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Ulcerative colitis: no rise in mortality in a European-wide population based cohort 10 years after diagnosis

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Background: Population based studies have revealed varying mortality for patients with ulcerative colitis but most have described patients from limited geographical areas who were diagnosed before 1990.

Aims: To assess overall mortality in a European cohort of patients with ulcerative colitis, 10 years after diagnosis, and to investigate national ulcerative colitis related mortality across Europe.

Methods: Mortality 10 years after diagnosis was recorded in a prospective European-wide population based cohort of patients with ulcerative colitis diagnosed in 1991–1993 from nine centres in seven European countries. Expected mortality was calculated from the sex, age and country specific mortality in the WHO Mortality Database for 1995–1998. Standardised mortality ratios (SMR) and 95% confidence intervals (CI) were calculated.

Results: At follow-up, 661 of 775 patients were alive with a median follow-up duration of 123 months (107–144). A total of 73 deaths (median follow-up time 61 months (1–133)) occurred compared with an expected 67. The overall mortality risk was no higher: SMR 1.09 (95% CI 0.86 to 1.37). Mortality by sex was SMR 0.92 (95% CI 0.65 to 1.26) for males and SMR 1.39 (95% CI 0.97 to 1.93) for females. There was a slightly higher risk in older age groups. For disease specific mortality, a higher SMR was found only for pulmonary disease. Mortality by European region was SMR 1.19 (95% CI 0.91 to 1.53) for the north and SMR 0.82 (95% CI 0.45–1.37) for the south.

Conclusions: Higher mortality was not found in patients with ulcerative colitis 10 years after disease onset. However, a significant rise in SMR for pulmonary disease, and a trend towards an age related rise in SMR, was observed.

Ulcerative colitis is a chronic inflammatory disease of unknown origin affecting the colon and rectum to a varying extent. The average incidence in Western Europe is estimated to be 10 per 100 000¹ but the overall incidence varies considerably throughout the world.² The disease course may vary from a single attack to chronic disabling symptoms³ that seriously impairs quality of life.⁴ Whether or not the disease carries a higher mortality risk has not been fully established; some studies have shown lower and others higher mortality than background populations.^{5–6} In addition, there may be subgroups of patients at risk of death from disease related conditions.⁷

The aim of this European–Israeli population based multi-centre study was to compare mortality in patients with ulcerative colitis with mortality in the background population, and to examine disease specific causes of death in the various subgroups.

PATIENTS AND METHODS

Patients and centres

The present investigation was part of a follow-up study conducted by the European Collaborative Study Group of Inflammatory Bowel Disease (EC-IBD). In the EC-IBD study, a population based prospective diagnosed inception cohort of 2201 patients with inflammatory bowel disease were recruited from 20 treatment centres in different geographical areas in 12 European countries over a 2 year period between 1 October 1991 and 30 September 1993.⁸ Patients were classified according to the diagnostic criteria of Lennard-Jones and Truelove and Witts,⁹ and 1379 patients were classified with ulcerative

colitis, the rest having either Crohn's disease or indeterminate colitis.¹⁰

After 10 years, each of the 20 centres was invited to participate in the follow-up study reported here. Thirteen, with 1022 (74%) of the original 1379 patients with ulcerative colitis, agreed, and seven did not participate for technical or logistical reasons, such as difficulties in establishing administrative routines, and lack of qualified study personnel and hospital facilities necessary to carry out the follow-up. This did not alter the population based character of the study because every centre had met the criteria for population based patient inclusion at the formation of the cohort. Before data collection, a patient response rate per centre was set to a minimum of 60% to ensure the population based nature of the cohort. Patients were followed-up from the inception period (1 October 1991 to 30 September 1993) to the data inclusion period of the present study, between 1 August 2002 and 31 January 2004, or to a time prior to this period if the patient had died or been lost to follow-up.

This 10 year follow-up study was supported financially by the European Union. Further details of the planning, financing and methods used have been described in previous publications from the EC-IBD.^{10–11}

Abbreviations: 5-ASA, salazopyrine/5-aminosalicylic acid; AZA/6MP, azathioprine/6-mercaptopurine; CCS, clinical classification software; CRC, colorectal cancer; EC-IBD, European Collaborative Study Group of Inflammatory Bowel Disease; GCS, glucocorticosteroids; SMR, standardised mortality ratio

Table 1 Male, female and cohort specific mortality according to age (sex and country adjusted), disease extent at diagnosis (age, sex and country adjusted) and residence (age and sex adjusted)

