Predictors of Aggressive Inflammatory Bowel Disease

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Abstract: Inflammatory bowel disease comprises a group of conditions characterized by idiopathic inflammation of the gastrointestinal tract. The natural course of disease can range from an indolent course with prolonged periods of remission to aggressive, incapacitating disease. Predicting which patients are more susceptible to developing severe disease is important, especially when choosing therapeutic agents and treatment strategies. This paper reviews current evidence on the main demographic, clinical, endoscopic, histologic, serologic, and genetic markers that predict aggressive inflammatory bowel disease. In ulcerative colitis, we considered disease to be aggressive when patients had a high relapse rate, need for admission and/or surgery, development of colon cancer, or extraintestinal manifestations. We defined aggressive Crohn's disease as having a high relapse rate, development of penetrating disease, need for repeat surgery, or multiple admissions for flares. In Crohn's disease, involvement of the upper gastrointestinal tract and ileum, penetrating disease, early age at diagnosis, smoking, extensive ulceration of the mucosa, high titers of serum antibodies, and mutations of the *NOD2* gene are markers of aggressive disease. In ulcerative colitis, patients with more extensive involvement of the colon (pancolitis) have more symptomatology and are at higher risk for needing a colectomy and developing colon cancer. Also, plasmocytic infiltration of the colonic mucosa and crypt atrophy predict treatment failure. As with diagnosis, no single method can predict disease aggressiveness. Multiple serologic and genetic tests are being developed to refine the accuracy of prediction. Endoscopic findings can also predict the future course of disease. At present, clinical manifestations are the most useful way to make therapeutic decisions.

Inflammatory bowel disease (IBD) comprises a heterogeneous group of conditions affecting the gastrointestinal tract; Crohn's disease (CD) and ulcerative colitis (UC) are the 2 main recognized entities. The course of the disease is variable, as some patients have an indolent course with long periods of remission, while others present with much more aggressive disease. Lack of response to cur-

rently available treatments can affect quality of life and increase patients' morbidity and mortality.

Predicting severity of disease is important for several reasons. Not only does an accurate prediction help the clinician prepare the patient and his or her family for what to expect, but it is also very useful to the clinician in terms of individualizing management, as the heterogeneity of the clinical presentation and course of IBD requires a personalized approach.

In the past decade, we have seen huge advances in IBD therapeutics, with several emerging pharmacologic agents and strategies. We already know that initiation of more aggressive treatment early in the course of the disease can result in better outcomes.[1] However, we also know that more aggressive therapies can lead to a greater chance of toxicity and adverse effects such as infections and malignancy.[2-4] If clinicians could better predict the subgroups of patients most likely to have the worst outcomes and, therefore, the greatest benefit from therapy, they could better tailor therapy and select the ideal monitoring strategy for each patient. This approach would minimize toxicity and lead to more efficient use of resources.

Predicting outcomes can not only help guide the clinician's choice of the optimal initial therapy but may also be useful when adjusting treatment. For example, patients in remission with combination therapy who have a low probability of relapse or disease progression may be able to de-escalate to a single-agent regimen, possibly improving the safety profile of the treatment.

This review will summarize the most studied predictors of severe disease for both CD and UC (Tables 1 and 2). As with diagnosis, we still do not have a reliable way to predict which patients will develop more aggressive disease, but the combination of variables reviewed in this paper can help clinicians choose which strategy will most likely benefit their patients.

In this review, aggressive UC is defined as disease that is associated with a high relapse rate (need for 2 or more courses of steroids and/or hospitalization for flares of disease after initial diagnosis despite optimal treatment with mesalamine and an immunomodulator), need for surgery, development of colon cancer, or the presence of extraintestinal manifestations (EIMs). Aggressive CD is defined as being characterized by penetrating disease, hospitalization for flares or complications of the disease, need for surgery, or EIMs involving 2 or more extraintestinal systems. Although we also considered including stricturing disease in this group, it may not truly represent aggressive disease, since the natural history of CD suggests that persistent inflammation over long periods of time leads to fibrosis and stricturing, perhaps suggesting more indolent disease.[5,6] Patients with a poor response to currently available treatments were also considered to have aggressive IBD.

Table 1. Variables at Diagnosis Associated with Aggressive Crohn's Disease

- Younger age (<40 years)
- Perianal disease
- Stenotic disease
- Involvement of the upper gastrointestinal tract
- Need for corticosteroids on the first flare-up
- Lack of mucosal healing after induction of clinical remission
- Smoking
- Presence of epithelioid granulomas
- Higher titers of ASCA, anti-OmpC, and anti-CBir1
- Mutations in the *NOD2/CARD15*, *ATG16L1*, and *MDR1* genes

Anti-CBir1=antibody against flagellin expressed by Clostridial phylum; anti-OmpC=antibody to the outer membrane porin of *Escherichia coli*; ASCA=anti–*Saccharomyces cerevisiae* antibody.

