Clinical Course in Crohn's Disease: Results of a Norwegian Population-Based Ten-Year Follow-Up Study

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See Hutfless SM et al on page 1779 for companion article in the December 2007 issue of *Gastroenterology*.

Background & Aims: **Most studies concerning the clinical course in CD are retrospective or based on selected patient groups. Our aim was to assess the course of CD in a prospective population-based follow-up study and to identify possible prognostic risk factors for complications on the basis of information obtained at initial diagnosis.** ***Methods:*** **From 1990–1994, a population-based cohort of 843 new cases of inflammatory bowel disease was recruited in South-Eastern Norway. The cohort was systematically followed up at 1, 5, and 10 years after diagnosis.** ***Results:*** **Of 237 patients classified as CD, 197 completed the 10 years of follow-up, 18 died, and 22 were lost to follow-up. The cumulative relapse rate during the first 10 years was 90% (95% confidence interval, 86%–94%), and the cumulative probability of surgery was 37.9% (95% confidence interval, 31.4%–44.4%). Terminal ileal location ($P < .001$), stricturing ($P = .004$), penetrating behavior ($P < .001$), and age younger than 40 years ($P = .03$) at diagnosis were independent risk factors for subsequent surgery. A total of 53% (n = 105) of the patients had developed stricturing or penetrating disease at 10 years. A large proportion of patients (44%) were in clinical remission during the last 5 years of follow-up.** ***Conclusions:*** **The prognosis for CD seems better than previously reported. The probability of surgery was low, and fewer than expected developed complicated disease behavior. Nevertheless, the cumulative relapse rate of 90% and the finding of prognostic risk factors for subsequent surgery might call for attention to early effective medical treatment strategies.**

Crohn's disease is a chronic recurrent inflammation of the gastrointestinal tract of unknown origin, affecting young people and associated with serious morbidity.[1,2] The clinical spectrum is wide, and the course of disease has often been difficult to predict based on the initial presentation.[3,4] Accordingly, there is a need for more knowledge about factors influencing the course of disease that can be used as a basis for prognosis, optimal follow-up, and treatment.

Because of the heterogeneity of CD, a stratification of patients into clinical subgroups has been considered necessary when studying the outcome of disease.[5–7] Thus, the first standardized, clinical classification system to achieve broad acceptance, the Vienna classification, was introduced in 1998; based on patient age at diagnosis, disease location, and disease behavior. [8] The relevance of this classification in the determination of prognosis has subsequently been addressed.[9–16] However, the majority of studies concerning the prognosis and course of disease in CD have been performed on selected patient groups, in whom complicated disease is likely to be overrepresented.

The primary aim of the present study was to evaluate the course of disease in a well-characterized population-based cohort of CD patients followed prospectively for the first 10 years after diagnosis. We also wanted to identify prognostic risk factors for complications on the basis of information obtained at initial diagnosis. In addition, we wanted to relate the outcome of the study to the Vienna classification in an attempt to evaluate the relationship between subgroups of disease and prognosis.

Material and Methods

From January 1, 1990 to December 31, 1993 all newly diagnosed patients with IBD or possible IBD were prospectively recorded in 4 geographically well-defined areas in South-Eastern Norway (Inflammatory Bowel South-Eastern Norway [IBSEN] study).

On January 1, 1992 the total study population was 966,427. All general practitioners in these areas (1236) were invited to participate in the study, and at each of the 15 participating hospitals, a senior gastroenterologist was made responsible for the diagnostic procedures and the registration and inclusion of patients. The clinical information was subsequently reviewed by a gastroenterologist at a university hospital. The organization of the inception cohort has previously been described in detail.[17–19]

Prescheduled follow-up visits were carried out at 1, 5, and 10 years (±1 year) after inclusion, with a re-evaluation of diagnosis and assessment of course of disease. All the follow-up visits were managed by the same gastroenterologists at each center, and each visit included a structured interview, a clinical exam-

Abbreviations used in this paper: CI, confidence interval; IBSEN, Inflammatory Bowel South-Eastern Norway; OR, odds ratio.

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ination with laboratory tests, and, if indicated, an ileocolonoscopy.

In some cases when the patients were unable to meet at the hospital, the interview was conducted by telephone and supplemented by information from hospital records. In a few cases we used hospital records alone, provided that these had recently been updated. Medical and surgical treatments during follow-up were given in accordance with established clinical practice. The results of the 1- and 5-year follow-up studies have been published elsewhere.[20–23]

Classification and Definitions

Patients were initially classified as having UC, CD, indeterminate colitis, or possible IBD, as previously described.[18,19]

The diagnosis of CD was based on the presence of 2 or more of the following criteria: (1) typical clinical features including abdominal pain, diarrhea, and weight loss; (2) macroscopic appearance at operation or endoscopy of segmental, discontinuous, and/or patchy lesions with or without rectal involvement, discrete or aphtous ulcerations, fissuring or penetrating lesions, cobblestone formation, or strictures; (3) radiologic evidence of stenosis in the small bowel, segmental colitis, or findings of fistulas; and (4) histologic evidence of focal or transmural inflammation or epithelial granulomas with giant cells.