Age (y)	Males				Females				Entire cohort			
	n	Dead	Exp	SMR (95%CI)	n	Dead	Exp	SMR (95%CI)	n	Dead	Exp	SMR (95%CI)
Age at diagnosis (y)												
10–19	15	0	0.12	0 (–)	25	0	0.08	0 (–)	40	0	0.19	0 (–)
20–29	84	0	0.92	0 (–)	108	1	0.53	1.89 (0.02–10.53)	192	1	1.45	0.69 (0.01–3.84)
30–39	89	1	1.68	0.60 (0.01–3.31)	85	0	0.92	0 (–)	174	1	2.60	0.38 (0.01–2.14)
40–49	86	1	4.10	0.24 (0.00–1.36)	41	1	0.98	1.02 (0.01–5.65)	127	2	5.08	0.39 (0.04–1.42)
50–59	55	6	6.41	0.94 (0.34–2.04)	43	6	2.60	2.30 (0.84–5.02)	98	12	9.02	1.33 (0.69–2.33)
60–69	46	12	13.76	0.87 (0.45–1.52)	35	5	5.27	0.95 (0.31–2.22)	81	17	19.03	0.89 (0.52–1.43)
70–79	25	16	11.81	1.36 (0.77–2.20)	27	15	12.46	1.20 (0.67–1.99)	52	31	24.27	1.28 (0.87–1.81)
80–89	4	2	2.73	0.73 (0.08–2.65)	7	7	2.42	2.90 (1.16–5.97)	11	9	5.15	1.75 (0.80–3.32)
Disease extent at diagnosis												
Proctitis	91	8	6.53	1.22 (0.53–2.41)	134	10	7.70	1.30 (0.62–2.39)	225	18	14.23	1.27 (0.75–2.00)
Distal colitis	204	21	25.09	0.84 (0.52–1.28)	130	11	10.04	1.10 (0.55–1.96)	334	32	35.13	0.91 (0.62–1.29)
Extensive colitis	96	9	8.20	1.10 (0.50–2.08)	94	12	6.66	1.80 (0.93–3.15)	190	21	14.86	1.41 (0.87–2.16)
Country												
Greece	53	2	5.25	0.38 (0.04–1.38)	37	1	1.11	0.90 (0.01–5.00)	90	3	6.36	0.47 (0.09–1.38)
Israel	24	0	1.17	0 (–)	15	2	0.49	4.06 (0.46–14.66)	39	7	5.39	1.30 (0.52–2.68)
Italy	50	4	3.95	1.01 (0.27–2.59)	36	3	1.44	2.08 (0.42–6.07)	86	2	1.66	1.20 (0.14–4.35)
Spain	30	2	2.78	0.72 (0.08–2.59)	33	0	0.97	0 (–)	63	2	3.75	0.53 (0.06–1.93)
Denmark	38	6	4.04	1.49 (0.54–3.24)	50	9	5.88	1.53 (0.70–2.91)	88	15	9.91	1.51 (0.85–2.50)
Norway	129	21	15.59	1.35 (0.83–2.06)	140	16	12.66	1.26 (0.72–2.05)	269	37	28.25	1.31 (0.92–1.81)
The Netherlands	80	3	8.75	0.34 (0.07–1.00)	60	4	2.70	1.48 (0.40–3.79)	140	7	11.45	0.61 (0.24–1.26)
Southern centres	157	8	13.14	0.61 (0.26–1.20)	121	6	4.02	1.49 (0.55–3.25)	278	14	17.16	0.82 (0.45–1.37)
Northern centres	247	30	28.38	1.06 (0.71–1.51)	250	29	21.24	1.37 (0.91–1.96)	497	59	49.61	1.19 (0.91–1.53)
All patients	404	38	41.52	0.92 (0.65–1.26)	371	35	25.26	1.39 (0.97–1.93)	775	73	66.78	1.09 (0.86–1.37)

n, Number of patients; Exp, expected number of deaths; SMR, standardised mortality ratio.

Southern centres, centres in Greece, Israel, Italy and Spain.

Northern centres, centres in Denmark (Copenhagen), The Netherlands and Norway;

Twenty six patients without known disease extent were excluded from the analysis of disease extent and mortality.

Only patients over age 15 years were entered into the cohort.

Methods

The centres in Greece, Israel, Italy and Spain are referred to as southern centres and those in Denmark (the Copenhagen centre), the Netherlands and Norway as northern centres.