Clinical Factors

Age

Whether there is a difference in the exact etiology of IBD between patients with childhood-onset disease compared to those who develop the disease as adults remains unclear. Clinical and population-based studies have shown that patients who present at a younger age (particularly <40 years) have more extensive and complicated disease in both UC and CD and have a higher risk of developing fistulae and corticosteroid dependency in CD.[7-13] It is possible that if even younger patients (<20 years at presentation) are considered, disease may be even more aggressive.

In UC, age of diagnosis seems to have a variable impact on prognosis. In a study from the Netherlands, older age at diagnosis increased the risk for flares during the first year, but older patients had a more benign course over the long term.[14] Using the Mayo score as a severity scale, a Canadian study showed that patients diagnosed at a younger age had worse UC.[15] Lee and colleagues also found that, at presentation, patients younger than 40 years of age had more diarrhea, pancolitis, and use of corticosteroids.[9] These findings may be explained by the fact that patients with more genetic risk factors and environmental triggers will present with symptoms earlier.

Disease onset at a younger age has also been found to be an independent predictor of aggressive disease by Etchevers and coauthors.[16] One study showed that patients who present with UC at 45 years of age or older have fewer relapses.[17] Even though patients diagnosed with UC

Table 2. Variables at Diagnosis Associated with Aggressive Ulcerative Colitis

- Younger age (<40 years)
- Pancolitis
- Development of primary sclerosing cholangitis
- Lack of mucosal healing after induction of clinical remission
- Deep ulcerations in the colonic mucosa
- Higher levels of pANCA

pANCA=perinuclear antineutrophil cytoplasmic antibody.

at an earlier age may present with more severe disease, a Canadian study found that those diagnosed later in life (>40 years of age) had a higher risk of developing colon cancer.[18] Whether this finding is because the patients had undiagnosed colitis for a longer period of time or whether there is a distinct colitis-associated cancer pathway in these individuals remains uncertain. These results did not corroborate a Swedish study that reported that patients who were 15 years or younger at diagnosis had a significantly higher risk of developing colon cancer.[19]

Despite the fact that age does not appear to impact response to treatment, Ferrante and colleagues demonstrated that, among UC patients who were treated with infliximab (Remicade, Centocor), younger patients had a higher rate of disease remission, while patients with a disease duration of more than 2 years had a lower response rate to biologic medications.[20,21] Page and coauthors found that patients 60 years of age or older had an increased risk of developing complications and an increased length of stay after IBD-related surgery, which was not explained by a higher prevalence of comorbidities or immunosuppressive drugs.[22]

Gender

When comparing males and females, no differences have been found in the development of disabling CD or response to biologic agents, but women may have a higher risk of intestinal resection and requiring surgery in CD.[8,11,12,23] In UC, there has been no gender difference in outcomes.[17]

EIMs seem to be more frequent in females.[24] Bernstein and colleagues found several differences regarding gender, as iritis/uveitis and peripheral arthritis are seen more frequently in women; conversely, primary sclerosing cholangitis and ankylosing spondylitis are more common in men.[12,25,26]

Race and Ethnicity

Only a few studies have looked at the role that race and ethnicity play in the course of IBD. Early investigations with a small number of patients reported that IBD manifestations were more severe in the African-American (AA) population.[27,28] A large cohort study found that both Hispanic and non-Hispanic whites were less likely than AA patients to have undergone bowel resection for CD, but whites had a higher rate of perianal disease.[29] The same study found that Hispanics had a significantly higher rate of colectomy and refractory UC. Nguyen and coworkers also looked at the prevalence of EIMs; compared to the white population, Hispanic patients had more erythema nodosum, while AA patients were at higher risk for uveitis and sacroiliitis.[29] Several other studies have shown no differences in severity of disease among races.[30,31]

It is not clear if the varying results are due to underlying genotypic differences or disparities in access to healthcare; perhaps future genome-wide association studies can better address this question.[32,33] Also, race and ethnicity are usually self-reported, so these studies have inherent limitations created by inconsistencies in reporting.

