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Crohn's Disease
Prognostic Serological Marker Profile

Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disease causing considerable morbidity with a prevalence of 26 to 199 cases per 100,000 in North America.[1] The etiology of CD remains unclear, but it is thought to be caused by a combination of genetic, environmental, and immunoregulatory factors that lead to a wide variety of clinical presentations and manifestations.[2]

In order to help discern the individual patient's clinical course a classification system was created that subcategorizes disease behavior to noncomplicated disease (nonstricturing and nonpenetrating) or complicated disease (stricturing or penetrating) and also subcategorizes age at diagnosis and disease location.[3] Due to the clinical variability of the disease there is no single test for the diagnosis, prognosis, and assessment of CD activity and severity. The physician, therefore, must rely on a combination of symptoms, clinical examination, laboratory indices, radiology, endoscopy with histology, and (most recently) serological marker assays in order to choose the best treatment management scheme for the individual patient.[2-4]

The management of CD includes a variety of pharmacological and surgical interventions and depends on disease location, severity, and complications.[4, 5] There are numerous pharmacological/biological treatments available for CD patients. For patients with mild disease, physicians typically prescribe treatments that may have less efficacy but are associated with fewer side effects. As patients develop or present with more moderate to severe disease, treatments such as corticosteroids, immunomodulators, or biological therapy may be prescribed. These treatments are more efficacious but are associated with more serious side effects.

Given the heterogeneous nature of CD, the choice of therapy should be tailored to the patient's clinical course, and predictors of prognosis are necessary.[6] Glycomind's Crohn's disease prognostic profile using the IBDX serology panel employs serological markers that have been associated with more aggressive CD disease and aids in the prediction of the clinical course of CD patients.[7-11]

Marker Origin Related to Pathophysiology

Cellular and humoral immune responses rely heavily on interactions between glycans and specific glycan-binding proteins.[12] IBDX serological antibodies respond to cell surface glycan antigens. gASCA and AMCA antibodies are directed against mannan antigens, which are found in the cell wall of the yeast *S cerevisiae*.[7-9] ALCA, ACCA, Anti-L, and AMCA also appear to be directed against glycans found in the cell wall of the pathogenic fungus *Candida albicans*.[13] Furthermore, these antibodies were found to associate with CD susceptible mutations in pattern recognition receptor genes.[14] Most notable is that the antibodies included in the profile were reported as being elevated in serum of CD patients with more aggressive disease. Most recent study showed that besides bacterial dysbiosis, a distinct fungal microbiota dysbiosis in IBD characterised by alterations in biodiversity and composition. Moreover, a disease-specific inter-kingdom network alterations in IBD, suggesting that, beyond bacteria, fungi such as Saccharomyces cerevisiae and Candida albicans play a role in IBD pathogenesis.[15]

Stratifying CD Phenotypes

The Crohn's Disease Prognostic Profile is a serological marker profile based on the detection of circulating antibodies directed against glycans. The panel includes:

- ACCA -Antichitobioside Carbohydrate Antibodies
- ALCA -Antilaminaribioside Carbohydrate Antibodies
- AMCA-Antimannobioside Carbohydrate Antibodies
- gASCA-Anti-*Saccharomyces cerevisiae* Antibodies
- Anti-L-Anti-*Laminarin* Antibodes