The patient's vital status was assessed from hospital charts and contact with relatives and general practitioners by mail or telephone. In the Scandinavian countries, additional information was obtained from the national death certificate registries. Dates and causes of death were registered using single level clinical classical software (CCS)¹² based on the International Classification of Diseases (ICD-10).¹³ In the CCS, ICD-10 codes are broken down into a smaller number of clinically meaningful categories, thus creating broad diagnostic groups which are

more useful for descriptive statistics than individual ICD-10 codes. The CCS aggregates illnesses and conditions into 259 mutually exclusive categories, most of which are homogeneous.

Expected mortality was calculated from the WHO Mortality Database for the years 1995–1998 using ICD-9 (for the centres in Greece, Italy and Spain) and ICD-10 (for the centres in Denmark, Israel, Norway and The Netherlands).¹⁴ The relation between ulcerative colitis and the cause of death was evaluated separately for each individual case on the basis of the collected data. Disease extent was calculated from findings at endoscopy, if necessary supplemented by radiology and findings at surgery. Disease extent proximal to the splenic flexure was classified as extensive colitis, colonic inflammation distal to the splenic flexure as distal colitis and disease limited to the rectum 15 cm above the linea dentata as proctitis. Disease extent at diagnosis was based on results from endoscopy, and in a limited number of cases supplemented by radiology or findings at surgery.

Information on drug use was obtained from the medical records updated at each follow-up visit. A patient registered as having used a drug during one or more time periods during follow-up was classified as a drug user, and for these patients the proportion of time of follow-up in which the medication was given was calculated. The most common systemically used drugs were chosen for analysis. These were grouped into aminosalicylates (5-ASA), including sulfasalazine, glucocorticosteroids (GCS), and azathioprine and 6-mercaptopurine (AZA/6MP). The use of other drugs such as methotrexate and ciclosporin was considered to be negligible because of the small number of patients who used them, and was therefore not included in the analysis.

Statistical analysis

Standardised mortality ratio (SMR) was calculated by dividing observed mortality by expected mortality using country, age and sex specific data from the WHO Mortality Database (31

Figure 1 Total observed survival of the entire cohort (—) compared with expected survival (---) based on aggregated mortality statistics of all participating countries. Overall observed versus expected survival was 99.1% versus 99.3%, 95.9% versus 95.3% and 90.9% versus 90.9% 1 year, 5 years and 10 years after diagnosis, respectively. Note the limited scale range on the vertical axis. n, number of patients.

Table 2 Use of systemic drugs from time of inclusion to colectomy, death, lost to follow-up or study completion

	5-ASA				GCS				AZA/6MP			
	User n	Time of use	Non-user n	No data n	User n	Time of use	Non-user n	No data n	User n	Time of use	Non-user n	No data n
Vital status at the end of the study												
Dead	55	1.0	15	3	32	0.3	38	3	3	0.1	67	3
Alive	553	0.8	90	18	287	0.1	356	18	51	0.2	589	21
Unknown	31	0.9	9	1	10	0.1	30	1	1	0.5	39	1
Total	639	0.9	114	22	329	0.1	424	22	55	0.2	695	25

5-ASA, sulfasalazine/5-aminosalicylic acid; GCS, glucocorticosteroids; AZA/6MP, azathioprin/6-mercaptopurine; No data, no available information on drug use; Non-user, drug not used in follow-up; User, drug used in follow-up; Time of use, proportion of time on medication during follow-up, median value calculated for drug users only.

January 2004 update). Byar's approximation was used to calculate 95% confidence intervals (95% CI).¹⁵ The χ^2 test, t test and the Mann-Whitney U test were performed to identify possible differences in sex, age, geographical location and disease extent between patients followed up for the whole period and those lost to follow-up, and to compare subgroups of patients during follow-up regarding time of survival, smoking and medical treatment. Observed survival was calculated using the Kaplan-Meier technique. Expected survival curves were calculated using age specific mortality and age and sex specific distribution of person-years of the cohort. Cox regression analysis was used to identify risk factors for mortality using the proportional hazards assumption.

RESULTS

Follow-up

Nine of the 13 centres met the threshold limit of 60% response, giving a total of 781 patients from these centres for follow-up. There were no significant differences in the distribution of sex or age at diagnosis or north-south location between these nine centres and the 11 non-participating centres of the original cohort. Of the 781 patients, 661 were known to be alive when the follow-up data collection was started in August 2004, and

73 patients had died during the follow-up period. The vital status at study end point was unknown in 47 patients who were lost to follow-up, 41 of whom were followed during varying time intervals (median follow-up time 35 months (range 1-91)). Six of these patients appeared to have a date of the most recent visit that was the same as the date of diagnosis. Thus a total of 775 patients were available for follow-up analyses (404 males and 371 females with a mean age of 37 years at diagnosis (range 16-88)). Patients with unknown vital status were no different from the rest of the cohort in terms of sex, age or proportion with extensive colitis at diagnosis.