The diagnoses were systematically re-evaluated at each prescheduled visit. At the 1-year visit the initial 4 classes were retained.[23] At the 5-year visit, however, the patients were reclassified as UC, CD, or non-IBD. When a clear diagnosis of either UC or CD was difficult, the most probable diagnosis for each case was made on the basis of discussion and consensus between the gastroenterologists in the study group.

On the basis of available information gathered at diagnosis and at 5 years, the patients were classified in retrospect according to the later Vienna classification.[8] At the 10-year examination, however, patients were prospectively classified according to the disease phenotypes of the Vienna classification.

Relapse was recorded after achieving remission from the first attack at diagnosis and defined as an aggravation of CD symptoms leading to the need for more intensive medical and/or surgical treatment.

Surgery from the time of diagnosis and during follow-up was defined as any intra-abdominal surgical procedure for active CD; thus, incision and drainage of perianal abscesses and simple perianal fistulectomy did not qualify as surgery in this outcome definition.

Patients without disease symptoms and who did not require a more intensive treatment were considered to be in clinical remission.

The clinical course from diagnosis onward was predefined in 4 curves, each of which reflected a different pattern of disease in terms of the severity of bowel symptoms during the whole follow-up period. The disease pattern for each curve is described

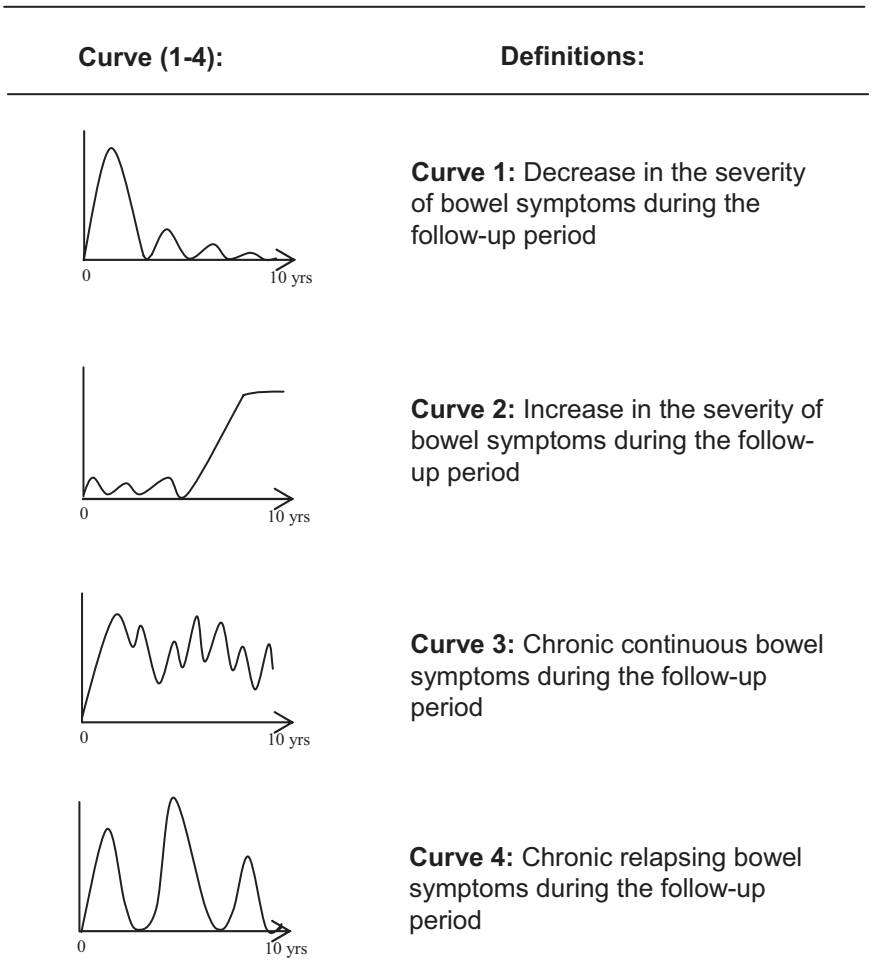

Figure 1. Four predefined curves reflecting different patterns of CD in terms of the severity of bowel symptoms from diagnosis to 10-year follow-up.

