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Clinical course of ulcerative colitis

M. Cottone *, D. Scimeca, F. Mocciaro, G. Civitavecchia, G. Perricone, A. Orlando

Department of Medicine, Pneumology and Nutrition Clinic, V. Cervello Hospital, University of Palermo, Palermo, Italy

Abstract

Aim: To provide a review of studies on prognosis in ulcerative colitis by reviewing the relevant population-based cohort studies. On the basis of incidence and population studies, ulcerative colitis has a favourable clinical course, with good quality of life, a chronic course characterized by at least one relapse, and a surgery rate of 30% after 10 years from diagnosis. Patients affected by severe ulcerative colitis have a higher risk of colectomy, and some clinical variables may predict the disease's clinical course. Most patients respond to steroids and only a low percentage become dependent, or non-responders to steroids. Patients who have a long-lasting ulcerative colitis (>10 years) or are affected by an extensive disease have an increased risk of developing colorectal cancer, while those treated with immunosuppressants for long period of time may have an increased risk of developing lymphomas. Data on mortality in ulcerative colitis patients are not homogeneous, but if a real risk exists it is in patients with extensive or severe disease. The evidence that patients with severe ulcerative colitis are often non-smokers may explain why in one study the mortality rate was lower.

Keywords: Cancer; Clinical course; Mortality; Ulcerative colitis

1. Introduction

To evaluate a disease course it is mandatory that the following criteria [1] will be met: a) cohort must be incident, consecutive and representative of patients assembled at a common point in the course of their disease; b) description of referral patterns must be of central importance in the assessment of the generalizability of the study results; c) follow-up of study must be complete and sufficiently long; d) objective outcome criteria must be applied in a blind fashion; and e) an adjustment for prognostic factors should be carried out.

2. Prognostic studies

In order to evaluate the clinical course of ulcerative colitis (UC), studies satisfying the above criteria should be selected. Table 1 shows some studies that, whether partially or completely, respected these criteria [2–11].

Table 1
Population-based inception cohort in studies on prognosis

Area	Population size	Period	Pros/retro	Number
Copenhagen	550,000	62–87	Pros	1161
IBSEN	970,000	90–94	Pros	454
Stockholm	1,200,000	55–84	Retro	1547
Uppsala	1,200,000	65–83	Retro	2508
Olmsted	110,000	40–93	Retro	278
Florence	650,000	78–92	Retro	231
EEC	n.a.	91–93	Pros	528

Among these studies, the Copenhagen cohort best satisfies these criteria. In fact, it is a population study performed on a consecutive-incident cohort in which the events are clearly defined, the follow-up is complete and an evaluation of prognostic factors was done.

The most relevant events in the course of UC are: remission, relapse, quality of life, extension of disease in time, surgery, cancer and mortality.

In the Copenhagen Study, among 1186 patients, the distribution of site of disease (relevant prognostic variable

* Address for correspondence: Mario Cottone, Ospedale V. Cervello, Divisione di Medicina Interna I, Via Trabucco 180, 90146, Palermo, Italy. Tel.: 0039 091-6803764; Fax: 0039 091-6885111.
E-mail address: dickens@tin.it

at diagnosis) was: 44% distal colitis, 36% left-side to transverse colitis, 18% pancolitis; in 1% of patients the site of disease was unknown. The distribution of disease activity was stable and about 50% of patients were in remission every year. After 10 years the colectomy rate was 24%; this probability varied in relation to the site of disease: patients affected by pancolitis had a higher risk of surgery. Cumulative probability of relapsing course was 90% after 25 years. The disease's clinical course varied from remission to relapse without significant predictors, excluding the disease activity during the first years of disease. Between the 3rd and the 7th years of disease, 25% of patients were in remission, 18% had a continuous disease activity (every year) and 57% had an intermittent disease. The disease activity in the first two years from diagnosis was correlated to the risk of having an active colitis in the next 5 years.

The systemic symptoms at diagnosis were inversely related to the following clinical course: a higher percentage of patients with these symptoms had a following period of longer remission. For the authors of this study, patients who have a severe active disease at diagnosis and respond to the treatment have a better prognosis. The probability of maintaining the ability to work after 10 years was 92%. Side effects associated with the disease (megacolon, bleeding, surgery) were related to extension of disease; pancolitis had a high probability of side effects.