Family History of Inflammatory Bowel Disease

Familial clustering of IBD has been well studied.[34] A correlation has also been found between phenotypes within families, especially in CD.[35,36] When comparing familial IBD (defined as having a first-degree family member with the disease) versus sporadic IBD, no differences in disease behavior have been reported, even though the familial cases are usually diagnosed at a younger age.[37] However, patients with IBD who have a positive family history have a higher chance of having medically refractory UC and EIMs.[38,39]

Disease Phenotype

The presentation and natural history of IBD can vary, with a wide spectrum of manifestations and locations of disease. For the purposes of this paper, we have characterized location and phenotype based on the Montreal classification system. CD is classified as ileal, colonic, ileocolonic, or isolated upper tract disease; UC is characterized as proctitis, left-sided disease, or extensive involvement.

Beaugerie and colleagues found that patients with CD who present with perianal disease at diagnosis had a significant risk of having a complicated disease course during the subsequent 5 years.[12] A study in Belgium validated these results and added weight loss (>5 kg), fever (>38° C), and stenotic disease as markers of poor prognosis.[40] The presence of strictures at diagnosis has been described as a predictor of subsequent development of penetrating disease and corticosteroid-refractory disease but not perianal disease.[7,41] Another analysis in an Asian population showed that involvement of the upper gastrointestinal tract was an independent predictor of more complicated disease, including hospitalizations.[42] This finding matches the results of several other studies in whites.[43] Patients with perianal disease also carry a higher risk of needing a permanent stoma.[44]

Fistulizing disease has repeatedly been found to be predictive of a more severe course, and studies have also shown that patients with fistulizing disease have a poor response to antimetabolites and a higher corticosteroid requirement.[45,46] Corticosteroid use may actually worsen the disease course in fistulizing disease by inhibiting wound healing. Patients who require corticosteroid therapy during their first CD flare are also more likely to develop more disabling disease, and the subgroup of CD patients who have upper tract involvement is more likely to become corticosteroid-dependent.[12,47] When compared to patients with ileal or ileocolonic involvement, patients with CD that is limited to the colon have a lower rate of surgery.[48,49] Interestingly, those CD cases that were initially diagnosed as UC have an increased risk of needing a surgical procedure.[8]

In UC, patients with pancolitis have a higher risk of developing intractable disease, experiencing rectal bleeding, and having difficulty maintaining weight compared to patients with left-sided colitis and proctitis.[50] The presence of EIMs at the time of diagnosis has also been found to increase the risk of colectomy.[7] The subgroup of patients with extensive disease (pancolitis) and those who develop primary sclerosing cholangitis are more prone to develop colonic malignancies.[51,52]

Endoscopic Findings

Endoscopy is a critical element in the diagnostic algorithm of IBD; it can also be used to predict disease behavior. A French study found that after a median follow-up period of 52 months, patients with active colonic or ileocolonic CD who exhibited deep and extensive ulcerations during colonoscopy had a higher risk of developing penetrating disease and requiring surgical intervention.[53] In UC, the presence of deep ulcerations and extensive disease is also predictive of more aggressive disease, failure of medical treatment, and a higher rate of colectomy.[54,55] Even though the extent of disease at diagnosis predicts subsequent need for immunomodulatory agents and the probability of needing a colectomy, it does not affect the risk of relapse.[56,57] It is important to mention that while this last study did not find a relationship between the extent of disease and risk of relapse, Henriksen and coauthors found that the 5-year relapse rate was 78%.[57]

Lack of mucosal healing after induction therapy has also been postulated to be a marker of aggressive disease. A large cohort study conducted in Norway, which included patients with UC and CD, found that patients who failed to achieve mucosal healing after their first year of disease subsequently had greater disease activity and an increased need for medical treatment, including corticosteroid therapy.[51] Schnitzler and coworkers found that, among patients with CD who showed a symptomatic response to infliximab, those who did not achieve mucosal healing had a higher chance of needing major abdominal surgery.[58] Similarly, results from an Italian study revealed that lack of mucosal healing after corticosteroid therapy in UC was associated with a more severe disease course.[18]

Environmental Factors

Smoking is one of the most studied prognostic factors in IBD; interestingly, the impact that smoking has on CD differs compared with UC. Not only is smoking considered to be a risk factor for developing CD, but it has also been found to have a detrimental effect on the clinical course of patients with CD.[59] Multiple studies have found that smokers with CD have a higher risk of requiring surgery, developing fistulae, having worse symptomatology, and relapsing.[25,59-62] These effects seem to be reversible with tobacco cessation.[63]

This phenomenon is not seen in UC, where data suggest that smoking may actually improve outcomes.[64] Van der Heide and colleagues found that, among patients from a university hospital in the Netherlands, smokers with UC required less corticosteroid and immunomodulator therapy and had a lower rate of admission for flares of UC when compared to nonsmokers.[64] However, the same authors failed to find a beneficial effect of smoking in a group of patients from a different community hospital.[65] Other studies have also shown no differences in the rates of UC relapse or response to treatment between smokers and nonsmokers.[66-68]

