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Family History and Serology Predict Crohn's Disease after Ileal Pouch-Anal Anastomosis for Ulcerative Colitis

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Abstract

Purpose—About 5 to 10 percent of patients undergoing ileal pouch-anal anastomosis with a diagnosis of ulcerative colitis are subsequently diagnosed with Crohn's disease. Preoperative predictors for Crohn's disease post-ileal pouch anal-anastomosis have not been prospectively defined.

Methods—Two hundred thirty-eight consecutive patients with ulcerative colitis or indeterminate colitis undergoing ileal pouch anal-anastomosis were prospectively enrolled into a longitudinal database. Clinical factors were assessed perioperatively. Serum drawn pre-operatively was assayed for anti-*Saccharomyces-cerevisiae*, anti-outer membrane porin-C, anti-CBir1, and perinuclear antineutrophil cytoplasmic antibody using enzyme-linked immunosorbent assay. Crohn's disease was defined by small-bowel inflammation proximal to the ileal pouch or a perianal fistula identified at least 3 months after ileostomy closure. Predictors were assessed in a multivariate Cox proportional hazards model to predict the rate of Crohn's disease after ileostomy closure.

Results—Sixteen patients (7 percent) were diagnosed with Crohn's disease; median time to Crohn's disease was 19 months (range, 1-41 months). Significant factors for postoperative Crohn's disease after ileal pouch anal-anastomosis included family history of Crohn's disease (hazard ratio 8.4, 95 percent confidence interval (CI) 2.96-24.1, $p < 0.0001$) and anti-*Saccharomyces-cerevisiae* -IgA seropositivity (hazard ratio 3.14, 95 percent CI 1.1-9.81, $p = 0.04$). Crohn's disease developed in only 8 of 198 (4 percent) patients without these predictors vs. 8 of 40 (20 percent) in those with at least one of these factors ($p = 0.002$). The cumulative risk of Crohn's disease among patients with 2 risk

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factors (67 percent) was higher than in patients with either risk factor (18 percent) or neither risk factor (4 percent, $p < 0.001$).

Conclusion—Patients with ulcerative colitis and indeterminate colitis with a family history of Crohn's disease or preoperative anti-*Saccharomyces-cerevisiae*-IgA seropositivity are more likely to be diagnosed with Crohn's disease after ileal pouch anal-anastomosis.

Keywords

Ileal pouch-anal anastomosis; Crohn's disease; ulcerative colitis; inflammatory bowel disease; indeterminate colitis; serology; pANCA; ASCA; OmpC

Introduction

Ileal pouch-anal anastomosis (IPAA) has become the standard operative approach for patients requiring colectomy for ulcerative colitis (UC) or in selected patients with indeterminate colitis (IC). Despite excellent functional results and high patient satisfaction,^{1, 2} about 5-10 percent of patients develop Crohn's disease (CD) of the pouch.³⁻⁸ Although many patients with CD of the pouch can be effectively treated medically, some require local remedial surgery or permanent fecal diversion.^{9, 10}

Although there is a body of literature examining the outcome of CD patients undergoing IPAA, ^{11, 12} little is known about the development of postoperative CD after IPAA for patients with either UC or IC. Several retrospective studies have attempted to identify risk factors for the development of CD.^{8, 13-16} A recent prospective clinical analysis identified that both a longer duration of IPAA and smoking were potential risk factors for CD of the pouch.¹⁷ However, this study is limited by referral center bias at a specialized 'Pouchitis Clinic'.

Serologic immune markers have been associated with inflammatory bowel disease (IBD). Perinuclear antineutrophil cytoplasmic antibodies (pANCA) are found in 60 to 80 percent of UC patients.¹⁸⁻²⁰ P-ANCA is also present in 15 to 25 percent of patients with CD, where it is associated with a 'UC-like' clinical picture.²¹ Anti-*Saccharomyces cerevisiae* antibodies (ASCA) are found in approximately 60 percent of CD patients.^{22, 23} While serum pANCA and ASCA are the best studied serologic markers for IBD, antibodies against the outer membrane porin C (anti-OmpC) of *Escherichia coli* and anti-CBir1 are also found in about 50 percent of patients with CD and to a lesser degree in UC patients.^{24, 25} The value of these disease markers in predicting CD development after IPAA has not been defined.

In this prospective study, we investigated the association of preoperative clinical and serologic factors with the development of CD after IPAA in a longitudinally followed cohort of consecutive UC and IC patients operated on by a single surgeon.

Methods

Study Population

Consecutive UC or IC patients requiring colectomy for medically unresponsive disease or dysplasia over the eight-year period ending December 2005 were studied. All research related activities were approved by the Cedars-Sinai Medical Center Institutional Review Board. Complete mucosectomy was performed in all patients. All patients had a temporary diverting ileostomy constructed at the time of pouch creation. Patients were seen for follow-up examinations (including pouchoscopy) every three months for the first year after stoma closure and yearly afterwards.

