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Original Article

Mortality in Patients with Inflammatory Bowel Disease: Results from 30 Years of Follow-up in a Norwegian Inception Cohort (the IBSEN study)

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Abstract

Background and Aims: Patients with longstanding inflammatory bowel disease [IBD] may be at an increased risk of death compared to the general population, especially elderly patients. The Inflammatory Bowel South-Eastern Norway [IBSEN] study has previously detected a small but not statistically significant increase in mortality 20 years after diagnosis. The aim of this study was to evaluate the overall and cause-specific mortality at 30 years of follow-up.

Methods: The IBSEN cohort included 519 incident patients with ulcerative colitis [UC] and 237 patients with Crohn's disease [CD] between 1990 and 1993, each matched with five controls. Death certificate data were obtained from the Norwegian Cause of Death Registry. The underlying causes of death were categorized into five groups: all cancers, gastrointestinal cancers, cardiovascular diseases, infections and all other causes. Hazard ratios [HRs] were modelled using Cox regression.

Results: There was no statistically significant difference in the overall mortality rates. However, in patients with CD, male sex (HR = 1.65 [95% CI: 1.04–2.62]), onset after 40 years of age (HR = 1.72 [1.19–2.48]), colonic disease (HR = 1.57 [1.05–2.35]) and penetrating behaviour (HR = 3.3 [1.41–7.76]) were clinical factors associated with an increased mortality. IBD patients were at a higher risk of death due to cardiovascular disease: HR = 1.51 [1.10–2.08] for UC and 2.04 [1.11–3.77] for CD. When taking into account both the underlying and the immediate cause of death, infection was more frequent in patients with IBD.

Conclusions: Overall, all-cause mortality rates were similar between patients with IBD and controls. However, clinicians should remain alert to cardiovascular diseases and infections, particularly in specific subgroups of CD patients.

Key Words: Inflammatory bowel disease; mortality; population-based study

1. Introduction

Inflammatory bowel diseases [IBD], including Crohn's disease [CD] and ulcerative colitis [UC], are chronic diseases of the gastrointestinal tract with a heterogeneous clinical course. A severe clinical disease course can lead to serious complications.[1,2] Furthermore, longitudinal studies have shown that patients with IBD have a higher mortality rate compared to the general population, particularly for CD patients from the second and third decade after diagnosis.[3–5]

In most cases, IBD-related mortality is a consequence of cardiovascular disease, malignancies, infections, postoperative complications, gastrointestinal and hepatic diseases, and pulmonary disease.[6–13]

Although treatments and clinical strategies have gradually improved, particularly with the emergence of tumour necrosis factor [TNF]-α inhibitors, the rising proportion of elderly patients poses new challenges.[14–17] For example, therapeutics that compromise the immune system may raise the risk of serious infections or malignancies in elderly patients.[18–22] Studies centered on elderly IBD patients repeatedly found increased mortality rates.[10,23,24]

Studies on the Inflammatory Bowel South-Eastern Norway [IBSEN] cohort detected a small but not significant increase in mortality 20 years after diagnosis.[25,26]

While the proportion of elderly patients in this cohort has grown, the aims of this study were primarily to determine the hazard ratios [HRs] for mortality within 30 years following diagnosis, and secondarily to identify specific causes of mortality and subgroups of patients most at risk.

2. Methods

The IBSEN study's design, methods and procedures have been described in detail before.[27,28] In summary, all newly diagnosed IBD patients from January 1, 1990 to December

Table 1. Characteristics of IBSEN patients.