Overall mortality

Table 1 shows the total mortality, and mortality according to age, sex, residence and disease extent at diagnosis

At the end of follow-up, 661 patients were known to be alive (median follow-up time 123 months (range 107-144)). Seventy three patients had died (median time from diagnosis until death 61 months (range 1-133)), and 66.8 were expected to die (SMR 1.09 (95% CI 0.86 to 1.37)). When the observed survival curve was compared with the expected curve based on aggregated mortality statistics of all participating countries, as shown in fig 1, there was no significant increase in overall

Table 3 Disease specific mortality for the main diagnostic groups (age, sex and country adjusted) and disease location at diagnosis (age, sex and country adjusted)

	n	Cancer causes CCS ICD-10: 011-044			Cardiovascular causes CCS ICD-10: 099-118			Pulmonary causes CCS ICD-10: 122-134			Gastrointestinal causes CCS ICD-10: 138-155		
		Dead	Exp	SMR (95%CI)	Dead	Exp	SMR (95%CI)	Dead	Exp	SMR (95%CI)	Dead	Exp	SMR (95%CI)
Sex													
Male	404	12	12.31	0.97 (0.50-1.70)	16	16.15	0.99 (0.57-1.61)	6	3.27	1.83 (0.67-3.99)	2	1.52	1.31 (0.15-4.75)
Female	371	7	6.63	1.06 (0.42-2.18)	12	10.05	1.19 (0.62-2.09)	5	2.19	2.28 (0.74-5.32)	3	0.94	3.18 (0.64-9.29)
Disease extent at diagnosis													
Proctitis	225	5	4.19	1.19 (0.38-2.79)	7	5.16	1.36 (0.54-2.80)	3	1.13	2.65 (0.53-7.73)	0	0.58	0 (-)
Distal colitis	334	9	9.81	0.92 (0.42-1.74)	12	14.13	0.85 (0.44-1.48)	3	3.04	0.99 (0.20-2.88)	3	1.26	2.39 (0.48-6.97)
Extensive colitis	190	5	4.19	1.19 (0.38-2.79)	7	5.88	1.19 (0.48-2.45)	5	1.13	4.44 (1.43-10.35)	2	0.53	3.74 (0.42-13.51)
Country													
Greece	90	2	1.89	1.06 (0.12-3.83)	1	2.74	0.37 (0-2.03)	0	0.33	0 (-)	0	0.18	0 (-)
Italy	86	0	1.82	0 (-)	6	1.83	3.29 (1.20-7.15)	0	0.25	0 (-)	1	0.31	3.26 (0.04-18.15)
Israel	39	1	0.45	2.24 (0.03-12.46)	0	0.52	0 (-)	1	0.07	13.37 (0.17-71.41)	0	0.05	0 (-)
Spain	63	2	1.22	1.64 (0.18-5.91)	0	1.11	0 (-)	0	0.31	0 (-)	0	0.23	0 (-)
Denmark	88	3	2.85	1.05 (1.21-3.08)	3	3.56	0.84 (0.17-2.46)	7	0.90	7.79 (3.12-16.04)	1	0.46	2.17 (0.03-12.09)
Norway	269	11	6.88	1.60 (0.80-2.86)	13	12.31	1.06 (0.56-1.81)	3	2.62	1.15 (0.23-3.35)	1	0.85	1.18 (0.02-6.55)
The Netherlands	140	0	3.84	0 (-)	5	4.14	1.21 (0.39-2.82)	0	0.98	0 (-)	2	0.38	5.28 (0.59-19.08)
Southern centres	278	5	5.38	0.93 (0.30-2.17)	7	6.19	1.13 (0.45-2.33)	1	0.96	1.04 (0.01-5.77)	1	0.78	1.29 (0.02-7.16)
Northern centres	497	14	13.56	1.03 (0.56-1.73)	21	20.01	1.05 (0.65-1.60)	10	4.50	2.22 (1.06-4.09)	4	1.69	2.37 (0.64-6.07)
All patients	775	19	18.94	1.00 (0.60-1.57)	28	26.20	1.07 (0.71-1.54)	11	5.46	2.01 (1.00-3.60)	5	2.47	2.03 (0.65-4.73)

n, Number of patients; Exp, expected number of deaths; SMR, standardised mortality ratio; CCS, clinical classifications software; ICD, International Classification of Disease.