Assessment of Clinical Characteristics

Detailed clinical profiles assessing demographic information and characteristics of the disease and its treatment were prospectively collected using chart review and patient interview immediately after colectomy and at routine postoperative visits. Demographic information included patient age at surgery, gender, smoking history, and length of follow-up after surgery. Patients who smoked at the time of surgery and/or after colectomy were considered to be smokers. Both current smokers and ex-smokers comprised the smoking patient group. Disease characteristics examined included disease duration and extent, presence of extraintestinal manifestations (EIM), backwash ileitis, detailed family history of inflammatory bowel disease (IBD), and type of colitis (UC vs. IC). Disease duration referred to the time interval between IBD diagnosis and the date of colectomy. Anatomic location of disease was grouped postoperatively into categories of pancolitis, left-sided colitis, and proctitis. EIMs noted before colectomy included primary sclerosing cholangitis (PSC), skin lesions (pyoderma gangrenosum, erythema nodosum), bone/joint disease (arthritis, ankylosing spondylitis, sacroileitis) or eye disease (uveitis, episcleritis) considered by the investigators and the patients' physicians to be manifestations of IBD. The diagnosis of PSC was based on clinical findings and confirmed with liver biopsy and/or ERCP. Backwash ileitis was defined by macroscopic or histologic inflammation restricted to the distal 3 cm of the terminal ileum not thought to be CD. Treatment characteristics included the nature of medical therapy before colectomy (steroids alone vs. the use of other immunomodulators) and the indications for surgery (medically-refractory disease vs. dysplasia/cancer). Blood drawn on the day before surgery was analyzed for platelet count (normal range $150 \times 10^9/\text{L}$ to $450 \times 10^9/\text{L}$) using standard automated laboratory techniques.

Family History of IBD

Family history was initially obtained by patient interview and confirmed among those patients who consented for separate genetics investigation at Cedars-Sinai Medical Center. When relatives reported to have either UC or CD were either not participants in our local genetics projects or not patients of our own hospital, we evaluated their diagnoses by asking the index patients detailed information regarding the symptoms, treatment, and course of disease in their relatives. Only relatives in whom we could confirm a diagnosis of UC or CD were regarded as having either disease. A patient with a family history of both UC and CD would be considered to have both a family history of IBD as well as a family history of CD. Because of the stronger genetic influence from first-degree relatives (in contrast with that from more distant family members), an individual 'family history score' (FHS) was calculated as follows: $\text{FHS} = [2 \times (\text{number of affected first-degree relatives}) + 1 \times (\text{number of second-degree relatives})]$. FHS for a group of patients was calculated by dividing the aggregate FHS sum by the total number of patients in that group. This scoring measure was designed to provide a greater weight to the potential genetic influence from a first-degree relative. Thus, a patient with an affected parent (first-degree relative) and uncle (second-degree relative) would have an $\text{FHS}=3$, while a patient with 2 affected siblings but no other affected relatives would have an $\text{FHS}=4$. FHS was not included in the multivariate model.

Diagnosis of Ulcerative and Indeterminate Colitis

Clinical, endoscopic, and pathologic criteria were reviewed in all patients to determine if they were UC, IBD-U, or IC. Clinically, UC patients had no perianal disease, and endoscopic and histologic features included continuous inflammation extending proximally from the dentate line. All patients underwent radiologic evaluation with small bowel follow-through to exclude small-bowel disease. Patients with histologic granulomata were excluded. Additionally, the diagnosis was revisited upon review of intraoperative findings and pathologic evaluation of the resected specimen. Using the Montreal classification²⁶, patients were classified as having

IBD-type unclassified (IBD-U) or postoperative IC when they had clinical features of UC with some features suggestive but not diagnostic of CD. Preoperative features of IBD-U included skip lesions possibly related to medical therapy, distant history of an anal fistula or ulcer, or small bowel inflammation more than 3 cm proximal to the ileocecal valve. Postoperative features of IC included gross or microscopic transmural colonic inflammation or discontinuous histologic involvement of the colon possibly related to medical therapy. We used an inclusive definition of postoperative IC that included all patients with IBD-U in addition to those patients with UC that were reclassified as IC on the basis of colectomy specimen. Patients with extensive small bowel inflammation, active anal disease, or those with granulomatous inflammation on histopathologic examination were deemed to have CD and were excluded from study analysis.

Diagnosis of Crohn's Disease after Surgery

CD after IPAA was diagnosed either when mucosal inflammation (5 or more ulcers) involved the small bowel mucosa proximal to the ileal pouch²⁷ anytime after surgery and/or when a pouch fistula or other perianal complication developed more than 3 months after ileostomy closure. Stool studies were obtained in all cases to exclude infection. Time to diagnosis of CD was defined as the time period from ileostomy closure. Patients in whom the ileostomy was not closed, those who did not consent to have blood drawn for research purposes and those using nonsteroidal anti-inflammatory drugs were excluded from analysis.

Serologic Analysis

Serum was drawn immediately before colectomy, coded, and stored for future analysis. All sera were analyzed in a blinded fashion by Prometheus Laboratories (San Diego, California, USA) or performed at Cedars-Sinai Medical Center.

Stored serum was analyzed for expression of IBD-associated antibodies, including ASCA, anti-OmpC, anti-CBir1, and pANCA in a blinded fashion by enzyme-linked immunosorbent assay (ELISA), as previously described.^{25, 28} Antibody levels were determined and results expressed as ELISA units (EU/ml) which are relative to a Cedars-Sinai laboratory (OmpC-IgA and anti-CBir1) or a Prometheus Laboratory standard (San Diego, CA; ASCA-IgA and IgG) derived from a pool of patient sera with well-characterized disease found to have reactivity to these antigens. Qualitative positivity to any antibody was defined as being greater than cut-off values greater than 2 standard deviations above mean control titers for each assay. Qualitative positivity for ASCA was considered separately for having positivity to either or both of the IgA or IgG antibodies. The magnitude of quantitative antibody seroreactivity was logarithmically transformed and standardized. All assays were performed blindly without knowledge of patient clinical characteristics. Similarly, clinical course after IPAA was assessed without knowledge of the patient's serologic profile.

