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Predictors of Proctocolectomy in Children with Ulcerative Colitis

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Abstract

Objectives—Few clinical predictors are associated with definitive proctocolectomy in children with ulcerative colitis (UC). The purpose of this study was to identify clinical predictors associated with surgery in children with UC using a disease specific database.

Methods—Children diagnosed with UC at age <18y were identified using the Pediatric Inflammatory Bowel Disease Consortium (PediIBDC) database. Demographic and clinical variables from January 1999–November 2003 were extracted alongside incidence and surgical staging.

Results—Review of the PediIBDC database identified 406 children with UC. Approximately half were female (51%) with an average age at diagnosis of 10.6±4.4 years in both boys and girls. Average follow-up was 6.8 (±4.0) years. Of the 57 (14%) who underwent surgery, median time to surgery was 3.8 (IQR 4.9) years after initial diagnosis. Children presenting with weight loss (HR 2.55, 99% CI 1.21–5.35) or serum albumin <3.5g/dL (HR 6.05, 99% CI 2.15–17.04) at time of diagnosis, and children with a first-degree relative with UC (HR 1.81, 99% CI 1.25–2.61) required earlier surgical intervention. Furthermore, children treated with cyclosporine (HR 6.11, 99% CI

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3.90–9.57) or tacrolimus (HR 3.66, 99% CI 1.60–8.39) also required earlier surgical management. Other symptoms, laboratory tests and medical therapies were not predictive for need of surgery.

Conclusions—Children with UC presenting with hypoalbuminemia, weight loss, a family history of UC and those treated with calcineurin inhibitors frequently require restorative proctocolectomy for definitive treatment. Early identification and recognition of these factors should be used to shape treatment goals and initiate multidisciplinary care at the time of diagnosis.

Introduction

The natural course of UC in children is often more severe than in their adult counterparts (1). Twenty to thirty percent of all cases of inflammatory bowel disease (IBD) are diagnosed during childhood (2), with ulcerative colitis (UC) affecting 22% of all children diagnosed with IBD(1). For the pediatric patient, UC is a lifelong disease making optimization of medical and surgical therapy paramount. Although significant advances have been made in medical management of UC, a large proportion of children ultimately require restorative proctocolectomy for definitive control of their disease.

Early studies of UC in children attempted to define severity of illness and risk of colectomy based on the number of bloody stools per day. This measurement can be highly subjective and difficult to replicate. While more recent reports have found stooling patterns to be highly predictive of failure of corticosteroid management (3), these reports relate to hospitalized acute severe colitis with short term outcome evaluation, which differs from the majority of children with UC who are ambulatory and receive care over a longer duration of time. It is possible that a more accurate definition of disease severity would take into account patient history and laboratory findings in addition to stooling patterns. Preliminary studies in France and Japan have identified such clinical predictors of colectomy in adults with UC, but few studies have been performed in the United States, and fewer in children (1, 4).

Unfortunately, children may present to the surgeon after a prolonged course of failed medical management and immunosuppression, with surgery rates as high as 60% in children with steroid refractory UC (5). Patients with a prolonged severe course of medically refractory disease often require prolonged hospitalization and experience increased post-operative complications (6). Furthermore, while previous reports have explored indicators for surgery in children with Crohn’s disease (7), few studies have identified predictors of surgery in children with UC. The primary goal of this study was to utilize a large, multi-center disease specific database in order to identify clinical predictors of surgical intervention in children with ulcerative colitis.

Materials and Methods

Patient Population

This retrospective cohort study was performed after obtaining IRB approvals from each individual institution and the Pediatric Inflammatory Bowel Disease Consortium (PediIBDC). Data was obtained from the PediIBDC Database, a registry established in January 2000 which collects demographic, clinical, and epidemiologic data reported by