Ulcerative colitis [UC]				Crohn's disease [CD]			
At diagnosis	**Percentage**	**Those who died**	**Percentage of all UC**	**At diagnosis**	**Percentage**	**Those who died**	**Percentage of all CD**
Male	267 51.4	85	16.6	**Male**	119 50.2	26	11.2
Female	252 48.6	63	12.3	**Female**	118 49.8	28	12.0
Median age, years		**At death**		**Median age, years**		**At death**	
Male	38.3 [7–83]	78.8		Male	27.8 [5–88]	67.8	
Female	36.6 [11–84]	81.1		Female	29.6 [3–88]	78.7	
Age < 17 years	20 3.9	1	0.2	**Age < 17 years**	29 12.2	2	0.9
Age 17–39 years	269 51.8	13	2.5	**Age 17–39 years**	138 58.2	7	3.0
Age ≥ 40 years	230 44.3	134	26.2	**Age ≥ 40 years**	70 29.5	45	19.3
Disease location at diagnosis							
Proctitis	171 32.9	27	5.3		— —	—	—
Left-sided colitis	182 35.1	68	13.3		— —	—	—
Pancolitis	166 32.0	53	10.4		— —	—	—
Ileal	— —	—	—		64 27.0	10	4.3
Colonic	— —	—	—		115 48.5	36	15.5
Ileocolonic	— —	—	—		54 22.8	8	3.4
Upper disease	— —	—	—		4 1.7	0	0.0
				Disease behaviour at diagnosis			
	— —	—	—	Non-stricturing, non-penetrating	147 62.0	32	13.7
	— —	—	—	Stricturing	64 27.0	12	5.2
	— —	—	—	Penetrating	26 11.0	10	4.3

31, 1993 residing in four geographically well-defined areas [counties] in Southeast Norway were included. In total, the population-based inception cohort included 519 patients with UC and 237 with CD.[29,30] The diagnosis and inclusion of the patients were made according to Lennard-Jones criteria.[31]

Predetermined follow-up visits were undertaken at 1, 5, 10 and 20 [±1] years after inclusion. Colonoscopies were performed unless the patients objected. Based on the clinical information gathered at the time of diagnosis, the disease phenotype was retrospectively classified according to its location and behaviour.

2.1. Definitions and causes of death classifications

Data on the cause of death were obtained from the Norwegian Cause of Death Registry which compiles all death certificates in Norway.[32] Medical doctors in Norway are required by law to complete a death certificate for every occurrence. The death certificate structure and the resulting underlying cause of death follow international guidelines published by the World Health Organization, the underlying cause of death being defined as the disease or injury which initiated the train of morbid events leading directly to death. Since 2005, the contributing cause of death is recorded when appropriate.

Causes of death were classified into five categories according to the International Classification of Diseases 10th revision [ICD-10]: all cancers [C00–D46], gastrointestinal cancers only [C15–C26], cardiovascular diseases [I00–I99], infections [A00–B99] and all other causes. Additional infection codes that are not specified in the ICD-10 A00–B99 chapter were also taken into account.[10] ICD-9 codes that were present before 1996 were converted into the ICD-10 format.

2.2. Statistical analysis

All Norwegian citizens are assigned a unique digital identification number, which enables the linking of data between different registries. Each patient in the IBSEN cohort was matched for age and sex with five controls from the same geographical area at the time of diagnosis, randomly drawn from the Norwegian Population Register.

Continuous variables were described as medians and ranges, while categorical data were presented as counts and percentages.

Survival time was defined from the date of diagnosis to the date of death or the end of follow-up on December 31, 2020, whichever came first.

Crude cumulative mortality was estimated using the Kaplan–Meier method, and survival differences between cases and controls were assessed using the log-rank test.

The HRs of all-cause and cause-specific mortality for the patients compared to matched controls were modelled using Cox regression stratified by matched case-controls sets. The results are presented with 95% confidence intervals [CIs]. The p-values less than 0.05 were considered statistically significant. When the analysis was restricted to subgroups of the dataset, HRs were also modelled using Cox regression stratified by matched sets. All analyses were considered exploratory and therefore no correction for multiple testing was done.

All analyses were performed using R statistical software version 4.1.3 and the survival package version 3.2.

2.3. Ethical considerations

The study has been approved by the Regional Committee for Medical Research Ethics of Southeast Norway.