Statistical Analysis

Statistics were performed using JMP®, version 5.1 and SAS®, version 8.2 (both from the SAS Institute, Carey, NC). For continuous covariates, medians were compared with the use of Wilcoxon nonparametric tests. Categorical variables were compared with the use of chi squared or Fishers' exact test. Serologic statistical analyses were performed for log-transformed quantitative sero-reactivity, as well as for qualitative sero-reactivity using prespecified thresholds described above (positive/negative). The Cox proportional hazards model was used to simultaneously evaluate all factors; those factors with simultaneous $p < 0.15$ were retained in the final model after stepwise backward elimination. Hazard ratios (HR) and 95 percent confidence intervals (CI) were calculated. The performance of the multivariate model was evaluated with the Concordance (C) statistic. The risk of CD development over time was plotted using the Kaplan-Meier method. The log-rank test was used to compare these incidence curves

to assess the role of serologic risk factors in the cumulative incidence of CD over time. All hypothesis testing was two-sided with p value of less than 0.05 considered statistically significant.

Results

Patient Demographics and Clinical Characteristics

Patient demographic and clinical characteristics of the 238 study patients are shown in Table 1. All patients underwent stoma closure and no patients were 'lost' to follow-up. A majority of the patients were male. Of the 199 patients with medically unresponsive disease, 34 (17 percent) were steroid-dependent and 165 (83 percent) were refractory to other immunosuppressive therapy, including thiopurines ($n=145$), cyclosporin ($n=96$) and/or infliximab ($n=30$). Forty patients (17 percent) had EIMs associated with their disease, including arthritis ($n=26$), skin disease ($n=7$), PSC ($n=5$), or uveitis ($n=1$). Twenty-four of the 174 patients (14 percent) with pancolitis had backwash ileitis. Fifty-seven patients (25 percent) had a family history of IBD. There were 29 subjects with affected first-degree relatives and 28 additional patients with more distant affected relatives. Among 20 patients with a family history of CD, 7 (35 percent) had affected first-degree relatives and 13 (65 percent) had more distant affected family members. Although the majority of patients had surgery for medically-refractory disease, IPAA was performed in 26 patients for dysplasia and 13 patients for an established carcinoma.

Ulcerative Colitis, IBD-Unspecified, and Indeterminate Colitis

Surgery was initially performed for UC in 195 patients (82 percent) and IBD-U in 43 patients (18 percent). Within the IBD-U group were patients with discontinuous colonic inflammation ($n=18$), small bowel inflammation not considered to be backwash ileitis ($n=12$), deep ulceration noted during colonoscopy or leading to colon perforation ($n=7$), and prior history of anal disease ($n=6$). Twenty-seven of the UC patients (14 percent) were reclassified as IC after colectomy. Reasons for a postoperative change of diagnosis from UC to IC included histopathologic evidence of transmural inflammation on the colectomy specimen ($n=23$) and severe mesenteric thickening noted at surgery ($n=4$). In total, there were 168 patients (71 percent) with UC and 70 patients (29 percent) with either IBD-U or IC.

Crohn's Disease Development

After a median follow-up time after ileostomy closure of 47 months (range, 1 to 142 months), 16 patients developed CD, representing an overall incidence of 7 percent. Median time to diagnosis of CD was 19 months (range, 1 to 41 months). One patient developed CD of the pouch and proximal limb of the ileostomy one month after IPAA creation. All of the remaining patients developed CD more than 3 months after ileostomy closure. CD was diagnosed on the basis of afferent ileal limb disease ($n=12$) and new perianal disease ($n=4$). Ten patients were maintained on immunosuppressive therapy, two patients were controlled with antibiotics alone, and four patients required a diverting ileostomy to control persistent symptoms after failing aggressive immunosuppression.

Serologic Analysis

Serum pANCA, anti-OmpC, ASCA and anti-CBir1 were detected in 171 patients (72 percent), 53 patients (22 percent), 48 patients (20 percent), and 46 patients (19 percent), respectively (Table 3). Within the 48 ASCA-positive patients were 32 patients who were ASCA IgA+, 16 patients who were ASCA IgG+ and 7 patients who expressed both forms of ASCA. There were no significant differences in clinical characteristics in patients who were serologically-positive compared to patients who did not express these markers (data not shown).

Clinical and Serologic Factors Predicting Postoperative CD

Demographic and clinical factors among the CD cases and non-CD controls in the entire patient group are shown in Table 1. Fifty percent of the CD group had a family history of IBD as compared with 22 percent of those without CD ($p=0.07$). Patients developing CD after IPAA however were significantly more likely to have a family history of CD ($p=0.0008$) vs. patients who did not develop postoperative CD. Family history score was also higher in those with a CD diagnosis ($p=0.03$). There were no other significant differences in demographic and clinical factors between the CD and non-CD patient groups.

The association between serologic marker expression and clinical course after IPAA is shown in Table 2. Univariate analysis of quantitative and qualitative seroreactivity to IBD-associated antibodies did not show significant differences among those with CD as compared to non-CD controls. However, ASCA IgA positivity and pANCA levels were increased among those with CD ($p=0.055$ and 0.12 , respectively). OmpC levels tended to be higher among those without CD ($p=0.10$).