Another study concerning the clinical course and prognosis of UC was the IBSEN study, performed in 4 southeastern areas of Norway [11]. From 1990 to 1994 an inception cohort of 454 patients was observed and followed prospectively for 5 years. The authors concluded that the disease course and prognosis of UC appeared to be better than previously described in the literature: at 5 years, the frequency of surgery was low (7.5%), a relapse-free course was observed in 22% of patients, the majority of the patients (57%) had no intestinal symptoms while only 7% had symptoms that interfered with everyday activities. Among patients initially diagnosed with proctitis 28% had progressed during the observation period (10% to extensive colitis).

Recently, a 10-year European-wide population-based cohort from 9 centers (3 northern and 6 southern) was published [12]. A total of 781 patients from these centers were eligible for follow-up and 617 of these (79%) completed the study. The median follow-up was 123 months (range 107–144). The 10-yr cumulative relapse rate was 67% (95% CI: 0.63–0.71) for the first relapse after diagnosis. The Hazard Ratio (HR) for relapsing disease was significantly higher for patients with a high level of education than for those with a low level (HR 1.4, CI: 1.1–1.8). The Poisson regression showed a significantly higher risk of relapse for women than for men (HR 1.2, CI: 1.1–1.3); for those who stopped smoking during follow-up than for those who had never smoked (HR 1.1, CI: 0.8–1.6); and for those using 5-ASA and steroids. Patients who experienced their first relapse within 1 year of diagnosis had a greater total number of relapses compared with patients having the first relapse between 1 and 2 years, and 2 years after diagnosis. These differences were statistically significant ($p < 0.001$). The authors concluded that smoking status, level of education and, perhaps, female gender influenced the risk of relapse.

An important prognostic variable is clinical presentation at diagnosis. Truelove identified three kinds of clinical presentation related to severity: mild, moderate and severe. Sandborn (Table 2) modified this classification by introducing the fulminant pattern in severe colitis [13]. This stratification of severity is useful both for prognosis and therapy of the disease.

Travis and colleagues [14] observed that, at the third day from admittance, the presence of 8 bloody stool movements and CRP levels > 45 ng/ml predicted surgery in severe UC treated with steroids and parenteral nutrition. Ho et al. [15] made a prognostic numerical score with the following variables (Table 3): stool frequency, colonic dilatation and albumin levels. Patients with a score ≥6 had a high risk of surgery.

The introduction of cyclosporine [16] and, recently, of infliximab in clinical management of severe colitis has reduced the number of patients undergoing surgery [17].

A cohort study, on incident patients, performed in Olmsted County [18], allowed for the evaluation of the short and long clinical course of the disease in patients treated with steroids. Fifty-four percent of treated patients were in complete remission, 16% did not respond to steroids, and 30% achieved a partial remission of disease. After one year, 49% of patients had a sustained response, and 22% became steroid-dependent.

Table 2
Truelove and Witts' criteria for evaluating the severity of ulcerative colitis, modified by Sandborn [13]

Variable	Mild Disease	Severe Disease	Fulminant Disease
Stools	<4 per day	>6 per day	>10 per day
Blood in stools	Intermittent	Frequent	Continuous
Temperature	Normal	>37.5°C	>37.5°C
Pulse	Normal	>90 bpm	>90 bpm
Haemoglobin	Normal	<75 of normal value	Transfusion required
Erythrocyte sedimentation rate	≤30 mm/hr	>30 mm/hr	>30 mm/hr
Colonic features on X-ray	Normal	Air, edematous wall, thumb-printing	Dilatation of colon (>5.0 cm diameter)
Clinical signs	Minimal tenderness	Abdominal tenderness	Increased abdominal distension, tenderness

Table 3
Integer risk score attributable to each category derived from coefficients of the logistic regression [15]

Variables	Score
Mean stool frequency:	
<4	0
4–6	1
6–9	2
>9	3
Colonic dilatation (>5,5 cm)	4
Hypoalbuminemia (<30 g/l)	4

Steroid-dependent patients were usually treated with azathioprine, and 65% of them responded to the treatment [19].

In some studies genetic and environmental prognostic variables were identified [20–24].

3. Genetic and environmental prognostic factors

Some HLA haplotypes (HLADR*103), multi-drug resistance (MDR) genes and interleukin 1 gene cause an unfavourable clinical course with a higher percentage of severe colitis and surgery [20].

A smoking habit is a protective factor in UC, as showed by Calkins's meta-analysis on case-control studies [21]. Studies on clinical course showed that smoking status protects patients from disease extension, reduces immunosuppressive use and need for surgery. Ex smokers have an increased risk of developing an unfavourable clinical course [22,23]. This observation was recently confirmed in a case-control study by De Saussure and colleagues [24], showing a strong negative correlation between tobacco smoking and UC (OR 2.4, 95% CI: 1.31–4.38; $p = 0.004$).