Twenty six patients without known disease extent were excluded from the analysis of disease extent and mortality.

Table 4 Cause of death possibly or probably related to ulcerative colitis

Patient and UC related death	Centre	Sex	Disease extent at diagnosis	Age at diagnosis (y)	Survival after diagnosis (months)	Surgery related	Cause of death	CCS ICD-10 code
Gastrointestinal causes								
1 Probable	Oslo	M	Distal	79	29	Yes	Acute myocardial infarction at partial colectomy for CRC	144
2 Probable	South Limburg	F	extensive	59	37	Yes	Cardiac complications at total colectomy for resistant UC	144
3 Probable	Copenhagen	F	Extensive	87	3	Yes	Active UC. Subtotal colectomy, abscess found	148
4 Probable	South Limburg	F	Distal	71	99	Yes	Peritonitis and septicaemia. Acute subtotal colectomy, findings of abscess and perforation.	148
Cardiovascular causes								
5 Possible	Cremona	M	Extensive	63	14	No	Acute cerebrovascular disease. Disease activity within the last 2 months of death, use of topical and systemic GCS and ciclosporin	109

CCS, clinical classifications software; ICD, International Classification of Diseases; UC, ulcerative colitis.

mortality risk. Observed mortality was almost identical to the expected numbers after 1 year, 5 years and 10 years of follow-up. No significantly higher mortality risk was found for females (SMR 1.39 (95% CI 0.97 to 1.93)), males (0.92 (95% CI 0.65 to 1.26)), northern (1.19 (95% CI 0.91 to 1.53)) or southern (0.82 (95% CI 0.45–1.37)) European centres even though there was a trend towards higher mortality for females and for northern centres.

Phenotype at diagnosis and associated mortality

Mortality according to age and disease extent at diagnosis, sex and country is presented in table 1. The number of cases of proctitis was 30% for the whole cohort, with a male/female ratio of 0.6. There were no statistically significant differences in SMR according to disease extent at diagnosis. Table 1 shows that SMR tended to increase with age at diagnosis but age at diagnosis was only statistically significant in females of 80 years and over. The overall SMR for females showed only a non-significant increase.

Use of drugs and mortality

Data on drug treatment according to vital status at the end of follow-up are presented in table 2.

With regards to the number of patients on medication, there were no significant differences between the dead and survivors for any of the three groups of drugs. However, duration of treatment was higher in the mortality group than in patients who survived throughout the follow-up period, both for 5-ASA ($p = 0.04$) and for GCS ($p = 0.01$), but not for AZA/6MP ($p = 0.7$).

Disease specific mortality

Table 3 shows disease specific mortality for the whole cohort.

The cause of death was poorly defined in two patients. Of the four main diagnostic groups, a significantly higher mortality was found for pulmonary disease (SMR 2.01 (95% CI 1.00 to 3.60)). Of the 11 patients who died from pulmonary disease, seven were in the Copenhagen cohort (Denmark), giving an SMR of 7.79 (95% CI 3.12 to 16.04). There was no increase in SMR for malignant disease. Only one death related to colorectal cancer (CRC) was observed, and the patient died of surgical complications. In two other cases, CRC was diagnosed in the last five months before death but was not considered to be the cause of death. No rise in mortality from non-malignant gastrointestinal disease was observed.

Mortality and relation to ulcerative colitis

Table 4 shows details of the five patients in whom the cause of death was considered to be possibly or probably related to ulcerative colitis. Table 5 shows the patients with causes of death unlikely to be related to ulcerative colitis.

Mean age at diagnosis was 71.8 years in the ulcerative colitis related group and 68.5 in the non-ulcerative colitis related mortality group (95% CI to 13.7–7.3). Median survival time was 29 months for ulcerative colitis related compared with 61.5 months in non-ulcerative colitis related deaths ($p = 0.09$). Four patients died in association with surgery, two of intra-abdominal infections and two of acute cardiac complications. One death, from acute cerebrovascular disease, was considered to be possibly caused by adverse effects of medical treatment for ulcerative colitis. The Cox regression model for total mortality was dominated by the age specific effects on total mortality and therefore did not yield any independent risk factor for ulcerative colitis related mortality.

DISCUSSION

The overall mortality in this European population based multicentre cohort was no higher than that of the background population. None of the factors that were analysed for a possible impact on mortality were statistically significant. Older age groups at diagnosis and female sex only showed a trend towards higher mortality.

