

Predictive factors for a severe clinical course in ulcerative colitis: Results from population-based studies

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Abstract

Ulcerative colitis (UC) is characterized by chronic inflammation of the large bowel in genetically susceptible individuals exposed to environmental risk factors. The disease course can be difficult to predict, with symptoms ranging from mild to severe. There is no generally accepted definition of severe UC, and no single outcome is sufficient to classify a disease course as severe. There are several outcomes indicating a severe disease course, including progression of the disease's extension, a high relapse rate, the development of acute severe colitis, colectomy, the occurrence of colorectal cancer and UC-related mortality. When evaluating a patient's prognosis, it is helpful to do so in relation to these outcomes. Using these outcomes also makes it easier to isolate factors predictive of severe disease. The aims of this article are to evaluate different disease outcomes and to present predictive factors for these outcomes.

Key words: Ulcerative colitis; Disease course; Prognosis; Severity; Colectomy; Relapse; Acute severe colitis; Cancer; Mortality

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Core tip: The disease course of ulcerative colitis (UC) can be difficult to predict. There is no generally accepted definition of severe UC. There are several outcomes indicating a severe disease course, including progression of the disease extension, a high relapse

rate, the development of acute severe colitis, colectomy, the occurrence of colorectal cancer and UC-related mortality. Using these outcomes is helpful when determining patient prognosis and also makes it easier to isolate predictive factors for severe disease. The aim of this article is to evaluate different disease outcomes and to present predictive factors for these outcomes.

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INTRODUCTION

Ulcerative colitis (UC) is a chronic relapsing inflammatory disease of the colon. Risk factors may be both genetical and environmental^[1]. Disease onset usually occurs in young adults, and the symptoms range from mild to severe. The course of the disease is unpredictable, and with the prospect of a life-long disease, it is crucial for patients and physicians to have the most precise information possible regarding disease course and treatment options. The natural progress of the disease, the medical treatment including the benefits and side effects, and the possibility of having surgery at a young age are among the issues specialists are faced with.

There is no generally accepted definition of severe UC. However, there are several outcomes that indicate a severe disease course, including progression of the disease's extension, a high relapse rate, the development of acute severe colitis (ASC), colectomy, the occurrence of colorectal cancer (CRC) and UC-related mortality^[2]. When evaluating a patient's prognosis, it can be helpful to do so in relation to these disease outcomes. This approach can simplify the process of determining predictive factors for severe disease as factors for each outcome can be identified separately.

The aims of the present article are firstly to describe the different outcomes used to determine whether a course of UC is severe or not, and secondly to present predictive factors for the different disease outcomes.

Study methods

This overview includes population-based studies published between 1993 and 2015 in the English language. We performed electronic searches in the PubMed, Cochrane, and Medline databases with the following key words: "ulcerative colitis" and "inflammatory bowel diseases", combined with free text searches for "diagnosis", "population based", "clinical", "course", "prognosis", "surgery", "colectomy", "relapse", "recurrence", "progression", "disease extension", "acute severe colitis", "complications", "cancer", "colo-rectal

cancer", and "mortality".

WHAT CONSTITUTES SEVERE UC?

As of today, there is no generally accepted definition of what constitutes a severe clinical course of UC. The disease course varies markedly between patients, and the decision whether to classify a certain disease phenotype as severe can be based on several possible disease outcomes, each of which depicts ways that severe UC can behave. One example is whether a course of quiescent disease for several years abruptly ending in an episode of acute severe colitis and colectomy is more or less severe than a course characterized by frequent flares barely manageable by medication. Both of these disease courses could at some point be described as severe.

In the following, six of the most commonly seen disease outcomes are evaluated, and predictive factors for these outcomes are presented.