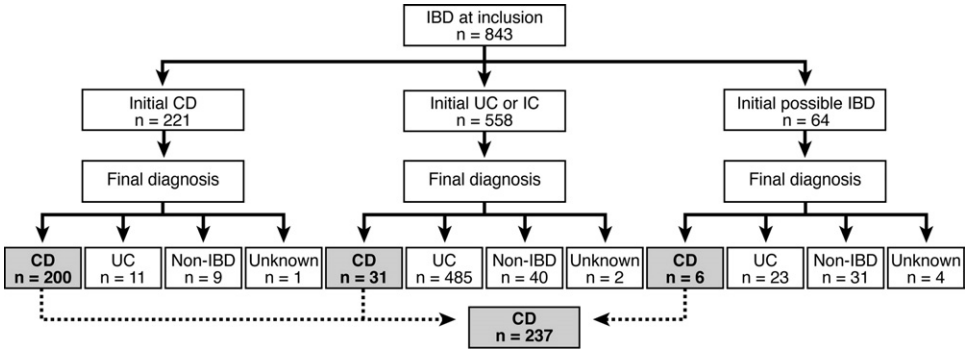

Figure 2. Flow chart of the study population; final diagnosis in relation to initial diagnosis.

in Figure 1. At the interview the patients were asked to choose the curve that best described their disease course during the previous 10 years.

Smoking behavior was recorded at diagnosis and at the 5-year and 10-year interviews. Smokers were patients who had smoked more than 7 cigarettes per week during the observation period. For ex-smokers, the years when they started and stopped smoking were compared with the year of diagnosis and, for operated patients, the year of first surgery. Patients who had stopped smoking during the calendar year of diagnosis or first surgery were defined as smokers until that point of time. The mean consumption of cigarettes was recorded at diagnosis and at 10 years.

Study Population

The inception cohort consisted of 843 IBD patients. Figure 2 provides a flow chart of the classification of the study cohort at inclusion compared with the final diagnosis. In accordance, 756 patients were classified as IBD 10 years after diagnosis, including 237 CD patients.

Statistics

To compare groups we used Pearson χ^2 tests or Fischer exact tests where appropriate. Mann-Whitney Wilcoxon test was used to compare age distributions in the groups. Binary logistic regression analysis with a backward elimination procedure was applied to determine the risk of complicated disease behavior and the risk of azathioprine treatment during follow-up, adjusting for clinically relevant co-variables. Life-table analysis with cumulative probabilities of surgery from diagnosis to the end of follow-up was calculated for the total cohort by using the Kaplan-Meier method. Cox proportional hazard analysis with forward selection method was used to identify risk factors at diagnosis that were possibly associated with surgery during follow-up. The following variables at diagnosis were included in the model: gender, smoking status, the need for systemic steroids, age, disease location, and disease behavior according to the Vienna classification. All analyses were calculated with the statistical software package version 14 (SPSS Inc, Chicago IL). *P* values less than .05 were considered to be statistically significant.

Ethics

The Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate approved the study. Confidentiality of both patient identity and records was maintained, with guidelines suggested by the National Health Department.

Results

Follow-up Cohort

A complete 10-year follow-up was achieved in 197 of 237 patients (83.1%). The median follow-up time for these patients was 124 months (range, 108–144 months). Eighteen patients (7.6%) had died (median follow-up, 28 months; range, 0–83 months), and 22 patients (9.3%) were lost to follow-up (median follow-up, 53 months; range, 0–100 months). Of the patients lost to follow-up, 9 were not willing to participate further in the study, 7 had moved out of the area, 4 were untraceable, and 2 had other serious comorbidities.

Clinical characteristics at diagnosis are shown in Table 1.

Table 1. Clinical Characteristics at Diagnosis of CD Patients Who Completed the 10-Year Follow-up (FU) Compared With Those Who Died or Were Lost to FU

Characteristics at diagnosis	Total	Complete FU	Dead	Lost to FU
Age				
A1, <40 *y*	165	148 (89.7)	0	17 (10.3)
A2, ≥40 *y*	72	49 (68.0)	18 (25.0)	5 (7.0)
Gender				
Male	119	102 (86.0)	7 (6.0)	10 (8.0)
Female	118	95 (81.0)	11 (9.0)	12 (10.0)
Disease location				
L1, terminal ileum	64	51 (79.7)	6 (9.4)	7 (10.9)
L2, isolated colon	115	94 (81.7)	12 (10.4)	9 (7.8)
L3, ileocolon	54	48 (89.0)	—	6 (11.0)
L4, upper gastrointestinal	4	4 (100)	—	—
Disease behavior				
B1, inflammatory	147	127 (86.4)	9 (6.1)	11 (7.5)
B2, stricturing	64	50 (78.1)	6 (9.4)	8 (12.5)
B3, penetrating	26	20 (77.0)	3 (11.5)	3 (11.5)
Systemic steroid				
No	106	86 (81.1)	10 (9.4)	10 (9.4)
Yes	129	109 (84.5)	8 (6.2)	12 (9.3)
Missing	2	2	—	—
Total	237	197 (83.1)	18 (7.6)	22 (9.3)

( ), percentage of total.