investigators at hospitals specializing in pediatric IBD care. The data used for our study reflected information submitted from seven regional IBD centers, including the current authors' associations and the Barbara Bush Children's Hospital at Maine Medical Center (8). Subjects eligible for inclusion in the database include all patients with IBD (ulcerative colitis, Crohn's disease, and inflammatory bowel disease-unspecified (IBD-U)) diagnosed before 18 years of age and actively followed in a pediatric gastroenterology clinic at one of the participating hospitals. Both the initial and final diagnosis of IBD are recorded in the database. Children with both existing and newly diagnosed IBD are prospectively enrolled. Data for patients examined in this report was retrieved from January 1999 through November 2003. This time period represents the original and most complete version of the PediIBDC dataset. Eligible patients included all children enrolled in the database with a final diagnosis of UC at the time of enrollment through November 2003. UC is defined in the database as continuous disease confined to the colon and no evidence of small intestinal disease (other than backwash ileitis) on biopsy or radiographically (8). Diagnosis of UC was present for each patient at the initiation of and through the entire course of clinical care. For example, if a patient was diagnosed with Crohn's disease discovered on surgical pathology after colectomy, they were not included in the cohort.

Predictor and Outcome Variables

Demographic information including age at diagnosis, gender, race, BMI and time interval prior to surgery was extracted from the database. Clinical history including family history of IBD (including Crohn's disease, ulcerative colitis and IBD-U) and preoperative medical therapy (5-ASA, 6-MP, azathioprine, azulfidine, cyclosporine, infliximab, methotrexate, steroids and tacrolimus) was also retrieved. Symptoms present at time of diagnosis of inflammatory bowel disease including abdominal pain, abnormal labs, diarrhea, joint pain, fatigue, fever, nausea, poor growth, dermatologic complications, rectal bleeding, vomiting and weight loss were also included in our analysis. Initial laboratory values measured at the time of diagnosis including serum ESR, CRP, albumin, and hemoglobin were also evaluated. Although many of the lab values evaluated vary with age and gender, clinically relevant lab cutoffs were defined (ESR >20 mm/h, CRP >5.0 mg/dL and hemoglobin <10 g/dL) as no significant association was appreciated on bivariate analysis of continuous lab values. Albumin was initially analyzed in the regression as a continuous variable but a cutoff of < 3.5 g/dL was later found to be statistically significant (see discussion below).

All potential predictors were evaluated at time of diagnosis. For children prospectively enrolled (those with new onset disease from January 1999- November 2003), time of diagnosis coincided with time of enrollment. For children retrospectively enrolled (those with existing disease diagnosed prior to Nov 1999), a retrospective chart review identifying the clinical encounter during which time they were diagnosed with UC was used to identify symptoms and lab values present at time of diagnosis. There was no missing data for any parameter in this cohort.

Statistical Methods

Bivariate statistical comparisons were made using χ^2 and Student T-statistics stratified by surgery. Factors associated with colectomy two years after diagnosis and overall colectomy

were identified using Cox proportional-hazards regression analysis. Patient demographics, clinical history, presenting symptoms and laboratory values were included in the models as covariates. Statistical analyses were performed using SAS version 9 (SAS Inc., Cary, NC) and Stata/IC version 10.1 (Stata Corp., College Station, TX). Because many variables were analyzed as potential surgical predictors, a p-value of <0.01 was considered significant to counter balance the risk of a Type I error due to multiple comparisons.

Results

Query of the PediIBDC Database yielded 406 children with ulcerative colitis eligible for inclusion (Table 1). Approximately half of the cohort was male (49%) and Caucasian (42%) with an average age at diagnosis of 10.6 ± 0.22 years. Of the 57 (14%) children who underwent colectomy, median time to surgery was 3.8 (IQR 4.9) years after diagnosis. Average follow-up was 6.8 (±4.0) years. One- and two-year colectomy rates were 4% (n=18) and 7% (n=30), respectively. Bivariate statistical comparisons of patient demographics, presenting symptoms and lab values stratified by surgery revealed there was a higher proportion of Hispanic (p=0.04) and Non-Caucasian children (p=0.042) in the surgical cohort, but these children represented a small minority of the overall population of this study. Additionally, there was a higher proportion of children presenting with weight loss at the time of initial diagnosis in the surgical cohort compared to the non-surgical cohort (p<0.006). Comparisons of family history and use of immunosuppressants stratified by surgery revealed that use of cyclosporine or tacrolimus (p<0.001 and p<0.001) at any time during medical treatment was also seen in a higher proportion in the surgical cohort..