Progression of disease extension

UC always affects the rectum and extends proximally. However, how far proximally it extends at the time of diagnosis varies greatly, from involving the rectum alone (proctitis) to involving the whole colon (pancolitis)^[3]. Furthermore, it is not uncommon that the distribution of the disease may change. In a one-year follow-up study, Moum *et al.*^[4] found that in 399 patients diagnosed with UC, 66% had changes in colonic involvement from the time of diagnosis to follow-up, 14% had extended proximally, 22% had regressed, and 30% showed normalization at colonoscopy after initial medical treatment.

In a population-based follow-up cohort of 423 cases, the Inflammatory Bowel South East Norway (IBSEN) study identified 288 patients with disease extension distal to the splenic flexure at time of diagnosis. Sixty-one of these patients (21.2%) experienced progression to extensive colitis; 39 of the patients (13.5%) experienced progression within the first five years, and 22 of the patients (7.6%) experienced progression during the subsequent five years^[5]. Additionally, 39 of 140 patients (28%) initially diagnosed with proctitis had extended to left-sided colitis. A review from 2012 found similar numbers, stating that 25%-50% of patients with distal colitis experienced progression to more extensive disease over time^[3].

Progression of disease extension indicates a poor prognosis. Etchevers *et al.*^[6] compared patients with stable distal UC (disease limited to rectum and sigmoid colon) with patients having disease progression from distal to extensive (disease with involvement of at least the descending colon). In the group with progression of disease distribution, there was a significantly higher prevalence of extra-intestinal manifestations, steroid-refractory disease course, requirement for immunosuppressive and -modulating medications (including thiopurines, cyclosporine and infliximab) and surgery

than in the group with stable distal UC. However, these differences were not found when comparing stable extensive disease with those having disease progression from distal to extensive. A South Korean study^[7] found a higher prevalence of chronic disease activity (> 6 mo), relapse, and hospitalization due to UC relapse in patients with disease progression than in patients with stable disease distribution.

Several factors predictive of disease progression have been identified. Factors at time of diagnosis include a higher Mayo score and the use of corticosteroids. During follow-up, disease progression has been significantly associated with chronic disease activity after diagnosis, as well as hospitalization and disease relapse^[7]. Preexisting independent factors predictive of disease progression include younger age at diagnosis and the presence of primary sclerosing cholangitis (PSC)^[5,6].

Relapse rate

A relapse is defined as an increase in UC-related symptoms requiring consultation with a physician and leading to changes in medication or surgery^[8,9]. The course of UC is usually characterized by relapses that alternate with periods of remission. The severity of relapses varies from mild increases in symptoms to life-threatening colitis requiring surgery^[10].

Relapse rates have been evaluated in several studies. One year after a diagnosis of UC, 50% of patients in the IBSEN study had registered one or more relapse^[11]. Five years after diagnosis, 78% had registered at least one relapse^[9], and the 10-year cumulative relapse rate was 83%^[5]. This number is higher than reported in a European population-based cohort study^[8], where a 10-year cumulative rate of 67% for the first relapse after diagnosis was established. A Danish study^[12] reported a cumulative risk of first relapse after diagnosis of 51%, 75% and 79% at one, five and seven years, respectively, whereas a study from the Netherlands^[13] found an overall relapse rate of 85% after 10 years of disease.

Factors predictive of a higher relapse rate have been identified in several studies. The 5-year follow-up IBSEN study^[9] found that relapse was more frequent in young patients (mean age 38.5 in patients with relapse vs 46.0 years in patients without relapse), and at the 10-year follow-up^[5], they found that patients older than 50 years of age had a reduced risk compared to patients younger than 30 years of age. The study also found that relapse was more frequent in female patients. Additionally, during the last five years of the 10-year follow-up, a smaller proportion of patients who initially had an ESR > 30 mm experienced relapse than those with initial ESR < 30 mm (30% vs 50%; $P < 0.001$).

The results from a large population-based inception cohort^[8] support age as a predictive factor, with a higher total number of relapses in patients younger than 20 years of age than in patients older than 30 years of

age. The study also found that the total number of relapses was higher in never-smokers than in current smokers. Furthermore, patients who experienced their first relapse < 1 year after diagnosis experienced an increased number of relapses in the subsequent years compared with those with their first relapse between 1-2 years after diagnosis and > 2 years after diagnosis.