The Cox multivariate proportional hazards model retained 3 factors with $p<0.15$, including family history of CD, ASCA IgA+, and pANCA+ (Table 3). The 2 significant factors that were independently associated with the development of CD after IPAA were family history of CD (hazard ratio (HR)=8.4; 95 percent CI, 2.96-24.1; $p<0.0001$) and ASCA-IgA+ (HR=3.14; 95 percent CI, 1.1 - 9.81; $p=0.04$). CD developed in only 8 of 198 (4 percent) patients without these predictors vs. 8 of 40 (20 percent) in those with at least one of these factors. This difference in CD development after IPAA response based on family history of CD and preoperative ASCA IgA serologic expression was highly significant ($p=0.002$). The positive predictive value (PPV) and the negative predictive value (NPV) of family history of CD in our population were 0.30 and 0.95, respectively. Those for ASCA IgA-positivity were 0.17 and 0.94, respectively. When both factors were present, PPV and NPV were 0.67 and 0.94.

The cumulative incidence of developing CD over time in patients with these two risk factors is shown in Figure 1. The cumulative risk of developing CD in patients who did not have a risk factor ($n=198$) was only 4 percent. Compared to the no risk factor patient group, patients with a single risk factor ($n=37$) had a significantly higher cumulative incidence of CD (16 percent) ($p=0.004$). Furthermore, patients with 2 or more risk factors ($n=3$) had a significantly higher cumulative incidence of CD (67 percent) compared to patients with only one risk factor ($p=0.02$) or no risk factor ($p<0.001$).

There was no significant difference in the incidence of CD development between the UC (7 percent), IBD-U (5 percent) and IC (7 percent) patient groups. Using multivariate analysis of clinical and serologic factors in the UC patient subgroups, we found that although family history of CD was again predictive (HR=6.8; 95 percent CI 2.01-20.5; $p=0.003$) of postoperative CD, the association of ASCA-IgA positivity approached but did not reach statistical significance (HR=3.5; 95 percent CI 0.94-10.4; $p=0.06$). No statistical modeling was performed in the IBD-U or IC patient groups because of the paucity of CD events in these groups.

Discussion

The development of CD after IPAA is associated with both a significantly lower quality of life²⁹ and higher incidence of ultimate pouch failure.^{5, 6, 8, 9, 30, 31} The identification of possible predictors of CD in these patients is therefore important for proper surgical management and prognostication for these patients. We identified two independently significant predictors of postoperative CD: a family history of Crohn's disease and seroreactivity to ASCA IgA. Furthermore, we found that those with a postoperative change in

diagnosis had a median of only 5 months from ileostomy closure, before the diagnosis of CD was made. The study described herein was prospective in design, all procedures were performed by a single surgeon in one hospital, and all patients had consistent, longitudinal follow-up.

Published retrospective studies have attempted to identify risk factors placing patients at risk for the development of CD. Potential risk factors have included IC,^{8, 13-16} female gender and perianal disease.⁴ Many of these previous reports have been hampered by their retrospective design, suboptimal patient follow-up and referral center bias. A recent prospective study at a tertiary Pouchitis Clinic showed that both a long duration of IPAA and active smoking were risk factors for postoperative CD development and that family history of IBD was not a significant factor; serologies were not assessed in that study.¹⁷ While smoking is an established risk factor for Crohn's disease, we did not find smoking to be a risk factor for CD. The reason for this is unclear, although the overall incidence of 'smokers' in our UC population is roughly half that of the population studied by Shen *et al*.¹⁷ suggesting a potential type II error in the present study.

The prevalence of CD after IPAA in the present study (7 percent) compares favorably with the 1 percent to 14 percent reported in other series.³⁻⁸ Mechanisms accounting for the change in diagnosis from UC to CD are unknown. Although most likely related to the inability to accurately distinguish the two diseases before surgery, particularly in the fulminant phase,¹³ it is interesting to speculate that the change in diagnosis reflects an inherent biologic behavior. In a large population study, almost 3 percent of nonoperated UC patients evolved into CD,³² similar to the incidence of CD development in the current prospectively followed patient cohort. A recent report by Melmed and colleagues³³ showed that two clinical factors (nonbloody diarrhea and weight loss >10 percent at initial clinical presentation) independently predict a change in diagnosis in the unoperated UC patient. No significant association was found however with any serologic expression and a diagnosis change. In the present study, CD development after IPAA was influenced family history of CD and ASCA IgA seropositivity. It therefore appears that unoperated and operated UC patients have different risk factors for CD development. This finding reinforces the theory that UC is likely a heterogeneous inflammatory disorder with different immunopathogenetic mechanisms. A better understanding of these processes may help gain insight into the etiology of UC and perhaps provide possible therapeutic options for its treatment.

The incidence of a family history of IBD in this study (24 percent) compares favorably to another surgical study which commented on this clinical factor.³⁴ A novel finding in the current study however was the significant influence of family history of CD on the eventual development of CD after surgery. While Shen *et al*.¹⁷ did not find an association between "family history of IBD" with CD post-IPAA, we found that detailing the history further by type of IBD was strongly associated with a postoperative change in diagnosis. Furthermore, our findings are corroborated by our utilization of the family history score that attributed a higher weight to first-degree family members as compared to more distant relatives with IBD. A positive family history has been found to be the strongest risk factor for the initial development of IBD, and first-degree family members are at highest risk.^{35, 36} Preoperative evaluation of UC patients contemplating an IPAA should therefore include a detailed family medical history to provide the best possible prognostic information to patients and their families.