Statistically significant clinical factors identified in bivariate analysis (weight loss at diagnosis, medical therapy) and factors thought to be clinically relevant (age, gender, Caucasian race, lab values present at time of diagnosis, family history of IBD) were included in the multivariate analysis (Table 2). Children presenting with weight loss (HR 2.55, p<0.001) or serum albumin <3.5g/dL (HR 6.05, p<0.001) at the time of diagnosis, and children with a first-degree relative with UC (HR 1.8, p<0.001) required earlier surgical intervention than children without these characteristics. Furthermore, children treated with cyclosporine (HR 6.1, p<0.001) or tacrolimus (HR 3.66, p<0.001) also required earlier surgical management of their UC compared to children not treated with calcineurin inhibitors. Of note, albumin <3.5gm/dL at time of diagnosis and having a first degree relative with UC were not predictive of two-year risk of colectomy while they were predictive of overall risk of colectomy. History of azathioprine (HR 0.06, 99% CI 0.01–0.27) or 6-mercaptopurine (HR 0.21, 99% CI 0.05–0.88) use was associated with a decreased two-year risk of colectomy while these factors did not impact overall risk of colectomy. Each factor predictive of overall colectomy was associated with an increased rate of two-year and overall colectomy (Table 3). However, for albumin <3.5 g/dL and having a first degree relative with UC, the risk of colectomy two years after diagnosis was notably attenuated (Figure 2).

Discussion

This is the first study to utilize a large, multi-center disease specific database in order to identify clinical predictors of colectomy in children with ulcerative colitis. Our analysis identified hypoalbuminemia and significant weight loss at time of diagnosis as predictive of earlier colectomy indicating that nutritional status and/or extent of protein losing enteropathy play an integral role in the clinical severity of UC in children. This finding underscores the importance of thoroughly assessing nutritional status at the time of diagnosis of UC. We also found that having a first degree relative with UC and previous use of cyclosporine and tacrolimus predicted an earlier need for surgery. Overall, our results indicate that children with more severe disease burden at time of diagnosis likely do not have sufficient physical reserve (i.e. low albumin, immunosuppression, muscle wasting), develop recalcitrant symptomatology and ultimately require colectomy for optimal disease control.

Poor nutritional status has previously been identified in the literature as predictive of clinical course in patients with UC. Low albumin levels after first induction therapy were reported by Shiga et al. to predict UC relapse and need for colectomy (4). However, Shiga et al.'s study did not find low albumin at time of diagnosis to be predictive of surgery. In our initial analysis, we examined albumin as a continuous variable and found that it was not independently predictive of colectomy. However, when albumin was analyzed as a dichotomous variable with a cutoff of <3.5 g/dL, albumin levels became significantly predictive in our model. This implies that once a nutritional threshold is passed, children with UC are likely not able to recover as robustly as their more healthy counterparts. Furthermore more than 20% of our subjects had an albumin <3.5 g/dL indicating that our cohort was likely to detect a difference between groups.

The greatest risk factor for developing UC in childhood is having a first degree relative with UC, albeit lesser than the genetic contribution observed in Crohn's disease (9, 10). Our results agree with previous reports that there is a hereditary component to UC, although the UC phenotype is likely more driven by environmental factors. The present findings imply that children with a first degree relative with UC likely have more severe clinical manifestations of UC thereby requiring colectomy at an earlier date. While multiple genetic contributors of ulcerative colitis have been established (11), the pathogenesis of ulcerative colitis is very likely multifactorial and those with a familial predisposition may express a more severe phenotype than those without a genetic contribution.