Acute severe colitis

The development of acute severe colitis is considered a medical emergency and is potentially life-threatening. Diagnosis of this condition is often based on Truelove and Witts' severity index: bloody stool frequency ≥ 6 per day, plus at least one of the following: Pulse > 90/min, temperature > 37.8 °C, Hb < 10.5 g/dL, or ESR > 30 mm/h^[14-16]. Modifications of these criteria can be applied, such as using CRP > 10 instead of ESR elevation^[17].

Two recent studies indicate that ASC affects approximately 25% of UC patients^[17,18]. Data from the United Kingdom show that ASC is the presenting feature leading to hospitalization and diagnosis in 10%-20% of patients^[17]. An Oxford-based cohort consisting of 750 UC patients also found that ASC occurred in approximately 25% of the patients (186/750); in these patients, ASC occurred as a presenting feature or occurred within one year of diagnosis, at a cumulative total of 54%. In 18% of the patients, ASC occurred for the first time 1-5 years after diagnosis, and it occurred after five years in 28% of the patients^[14].

The first-line medical treatment for ASC is intravenous corticosteroids^[17]. If the patient does not respond to this ("steroid-refractory colitis"), second-line therapy with infliximab or cyclosporine is considered. The results on the efficacy of these treatments are not conclusive^[15,17-19], but the risk of in-hospital mortality is no higher for patients treated with second-line medical therapy than for those undergoing surgery^[17]. The proportion of patients with ASC undergoing surgery varies from 17% to 40%^[14,17,20]. A trend toward fewer surgical interventions for ASC was noted from 2008 to 2010, with 34% vs 25% operated in the respective years^[17]. Delayed surgery for ASC patients not responding to medical rescue therapy might increase the risk of postoperative complications^[16].

Mortality in ASC patients is relatively low compared to that of the background population. A Canadian study^[20] found a total mortality rate among 1991 ASC patients of 1%. However, among those who underwent surgery, the mortality rate was approximately 3.8%. A Danish cohort that included UC patients undergoing acute or elective colectomy between 1996 and 2010, with a 30-d follow-up, found a mortality rate of 5.2% among those who underwent emergency surgery^[21]. United Kingdom data also suggest a total mortality rate among ASC patients close to 1%. However, this rate increases to close to 3% among those with steroid-refractory colitis^[17].

In the literature, predictive factors for ASC are

scarce. However, in an abstract, Cesarini *et al.*^[22] presented a prognostic index for the development of ASC within 3 years to be applied at the time of diagnosis. The three factors included in this index were extensive disease, CRP > 10 mg/L and Hb < 12.1 g/dL (women)/< 13.8 g/dL (men). The index was tested on three cohorts in England and Sweden, and of the patients who scored 3/3 at diagnosis, 8/11 (73%), 18/18 (100%) and 13/14 (93%) subsequently developed ASC. Another study supports disease extension being predictive of ASC, with a significantly higher number of patients with extensive disease in the ASC cohort than in the non-ASC cohort (30% vs 11%)^[14]. The same was seen with regard to patients whose disease had progressed from proctitis and left-sided colitis to extensive colitis (81% vs 21%).

Colectomy

Colectomy indications can be categorized into those for acute surgery and those for elective surgery^[23]. An emergency colectomy is performed when a hospitalized colitis patient develops life-threatening complications unresponsive to medical treatment. Elective colectomy is most frequently performed due to either refractory disease, intolerance to medical treatment or colonic neoplasia.

Colectomy rates for UC have varied between cohorts and across time^[24]. In 1994, a Danish study reported that 25% of UC patients underwent colectomy within the first ten years of diagnosis^[25]. The reason for this high rate may have been a tendency of specialists to choose colectomy after the second relapse over conservative medical treatment.

