in women admitted for CD. All-cause mortality also declined in men and women admitted for UC during the study period (Table 3). The 1-year all-cause mortality rate decreased from 7.1% to 5.3% (adjusted HR, 0.70; 95% CI, 0.55–0.88) in men and from 5.4% to 4.8% (adjusted HR, 0.76; 95% CI, 0.59–0.99) in women admitted for UC between the periods 1998–2004 and 2005–2010. Both 1-year and 5-year mortality rates were higher in men than in women and were higher in UC patients than in CD patients.

After correcting for covariables, risk of 1-year all-cause mortality was increased in both men and women admitted for CD compared with individuals from the general Dutch population with adjusted HRs of 2.68 (95% CI, 2.16–3.32) and 2.11 (95% CI, 1.73–2.57), respectively (Table 4). Corresponding HRs in UC patients were 2.11 (95% CI, 1.72–2.58) and 1.67 (95% CI, 1.36–2.05). Similarly, risk of all-cause mortality was increased in both CD and UC patients as compared with individuals from the general population after 5 years of follow-up, although this proved not to be significant in women with UC (Table 4). Hazard ratios were smaller at 5-year follow-up than at 1-year follow-up.

Male sex, increasing age, not being married or living together, and increasing comorbidity were independent predictors of 1-year and 5-year all-cause mortality in patients with a first hospital admission for IBD (Table 5). Furthermore, patients admitted for UC had a higher risk of 1-year all-cause mortality (adjusted HR, 1.30; 95% CI, 1.22–1.38) and 5-year all-cause mortality (adjusted HR, 1.12; 95% CI, 1.08–1.17) than those admitted for CD. Within the cohort, patients hospitalized in the period 2005–2010 had a reduced risk of all-cause mortality at 1-year follow-up and 5-year follow-up compared with patients hospitalized in the period 1998–2004, with adjusted HRs of 0.64 (95% CI, 0.57–0.72) and 0.72 (95% CI, 0.66–0.78), respectively.

The main causes of death were cardiovascular disease and cancer in both IBD patients and individuals from the general population (Table 6). Patients with CD and UC died more often from cancer (CD: 30.1%; UC: 27.0%), including colorectal cancer (CD: 6.1%; UC: 5.8%) and gastrointestinal

TABLE 1. Characteristics of Patients With a First Hospital Admission for Crohn's Disease and Ulcerative Colitis in the Netherlands Between 1998 and 2010 and Individuals From the General Dutch Population

	Crohn's Disease		Ulcerative Colitis		General Population	
	Men (n = 5152)	Women (n = 7972)	Men (n = 4957)	Women (n = 4922)	Men (n = 22,479)	Women (n = 28,793)
Age, mean (SD), y	41.6 (19.9)	42.5 (19.3)	48.8 (20.4)	47.9 (21.4)	44.9 (27.1)	55.5 (30.7)
Marital status, % married or living together	50.8	48.0	58.2	46.7	44.9	30.9
Ethnic origin, % native people	82.9	84.5	85.6	85.5	82.7	84.1
Charlson comorbidity index,[27] %						
0	89.2	91.8	83.5	88.7	90.5	89.5
1	6.3	4.4	9.1	6.2	5.4	5.9
≥2	4.5	3.8	7.3	5.1	4.1	4.6
Follow-up, median (IQR), y	4.8 (2.0–8.1)	4.8 (2.0–8.4)	4.6 (2.0–7.8)	4.7 (2.0–8.0)	6.0 (5.9–6.0)	6.0 (3.6–6.0)

Abbreviation: IQR, interquartile range.

TABLE 2. Time Trend in 1-Year and 5-Year All-Cause Mortality in Patients With a First Hospital Admission for Crohn's Disease in the Netherlands Between 1998 and 2010, Stratified by Sex and Age