The role of smoking as a protective factor in the development of pouchitis after a total colectomy has also been controversial.[69] Smoking does not seem to affect the incidence of colon carcinoma in these patients.[59] Nonetheless, smoking increases the risk of developing surgical complications in both UC and CD.[70]

Appendectomy is another common environmental factor that can influence both the risk of developing disease and the course of both UC and CD. As with smoking, appendectomy seems to have opposite effects based on the disease. Appendectomy as a risk factor for the development of CD has been a controversial topic; while some studies show that appendectomy can increase the risk of CD, other studies contest these findings.[71-73] Appendectomy has been shown to increase the risk for surgical resection in CD, but other studies have not found an increase in disease severity.[72,74]

In UC, appendectomy not only decreases the risk of developing the disease but also protects the patient against developing severe disease and reduces the need for colectomy.[71,75,76] This benefit seems to be associated with appendectomies performed for inflammatory conditions (appendicitis and lymphadenitis), and this benefit is seen in all age groups.[82,83]

Use of oral contraceptives (OCPs) has also been considered as a potential predictor of more aggressive CD. A prospective study found that women exposed to OCPs (current or former) were at increased risk for CD relapse.[77] However, these findings could be confounded by the fact that younger women (<40 years of age) use more OCPs, and, as mentioned before, younger age is an independent risk factor for worse prognosis. Intriguingly, the potential influence of OCPs in the natural course of CD may be dependent on the dose and the concomitant use of cigarettes.[78] Overall, strong evidence to support the restriction of OCPs in these patients is lacking.

Histopathology

Epithelioid granulomas are one of the most characteristic findings in biopsies of patients with CD, although only approximately 15–25% of patients with CD present with epithelioid granulomas.[79,80] Their presence has been linked to more complicated disease (stricturing or penetrating complications, need for surgery, and hospitalizations for flares) in both adults and children.[79,81,82] Bataille and coauthors found that an excess of lymphocytes and eosinophils in the lamina propria, crypt atrophy, and the absence of lymphocytes in the epithelium were predictive of uncomplicated disease.[43]

In UC, infiltration of plasma cells in the lower one third of the mucosa and crypt atrophy were associated with a shorter time to relapse.[66] An interesting study by Melson and colleagues showed that the histologic predictors of refractory UC seem to differ by age groups.[83] In this analysis, lymphoid follicles were predictive of medically refractory disease in patients 38 years of age and younger, while severe cryptitis was more predictive in the older population.[83] Severe pancolitis, fissuring ulcers, and appendiceal ulceration in the resected specimen increase the risk of pouchitis among patients who have undergone a total proctocolectomy (TPC) with ileal pouch–anal anastomosis (IPAA).[84]

Biomarkers

Serologic Markers

Serologic markers exploit the antibody response to self or foreign antigens. Several immune-mediated antibodies against microbial antigens have been described in both CD and UC.[85] Because of the great complexity of the pathophysiology of IBD, the number of potential antibodies is high, but the most studied antibodies are perinuclear antineutrophil cytoplasmic antibody (pANCA), anti–*Saccharomyces cerevisiae* antibody (ASCA), antibody to the outer membrane porin of *Escherichia coli* (anti-OmpC), antibody against flagellin expressed by Clostridial phylum (anti-CBir1), anti–chitobioside carbohydrate antibody, anti–laminaribioside carbohydrate antibody, and anti–mannobioside carbohydrate antibody. Evidence suggests that these antibodies can help to establish a diagnosis of IBD and to differentiate CD from UC, particularly when used in combination.[86,87] Can these antibodies help to predict disease severity? Data suggest that the presence and level of these antimicrobial antibodies correlate with disease complications, need for surgery, and response to treatment.[20,88]

In CD, multiple studies have linked the presence of these antibodies to more complicated disease, including fibrostenosis, internal penetrating disease, and increased need for surgical interventions involving the small bowel.[89,90] ASCA has been associated with internal penetrating disease and early need for surgery.[8,91] By using the quartile sum score technique based on the number of elevated antibodies, Dubinsky and coworkers examined how the degree of immune response to ASCA, anti-OmpC, and anti-CBir1 correlated with internal penetrating and stricturing disease and the need for surgery in a large pediatric CD cohort.[92] This study found that both the number and level of immune responses to the studied antibodies were predictive of aggressive disease phenotypes.[92]