Children with a more severe disease burden typically require more potent immunosuppressive regimens and require colectomy at a higher rate. Tacrolimus and cyclosporine are used most commonly in steroid-refractory UC, so it was not surprising that use of these calcineurin inhibitors was highly predictive of early colectomy in the cohort. Our results imply that calcineurin inhibitors are likely a proxy for disease severity. This is in agreement with prior studies reporting colectomy rates in up to 60% of children with steroid refractory UC treated with tacrolimus (5). Furthermore, our results also coincide with studies showing that azathioprine, 6-mercaptopurine and infliximab use do not predict colectomy (12). Of note, one limitation in our study is that use of infliximab for refractory

UC has increased in the past 10 years and the present study took place before this clinical trend was more established. Our findings, however, disagree with Tremaine et al.'s report of increased colectomy in patients receiving aminosalicylate, prednisone and azathioprine/6-mercaptopurine therapy (13). The final regression analysis in this latter study did not examine the use of more potent immunosuppressants such as cyclosporine and tacrolimus as the number of participants using these drugs was very small. Due to the exclusion of calcineurin inhibitors, it may be that maximal medical therapy was thereby defined as patients who received aminosalicylate, prednisone, azathioprine or 6-mercaptopurine. Patients receiving these drugs therefore had a more severe disease burden compared to the rest of their cohort and therefore were in higher proportion in the colectomy arm. Additionally, Tremaine conducted a single institution study in a predominantly adult population and therefore the external validity of the study's conclusions may be limited in the pediatric setting.

Factors predictive of two-year risk of colectomy did not entirely coincide with those predictive of overall risk of colectomy. Albumin <3.5gm/dL at time of diagnosis and having a first degree relative with UC were not predictive of two-year risk of colectomy while they were predictive of overall risk of colectomy. This implies that these factors may have less impact on short term risk of colectomy for children with UC but maintain significance when predicting overall risk of colectomy. Furthermore, history of use of azathioprine or 6-mercaptopurine was associated with a decreased two-year risk of colectomy while these factors did not impact overall risk of colectomy. This latter finding likely implies that use of azathioprine and 6-mercaptopurine may delay early disease progression significantly for children with UC but that overall, their long-term clinical benefit may be uncertain. Finally, weight loss at diagnosis and previous use of cyclosporine and tacrolimus remained significant predictors of both two-year and overall colectomy risk. This finding underscores the prognostic significance of a child's nutritional status at the time of diagnosis and also affirms the use of calcineurin inhibitors in this study cohort as the probable limit of medical therapy for UC prior to proceeding with colectomy.

Contrary to the most recent single-center report by Moore et al. (14), low hemoglobin and leukocytosis at the time of diagnosis did not predict colectomy in our analysis. This may be due to the abnormally high colectomy rate reported in Moore's cohort (16.7% at one year and 35.6% at three years). The overall cumulative rate of colectomy in children with UC is typically lower, with rates reported from 5–8% at one year after diagnosis, and up to 20% at five years (1, 15). The overall colectomy rate in our study was 14% with a median time to surgery of 3.8 years which is closer to reported average colectomy rates for children with UC. Due to the profound impact UC has on overall development and growth in children, we agree with the authors in concluding that creation of a risk stratification tool would facilitate counseling at time of diagnosis. However, the risk score calculated in their study may only be most applicable within their institution.

Unfortunately, patients with UC and their families often do not have an accurate understanding of what their medical treatment may entail (16). Knowledge of the clinical factors identified in this study will likely facilitate more accurate risk stratification at the time of diagnosis and throughout medical treatment. This will ultimately encourage earlier

preoperative counseling and surgical referral. Children undergoing restorative proctocolectomy for UC have a very high quality of life after surgery (17–19) and consideration of earlier surgical intervention for children with UC has been reported (20).

One limitation of this study is that our analysis did not incorporate more global measurements of disease severity such as the Pediatric Ulcerative Colitis Activity Index (PUCAI). First validated in 2007 (21), the PUCAI has been demonstrated to aid in determining timely introduction of second-line therapy in severe acute UC (22). Furthermore, the FDA recently endorsed the PUCAI as a substitute to endoscopic evaluation for the primary outcome measure in a pediatric clinical trial evaluating a 5-aminosalicylate (5-ASA) regimen. The PediIBDC dataset used for this study predates the PUCAI, and included only dichotomized information on stooling patterns as opposed to the numerical gradations found in the PUCAI. Non-invasive, global clinical assessments like the PUCAI are likely to have high predictive capabilities when determining need for colectomy in children with UC. Looking ahead towards future uses of the PediIBDC, now with 18 centers throughout the United States, Austria and Hungary submitting data, a richer source of data may lead to further findings.