Previous studies from different geographical regions are not in complete agreement as to whether ulcerative colitis is a risk factor for mortality^{5 16–19} or not.^{6 7 20–22} Many of these studies were hospital based, retrospective or covered periods of many years. Thus their results must be interpreted with caution as they used different criteria for selection of patients, and as both treatment and disease behaviour change over time.²³ The present study had a short inclusion period of 2 years, patients were selected from a range of centres across Europe and Israel, the geographical areas were well defined and it was population based and employed uniform diagnostic criteria. All of the patients were followed-up for the same time period so that those who completed follow-up had comparable observation times.

A higher mortality risk in ulcerative colitis has mostly been reported in older studies^{16–18} while more recent ones have shown a mortality rate comparable to that of the background population, which is in accordance with the findings in our study.^{6 21} This may be due to a more favourable disease pattern or to improvements in treatment in recent decades although

Table 5 Causes of death not likely to be related to ulcerative colitis

Patient No	Centre	Sex	Disease extent at diagnosis	Age at diagnosis (y)	Survival after diagnosis (months)	Cause of death	CCS ICD-10 code	Circumstances at death
Cancer								
1	Copenhagen	F	Extensive	77	58	Cancer of head and neck	11	Long term use of systemic GCS followed by azathioprine
2	Copenhagen	M	Proctitis	52	50	Cancer of stomach	13	No immunosuppressives
3	Heraklion	F	Proctitis	62	63	Cancer of stomach	13	No immunosuppressives
4	Oslo	M	Distal	74	72	Cancer of stomach	13	No immunosuppressives
5	Oslo	M	Extensive	65	1	Cancer of the liver	16	No immunosuppressives
6	Oslo	M	Proctitis	87	26	Cancer pancreatitis	17	Systemic GCS used
7	Beer Sheeva	F	Extensive	54	58	Cancer of the gall bladder	18	No immunosuppressive. No sign of UC related liver disease
8	Heraklion	M	Proctitis	56	133	Bronchus carcinoma	19	No immunosuppressives
9	Vigo	M	Distal	59	45	Bronchus carcinoma	19	No immunosuppressives
10	Oslo	F	Extensive	53	110	Breast cancer	24	No immunosuppressives
11	Oslo	F	Extensive	83	23	Breast cancer	24	No immunosuppressives
12	Oslo	F	Proctitis	61	40	Cancer of uterus	25	No immunosuppressives
13	Vigo	M	Distal	72	51	Cancer of prostate	29	Long term use of systemic GCS
14	Oslo	M	Distal	61	105	Cancer of brain and nervous system	35	No immunosuppressives
15	Oslo	M	Distal	59	106	Non-Hodgkin's lymphoma	38	No immunosuppressives
16	Oslo	M	Distal	67	8	Leukaemia	39	No immunosuppressives
17	Oslo	M	Distal	74	83	Cancer of the prostate	29	No immunosuppressives
18	Oslo	F	Distal	79	124	Myelofibrosis	39	No UC activity. CRC surgery 5 months before death.
19	Copenhagen	M	Distal	73	93	Multiple myeloma	40	No immunosuppressives
Cardiovascular causes								
20	Reggio Emilia	F	Unknown	63	70	Acute cerebral haemorrhagia	85	No immunosuppressives
21	Oslo	M	Proctitis	49	132	Acute myocardial infarction	100	No UC activity. Topical GCS
22	Oslo	M	Distal	67	38	Acute myocardial infarction	100	No UC activity
23	Oslo	M	Extensive	68	89	Acute myocardial infarction	100	No UC activity
24	Reggio Emilia	M	Extensive	73	21	Acute myocardial infarction	100	No UC activity
25	South Limburg	M	Distal	63	125	Acute myocardial infarction	100	No UC activity
26	South Limburg	F	Distal	67	10	Acute myocardial infarction	100	Systemic GCS
27	South Limburg	M	Extensive	69	113	Acute myocardial infarction	100	No UC activity
28	Oslo	M	Distal	69	107	Coronary atherosclerosis	101	No UC activity
29	Copenhagen	F	Proctitis	77	115	Other and ill defined heart disease	104	No UC activity
30	Cremona	F	Proctitis	85	18	Congestive heart failure	108	No UC activity