Newer assessments have shown a 10-year cumulative colectomy rate of approximately 10%^[5,26]. Hoie *et al.*^[27] found a 10-year cumulative colectomy rate of 8.7% and a significant difference between southern and northern European centers (3.9% vs 10.4%). In the province of Manitoba, Canada, the 10-year colectomy rate decreased significantly over time from 12.7% (1987-1991) to 9.3% (1997-2001)^[26]. Thus, a trend can be seen toward a lower colectomy rate in UC patients. This is supported in a review from 2013; in the review 10-year surgery rates as high as 35% were reported before 1990, and rates declining to < 10% were reported after 1990^[28]. This observation is also supported by Kaplan *et al.*^[24], who reported a significant decrease in colectomy rates in UC patients between 1997 and 2009. However, the study showed that the rate of emergency colectomies remained stable.

In a population-based surveillance cohort identifying 666 UC patients who underwent surgery, a total of 27% of the patients had a postoperative complication, whereas postoperative mortality occurred at 1.5%. The main independent predictors of complications were advanced age, comorbidity and emergency surgery^[29]. Although mortality related to severe attacks of UC has substantially decreased to less than 1% in past decades, a delay in surgery can increase the risk of

postoperative complications and mortality^[16,20,29]. Sixty percent of patients treated with emergency colectomy experienced some sort of complication during follow-up^[16].

In a systematic review from 2014, Dias *et al.*^[30] identified clinical predictors of colectomy in patients with UC. They found a reduced colectomy risk for female patients and for smokers, whereas a higher risk was noted for patients with extensive disease, for patients who took corticosteroids at least once and for patients who were hospitalized.

Cancer development

UC may be complicated by the development of CRC^[31]. Inflammatory bowel disease (IBD)-associated CRC (IBD-CRC) affects patients at a younger age than sporadic CRC. The prognoses for sporadic CRC and IBD-CRC are similar, with a 5-year survival of approximately 50%^[32].

A Danish study reporting CRC risk in a nationwide cohort of 47374 patients with IBD over a 30-year period found that the relative risk (RR) of developing CRC in UC patients was 1.07 (95%CI: 0.95-1.21), which means that the risk for CRC in UC patients was comparable to that in the general population^[33]. The overall RR for CRC in UC patients decreased from 1.34 (95%CI: 1.13-1.58) in 1979-1988 to 0.57 (95%CI: 0.41-0.80) in 1999-2008.

A meta-analysis to determine CRC risk in UC patients showed that UC increases the risk of CRC 2.4-fold, which represents a total CRC occurrence of 1.6% during the first 14 years of follow-up^[34]. The authors concluded that Eaden *et al.*^[35] overestimated the long-term CRC risk among UC patients in reporting a cumulative incidence of CRC of 2% at 10 years and 8% at 20 years of follow-up for any patient with UC. In this meta-analysis^[34], restricted to unselected patients in population-based cohorts and including sporadic CRC cases, the numbers were only 0.4% and 1.1%-5.3%, respectively. The authors conclude that a UC diagnosis no longer seems to be associated with increased CRC risk, although subgroups of patients remain at increased risk. A recent systematic review supports this observation^[36]. The decreasing risk of CRC might result from improvements in therapy.

However, a Finnish study found a higher cancer incidence in male IBD patients, with UC patients at increased risk for developing CRC and biliary tract cancer^[37]. In addition to this finding, a study from 2009 found a significantly increased risk of CRC development in IBD patients with concomitant PSC^[38]. The 10- and 20-year risk rates were 14% and 31%, respectively, compared to 2% and 2% in PSC patients without IBD.

The association between IBD and cancer in general was evaluated in the fifteen-year follow-up of the European Collaborative Study Group of Inflammatory Bowel Disease^[39]. The total cancer prevalence was 9.1%, with most patients having a single extra-intestinal neoplasm. In Northern centers there were more

intestinal cancers, whereas in southern centers there were more extra-intestinal cancers. In this IBD cohort, the frequency of observed cancers was not different from that expected in the background population.