Unfortunately, like much of the literature examining clinical predictors of colectomy in children with UC, the present study is also limited by the relatively low number of children undergoing colectomy in the cohort. This limits the external validity of our predictors and those identified by previous groups, which may explain why there is notable variation between studies. Our results highlight the fact that even within centers of excellence in pediatric IBD care, there are relatively low numbers of colectomies performed overall. This makes identifying reliable surgical predictors a challenge for anyone examining healthcare utilization for children with UC and highlights the increased need for large, trans-national, multi-institutional collaborations.

In conclusion, children with a more severe disease burden are more likely to undergo surgical management of their UC. Specifically, children presenting with clinical and laboratory evidence of malnutrition, those with a first degree family member with UC and those treated with calcineurin inhibitors have an increased likelihood of undergoing surgery. Early identification and recognition of these factors should be used to facilitate preoperative counseling and patient-based planning for medical and surgical care of children with UC.

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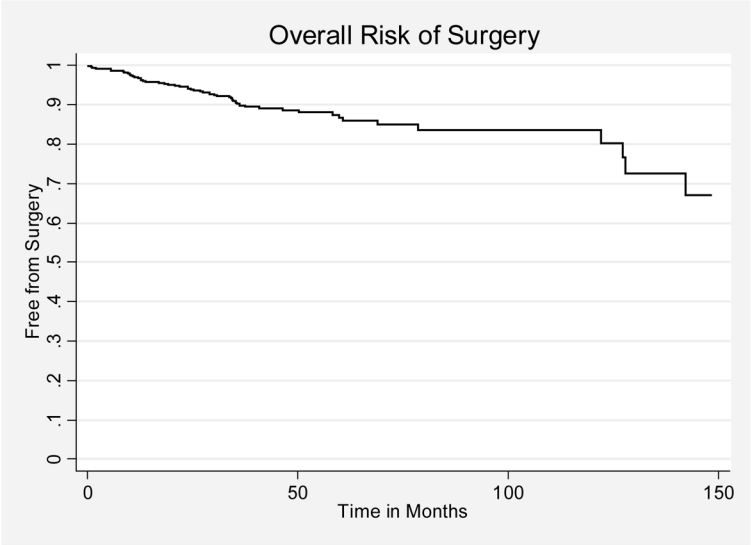