31	Oslo	M	Extensive	67	80	Congestive heart failure	108	No UC activity
32	Oslo	F	Distal	70	110	Congestive heart failure	108	No UC activity
33	Oslo	F	Distal	73	13	Congestive heart failure	108	No UC activity
34	Oslo	F	Extensive	80	110	Congestive heart failure	108	No UC activity
35	Oslo	M	Distal	88	56	Congestive heart failure	108	No immunosuppressives
36	Reggio Emilia	M	Distal	71	130	Congestive heart failure	108	No UC activity
37	Copenhagen	F	Distal	58	51	Acute cerebrovascular disease	109	No UC activity
38	Cremona	F	Distal	75	40	Acute cerebrovascular disease	109	No UC activity
39	Oslo	M	Extensive	77	27	Acute cerebrovascular disease	109	No UC activity
40	Oslo	M	Proctitis	80	49	Acute cerebrovascular disease	109	No UC activity
41	South Limburg	M	Proctitis	33	99	Acute cerebrovascular disease	109	No UC activity
42	South Limburg	F	Distal	54	103	Acute cerebrovascular disease	109	No UC activity
43	Oslo	M	Proctitis	58	37	Peripheral atherosclerosis	114	No UC activity
44	Copenhagen	F	Unknown	77	35	Arteriosclerosis	115	No immunosuppressives
45	Ioannina	M	Distal	72	25	Phlebitis, thrombophlebitis and thrombosis	118	No UC activity
46	Oslo	F	Proctitis	80	6	Phlebitis, thrombophlebitis and thrombosis	118	No UC activity
Pulmonary causes								
47	Beer Sheeva	F	Extensive	58	103	Pneumonia	122	Possible steroid use
48	Copenhagen	M	Extensive	66	24	Pneumonia	122	No immunosuppressives
49	Copenhagen	F	Extensive	67	61	Pneumonia	122	No immunosuppressives
50	Copenhagen	M	Proctitis	67	61	Pneumonia	122	No immunosuppressives
51	Copenhagen	M	Distal	70	36	COPD	127	No UC activity
52	Copenhagen	F	Proctitis	70	70	COPD	127	No UC activity
53	Copenhagen	M	Extensive	74	93	Pneumonia	122	No immunosuppressives
54	Copenhagen	F	Extensive	77	109	Pneumonia	122	No immunosuppressives
55	Oslo	F	Proctitis	56	83	COPD	127	No UC activity
56	Oslo	M	Distal	70	57	Pneumonia	122	No immunosuppressives
57	Oslo	M	Distal	70	57	Pneumonia	122	No immunosuppressives
Gastrointestinal causes								
58	Cremona	male	distal	58	2	Gastrointestinal haemorrhage	153	Bleeding oesophageal varices in cirrhosis from hepatitis B
Other causes								
59	Oslo	F	Distal	76	111	Septicaemia	2	No immunosuppressives
60	Oslo	M	Distal	71	97	Diabetes mellitus with complications	50	No UC activity
61	Copenhagen	F	Proctitis	77	63	Fluid and electrolyte disorder	55	No UC activity
62	Oslo	F	Distal	82	78	Organic mental disorder	68	No UC activity
63	Oslo	F	Extensive	79	30	Hip fracture	226	Use of systemic GCS
64	Oslo	F	Distal	28	62	Residual code, unclassified	259	No UC activity
65	Oslo	M	Distal	74	110	Residual code, unclassified	259	No UC activity
66	Oslo	F	Proctitis	74	123	Residual code, unclassified	259	Use of systemic GCS
67	Oslo	F	Extensive	82	2	Residual code, unclassified	259	No immunosuppressives
68	Oslo	F	Proctitis	88	30	Residual code, unclassified	259	No immunosuppressives

GCS, glucocorticosteroids; CCS, clinical classifications software; ICD, International Classification of Disease; UC, ulcerative colitis.

long term follow-up studies from Denmark and the UK have failed to show any change in mortality over time.^{7, 21} Excess mortality during the first year of ulcerative colitis has been reported,²¹ a finding that is not supported by our study. The values for survival in our cohort were almost identical to those expected throughout the entire 10 years. Our study also failed to show any rise in SMR for non-malignant gastrointestinal disease, as has been reported in earlier studies.^{5, 17, 18} A large study from Copenhagen showed excess mortality related to ulcerative colitis as a result of postoperative complications.⁷ Our data did not support the finding of higher mortality related to colectomy in ulcerative colitis, despite the occurrence of four surgery related deaths.