Appendix seems to have an unclear correlation with UC. Case-control studies have shown that patients who have undergone appendectomy had a lower risk of developing UC [25]. On the basis of this evidence, studies on small series of patients were performed, showing that patients who underwent appendectomy had a more favourable course [26,27] with low rates of immunosuppressants use and surgery. In De Saussure's study the pairwise-matched OR of UC for previous appendectomy was 0.10 (95% CI: 0.005–0.21; $p < 0.0001$) [24].

4. Risk of cancer

Several studies have been carried out to evaluate cancer risk in UC, with divergent results. Some studies have also evaluated the risk of developing non-Hodgkin's lymphoma. The variability in results depends on the selection of population sample: incident, prevalent or hospital cohort.

4.1. Risk of colorectal cancer

Recently a meta-analysis on risk of colorectal cancer in UC development was published [28]. The overall prevalence of colorectal cancer in UC, analysed in 116 studies, was 3.7%. Forty-one of 116 studies reported the UC duration time. In these studies, the global incidence was 3/1000 person years duration. In children, the global incidence was 6/1000 person years duration. Nineteen of 41 studies reported results stratified into 10-years intervals of disease duration. In the first 10 years of disease the incidence rate was 2/1000 person years duration, 7/1000 in the second decade and 12/1000 in the third decade. These rates corresponded to a cumulative probability of 2% at 10 years, of 8% at 20 years, and of 18% at 30 years. Incidence of cancer also had a geographic variability: 5/1000 person years duration in USA, 4/1000 in United Kingdom and 2/1000 in Scandinavian countries. Since 1955, the incidence of cancer had increased over the years, but this evidence was not statistically significant. The variability of colorectal cancer incidence may be related to different clinical approaches in different countries. In Denmark, for example, patients affected by pancolitis and with more than 10 years of disease history underwent colectomy; this evidence may explain the low rate of cancer risk observed in Danish studies [29].

In a recent population-based study, Jess et al. observed a standardized incidence ratio (SIR) of 1.1 (95% CI: 0.4–2.4), showing an overall no increased risk of colorectal cancer among UC patients. It is important to underline that in the sub-group of patients with extensive or total colitis the risk of colorectal cancer appeared to be increased (SIR 2.4; 95% CI: 0.6–6.0) [30].

Concerning the risk or protective factors of cancer development, Velayos et al. performed a population case-control study in which they analyzed 188 patients with UC-related cancer, and controls matched for extent and duration of chronic ulcerative colitis. In the final multiple variable model, the authors observed that the most important factors associated with colorectal cancer were a history of pseudopolyps (OR 2.5; 95% CI: 1.4–4.6), 1 or 2 surveillance colonoscopies (OR 0.4; 95% CI: 0.2–0.7), smoking (OR 0.5; 95% CI: 0.2–0.9) and use of corticosteroids (OR 0.4; 95% CI: 0.2–0.8), aspirin (OR 0.3; 95% CI: 0.1–0.8), non-steroid anti-inflammatory drugs (OR 0.1; 95% CI: 0.03–0.5), and 5-ASA agents (OR 0.4; 95% CI: 0.2–0.9). Primary sclerosing cholangitis and immunosuppressants use were not statistically significant. The authors concluded that surveillance colonoscopy and use of anti-inflammatory medications may reduce the risk of colorectal cancer, while a history of post-inflammatory pseudopolyps appeared to be a predictive factor for cancer development [31].

To underline the relevance of colonoscopy surveillance in UC patients, a recent meta-analysis by Thomas et al. analysed the risk of cancer or any advanced lesion once low-grade dysplasia was diagnosed. They observed a cancer incidence of 14/1000 (95% CI: 5.0–34) person

years duration and an incidence of any advanced lesion of 30/1000 (95% CI: 12–76) person years duration. When low-grade dysplasia was detected on surveillance there was a 9-fold risk of developing cancer (OR 9.0; 95% CI: 4.0–20.5) and a 12-fold risk of developing any advanced lesion (OR 11.9; 95% CI: 5.2–27). The authors concluded that the risk of developing cancer in patients with low-grade dysplasia is high. These estimates are valuable for decision-making when low-grade dysplasia is encountered on surveillance [32].