Serology has also been used to predict EIMs, risk of complications, and response to treatment. A positive pANCA test result correlates with the likelihood of developing erythema nodosum.[93] In patients with UC who undergo TPC with IPAA, higher preoperative levels of pANCA and anti-CBir1 are predictors of development of chronic pouchitis.[94,95] Conversely, patients with negative serology test results for pANCA have a better response to infliximab.[23]

Inflammatory Markers

The most commonly used surrogate markers of systemic inflammation are C-reactive protein and erythrocyte sedimentation rate. These markers are readily available but have not proven to be good predictors of disease behavior, even though patients with higher levels of these markers are more prone to relapse and require more corticosteroid therapy.[46,66,96,97] Some studies have tried to use these inflammatory markers as predictors of colectomy; although there is some correlation with risk for colectomy, the predictive value of these markers is poor.[98] Other markers, including plasma cytokines—interleukin (IL)-1B, IL-6, IL-8, and tumor necrosis factor-α (TNF-α)—have not been found to be associated with risk of UC relapse.[99,100]

In CD, serum levels of ILs have also been studied. Even though higher concentrations of these markers correlate with the risk of relapse, their role in disease prognosis and their clinical application are limited.[101,102]

Fecal Markers

Stool biomarkers have been studied to evaluate their ability to predict the level of gastrointestinal tract inflammation and disease phenotype.[103] Several markers have been described to date. Calprotectin is a calcium-binder protein found in neutrophils. High levels of fecal calprotectin correlate with higher relapse rates in both UC and CD.[79,104,105] Lactoferrin is an iron-binding glycoprotein found in the secretory granules of neutrophils that has also been found to predict relapse in IBD.[105]

M2-pyruvate kinase (M2-PK) and S100A12 are 2 other fecal inflammatory markers that have been proposed for clinical use in IBD. M2-PK is an enzyme that participates in the production of adenosine triphosphate and can be found at high levels in patients with IBD. S100A12 is a protein expressed by activated granulocytes that are involved in the innate immune response.[106,107] In a prospective, multicenter study, Turner and coworkers found that, while M2-PK can predict intravenous corticosteroid treatment failure in severe UC, S100A12 was not found to have any predictive utility.[108]

Genetic Markers

The development of IBD is determined by the influence of the environment in a genetically susceptible individual. Multiple genes have been associated with the risk of developing IBD, but only a few genes have been linked with the development of a more complicated disease course.[109]

The most studied gene in IBD is *NOD2/CARD15*. Several mutations in this gene have been found to predict the development of small bowel stenosis and the need for early surgery in CD.[110-114] Among the most analyzed polymorphisms, 3020insC and G908R have been associated with stricturing disease in CD, and the 3020insC polymorphism has also been linked with the need for surgery.[115] Studies have failed to find a clear relationship between *NOD2/CARD15* polymorphisms and the likelihood of response to anti-TNF agents.[109,112]

The *ATG16L1* gene encodes for a protein that participates in autophagy.[116] Mutations in this gene have been associated not only with stricturing disease but also with perianal involvement in CD.[115,117]

The multidrug resistance 1 gene (*MDR1*) encodes a glycoprotein expressed in the bowel epithelium and lymphocytes that transports substrates (including drugs) across the cell membrane.[118] Mutations in the *MDR1* gene have been associated not only with more severe IBD but also with resistance to treatment.[119]

Finally, multiple studies have observed a relationship between TNF-α gene polymorphisms and lack of response to infliximab, but results of these studies have been variable.[21] By using microarray technology, Arijs and coworkers compared mucosal expression of messenger RNA in patients with UC who responded to infliximab versus expression in patients who did not respond.[120] Nonresponders expressed higher levels of genes involved in the inflammatory pathway.[120]

Conclusion

Predicting prognosis in patients with IBD is not easy. The pathophysiology of IBD is extremely complex, as multiple environmental factors interact with the genotype of an individual to cause expression of disease. The ability to predict which patients will develop aggressive disease and target more intensive, early treatment to that group would be invaluable.

Clinical variables, phenotypes of disease, serologic and fecal markers, and genetic tests are available, but unfortunately none of them is highly predictive when used alone. Biologic and genetic markers are currently being developed, and some of them may prove to be highly predictive; however, clinical indices are still superior today, as they are more accessible and cost-effective. Endoscopic criteria (particularly mucosal healing) have also been shown to be helpful for predicting prognosis, which raises the question of whether clinicians should be aiming for symptomatic remission or endoscopic remission. Further studies are warranted to assess whether the previously mentioned prognostic variables improve decision-making and affect patient outcomes.

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