Patients who had been lost to follow-up did not differ significantly from those who completed the 10-year follow-up in terms of gender, age, disease location, disease behaviour, or the need for systemic steroids at diagnosis. Patients who died, however, were older (median age at diagnosis, 73 vs 28 years; $P < .001$). Two deaths during follow-up were probably CD-related; one patient aged 84 died of a spontaneous colonic perforation, and one patient aged 68 died of septicemia.

Clinical Behavior

The overall percentage of patients with stricturing (B2) or penetrating disease behavior (B3) was 36% (n = 70) at diagnosis, 49% (n = 97) at 5 years, and 53% (n = 105) at 10 years. Of these, 31% (n = 61) and 22% (n = 44) were classified as B2 and B3, respectively, at 10 years. Complicated disease behavior during follow-up, defined as at least one stricturing or penetrating event from the time of diagnosis, was associated with initial location in terminal ileum (L1) (86%) compared with colonic (L2) (30%, $P < .001$) and ileocolonic location (L3) (60%, $P = .005$), adjusted for sex ($P = .4$) and age at diagnosis (A1 vs A2) ($P = .2$). Stricturing complications during follow-up was strongly associated with L1 location, compared with L2 and L3 location at diagnosis ($P < .001$ and $P = .01$), but not with age ($P = .2$). On the other hand, penetrating complications correlated with age younger than 40 years at diagnosis ($P = .02$) but not with initial disease location ($P = .9$). Approximately one half of patients who were classified as B3 after 10 years had intestinal penetrating disease (n = 21), whereas the remaining (n = 23) had perianal fistulas. All patients with upper gastrointestinal disease (L4) at diagnosis (n = 4) had developed stricturing complications.

Relapse

Overall relapse rates for the first and second 5-year periods after diagnosis were recorded, as were the annual relapse rates for the first, fifth, and tenth years of follow-up. One hundred seventy-seven of 197 patients had relapsed during the follow-up period, and the cumulative relapse rate was 53% (95% confidence interval [CI], 47%–60%), 85% (95% CI, 80%–90%), and 90% (95% CI, 86%–94%) at 1, 5, and 10 years, respectively. Table 2 shows the cumulative rates of patients with relapsing disease, comparing the periods 0–1 year, 1–5 years, and 5–10 years according to clinical and demographic variables at baseline. Patients who needed systemic steroids for treating the first flare at diagnosis had increased risk of relapsing disease during these periods. However, we found no significant difference in overall relapse rate in relation to gender, smoking status, disease location, or disease behavior at diagnosis (Table 2).

As many as 44% (n = 86) were in clinical remission during the second 5-year period, of which the majority (n = 75) did not use any immunosuppressive medication. Clinical remission during the second 5-year period, however, was inversely associated with age younger than 40 years at diagnosis (Table 2). Surgery for active CD within the first 5 years of disease did not influence the proportion of patients with clinical remission during the subsequent 5-year period (46% in operated [24/52] vs 43% in nonoperated patients [62/145], $P = .7$). Finally, in the

Table 2. Cumulative Rate (Cum %) of CD Patients With Relapsing Disease During the First Year and in the Periods 1–5 Years and 5–10 Years After Diagnosis

Variables at diagnosis	Total in each subgroup	Relapse during the 1st y		Relapse between 1–5 y		Relapse between 5–10 y	
		Cum % (CI)	*P* value	Cum % (CI)	*P* value	Cum % (CI)	*P* value
Age groups							
A1, <40 *y*	148	54 (50–58)	.7	80 (77–83)	.6	61 (57–65)	.03
A2, ≥40 *y*	49	51 (44–58)		76 (70–82)		43 (36–50)	
Gender							
Female	95	54 (49–59)	.9	76 (72–80)	.4	56 (51–61)	.9
Male	102	53 (48–58)		81 (77–85)		57 (52–62)	
Location							
L1, terminal ileum	51	54 (47–61)	.4	78 (72–84)	.8	57 (50–64)	.1
L2, colon	94	57 (52–64)		76 (72–80)		49 (44–54)	
L3, ileocolon	48	44 (37–51)		81 (75–87)		69 (62–76)	
L4, upper gastrointestinal	4	75 (53–97)		100		75 (53–97)	
Behavior							
B1, inflammatory	127	56 (52–60)	.7	79 (75–83)	.6	54 (50–58)	.4
B2, stricturing	50	49 (42–56)		74 (68–78)		64 (57–71)	
B3, penetrating	20	50 (39–61)		85 (77–93)		55 (44–66)	
Systemic steroids							
No	86	47 (42–52)	.08	69 (64–74)	.008	47 (42–52)	.02
Yes	109	59 (54–64)		85 (82–88)		63 (58–68)	
Missing	2	—		—		—	
Smoking status							
Never	82	52 (47–57)	.5	79 (75–84)	.9	59 (54–64)	.09
Current smoker	82	57 (52–62)		79 (75–84)		61 (56–66)	
Ex-smoker	29	45 (36–54)		76 (68–84)		38 (29–47)	
Missing	4	—		—		—	
Total	197	54 (50–57)		79 (76–82)		56 (53–60)	

χ^2 comparisons within each subgroup.

tenth year of follow-up, overall 62% of patients (n = 123) were in clinical remission.