	1-y All-Cause Mortality			5-y All-Cause Mortality		
	1998–2004, %	2005–2010, %	Adjusted HR (95% CI)	1998–2004, %	2005–2010, %	Adjusted HR (95% CI)
Men						
0–19 y	0	0	-	0.3	1.9	5.90 (0.65–53.9)
20–39 y	0.7	0.5	0.89 (0.25–3.21)	1.7	2.1	1.23 (0.54–2.84)
40–59 y	3.0	2.1	0.64 (0.33–1.26)	7.1	5.4	0.70 (0.43–1.14)
60–79 y	16.4	12.0	0.69 (0.48–1.00)	33.9	27.7	0.77 (0.59–1.02)
≥80 y	30.4	38.5	1.32 (0.79–2.21)	76.1	70.1	0.93 (0.65–1.35)
Total	4.9	4.4	0.81 (0.62–1.06)	11.3	10.5	0.83 (0.69–1.01)
Women						
0–19 y	0	0	-	0	0	-
20–39 y	0.6	0.3	0.67 (0.19–2.31)	1.6	0.8	0.51 (0.22–1.21)
40–59 y	2.9	1.7	0.62 (0.34–1.12)	7.0	5.4	0.78 (0.52–1.15)
60–79 y	10.8	9.8	0.90 (0.63–1.29)	28.8	24.8	0.79 (0.61–1.01)
≥80 y	28.7	23.4	0.73 (0.47–1.13)	67.3	62.3	0.77 (0.57–1.05)
Total	4.1	3.4	0.76 (0.59–0.96)	10.6	9.5	0.75 (0.63–0.89)

Hazard ratios are adjusted for age, marital status, ethnic origin, and the Charlson comorbidity index.[27]
Abbreviations: CI, confidence interval; HR, hazard ratio.

TABLE 3. Time Trend in 1-Year and 5-Year All-Cause Mortality in Patients With a First Hospital Admission for Ulcerative Colitis in the Netherlands Between 1998 and 2010, Stratified by Sex and Age

	1-y All-Cause Mortality			5-y All-Cause Mortality		
	1998–2004, %	2005–2010, %	Adjusted HR (95% CI)	1998–2004, %	2005–2010, %	Adjusted HR (95% CI)
Men						
0–19 y	0.6	1.0	1.33 (0.12–15.0)	2.5	1.8	1.00 (0.20–4.91)
20–39 y	0.9	0.7	0.62 (0.18–2.16)	2.1	1.8	0.70 (0.28–1.77)
40–59 y	1.9	2.2	1.11 (0.53–2.30)	6.1	7.1	1.12 (0.70–1.80)
60–79 y	14.3	10.3	0.67 (0.49–0.92)	35.2	27.9	0.72 (0.58–0.90)
≥80 y	39.0	23.1	0.54 (0.35–0.83)	78.8	62.3	0.64 (0.47–0.87)
Total	7.1	5.3	0.70 (0.55–0.88)	17.3	15.1	0.76 (0.65–0.90)
Women						
0–19 y	0	0.5	-	0.6	0.5	77.0 (<0.1–≥10)
20–39 y	0.2	0.2	0.65 (0.06–7.57)	1.1	0.3	0.42 (0.09–2.03)
40–59 y	2.2	1.3	0.50 (0.20–1.23)	4.6	3.6	0.72 (0.39–1.34)
60–79 y	11.8	10.2	0.75 (0.52–1.11)	28.1	24.6	0.78 (1.33–1.64)
≥80 y	24.2	21.0	0.82 (0.55–1.23)	61.0	50.4	0.77 (0.58–1.02)
Total	5.4	4.8	0.76 (0.59–0.99)	13.5	11.9	0.75 (0.63–0.91)

Hazard ratios are adjusted for age, marital status, ethnic origin, and the Charlson comorbidity index.[27]
Abbreviations: CI, confidence interval; HR, hazard ratio.

disease (CD: 17.3%; UC: 15.1%), and less often from cardiovascular disease (CD: 24.4%; UC: 26.3%), than those from the general Dutch population (cancer: 16.7%; colorectal cancer: 2.8%; gastrointestinal disease: 8.1%; cardiovascular disease: 31.3%).

DISCUSSION

This nationwide registry linkage study from the Netherlands showed that mortality of patients after hospitalization for CD and UC decreased over time. Mortality of patients admitted for IBD was increased compared with individuals

TABLE 4. Difference in Risk of 1-Year and 5-Year All-Cause Mortality in Crohn's Disease and Ulcerative Colitis Patients Compared With Individuals From the General Dutch Population Between 2005 and 2010, Stratified by Sex

	Adjusted HR (95% CI) Crohn's Disease vs General Population	Adjusted HR (95% CI) Ulcerative Colitis vs General Population
Men		
1-y all-cause mortality	2.68 (2.16–3.32)	2.11 (1.72–2.58)
5-y all-cause mortality	2.42 (1.15–5.12)	1.59 (1.39–1.83)
Women		
1-y all-cause mortality	2.11 (1.73–2.57)	1.67 (1.36–2.05)
5-y all-cause mortality	1.45 (1.26–1.66)	1.13 (0.98–1.31)

Hazard ratios are adjusted for age, marital status, ethnic origin, and the Charlson comorbidity index.[27]
Abbreviations: CI, confidence interval; HR, hazard ratio.