3. Results

Characteristics of the patients of the IBSEN cohort are summarized in Table 1. The median follow-up time was 28 years and the median age of the cohort was 60 years at the end of the study. Twelve patients were lost to follow-up when emigrating.

3.1. All-cause mortality

The proportion of IBD patients who died after 30 years of follow-up was similar to the matched controls. There were 202 [26.7%] and 998 deaths [26.4%] among IBD patients and controls, respectively. Figure 1 displays the Kaplan–Meier plot of overall survival throughout the observational study period.

There was no significant difference in overall mortality between UC or CD patients and controls [p = 0.6 and 0.2, respectively]. Although the mortality HR was increased for CD patients, when stratifying the analysis according to gender, the increase was significant only for male CD patients [Table 2].

Disease onset after 40 years of age, colonic disease and penetrating behaviour were clinical characteristics associated with a higher mortality rate in CD patients compared to their matched controls [Table 2]. In patients with onset of CD before 17 years of age, the mortality HR was high (HR = 3.33 [0.56–19.95]) although not statistically significant.

3.2. Cause-specific mortality

Cardiovascular disease was the most common cause of death in this cohort. Compared to controls, patients with

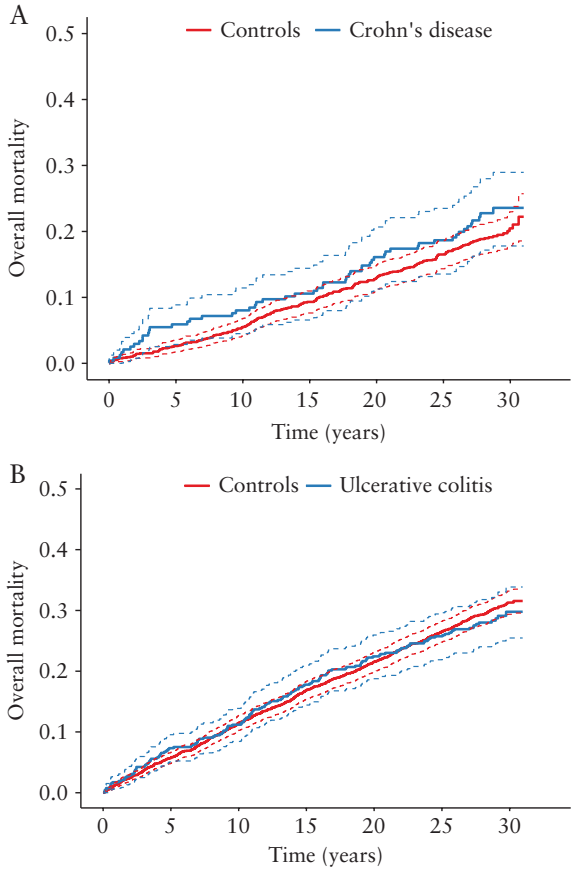

Figure 1. Kaplan–Meier plot of overall mortality for Crohn's disease [a] and ulcerative colitis patients [b] and matched controls.

UC and CD were at a higher risk of death due to cardiovascular disease, with HR of 1.51 [1.10–2.08] and 2.04 [1.11–3.77], respectively [Table 3]. Specifically, myocardial infarction [*n* = 21], chronic ischaemic heart disease [*n* = 14] and intracerebral haemorrhage [*n* = 7] frequently occurred in patients with IBD.

The HRs for all cancers, or gastrointestinal cancers, or infections as the underlying cause of death were not significantly different between patients and controls.

CD was explicitly reported as the underlying cause of death for six patients. Similarly, UC was recorded for eight patients. In these cases, the immediate causes of death recorded on the death certificates were most often infections [*n* = 6] or cardiovascular diseases [*n* = 4].

In addition, IBD was noted as a contributing cause of death in 19 cases, frequently in conjunction with cancer as the underlying cause [*n* = 9].