Patterns of Disease

In terms of the predefined curves, 43% (n = 85) of the patients reported a decrease in the severity of bowel symptoms during follow-up (curve 1), whereas only 3% (n = 6) reported an increase in symptom severity (curve 2) (Figure 1). Chronic continuous symptoms (curve 3) and chronic relapsing symptoms (curve 4) were reported by 19% (n = 37) and 32% (n = 63) of the patients, respectively. Data for 6 patients were missing (3%).

The need for systemic steroids for treating the first flare at diagnosis increased the risk of chronic continuous symptoms during follow-up (crude odds ratio [OR], 2.32; 95% CI, 1.04–5.14; $P = .035$). Furthermore, age younger than 40 years at diagnosis was positively associated with chronic relapsing symptoms (crude OR, 2.63; 95% CI, 1.18–5.88; $P = .016$) and inversely associated with a decrease in the severity of symptoms during follow-up (crude OR, 2.33; 95% CI, 1.20–5.88; $P = .016$). No significant differences in pattern of disease were found in terms of gender, smoking status, disease location, or disease behavior at diagnosis (data not shown).

Medical Treatment

After initial treatment at diagnosis, the cumulative rate of a second course of systemic steroids was 34% (95% CI, 27%–41%), 73% (95% CI, 66%–79%), and 77% (95% CI, 71%–82%) at 1, 5, and 10 years, respectively. Azathioprine was mainly prescribed during follow-up to steroid-dependent or -resistant patients and was taken by overall 6% (95% CI, 3%–9%) during the year of diagnosis and then by 21% (95% CI, 17%–28%) and 33% (95% CI, 26%–39%), respectively, 5 and 10 years after diagnosis. The need for systemic steroids at diagnosis was a risk factor for receiving azathioprine treatment during follow-up (OR, 3.7; 95% CI, 1.7–6.9; $P = .001$), adjusted for gender, smoking status, disease location, disease behavior, and age at diagnosis.

Figure 3 shows the cumulative drug consumption during the first and second 5-year periods. Oral sulfasalazine and mesalamine were the most frequently prescribed drugs during both periods, but the number of patients treated decreased significantly during the second 5-year period (88% vs 64%).The same trend was seen in the use of systemic steroids (73% vs 42%), whereas the use of azathioprine slightly increased (21% vs 26%). In agreement with the treating physician, 25% of the patients (n = 49) did not use any medication for CD during the last 5 years of follow-up, which was not significantly influenced by age, disease location, or disease behavioral characteristics at diagnosis (data not shown).

Surgery

The Kaplan-Meier method was used to calculate the cumulative probability of surgery, which was 13.6%, 27.0%, and 37.9% at 1, 5, and 10 years after diagnosis (Figure 4). Table 3 also provides the cumulative rates of surgery at 1, 5, and 10 years for each of the subgroups of the Vienna classification.

Clinical and epidemiologic variables at diagnosis associated with surgery by univariate and multiple Cox regression are shown in Table 4. Surgery was strongly associated with terminal ileal location compared with colonic ($P = .001$) and ileocolonic ($P < .001$) location and with stricturing ($P = .004$) or penetrating ($P < .001$) disease behavior as compared with pure inflammatory disease. Furthermore, there was an increased risk for surgery in patients younger than 40 years of age at diagnosis ($P = .03$). The results for penetrating behavior were significant also if the group was subdivided into perianal (n = 26; hazard ratio, 5.0; 95% CI, 2.5–10.0) or intestinal penetrating fistulas at diagnosis (n = 6; hazard ratio, 11.8; 95% CI, 4.4–30.1). All patients classified as L4 at diagnosis were operated, but the sample was too small for statistical conclusion. Gender, the need for systemic steroids, or smoking habits at diagnosis did not influence the risk of surgery significantly. However, there was a nonsignificant increase in the hazard ratio for surgery in patients who smoked more than 10 cigarettes per day at diagnosis compared with nonsmokers (unadjusted hazard ratio, 1.9; 95% CI, 0.8–2.6; Table 3).

Finally, of 197 patients with a complete 10-year follow-up, 74 (38%) had required at least 1 operation, whereas 17 (9%) had required 2 or more operations.