A recent nested case-control study from Copenhagen, Denmark and Olmsted counties showed a greater risk of colorectal neoplasia in inflammatory bowel disease patients (those with primary sclerosing cholangitis, severe long-standing disease, and exposure to X-ray). The protective effect of close follow-up colonoscopy and treatment with 5-ASA was questionable [33].

4.2. Risk of lymphoma

Data on risk of lymphoma in UC are controversial, independently of the therapies. Only a few studies showed an increased risk of developing lymphoma [34]. It is unclear if immunosuppressive therapy has a role in risk lymphoma: a retrospective study performed at St. Mark's Hospital showed no increased risk of lymphoma in inflammatory bowel disease patients treated with immunosuppressants [35]. A recent meta-analysis [36] pooled 5 studies in which risk of lymphoma was evaluated in patients treated with immunosuppressive therapy; the analysis showed that, although the studies were heterogeneous, inflammatory bowel disease patients had a 4.4-fold higher risk of lymphoma than the general population.

Palli's study [37], on a retrospective incident cohort of 688 patients, showed a high risk of developing Hodgkin's lymphoma. The number of cases observed was 4, while expected cases were 0.4. Obviously it is difficult to draw firm conclusions from small numbers, but the authors suggest that risk is increased in developed countries with a low birth-rate, which reduces exposition to common viral infections.

5. Mortality

Data on mortality in UC are not homogeneous. Some studies have shown an increased mortality rate in patients affected by UC [7,38,39], while others have shown no difference of mortality between UC patients and the general population (Table 4) [40]. An Italian study [41] on UC patients showed a decreased risk of mortality. The divergent results in the studies persist even when comparing cohorts with comparable study methodology (Table 4).

The increased mortality is due to the adverse events related to severe UC: megacolon, severe bleeding, and surgery. The Italian study showed a reduction in mortality rate due to the low incidence of lung cancer and cardiovascular disease. This reduction is explained by the low percentage of smokers among UC patients.

Table 4
Studies on mortality

Author	No. pts	Inception period	No. deaths	SMR *
Ekbom [7]	2509	1965–1983	505	1.4
Palli [9]	689	1978–1992	81	0.67
Probert [38]	1014	1972–1989	93	0.9
Persson [39]	1547	1955–1984	255	1.4
Farrokhyar [40]	354	1978–1986	41	1.03
Höie [42]	775	1991–2001	73	1.09

* Standardized mortality ratio.

Recently a European-wide population based cohort study [42] found no higher mortality rate in patients with UC 10 years after the onset of disease.

A recent meta-analysis by Jess et al. [43] pooled 10 studies in which the overall mortality and the specific causes of death in UC were evaluated. The analysis showed SMRs (standardized mortality ratio, observed/expected death) varying from 0.7 to 1.4; the overall pooled estimate was 1.1 (95% CI: 0.9–1.2, $p = 0.42$). Greater risk of dying was observed during the first years of follow-up, in patients with extensive colitis, and in patients from Scandinavia. Meta-regression analysis showed an increase in SMR by increasing cohort size. UC-related mortality accounted for 17% of all death; mortality from gastrointestinal disease, non-alcoholic liver diseases, pulmonary embolisms, and respiratory diseases was reduced. The authors concluded that the overall risk of dying in patients with UC did not differ from that of the background population, although subgroups of patients were at greater risk of dying.

These data agree with the time trends that seem to show a reduction of mortality from UC over the past 50 years [44].

Conflict of interest statement

All authors declare that they have no conflict of interest.

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Practice points

- We provide a review of studies on prognosis in ulcerative colitis by reviewing the relevant population-based cohort studies.
- The most relevant events in the course of ulcerative colitis are: remission, relapse, quality of life, extension of disease in time, surgery, cancer and mortality.
- Between the 3rd and the 7th year of disease, 25% of patients were in remission, 18% had a continuous disease activity (every year) and 57% had an intermittent disease.
- Patients with long-lasting or extensive ulcerative colitis or with low grade dysplasia have an increased risk of developing colorectal cancer. Surveillance colonoscopy may reduce this risk. It is unclear if immunosuppressive therapy has a role in risk of lymphoma.
- Data on mortality in UC are not homogeneous. In a recent meta-analysis the overall risk of dying in patients with ulcerative colitis does not differ from that of the background population, although subgroups of patients were at greater risk of dying.

Research agenda

- Genetic and environmental prognostic factors should be fully studied in order to predict the clinical course and, consequently, the best treatment approach in ulcerative colitis.
- In the future, creation of national registry for ulcerative colitis patients could improve knowledge concerning risk or protective factors on clinical course, cancer development and mortality rate in comparison with general population.

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