Do clinical factors help to predict disease course in inflammatory bowel disease?

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Abstract

While therapeutic strategies able to change the natural history of the disease are developing, it is of major importance to have available predictive factors for aggressive disease to try and target these therapeutic strategies. Clinical predictors have probably been the most broadly studied. In both Crohn’s disease (CD) and ulcerative colitis (UC), age at diagnosis, disease location and smoking habit are currently the strongest predictors of disease course. A younger age at onset is associated with more aggressive disease both in CD and UC. Disease location in CD is associated with different types of complications: surgery and recurrence in upper gastrointestinal and proximal small bowel disease; and surgery in distal small bowel disease and peri-anal lesions in rectal disease. In UC, extensive colitis is clearly been associated with more severe disease. Finally, active smoking globally increases disease severity in CD but decreases it in UC. Besides these important factors, others may predispose to some specific disease evolution and complications, and are also reviewed in the present paper.

INTRODUCTION

The clinical course of the disease varies greatly among patients with inflammatory bowel diseases (IBD). It usually follows a pattern of more or less frequent relapses of variable duration interspersed with remission periods, but some patients may experience progressive decrease and even disappearance of disease activity over time, while others may have chronic active disease without remission periods. Furthermore, the natural history of IBD progressively leads to the development of complications in approximately two-thirds of Crohn’s disease (CD) patients and less than one-third of ulcerative colitis (UC) patients. In CD, the main complications are the development of fibrotic strictures that lead to intestinal obstruction and the development of intra-abdominal and peri-anal fistulae and abscesses. In UC, the main complications are fulminant colitis that leads to emergency colectomy and the development of colorectal cancer.

To be able to predict the course and complications of IBD has become particularly important since drugs able to change the natural history of the disease have become available: this is particularly the case for anti-tumor necrosis factor treatment but probably also, albeit to a...
lesser extent, immunosuppressive treatment if it is used early enough[1].

Among other markers that can help clinicians to predict disease course in IBD, demographic and clinical characteristics are important because they are probably the easiest to use. The value of clinical parameters has been studied for the prediction of various types of disease outcomes, including the development of complications, need for surgery, or more elaborate definitions of disabling or severe disease.

**CD**

The variable course of CD has been well described in several Scandinavian population-based studies[8,9]. In particular, four subtypes have been described: 1, severe flare at diagnosis but with rapid decrease and disappearance of disease activity; 2, mild activity at the beginning with secondary progressive worsening of the disease; 3, recurrent flares interspersed with periods of full remission; and 4, chronic active disease with fluctuating but constant disease activity. In a recent population-based Norwegian study, types 1, 2, 3 and 4 affected 43%, 3%, 32% and 19%, respectively[8]. To date, no clinical predictive factor has been associated with these different profiles of disease evolution. More numerous studies have been devoted to the search for predictive factors of disease complications.

The characteristic of CD that is associated most strikingly with the course of the disease is disease location. Terminal ileal location has been very strongly associated with the risk of stricture and internal penetrating behavior in several independent studies[10,11,12,13]. Hence, it has also been associated with the risk of surgery[14,15]. Proximal small bowel and upper gastro-intestinal tract location (category L4 in the Montreal classification) has been associated in a European population-based study with the risk of recurrence[16]. In a recent Asian study, it was also associated with the risk of surgery[17]. Colonic disease, and particularly rectal disease, is associated with the development of peri-anal disease, and such a complication develops in 12% of patients with ileal disease, 41% of those with colonic disease, and 92% of those with rectal disease[18].

The behavior of the disease at diagnosis can also influence the course of the disease, since a fibro-stenosing or a perforating phenotype is already the sign of the presence of complications. By itself, a particular phenotype may necessitate surgery or the use of immunosuppressive drugs. Beyond this, the predictive value of the phenotype at diagnosis is more difficult to imagine. One of the reasons is that the phenotype of CD is a dynamic process, and after 10 years, almost 50% of the patients with an inflammatory phenotype at diagnosis develop fibro-stenosing or perforating complications that affect the course of the disease[19]. However, it must be remembered that, if only a minority of CD patients remain complication-free over time (30% at 10 years and <20% at 20 years), among those developing complications, these will occur with a variable delay after diagnosis. This can be interpreted as a different inclination to develop such complications, that is, patients who have already developed complications at diagnosis are the most prone to develop such complications. This difference may then influence the course of the disease.