In addition to the use of clinical, endoscopic, radiologic and histologic evaluation, specific seromarker expression has been used to help classify patients with IBD as either UC or CD. In the surgical patient, preoperative seromarker expression has been associated with chronic pouch inflammation after IPAA for IC³⁷ and the development of chronic pouchitis after IPAA

in UC.³⁸ Little is known regarding the significance of serologic studies and the development of CD after IPAA. In the only study to date of a highly selected group of UC patients, Dendrinis and coworkers showed that ASCA-positive patients were at greater risk of developing postoperative pouch fistulas (and presumably CD) than ASCA-negative patients.³⁹ This study did not comment on the distribution of IgA and IgG ASCA subtypes, and sera were drawn at varying timepoints after surgery. Data from the current study showed a strong association between preoperative ASCA-IgA expression and the onset of CD after IPAA in patients with UC and IC. Although the mechanisms by which ASCA-IgA positivity influences postoperative inflammation are unknown, it is well known that ASCA expression is associated with aggressive disease course, including the need for small bowel surgery, in both adults and children with CD.^{21, 28, 40} Serologic testing should therefore also be strongly considered in the preoperative evaluation of patients requiring IPAA.

There are three milestones when the diagnosis of CD should be entertained in a UC or IC patient undergoing IPAA, namely before colectomy, after histologic review of the resected specimen, and finally after ileostomy closure. Although the presence of granulomas is conclusive,⁴¹ many studies have also included 'minor' pathologic criteria such as transmural inflammation, discontinuous disease, and fissuring ulcers in the surgical specimen to establish the diagnosis of CD immediately after colectomy.^{7, 9, 12, 15, 16, 34, 39, 42-47} We consider patients with these minor criteria to have IC and not CD since these features can not only be observed in fulminant UC but may also reflect treatment effect. Furthermore, we found no significant difference in clinical outcome (i.e., CD development) after IPAA between the UC, IBD-U, and IC patient subgroups. Patients with preoperative clinical features of UC who have minor CD features on the colectomy specimen appear to have an uncomplicated course after IPAA, confirming the results of other investigators.^{10, 12, 44, 46, 48} In order to introduce uniform diagnostic criteria, we recommend that future studies examining the results of IPAA in CD patients only include IBD patients with strictly defined characteristics of CD, *i.e.* granulomas on endoscopic biopsies or in the resected specimen, those with active anal disease, or patients with significant small bowel inflammation.

Older studies suggested that most patients who develop CD in their pouch required fecal diversion for symptom control.^{10, 11, 42} One-quarter of the patients with CD in this study required a permanent diverting ileostomy, corresponding well to the 34 percent stoma rate noted in another more recent study.⁷ Two publications in the last few years have demonstrated that the majority of patients who develop CD after IPAA do not require fecal diversion as they can be successfully managed using medical measures alone.^{49, 50} These results can only be expected to improve with the increasing use of potent therapies such as biologic agents.

What implications do our findings have on a physician counseling a patient with UC who is facing colectomy? While it is unlikely that the presence of one of these two predictors would alone alter a decision to undergo IPAA, prognostication of outcomes might be modified in the patient with ASCA seropositivity or a family history of CD, to include the possibility of postoperative CD and its inherent risk for pouch failure. In addition, close attention to a thorough preoperative diagnostic work-up to exclude CD is warranted among those with risk factors. Finally, postoperative evaluation for CD among symptomatic patients after IPAA may be warranted so that CD can be correctly diagnosed and treated.

In summary, this study comprehensively describes clinical and serologic risk factors for CD among patients with UC or IC undergoing IPAA. Our findings suggest that among these patients, those with a family history of CD or those who have seropositivity for ASCA IgA should be carefully evaluated for CD preoperatively. Validation of our findings will help determine the prognosis of patients with these identified risk factors in order to optimize preoperative counseling.