4. Discussion

We have measured the HRs for mortality at 30 years following diagnosis, and we further estimated the risk for specific causes of death corresponding to distinct patient subgroups within our population-based cohort.

Although HRs for mortality were higher, which is in line with results of similar studies, we did not detect a significant difference in overall mortality 30 years after diagnosis compared to the controls. Studies from Nordic countries carried

Table 2. Mortality hazard ratio for IBSEN patients compared to controls stratified by clinical covariates.

	Ulcerative colitis		Crohn's disease	
	All-cause mortality		All-cause mortality	
	HR	95% CI	HR	95% CI
	1.09	0.90–1.33	**1.61**	**1.16–2.22**
Female	1.15	0.85–1.55	1.56	0.99–2.47
Male	1.05	0.81–1.34	**1.65**	**1.04–2.62**
Age < 17 years	NA		3.33	0.56–19.95
Age 17–39 years	0.69	0.39–1.32	1.18	0.54–2.57
Age ≥ 40 years	1.16	0.94–1.43	**1.72**	**1.19–2.48**
Disease location at diagnosis				
Proctitis	0.87	0.67–1.35	—	—
Left-sided colitis	1.19	0.89–1.60	—	—
Pancolitis	1.11	0.81–1.53	—	—
Ileal	—	—	1.46	0.71–3
Colonic	—	—	**1.57**	**1.05–2.35**
Ileocolonic	—	—	2.17	0.91–5.21
Upper disease	—	—	NA	
Disease behaviour at diagnosis				
Non-stricturing, non-penetrating	—	—	1.48	0.97–2.25
Stricturing	—	—	1.33	0.69–2.59
Penetrating	—	—	**3.3**	**1.41–7.76**

HR, hazard ratio; CI, confidence interval; NA, not applicable. Bold values indicates the significant results.

Table 3. Hazard ratios for causes of death categories for IBSEN patients compared to controls.

Underlying cause of death	Ulcerative colitis [UC]		Crohn's disease [CD]	
	Number	HR [95% CI]	Number	HR
Gastrointestinal cancer[a]	18	1.4 [0.80–2.45]	2	0.87 [0.19–3.96]
All cancers	42	1.02 [0.72–1.45]	17	1.50 [0.86–2.63]
Cardiovascular disease	58	**1.51 [1.10–2.08]**	17	**2.04 [1.11–3.77]**
Infection	7	1.49 [0.61–23.65]	2	4.23 [0.59–30.09]
Other causes	41	0.77 [0.53–1.11]	18	1.34 [0.77–2.32]

HR, hazard ratio; CI, confidence interval. Bold values indicates the significant results.
[a]Of which ten colorectal cancers in UC patients and one in CD patients.

out over similar time periods often observed a progressive decline in the mortality HR.[9,10,33,34] The gradual improvement of medical treatments may explain this observation. The IBSEN study did not detect elevated mortality at earlier follow-up time points.[25,26,29]

An elevated risk of death, specifically due to cardiovascular disease, was observed in our study. The association between IBD and death caused by cardiovascular disease aligns with the findings of several recent studies.[9–11,33] In Denmark, heart failure, ischaemic heart disease, myocardial infarction and cerebrovascular disease were found to be associated with IBD, and the risk of death from cardiovascular disease may be higher during flares.[35–37] The incidence of cardiovascular disease is highest in the older age groups.[38,39] Long-term ongoing chronic inflammation exacerbates the risk of cardiovascular disease, which could explain why the increased mortality was detected for the first time after 30 years of follow-up of the IBSEN study.[14,40]

In patients with CD, male sex, diagnosis after 40 years of age and colonic disease result in higher mortality. This association was also observed in a comparable Danish cohort.[13] In a recent Swedish register study, patients diagnosed after 60 years of age had the highest excess mortality, and colonic location and penetrating behaviour seemed to be associated with excess mortality.[34] Penetrating behaviour from the onset of CD was linked to a higher mortality in our cohort as well. Penetrating disease is a more severe behaviour that often results in surgical intervention, as has been observed within the IBSEN cohort 10 and 20 years after diagnosis.[41,42] Perioperative death, especially following emergency surgery, is a possible outcome.[6,43,44] However, our dataset does not allow for IBD-related perioperative mortality analysis, so it is not possible to assess if this explains our finding.