TABLE 5. Factors Associated With 1-Year and 5-Year All-Cause Mortality in Patients With a First Hospital Admission for Inflammatory Bowel Disease

	1-y All-Cause Mortality, Adjusted HR (95% CI)	5-y All-Cause Mortality, Adjusted HR (95% CI)
Ulcerative colitis (vs Crohn's disease)	1.30 (1.22–1.38)	1.12 (1.08–1.17)
Women (vs men)	0.87 (0.81–0.94)	0.91 (0.87–0.95)
Time period		
1998–2004	Reference	Reference
2005–2010	0.64 (0.57–0.72)	0.72 (0.66–0.78)
Age group		
0–19 y	Reference	Reference
20–39 y	3.71 (1.66–8.27)	3.59 (2.29–5.63)
40–59 y	16.4 (7.66–34.9)	16.6 (10.9–25.3)
60–79 y	84.6 (40.1–178)	89.8 (59.5–136)
≥80 y	412 (196–867)	516 (343–778)
Marital status		
Married or living together (vs not)	0.79 (0.72–0.87)	0.80 (0.76–0.85)
Ethnic origin		
Native people (vs non-native people)	0.96 (0.86–1.08)	1.00 (0.93–1.06)
Charlson comorbidity index[27]	1.33 (1.29–1.37)	1.31 (1.28–1.33)

Abbreviations: CI, confidence interval; HR, hazard ratio.

from the general population. Patients admitted for UC had a higher risk of all-cause mortality than patients admitted for CD. Causes of death in IBD patients differed from those in the general population. Patients hospitalized for CD and UC died more often from (colorectal) cancer and gastrointestinal disease and less often from cardiovascular disease.

Although mortality in IBD has been extensively studied, data on long-term survival of CD and UC patients requiring hospitalization are relatively scarce.[29–31] Approximately half of patients with IBD will be admitted to the hospital at some point through the course of their disease, especially in the first years after the diagnosis, although differences between countries have been observed.[2, 3, 16] The mortality rates in this study appear to be consistent with previous data. In a record linkage study from England investigating survival in patients with and without colectomy admitted to the hospital, overall 3-year mortality rates were 9% in CD and 12% in UC.[29] A nationwide linkage analysis from Scotland, based on smaller numbers, generated roughly similar results.[30, 31] Temporal data from these and other studies also demonstrated reduced mortality risks over time, mainly in patients with UC.[6, 30–32] Apart from changes in the general population, these improving mortality trends may indicate the introduction of better diagnostics, new drugs, such as biological agents, and changed therapeutic or surveillance strategies in IBD.

Patients admitted for IBD were found to have an approximately 2-fold increased risk of death at 1-year follow-up

TABLE 6. Causes of Death in Patients With a First Hospital Admission for Crohn's Disease and Ulcerative Colitis and Individuals From the General Dutch Population

Cause of Death	Crohn's Disease (n = 13,124), %	Ulcerative Colitis (n = 9879), %	General Population (n = 51,272), %
Cardiovascular diseases	24.4	26.3	31.3
Cancer	30.1	27.0	16.7
Lung cancer	7.1	5.3	3.2
Colon cancer	4.8	4.5	2.2
Breast cancer	1.5	1.6	1.4
Prostate cancer	1.3	2.0	1.1
Pancreatic cancer	1.4	1.2	0.8
Gastric cancer	0.7	0.9	0.6
Rectosigmoid cancer	1.3	1.3	0.6
Esophageal cancer	0.6	0.9	0.3
Biliary tract cancer	0.3	0.5	0.2
Liver cancer	0.3	0.5	0.2
Dementia	1.9	2.1	8.3
Gastrointestinal diseases	17.3	15.1	8.1
Lower respiratory tract infection	3.5	4.3	7.3
Chronic lower respiratory disease	5.0	5.5	4.2
Genitourinary diseases	2.4	2.3	3.1
Other causes	15.4	17.4	21.0

compared with individuals from the general population. This considerably increased risk decreased after 5 years of follow-up, possibly reflecting the severity of the initial complication for which the patient was admitted. Indeed, several studies have shown mortality risks in IBD patients to be increased particularly within the first years after diagnosis,[13, 14] most notably in patients with UC. Of note, the risk of death remained significantly elevated several years after hospital admission in both CD and UC patients in the present study. This might be explained by complications associated with longer disease durations, such as the development of strictures or (colitis-associated) colorectal cancer. The mortality risks in IBD patients relative to the general population found here are greater than the standardized mortality ratios found in previous studies and underscore the severe disease phenotype of hospitalized IBD patients.[5]

Few studies have investigated factors associated with mortality in patients with IBD. As observed in this study, male sex, increasing age, and comorbidity were previously found to be important predictors of mortality.[14, 30, 31] Other determinants that were identified in varying degrees in prior studies included socioeconomic status, emergency admission, length of hospital stay, and (emergency) surgery.[14, 30, 31] The greater risk of all-cause mortality in UC patients than in CD patients can possibly be ascribed to cases of fulminant colitis.