Discussion

This 10-year follow-up study of newly diagnosed CD patients demonstrated the clinical phenotype, course of disease, and results of treatment in a population-based cohort. In ad-

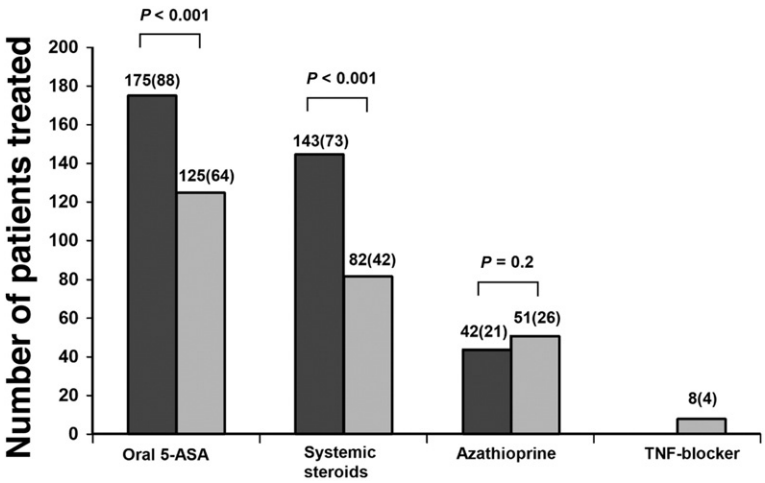

Figure 3. Cumulative drug consumption after initial treatment in CD patients during the first 5-year period (*patterned bars*) vs the second 5-year period (*grey bars*). ( ), percentage of total number.

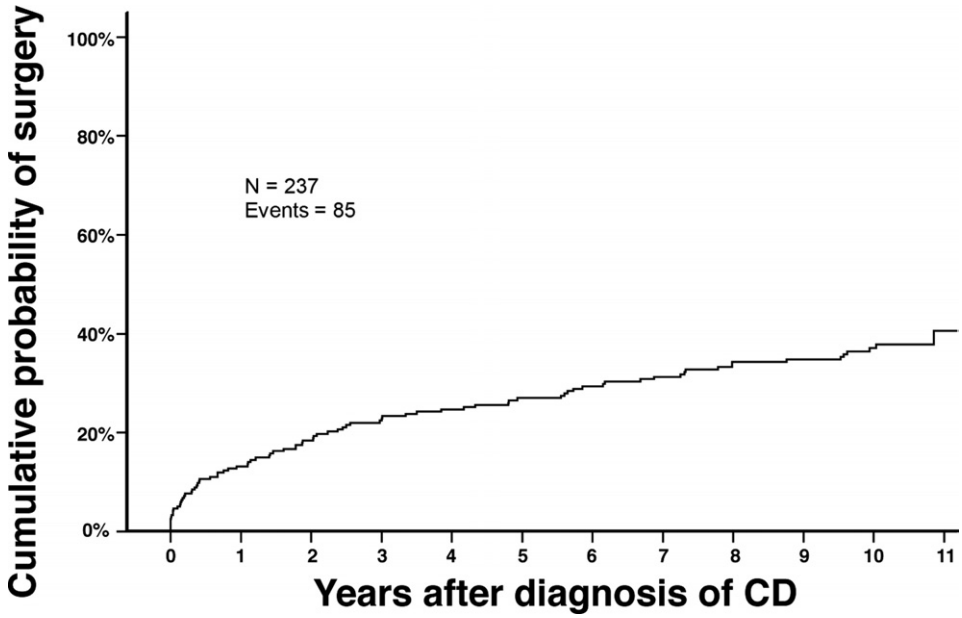

Figure 4. Kaplan–Meier one-minus survival curve showing the cumulative probability of surgery for the total group of CD patients during follow-up; it was 13.6% (95% CI, 9.0%–17.6%), 27.0% (95% CI, 21.3%–32.7%), and 37.9% (95% CI, 31.4%–44.4%) at 1, 5, and 10 years. *N*, total number at risk; *Events*, number of patients with first surgery.

dition, we have described potential risk factors for subsequent complications on the basis of clinical and epidemiologic variables at the time of the initial diagnosis.

This is one of few prospective population-based studies in this field,[4,16] and it has other methodologic advantages. First, the patients were uniformly recruited from a well-defined area during a limited period of time and followed up by a network of specialists with prescheduled visits at 1, 5, and 10 years. Thus, the patients had almost identical lengths of follow-up and were subjected to uniform classification criteria and treatment policies during the study period. Second, the diagnosis was systematically re-evaluated for each patient, and the follow-up-rate was high; complete data were obtained from 90% of the patients who were still alive 10 years after inclusion.

On the other hand, the information on doses of medication was recorded retrospectively at each prescheduled visit. An estimation of the area under the curve for drug consumption was therefore not justified. Moreover, a year-by-year examination of disease activity in the present study design was not planned, because all contacts outside the prescheduled visits were entirely based on patients' symptoms and individual follow-up in clinical practice.