IBD patients are regularly administered immunomodulatory treatments, glucocorticoids and in a few cases therapeutic biological products, which consequently increase the risk of infection.[18–21,45] Considering the main underlying cause of death, infection was not significantly more frequent in IBD patients than in the controls. This is in contrast to recent studies in which IBD patients, especially elderly, were vulnerable to opportunistic and serious infections.[9,10,33,46] However, when IBD was recorded as the main underlying cause in our study, infection was often the immediate cause of death. Therefore, the risk of infection remains a major concern for both patients and clinicians.

Compared to controls, there was no significant elevation in mortality due to cancer in general or to gastrointestinal cancer in particular. This differs from the results of a systematic review of population-based studies as well as several nationwide studies in Nordic countries, which revealed a modest increase.[9,10,33,47] It has been argued that excess mortality due to malignancy may not be as marked as it used to be.[48]

4.1. Strengths and limitations

The main strength of the present study is the well-defined inclusion criteria enforced by dedicated specialists and hospitals, and its prospective population-based design, which minimizes selection and observer bias. Continuous and thorough medical follow-up in a well-functioning health system, together with the precise characterization of the cohort, add value to the IBSEN study.

Norwegian national health registers and the national identity number facilitate data collection and analysis.[49] Each patient was age- and sex-matched with controls from the same county. The National Cause of Death Registry has good completeness.[32]

A limitation of our cohort is its moderate size, inherently weakening the statistical power, which results in imprecise estimates when the analysis relies on small subgroups with few individuals. The long follow-up time partially compensates for the moderate cohort size by increasing the cumulative number of events. In addition, no further clinical data were collected after 20 years of disease, and therefore it is not possible to associate recent medical treatment or disease course events with the outcomes.

It is an oversimplification to assume that death is due to a single cause, and it may not always be accurately reported. The format of the death certificate evolved over the time of our study.[32] However, the underlying cause of death has been systematically coded according to international World Health Organization guidelines, which allows comparison with studies from other countries. Furthermore, the classification bias would be the same for both patients and controls.

5. Conclusion

Overall, this long-term cohort study revealed a good prognosis for IBD patients regarding mortality, which testifies to the advances in IBD medical care and the broadening panel of therapeutic options. Clinicians should be particularly alert to cardiovascular diseases and infections since IBD patients are more likely to be affected, emphasizing the challenges associated with the ageing general population.

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Conflict of Interest

Ø.H. has received personal fees from AbbVie, Janssen-Cilag AS, Takeda and Ferring. L-P.J-J. has received personal fees for lectures and advisory boards for Takeda, Ferring and Tillots Pharmaceuticals. B.M. has received personal fees from Gilead, AbbVie, Janssen-Cilag, Takeda, Ferring, Pfizer, Norgine, Vifor France, Norsk elektronisk legehåndbok. None of these were related to the submitted work.

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Author Contributions

All of the authors made substantial contributions to the conception and design of the study, as well as the generation, collection and interpretation of the data. All of the authors also contributed to the drafting and revision of the article and approved the final version of the article. M. C. Småstuen had the main responsibility for the statistical analyses. B.

Follin-Arbelet, Ø. Hovde, Lars-Petter Jørgensen and B. A. Moum were responsible for drafting the article, for revising it critically, for important intellectual content and for the final approval of the version to be published. They also were partially responsible for the statistical analyses.

Data Availability

The data underlying this article cannot be shared publicly due to the restrictions imposed by the ethics committee, the public registers and the national legal framework.

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