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References

1. Fazio VW, Ziv Y, Church JM, et al. Ileal pouch-anal anastomoses complications and function in 1005 patients. *Ann Surg* Aug;1995 222(2):120–127. [PubMed: 7639579]
2. Meagher AP, Farouk R, Dozois RR, Kelly KA, Pemberton JH. J ileal pouch-anal anastomosis for chronic ulcerative colitis: complications and long-term outcome in 1310 patients. *Br J Surg* Jun;1998 85(6):800–803. [PubMed: 9667712]
3. Dayton MT, Larsen KR, Christiansen DD. Similar functional results and complications after ileal pouch-anal anastomosis in patients with indeterminate vs ulcerative colitis. *Arch Surg* Jun;2002 137(6):690–694. [PubMed: 12049540]discussion 694-695
4. Alexander F, Sarigol S, DiFiore J, et al. Fate of the pouch in 151 pediatric patients after ileal pouch anal anastomosis. *J Pediatr Surg* Jan;2003 38(1):78–82. [PubMed: 12592624]
5. Fazio VW, Tekkis PP, Remzi F, et al. Quantification of risk for pouch failure after ileal pouch anal anastomosis surgery. *Ann Surg* Oct;2003 238(4):605–614. [PubMed: 14530732]discussion 614-607
6. Tulchinsky H, Hawley PR, Nicholls J. Long-term failure after restorative proctocolectomy for ulcerative colitis. *Ann Surg* Aug;2003 238(2):229–234. [PubMed: 12894016]
7. Braveman JM, Schoetz DJ Jr, Marcello PW, et al. The fate of the ileal pouch in patients developing Crohn's disease. *Dis Colon Rectum* Oct;2004 47(10):1613–1619. [PubMed: 15540289]
8. Hahnloser D, Pemberton JH, Wolff BG, Larson DR, Crownhart BS, Dozois RR. Results at up to 20 years after ileal pouch-anal anastomosis for chronic ulcerative colitis. *Br J Surg* Mar;2007 94(3):333–340. [PubMed: 17225210]
9. Brown CJ, Maclean AR, Cohen Z, Macrae HM, O'Connor BI, McLeod RS. Crohn's disease and indeterminate colitis and the ileal pouch-anal anastomosis: outcomes and patterns of failure. *Dis Colon Rectum* Aug;2005 48(8):1542–1549. [PubMed: 15937625]
10. Peyregne V, Francois Y, Gilly FN, Descos JL, Flourie B, Vignal J. Outcome of ileal pouch after secondary diagnosis of Crohn's disease. *Int J Colorectal Dis* Feb;2000 15(1):49–53. [PubMed: 10766091]
11. Hyman NH, Fazio VW, Tuckson WB, Lavery IC. Consequences of ileal pouch-anal anastomosis for Crohn's colitis. *Dis Colon Rectum* Aug;1991 34(8):653–657. [PubMed: 1855421]
12. Regimbeau JM, Panis Y, Pocard M, et al. Long-term results of ileal pouch-anal anastomosis for colorectal Crohn's disease. *Dis Colon Rectum* Jun;2001 44(6):769–778. [PubMed: 11391134]
13. Koltun WA, Schoetz DJ Jr, Roberts PL, Murray JJ, Collier JA, Veidenheimer MC. Indeterminate colitis predisposes to perineal complications after ileal pouch-anal anastomosis. *Dis Colon Rectum* Oct;1991 34(10):857–860. [PubMed: 1914717]
14. Goldstein NS, Sanford WW, Bodzin JH. Crohn's-like complications in patients with ulcerative colitis after total proctocolectomy and ileal pouch-anal anastomosis. *Am J Surg Pathol* Nov;1997 21(11):1343–1353. [PubMed: 9351572]
15. Yu CS, Pemberton JH, Larson D. Ileal pouch-anal anastomosis in patients with indeterminate colitis: long-term results. *Dis Colon Rectum* Nov;2000 43(11):1487–1496. [PubMed: 11089581]
16. Delaney CP, Remzi FH, Gramlich T, Dadvand B, Fazio VW. Equivalent function, quality of life and pouch survival rates after ileal pouch-anal anastomosis for indeterminate and ulcerative colitis. *Ann Surg* Jul;2002 236(1):43–48. [PubMed: 12131084]
17. Shen B, Fazio VW, Remzi FH, et al. Risk factors for diseases of ileal pouch-anal anastomosis after restorative proctocolectomy for ulcerative colitis. *Clin Gastroenterol Hepatol* Jan;2006 4(1):81–89. [PubMed: 16431309]quiz 82-83
18. Saxon A, Shanahan F, Landers C, Ganz T, Targan S. A distinct subset of antineutrophil cytoplasmic antibodies is associated with inflammatory bowel disease. *J Allergy Clin Immunol* Aug;1990 86(2):202–210. [PubMed: 2200820]
19. Oudkerk Pool M, Ellerbroek PM, Ridwan BU, et al. Serum antineutrophil cytoplasmic autoantibodies in inflammatory bowel disease are mainly associated with ulcerative colitis. A correlation study