Even though most of the present follow-up study was performed before biologic treatment was introduced, the cumulative probability of bowel surgery was only 37.9% ten years after diagnosis. This is markedly lower than previous figures reported from population-based studies in Scandinavia. The corresponding 10-year probability of surgery in a cohort diagnosed from 1955–1989 in Stockholm County was 71%, and in the cohort from 1962–1987 in Copenhagen it was 61%.[3,24] Moreover, both of these studies showed a higher occurrence of early surgery, because nearly 60% of patients requiring surgery during the first 10 years were operated within the year of diagnosis, whereas this figure in our study was 36%. A time trend in the mode of surgical treatment toward a more conservative surgical approach in CD might explain some of these differences in rates of surgery. Other explanations might be improved and possibly earlier initiation as well as intensified medical treatment in our cohort compared with previous studies from Scandinavia. On the other hand, 70% of patients who required surgery in the present cohort were operated within the first 5 years after diagnosis, which might, because surgically induced remission often is not durable,[25] indicate a need for more potent immunomodulating therapy at an earlier stage in subgroups of patients.

We used the Vienna classification at diagnosis as basis for the analysis of clinical variables influencing the outcome of disease. This might not be optimal, because we know that, in

Table 3. Cumulative Rates (Kaplan-Meier Estimates) of First Surgery at 1, 5, and 10 Years After Diagnosis of CD in Relation to Main Categories of the Vienna Classification at Diagnosis

Classification at diagnosis	N	First surgery ≤1 y Cum % (CI)	First surgery ≤5 y Cum % (CI)	First surgery ≤10 y Cum % (CI)
Age				
A1, age <40 *y*	165	16 (11–21)	31 (24–38)	42 (34–49)
A2, age ≥40 *y*	72	10 (4–16)	18 (9–27)	26 (15–37)
Location				
L1, terminal ileum	64	37 (25–49)	53 (41–65)	65 (52–78)
L2, isolated colonic	115	5 (1–9)	15 (8–22)	23 (15–31)
L3, ileocolonic	54	8 (1–4)	19 (9–29)	34 (21–47)
L4, upper gastrointestinal	4	0	50 (1–99)	75 (36–100)
Behavior				
B1, inflammatory	147	7 (3–11)	16 (10–22)	23 (16–30)
B2, stricturing	64	20 (10–30)	39 (27–51)	64 (51–77)
B3, penetrating	26	39 (21–57)	63 (44–82)	63 (44–82)

Cum %, cumulative rate in each subgroup; N, total number in each subgroup at diagnosis.

Table 4. Risk Factors at Diagnosis Associated With Surgery During Follow-up Analyzed by Cox Regression

Variables at diagnosis (no. in analysis)	No. with surgery (%)	Unadjusted			Adjusted		
		HR	95% CI	*P* value	HR	95% CI	*P* value
Age							
A1, <40 *y* (165)	69 (42)	1	[Ref]	.03	1	[Ref]	.03
A2, ≥40 *y* (72)	16 (22)	0.5	0.3–0.9		0.5	0.3–0.9	
Gender							
Female (118)	40 (34)	1	[Ref]	.9	Not included		
Male (119)	45 (38)	1.0	0.7–3.6				
Location							
L1, terminal ileum (64)	38 (59)	1	[Ref]	.001	1	[Ref]	
L2, isolated colonic (115)	26 (23)	0.2	0.1–0.4		0.3	0.2–0.6	.001
L3, ileocolonic (54)	17 (32)	0.3	0.2–0.6		0.3	0.2–0.5	.001
L4, upper gastrointestinal (4)[a]	4 (100)	1.4	0.5–3.8		1.6	0.5–4.4	.4
Behavior							
B1, inflammatory (147)	32 (22)	1	[Ref]	.001	1	[Ref]	
B2, stricturing (64)	36 (56)	3.5	2.1–5.6		2.3	1.3–4.1	.004
B3, penetrating (26)	17(65)	4.9	2.7–8.8		5.4	3.0–9.9	.001
Smoking status[b]							
Never (103)	38 (37)	1	[Ref]	.2	Not included		
Current ≤10 cigarettes/day (57)	18 (32)	0.8	0.4–1.4				
Current <10 cigarettes/day (36)	18 (50)	1.9	0.8–2.6				
Ex-smoker (35)	11 (31)	0.8	0.4–1.6				
Systemic steroids[c]							
No (106)	36 (34)	1	[Ref]	.8	Not included		
Yes (129)	48 (37)	1.1	0.7–1.6				

Ref, reference variable; HR, hazard ratio; (), percentage of CD patients with surgery in each subgroup.
[a]Difficult to conclude because of insufficient number of patients.
[b]Data were unknown in 6 cases. There was none in the operated group.
[c]Data were unknown in 2 cases. There was one in the operated group.

particular, behavior of disease changes over time.[9] However, the recognition of prognostic risk factors before the development of complications might justify this approach. Furthermore, our inception cohort of unselected and treatment-naive patients should be a good design for studying early risk factors.