Regarding predictive factors for the development of CRC in UC patients, the aforementioned results indicate that it is debated whether a correlation exists between UC and a higher than normal risk of developing CRC. Thus, UC-specific factors predictive of CRC may not exist. However, a Finnish study found that male gender increased the risk of developing CRC in the context of UC, and concomitant PSC also increased CRC risk.

Mortality

Early studies on the prognosis in IBD showed significant reductions in survival, whereas reports from the last two decades have been more optimistic^[40-43]. In an updated examination of mortality in the Copenhagen cohort (median follow-up 19 years), no significant increase in overall mortality in UC was reported. The IBSEN study reported on mortality in an inception cohort gathered between 1990 and 1994 and followed the patients for 10 years^[5]. No elevated mortality was found, either overall or in subgroups of patients. These data have now been extended up to 20 years, still showing no overall increased mortality^[44]. In a population-based registry of 1254 Finnish adult IBD patients accrued between 1986 and 2007, the standard mortality rate (SMR) was 0.90 (95%CI: 0.77-1.06)^[45]. Similar data were seen in a large multicenter study in Europe following patients for 10 and 15 years, with no increase in overall mortality^[39,46].

In the modern era of managing patients with UC, mortality rates seem to have decreased. A recent meta-analysis comprising 22 studies did not detect an increased risk of death in UC patients compared to the background population. The pooled SMR from the 10 population-based inception studies was 1.1 (95%CI: 0.9-1.2)^[47].

Colectomy reduces mortality in UC by removing the risk of dysplasia/CRC and the inflammatory burden of the disease. However, peri- and postoperative mortality might lead to an increased total mortality risk. In the Danish IBD registry spanning from 1996 to 2010, 50% of patients admitted as emergency cases underwent colectomy^[21]. In UC patients undergoing emergency surgery, the 30-d mortality rate was 5.2% compared with 0.9% among elective cases. Low hospital total colectomy volume, comorbidity and advanced age were associated with increased 30-d mortality in UC patients undergoing emergency surgery.

UC occurs more frequently in nonsmokers; therefore, smoking-related mortality is decreased^[48]. However, one study concluded that in UC patients, mortality from respiratory disorders (smoking-related diseases, asthma, pulmonary embolism, and pneumonia) was significantly increased^[49]. Hematological malignancy mortality rates from leukemia and non-Hodgkin's lymphoma were not increased.

The overall mortality in UC has been declining, and today it is no higher than that in the background population. Hence, it is difficult to identify predictive factors related to the disease course that increase mortality. However, trends leading to an increased mortality risk in subgroups of UC patients are seen.

SUMMARY OF SEVERE UC AND ITS PREDICTIVE FACTORS

No generally accepted definition of severe UC exists. However, several disease outcomes can indicate a more severe disease course.

Progression of disease extension is a poor prognostic factor. Predictive factors include higher Mayo score, higher endoscopic score, corticosteroid use, younger age at diagnosis and presence of PSC at time of diagnosis.

Relapse of disease is frequently seen, with 70%-80% of UC patients experiencing at least one relapse. Predictive factors for a higher relapse rate include younger age, female gender, initial ESR < 30 mm, no smoking and early relapse (within 1 year after diagnosis).

Acute severe colitis is a potentially life-threatening condition occurring in approximately 25% of patients with a total mortality of 1%, increasing to 3% in those who undergo surgery. Predictive factors are scarce, but they include extensive disease, CRP > 10 mg/L and Hb < 12.1/13.8 (women/men).

Colectomy, whether an emergency procedure or elective, is performed when conservative treatments have not succeeded at inducing remission. Reduced colectomy risk was found in female patients and smoking patients, whereas higher risk was found in patients with extensive disease, corticosteroid use and hospitalization.

Neither CRC nor mortality has consistently been shown to be increased among UC patients. However, male UC patients and patients with PSC are at an increased risk of developing CRC. Additionally, trends leading to increased mortality risk in subgroups of UC patients are seen.

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