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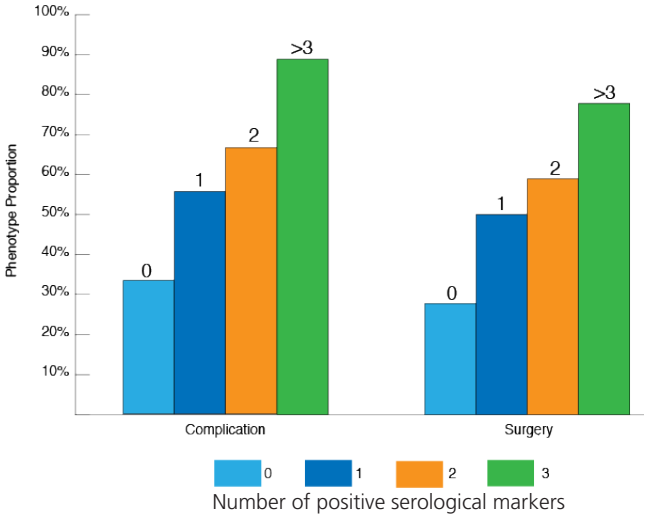
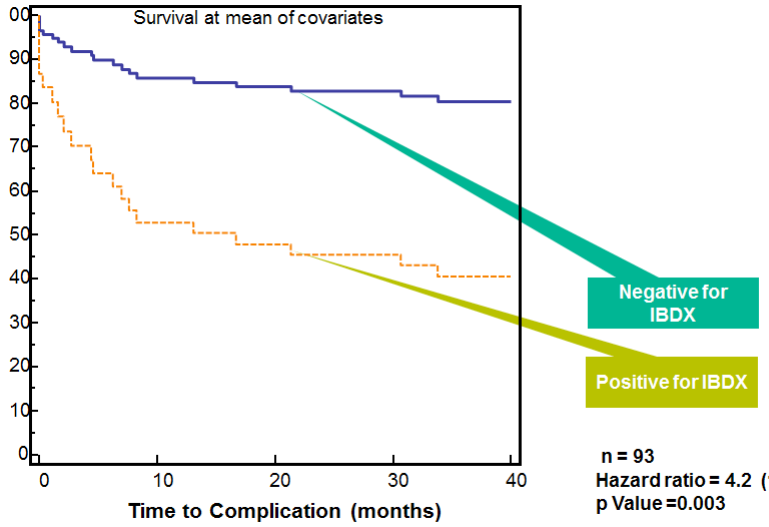


*adopted from Reider et. al. 2010 IBD 16 (2) 263-274



*adopted from Reider et al. 2010 IBD 16(8), 1367-1375

Patients positive for two or more IBDX Antibodies:

- **70% are likely to have complicated disease[8]**
- **60% are likely to require abdominal surgery[8]**

Patients positive for three or more IBDX Antibodies:

- **90% are likely to have complicated disease[8]**
- **80% are likely to require abdominal surgery[8]**

Chron's disease patients positive for at least two IBDX antibodies are likely to progress faster[4]

The IBDX antibodies are detected in patient serum or plasma by an indirect solid-phase enzyme-linked immunosorbent assay (ELISA).ALCA, ACCA, and AMCA were found to be positive in approximately 44% of ASCA-negative CD patients.[7] The Crohn's Disease Prognostic Profile panel of antibodies can be used by physicians to aid in stratifying patients already diagnosed with CD. The panel should not be used as a sole decision tool for deciding on a CD patient's treatment plan, but it should be used in conjunction with other clinical data and tests such as natural history of the patient's disease, family history, patient smoking status, and endoscopy results. CD patients are considered to b at greater risk for disease complication (stricturing or penetrating or surgery intervention if they are positive for two or more serological markers. Patients who had antibody response to two or more markers of complicated disease (OR: 3.12, 95% CI 2.27 to 4.29, p<0.0001), need for CD-related abdominal surgery (OR: 2.81, CI 2.07 to 3.80, p< 0.0001) and ileal involvement (OR: 2.19, 95% CI 1.50 to 3.30, p=0.0001) compared to patients with one or no positive antibody.[8]

In another cohort similar results were reported, whereas patients who had antibody response to two or more markers had an increased risk of complicated disease (OR: 2.92, 95% CI 1.92 to 4.46, p<0.0001), need for CD-related abdominal surgery (OR: 2.55, 95% CI 1.68 to 3.87, p<0.0001) and ileal involvement (OR: 2.16, 95% CI 1.35 to 3.43, p=0.007) compared to patients with no positive antibodies.[9] IBDX antibodies were also shown to be able to predict patients who are at a higher risk for first complication (HR: 2.8 to 3.1, p<0.007)[10]

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