In our study cohort, terminal ileal location (L1), stricturing (B2), penetrating disease behavior (B3), and age younger than 40 years (A1) at diagnosis were independent risk factors for subsequent bowel surgery. In addition, all patients with upper gastrointestinal disease (L4) at diagnosis were operated, but this analysis was limited by a low sample size.

Small bowel involvement in contrast to isolated colonic location is identified as an important risk factor for surgery in several studies.[11,14–16] The relationship between disease behavior according to the Vienna classification at diagnosis and the subsequent risk of surgery, however, has only been reported in 2 previous studies.[13,16] No significant correlation between behavior at diagnosis and the risk of surgery was found in a recent European-wide population-based study.[16] On the other hand, initial penetrating behavior was a positive risk factor for surgery in a referral-based study from Hungary,[13] which is in agreement with our results, despite the fact that we only included unselected and newly diagnosed patients. Our study design, with uniform classification of each case at diagnosis first by a local specialist and second by one from a university hospital, might be an important advantage of the present population-based study, as compared with the multi-center approach of the earlier mentioned European study.[16]

The finding of a lower risk of surgery among patients older than 40 years of age at diagnosis (A2) is in agreement with previous data[16] and might indicate a milder course of disease with increasing age.[26]

Of other factors influencing the course of CD, smoking is an established risk factor.[27] Our study failed to detect any significant association between smoking status at the time of diagnosis and the subsequent risk of surgery. This lack of association could possibly be explained by the rather low proportion of patients (16%) who smoked more than 10 cigarettes per day in the present cohort, because previous data have suggested a dose-dependent effect of cigarette consumption in CD.[27,28] This result might also be influenced by the relatively small number of patients who were operated on in our cohort.

Transmural gut inflammation with the development of stricturing and penetrating complications is a major characteristic of CD. In the present cohort, 53% of the patients had stricturing or penetrating disease behavior 10 years after diagnosis, whereas the corresponding figure in a previous study was almost 70%.[12] However, results are difficult to compare because previous figures are based on studies from referral centers in which patients with a more severe course of disease are likely to be overrepresented.[9,12]

There is a lack of good instruments for describing patients' symptoms over time in chronic diseases such as CD. Indices of disease activity or health-related quality of life questionnaires mainly provide information about patients' symptoms and level of functioning at the time of the examination. Thus, to assess time trends in the severity of symptoms in our patients, we used

4 predefined patterns of disease by which the patients could retrospectively assess their course of disease during follow-up. Although the curves were intuitively understood by the patients, this graphic description of the clinical course might have some limitations; a recent flare might have led the patient to choose a more severe pattern of disease, whereas adaptation to symptoms over time might have had the opposite effect.

Our study showed a high cumulative relapse rate of 90% during the first 10 years after diagnosis, which is in accordance with the relapse rate of 88% previously reported by Munkholm et al[4] in the Copenhagen study. As previously described in the Danish study, our study suggested a decline in the activity of CD over time. This was based on the increasing number of patients in clinical remission during the follow-up, with overall 44% of our patients in remission during the second 5-year period as compared with 21% between years 1–5 after diagnosis. Furthermore, most patients who developed a stricturing or penetrating disease behavior had done that within the first 5 years of disease. An improved course of disease was also supported by the patients' own experiences, because almost one half reported a decrease in the severity of bowel symptoms over time. These observations could not entirely be explained by a more intensified medical treatment, because only a few of our patients in remission during the last 5 years had received immunosuppressive medication. Alternative explanations are that the patient adjusted to the disease symptoms and/or that the inflammatory activity of disease burned out over time. However, an extended observation of our material is needed to clarify the long-term disease activity.

Use of systemic steroids for treating the first flare at diagnosis was recently suggested as an important risk factor for subsequent disabling 5-year course of disease in a referral-based study.[29] Our study might in part support this, because the need for systemic steroids at diagnosis was a risk factor for relapsing disease and chronic continuous symptoms during follow-up. However, the need for systemic steroids at diagnosis was not a predictor for subsequent surgery in our study.

In conclusion, this population-based 10-year follow-up study demonstrated a considerably lower probability of bowel surgery than previously reported from Scandinavia. Terminal ileal location, stricturing, penetrating behavior, and age younger than 40 years at diagnosis were prognostic risk factors for subsequent surgery. Moreover, the need for systemic steroids for treating the first flare at diagnosis appears to be a predictor for a more severe course of disease. Our study might suggest that the overall activity of CD declines over time. Nevertheless, the high cumulative relapse rate of 90% and the finding that the risk of complications and surgery was at the highest within the first 5 years of disease indicate that more effective medical treatment strategies should be considered at an early stage in subgroups of patients.

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