- between perinuclear antineutrophil cytoplasmic autoantibodies and clinical parameters, medical, and surgical treatment. *Gut* Jan;1993 34(1):46–50. [PubMed: 8432451]
20. Aitola P, Miettinen A, Mattila A, Matikainen M, Soppi E. Effect of proctocolectomy on serum antineutrophil cytoplasmic antibodies in patients with chronic ulcerative colitis. *J Clin Pathol* Jul; 1995 48(7):645–647. [PubMed: 7560172]
 21. Vasiliasukas EA, Plevy SE, Landers CJ, et al. Perinuclear antineutrophil cytoplasmic antibodies in patients with Crohn's disease define a clinical subgroup. *Gastroenterology* Jun;1996 110(6):1810–1819. [PubMed: 8964407]
 22. Quinton JF, Sendid B, Reumaux D, et al. Anti-Saccharomyces cerevisiae mannan antibodies combined with antineutrophil cytoplasmic autoantibodies in inflammatory bowel disease: prevalence and diagnostic role. *Gut* Jun;1998 42(6):788–791. [PubMed: 9691915]
 23. Sutton CL, Yang H, Li Z, Rotter JJ, Targan SR, Braun J. Familial expression of anti-Saccharomyces cerevisiae mannan antibodies in affected and unaffected relatives of patients with Crohn's disease. *Gut* Jan;2000 46(1):58–63. [PubMed: 10601056]
 24. Cohavy O, Bruckner D, Gordon LK, et al. Colonic bacteria express an ulcerative colitis pANCA-related protein epitope. *Infect Immun* Mar;2000 68(3):1542–1548. [PubMed: 10678972]
 25. Targan SR, Landers CJ, Yang H, et al. Antibodies to CBir1 flagellin define a unique response that is associated independently with complicated Crohn's disease. *Gastroenterology* Jun;2005 128(7): 2020–2028. [PubMed: 15940634]
 26. Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: Report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol* Sep;2005 19(Suppl A):5–36. [PubMed: 16151544]
 27. Wolf JM, Achkar JP, Lashner BA, et al. Afferent limb ulcers predict Crohn's disease in patients with ileal pouch-anal anastomosis. *Gastroenterology* Jun;2004 126(7):1686–1691. [PubMed: 15188163]
 28. Mow WS, Vasiliasukas EA, Lin YC, et al. Association of antibody responses to microbial antigens and complications of small bowel Crohn's disease. *Gastroenterology* Feb;2004 126(2):414–424. [PubMed: 14762777]
 29. Shen B, Fazio VW, Remzi FH, et al. Comprehensive evaluation of inflammatory and noninflammatory sequelae of ileal pouch-anal anastomoses. *Am J Gastroenterol* Jan;2005 100(1): 93–101. [PubMed: 15654787]
 30. Foley EF, Schoetz DJ Jr, Roberts PL, et al. Rediversion after ileal pouch-anal anastomosis. Causes of failures and predictors of subsequent pouch salvage. *Dis Colon Rectum* Aug;1995 38(8):793–798. [PubMed: 7634973]
 31. Tekkis PP, Heriot AG, Smith O, Smith JJ, Windsor AC, Nicholls RJ. Long-term outcomes of restorative proctocolectomy for Crohn's disease and indeterminate colitis. *Colorectal Dis* May;2005 7(3):218–223. [PubMed: 15859957]
 32. Henriksen M, Jahnsen J, Lygren I, et al. Change of diagnosis during the first five years after onset of inflammatory bowel disease: Results of a preprospective follow-up study (the IBSEN Study). *Scandinavian Journal of Gastroenterology* 2006;1(1):1–7.epub preview 2006
 33. Melmed GY, Elashoff R, Chen GC, et al. Predicting a change in diagnosis from ulcerative colitis to Crohn's disease: a nested, case-control study. *Clin Gastroenterol Hepatol* May;2007 5(5):602–608. [PubMed: 17478347]
 34. Rudolph WG, Uthoff SM, McAuliffe TL, Goode ET, Petras RE, Galandiuk S. Indeterminate colitis: the real story. *Dis Colon Rectum* Nov;2002 45(11):1528–1534. [PubMed: 12432302]
 35. Sachar DB. Crohn's disease: a family affair. *Gastroenterology* Sep;1996 111(3):813–815. [PubMed: 8780588]
 36. Annese V, Andreoli A, Astegiano M, et al. Clinical features in familial cases of Crohn's disease and ulcerative colitis in Italy: a GISC study. Italian Study Group for the Disease of Colon and Rectum. *Am J Gastroenterol* Oct;2001 96(10):2939–2945. [PubMed: 11693330]
 37. Hui T, Landers C, Vasiliasukas E, et al. Serologic responses in indeterminate colitis patients before ileal pouch-anal anastomosis may determine those at risk for continuous pouch inflammation. *Dis Colon Rectum* Jun;2005 48(6):1254–1262. [PubMed: 15868228]

38. Fleshner PR, Vasiliauskas EA, Kam LY, et al. High level perinuclear antineutrophil cytoplasmic antibody (pANCA) in ulcerative colitis patients before colectomy predicts the development of chronic pouchitis after ileal pouch-anal anastomosis. *Gut* Nov;2001 49(5):671–677. [PubMed: 11600470]
39. Dendrinos KG, Becker JM, Stucchi AF, Saubermann LJ, LaMorte W, Farraye FA. Anti-*Saccharomyces cerevisiae* antibodies are associated with the development of postoperative fistulas following ileal pouch-anal anastomosis. *J Gastrointest Surg* Jul-Aug;2006 10(7):1060–1064. [PubMed: 16843878]
40. Dubinsky MC, Lin YC, Dutridge D, et al. Serum immune responses predict rapid disease progression among children with Crohn's disease: immune responses predict disease progression. *Am J Gastroenterol* Feb;2006 101(2):360–367. [PubMed: 16454844]
41. Price AB. Overlap in the spectrum of non-specific inflammatory bowel disease--'colitis indeterminate'. *J Clin Pathol* Jun;1978 31(6):567–577. [PubMed: 670413]
42. Sagar PM, Dozois RR, Wolff BG. Long-term results of ileal pouch-anal anastomosis in patients with Crohn's disease. *Dis Colon Rectum* Aug;1996 39(8):893–898. [PubMed: 8756845]
43. Mylonakis E, Allan RN, Keighley MR. How does pouch construction for a final diagnosis of Crohn's disease compare with ileoproctostomy for established Crohn's proctocolitis? *Dis Colon Rectum* Aug; 2001 44(8):1137–1142. [PubMed: 11535853]
44. de Oca J, Sanchez-Santos R, Rague JM, et al. Long-term results of ileal pouch-anal anastomosis in Crohn's disease. *Inflamm Bowel Dis* May;2003 9(3):171–175. [PubMed: 12792222]
45. Morpurgo E, Petras R, Kimberling J, Ziegler C, Galandiuk S. Characterization and clinical behavior of Crohn's disease initially presenting predominantly as colitis. *Dis Colon Rectum* Jul;2003 46(7): 918–924. [PubMed: 12847366]
46. Panis Y, Poupard B, Nemeth J, Lavergne A, Hautefeuille P, Valleur P. Ileal pouch/anal anastomosis for Crohn's disease. *Lancet* Mar 30;1996 347(9005):854–857. [PubMed: 8622390]
47. Deutsch AA, McLeod RS, Cullen J, Cohen Z. Results of the pelvic-pouch procedure in patients with Crohn's disease. *Dis Colon Rectum* Jun;1991 34(6):475–477. [PubMed: 2036927]
48. Guindi M, Riddell RH. Indeterminate colitis. *J Clin Pathol* Dec;2004 57(12):1233–1244. [PubMed: 15563659]
49. Colombel JF, Ricart E, Loftus EV Jr, et al. Management of Crohn's disease of the ileoanal pouch with infliximab. *Am J Gastroenterol* Oct;2003 98(10):2239–2244. [PubMed: 14572574]
50. Kooros K, Katz AJ. Infliximab therapy in pediatric Crohn's pouchitis. *Inflamm Bowel Dis* Jul;2004 10(4):417–420. [PubMed: 15475750]