The presence at diagnosis of peri-anal lesions, is associated with a more frequent use of immunosuppressive treatment[17,18], poor mid-term outcome[19], and increased risk of surgical resection and postoperative recurrence[20]. A stricture or intra-abdominal penetrating lesion is associated with an increased risk of surgery[12,21]. Other studies have also shown that abdominal penetrating lesion at the time of first surgery is associated with more rapid recurrence and is an indicator of further surgery[22].

More recently, some studies have been performed in an attempt to define predictive factors for the development of disabling or severe disease over time. In a large cohort study that used retrospective analysis and prospective validation, the need for surgery, immunosuppressive treatment, biological agents, and hospitalization, demonstrated that peri-anal disease, together with young age at diagnosis and the need for steroids to treat the first flare, were factors associated with disabling chronic disease[22]. In a further study, these factors were partly confirmed, particularly the presence of peri-anal disease at diagnosis[23]. Furthermore, the presence of a stricture or penetrating disease at diagnosis, and peri-anal disease together with weight loss, fever and increased platelet count, were associated with development of severe disease, which was defined by surgical resection of two small bowel segments (or at least 70 cm) or any colonic segment, complex peri-anal disease, or definitive stoma[24]. However in a European population-based study, a stricture or penetrating behavior at diagnosis was not associated with recurrence after the first flare, need for surgery[10,11,25], or increased mortality[26].

Young age at onset is also associated with greater disease severity, particularly with the risk of disabling disease[22,23]. However, in contrast, older age at onset is associated with a slight increase in mortality[26].

As indicated earlier, weight loss at diagnosis is associated with more severe disease that is characterized by development of non-reversible tissue damage[23]. Obesity has been associated in a recent study with a more rapid need for surgery, which indicates a more aggressive disease in these such patients[25].

Finally, active smoking is associated with disease activity[26], as well as with the development of strictures and fistula complications[10,11,12,7]. In a recent study, low levels of smoking increased disease activity and hospitalization, but not the need for surgery[29].

**UC**

Disease course also varies greatly among patients with UC. In a recent population-based study from Norway, nearly one-fifth of the patients experienced no significant relapse over 10 years after diagnosis, while about half of
the patients had quiescent disease over the past 5 years. In UC, disease location is associated most strikingly with disease course. In particular, extensive colitis is associated with increased risk of colectomy and colon cancer, as well as a slight increase in mortality. Colectomy rate reached 35% in extensive colitis, while it was <20% in left-sided colitis and <10% in proctitis. The same is true for the risk of colon cancer, which reached 45% after 30 years of the disease in one early historic study, while it was around 30% in left-sided colitis and 10% in proctitis. These risks have been shown to be much lower in most recent studies. It has gone down to 5%-10% for cancer, probably due to sustained control of inflammation and perhaps surveillance, but still with an increased risk in extensive colitis. Likewise, in a recent population-based European study, the global risk of colectomy was 8.7% over 10 years.

In a recent study, patients with distal colitis were at increased risk of disease extension if they were younger at diagnosis or if they had sclerosing cholangitis. Furthermore after disease extension, these patients were at increased risk of more aggressive disease with resistance to treatment. In another recent pediatric study, disease extension was strongly associated with risk of colectomy. It was also the case, albeit to a lesser extent, for extra-intestinal manifestations.

In a recent Norwegian population-based study, age >50 years at diagnosis was associated with decreased risk of colectomy.

Finally, smoking is associated with a less aggressive disease course in UC and colon cancer and colectomy. In a recent study from Hungary, it even decreased the risk of colectomy.

CONCLUSION
Clinical presentation markedly influences disease course in CD and UC. It probably currently represents the strongest predictor for further disease evolution and complications. In both CD and UC, the clinical and demographic characteristics most constantly associated with disease course are age at diagnosis, disease location, and smoking. Younger age at onset is associated with a more severe course in both diseases. In CD, proximal small bowel and upper gastrointestinal tract location is associated with risk of recurrence and surgery; small bowel disease with risk of surgery; and colonic disease, and particularly rectal disease, is associated with increased risk of peri-anal lesions. In UC, extensive colitis is associated with increased risk of colorectal cancer and colectomy. Finally, smoking globally decreases disease severity in UC while it increases severity in CD.

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