Our findings are in line with the study of Farrokhyar *et al* that showed no relation between death and ulcerative colitis.²¹ Only one death from CRC was found in our study. A 10 year follow-up period is, however, too short to conclude whether or not CRC has an impact on ulcerative colitis related mortality because this cancer is known to have a long latency period. Patients with an ulcerative colitis related cause of death tended to have a shorter life expectancy from the time of diagnosis than patients who died from other diseases. This could have been due to the surgery related mortality which occurred in four of the five patients who died of ulcerative colitis related causes.

Older age at diagnosis has been shown to be a mortality risk factor by Winther and colleagues⁷ and Farrokhyar and colleagues,²¹ and there was also a trend towards higher mortality in the older age groups in our study. However, the effect of age on SMR may be partly due to older age related comorbidity. Higher mortality for males and those with extensive disease has been reported^{7, 16} but we found no impact of disease extent on SMR, and only a non-significant rise in SMR for females. Older females, on the other hand, had a significantly higher SMR. However, as there was only a small number of deaths in this group, the finding may be coincidental.

Differences in drug treatment may influence mortality through therapeutic or adverse effects. The difference in treatment duration of 5-ASA found between the patients who died and the survivors is probably of no clinical importance. The number of serious adverse events of possible importance to mortality was low compared with the extensive prescription of this group of drugs.²⁴ The increase in GCS treatment found in patients who died during follow-up could, however, be of some importance to mortality, even if this could not be established from our data. For AZA/6MP, the number of users may have been too small to detect any possible influence on mortality rate. Also, long term effects of drug treatment on mortality may not have been detectable in this study due to the short follow up period. Differences in drug treatments could also reflect differences in disease severity of importance to mortality. A difference in the incidence of ulcerative colitis between northern and southern European centres has been reported previously¹⁰ but we found no significant difference in SMR by place of residence, even though SMR was slightly higher for the northern than for the southern centres. But the lack of significance could be due to a type II statistical error.

Smoking has been suggested to be an important influence on mortality in ulcerative colitis. The lower mortality from cardiovascular and pulmonary disease in patients with ulcerative colitis has been attributed to the lower frequency of smoking in these patients, especially in comparison with patients with Crohn's disease.^{25, 26} We found a higher pulmonary SMR, which reached a significant level for the Copenhagen cohort from the Danish centre, and this is in line with the findings of Winther and colleagues.⁷ There is no obvious explanation for this finding. Of the 11 patients who died from

pulmonary disease, the cause of death was noted as pneumonia in eight and chronic obstructive pulmonary disease in three patients. Possible local differences in registration of the primary cause of death or of the records on comorbidity in this elderly, probably multimorbid patient group, might have biased the result. Also, the smoking status of these patients might not have been substantially different from the total cohort, and therefore not in conflict with ulcerative colitis as being a disease of non-smokers. Because data on smoking habits and comorbidity were not available, and the number of patients who died from pulmonary causes was low, this finding must be interpreted with caution.

It could be argued that the study shows that mortality in patients with ulcerative colitis who are "compliant" and attend follow-up, answer questionnaires and attend centres with the logistics necessary to maintain follow-up over a decade is normal. Mortality among the other patients could have made a difference. From the original cohort of patients described by Shivananda and colleagues,¹⁰ patients from centres who were in the follow-up analysis did not differ in baseline characteristics, such as age, sex or north-south location, compared with patients from centres that were not included. A similar uniformity in patient characteristics was found when comparing patients with unknown vital status to the rest of the patients included in the follow-up study. Our data do not seem to indicate that these results on mortality were not representative of the original cohort, even if the follow-up did not include all of the original centres.

Some of the subgroups may represent too small a sample for some analyses such as cause of mortality by sex, or mortality related to geographical region. The multivariate analysis was impeded by the relatively small number of deaths and the strong association between age and survival. There could have been a selection bias in the patients and centres participating in the follow-up study but a uniform standard of clinical management of ulcerative colitis was noted in the first year in all of the centres participating in the original cohort.²⁷

The high number of cases of proctitis, especially among females, could have biased the mortality rates found in our study. The initial disease distribution was however in line with what was previously found in the IBSEN cohort by Moum *et al*²⁸ who reported an initial incidence of proctitis of 32%, and a male/female ratio of 0.7. We therefore believe that our data should be acceptable and justified with regards to the low risk of selection bias.

In conclusion, our prospective European population based cohort study of mortality in ulcerative colitis has shown no rise in SMR at any time over 10 years of observation. No rise in mortality was found from gastrointestinal diseases. There was a trend towards higher mortality with disease onset at an older age. Long term follow-up studies of possible risk factors, such as drug treatment and smoking, for morbidity and mortality are needed.

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