Cause-specific mortality in patients hospitalized for IBD differed from that of individuals from the general population, which is in line with previous population-based studies.[6, 33, 34] Death from gastrointestinal disease occurred more frequently in patients with IBD. It is conceivable that this is related to (complications from) IBD, although the group of digestive diseases was not further specified. The risk of death from cancer was found to be almost 2-fold greater in both patients with CD and UC, which could be only partly attributed to colorectal cancer. Excess mortality from extraintestinal cancer has been observed in several studies.[15, 35–37] A meta-analysis of population-based cohort studies, for example, also noted an increased risk of lung and upper gastrointestinal cancer in CD patients and an increased risk of biliary tract and liver cancer in UC patients.[35] Other extra-intestinal malignancies reportedly associated with IBD include lymphoproliferative disorders and nonmelanoma skin cancers.[36, 37] Possible explanations for these findings may be smoking habits (especially in CD), extraintestinal manifestations of IBD, concomitant disorders such as primary sclerosing cholangitis, and immunosuppressive drugs. Remarkably, cardiovascular disease mortality was a less frequent cause of death in IBD patients. Although inflammatory disorders are frequently linked with cardiovascular disease,[38] some studies have indeed suggested that IBD does not appear to be a risk factor for cardiovascular disease mortality.[39, 40] Interestingly, lower respiratory tract infections were also less often found to be the cause of death in CD and UC patients than in individuals from the general population. With the introduction of new, powerful drugs, the prevalence of serious infections could be expected to rise. However, these results do not support this assumption and have been confirmed in recent reports.[41] Cause-specific mortality differed slightly between the

types of IBD, with death from cancer and gastrointestinal disease occurring more often and death from cardiovascular disease occurring less often in patients with CD than in patients with UC. Notably, risk of colorectal cancer (mortality) is often found to be higher in UC patients than CD patients, whereas this difference was not observed in this study, which may possibly reflect more careful surveillance in UC patients due to increased awareness.

The strengths of this study include the large size and nationwide coverage of the cohort, increasing the generalizability of the results because of the unselective population and complete follow-up. Data were collected prospectively from national registries in the Netherlands that have been previously shown to have high validity.[22, 23] In addition, linkage between these registries was found to be highly reliable.[24, 25] In contrast to previous studies, mortality risks were stratified by age, sex, and diagnosis (CD and UC) and adjusted for possible confounders, such as comorbidity. Lastly, causes of death were determined to provide cause-specific mortality.

This study also had limitations. Despite the high validity of the registries, misclassification could not be fully excluded. Identification of patients being admitted for IBD may sometimes have been incorrect. However, validation in a subgroup revealed that only 3% of IBD diagnoses were incorrect. Although all previous admissions to a maximum of 3 years were identified, it is conceivable that some patients were readmitted rather than hospitalized for the first time. As a result, mortality after hospitalization for IBD may have been somewhat overestimated. However, as the method was applied in a similar way over the entire study period, it is not likely that this affected the trend analysis. Mortality over time was evaluated by comparing data between 2 discrete time periods, as the sample size did not allow analysis of mortality from year to year. Controls from the general population were not matched for characteristics of the IBD patients. However, adjusting for potential confounders, including important mortality drivers such as sex and age, by using regression models is preferred to matching. If residual confounding might have still existed, it is likely that the reported HRs are actually underestimated because the reference group was comprised of more older individuals than the IBD population. In spite of the large sample size of this study, the confidence intervals were sometimes relatively wide. Finally, information on type of admission (elective vs emergency), length of hospital stay, surgery, medication, and disease characteristics, including disease duration and severity of disease as an indication for hospitalization, were not available. Although the lack of these data affects the ability to precisely point toward underlying explanatory processes, this does not invalidate the reported findings.

In conclusion, this nationwide registry linkage study found mortality of patients after hospital admission for IBD to have decreased over the last years. Patients hospitalized for IBD died more often from (colorectal) cancer and gastrointestinal disease and less often from cardiovascular disease relative to the general population. These findings help inform caregivers about the long-term prognosis of patients with CD and UC requiring hospitalization.

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