Figure 1.

Effects of family history of Crohn's disease (CD) and expression of anti-*Saccharomyces-cerevisiae* (ASCA)-IgA on the cumulative incidence of CD after ileal pouch-anal anastomosis (IPAA). The risk of developing CD after IPAA among patients with both factors was significantly higher than in patients with neither factor or only one factor.

Table 1
Patient Characteristics and Descriptive Statistics

	Whole Group (n=238)	CD Patients (n=16)	Non-CD Patients (n=222)	p value*
Sex (M/F)	137/101	8/8	129/93	0.6
Median age (years)	38	38	38	0.46
Median disease duration (months)	60	66	60	0.63
Disease extent (n)				
Pancolitis	174	12 (75)	162 (73)	
Left-sided	61	4 (25)	57 (26)	0.89
Proctitis	3	0	3 (1)	
Preoperative medication (n)				
Steroids	34	0	34 (15)	0.13
Immunomodulators	165	14 (88)	151 (68)	
Extraintestinal disease (percent)	40	5 (31)	35 (16)	0.16
Arthritis	26	3	23	
PSC	5	1	4	
Other	9	1	8	
Backwash ileitis (percent)	24 (10)	0	24 (11)	0.38
Remote or Current Smoking (percent)	72 (30)	3 (19)	59 (27)	0.77
Never smoked	166	13	153	
Remote smoker	59	2	57	
Current Smoking	13	1	12	
Family history of IBD (percent)	57	8	49	
Ulcerative colitis	37	2 (13)	35 (16)	0.91
Crohn's disease	20	6 (38)	14 (6)	0.0008
Family History Score	0.47	0.50	0.21	0.03
Type of Colitis (percent)				
Preoperative UC	195 (82)	14 (88)	181 (82)	1.0
IBD-U	43 (18)	2 (13)	41 (18)	
Postoperative IC	70 (29)	5 (31)	65 (29)	
Indication for IPAA (percent)				
Medically unresponsive	199 (84)	14 (88)	185 (83)	1.0
Cancer/Dysplasia	39 (16)	2 (12)	37 (17)	
Platelet count (range)	$354 \times 10^9/L$ (103 - 895)	$325 \times 10^9/L$ (103 - 895)	$310 \times 10^9/L$ (177 - 607)	0.56
Median duration of follow-up (months)		78	46	0.16

PSC primary sclerosing cholangitis

IPAA ileal pouch-anal anastomosis

IBD inflammatory bowel disease

UC ulcerative colitis

IBD-U Inflammatory bowel disease, type unclassified

IC indeterminate colitis

Table 2
Serologic Expression in Patients with and without Postoperative CD

	CD Patients (n=16)	Non-CD Patients (n=222)	p value
pANCA			
Positive	14 (88)	157 (71)	0.25
Mean level	1.64	1.49	0.12
ASCA			
IgA+	4 (25)	19 (9)	0.06
IgG+	1 (6)	15 (7)	0.94
Either IgA+ or IgG+	4 (25)	28 (13)	0.24
Both IgA+ and IgG+	1 (6)	6 (3)	0.38
Mean level IgA+	0.81	0.69	0.32
Mean level IgG+	0.92	0.81	0.40
anti-OmpC			
Positive	2 (13)	51 (23)	0.53
Mean level	0.97	1.13	0.10
anti-CBir1			
Positive	2 (13)	44 (20)	0.74
Mean level	1.18	1.25	0.51
Mean number of all seromarkers *	1.43	1.29	0.55
Mean number of CD markers ⁺	0.63	0.88	0.32

All levels expressed after logarithmically transformed

Values in parentheses expressed as percent

* pANCA, ASCA, anti-OmpC, anti-CBir1

⁺ ASCA, anti-OmpC, anti-CBir1

CD Crohn's disease

pANCA Perinuclear antineutrophil cytoplasmic antibodies

ASCA Anti-Saccharomyces cerevisiae antibodies

Omp-C Outer membrane porin-C

CD Crohn's disease

Table 3

Cox Proportional Hazards Multivariable Model for Prediction of CD after IPAA *

	Hazard ratio (HR)	95 percent Confidence Interval	p value
Family history of CD	8.44	2.96 - 24.1	< 0.0001
ASCA-IgA+	3.14	1.1 - 9.81	0.04
pANCA+	3.82	0.85 - 17.2	0.08

CD Crohn's disease

*
all items with simultaneous p<0.15 were retained