Figure 1.
Overall Predicted Risk of Colectomy for Entire Cohort

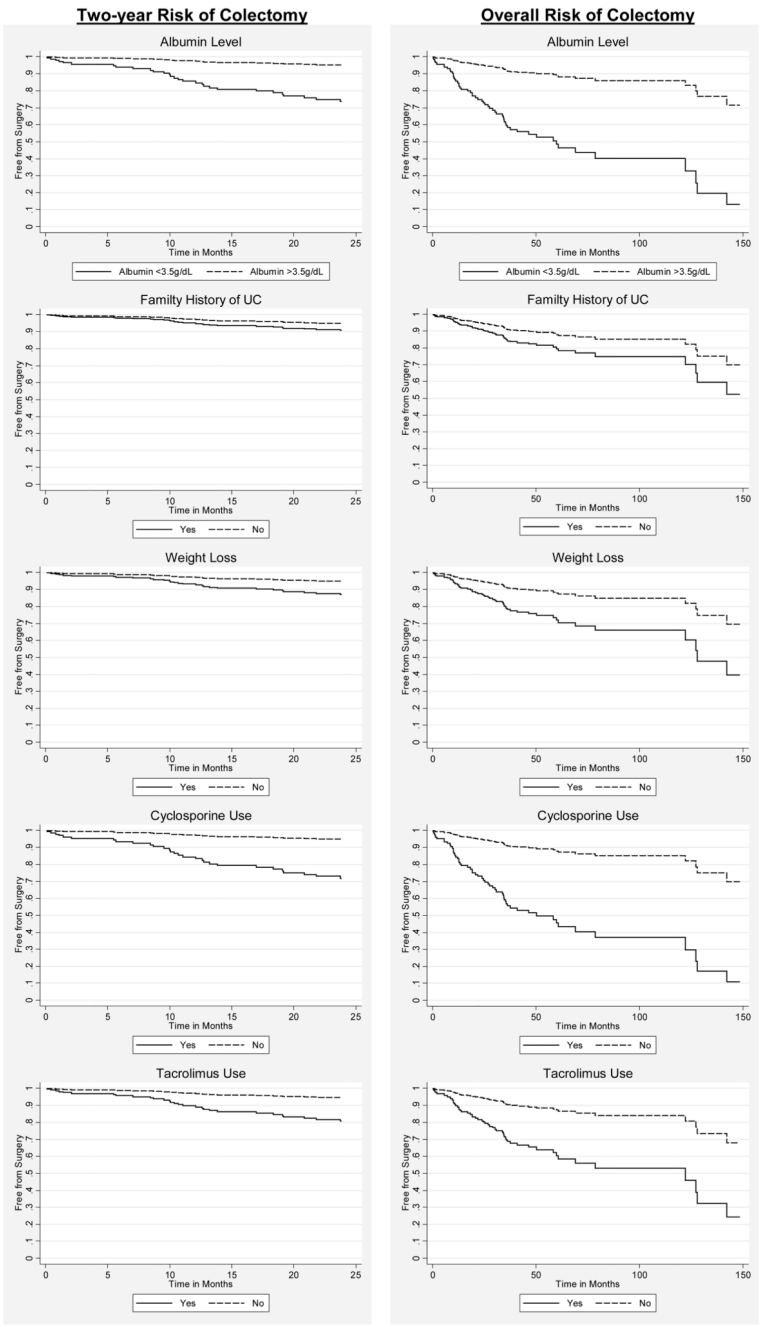

Figure 2.
Two-year and Overall Risk of Colectomy by Clinical Predictors

Table 1

Cohort Demographics and Clinical Factors Present at Time of Diagnosis

Demographics	Total N=406 (%)	No Surgery N=349 (%)	Surgery N=57 (%)	P-value
Male Gender	199 (49)	174 (49)	25 (44)	0.401
Race/Ethnicity				
Caucasian	331 (82)	283 (81)	48 (84)	0.573
Hispanic	16 (4)	11 (3.2)	5 (8.7)	0.043
African American	23 (5)	20 (5.7)	3 (5.3)	0.887
Other	36 (9)	35 (10)	1 (1.8)	0.042
Symptoms at Diagnosis				
Abdominal Pain	136 (33)	119 (34)	17 (30)	0.526
Diarrhea	170 (42)	143 (41)	27 (47)	0.364
Fatigue	24 (5.9)	22 (6.3)	2 (3.5)	0.407
Joint Pain	19 (4.7)	18 (5.2)	1 (1.8)	0.259
Fever	24 (5.9)	21 (6.0)	2 (3.5)	0.448
Nausea	13 (3.2)	12 (3.4)	1 (1.8)	0.503
Poor Growth	10 (2.4)	8 (2.3)	2 (3.5)	0.583
Rectal Bleeding	215 (53)	184 (53)	31 (54)	0.815
Skin Problem	3 (0.01)	3 (0.9)	0 (0)	0.482
Emesis	16 (3.9)	12 (3.4)	4 (7.0)	0.198
Weight Loss	43 (11)	31 (8.9)	12 (21)	0.006
BMI <18	127 (31)	110 (53)	17 (65)	0.247
Lab Values				
Albumin < 3.5 g/dL	41 (10)	31 (8.9)	10 (18)	0.044
Serum ESR >20 mm/h	86 (21)	78 (22)	8 (14)	0.154
Hemoglobin <10 g/dL	37 (9.1)	34 (9.7)	3 (5.3)	0.276
Serum CRP >5.0 mg/dL	14 (3.4)	11 (3.2)	3 (5.3)	0.418
Family History				
IBD	120 (30)	99 (28)	21 (37)	0.194
UC	77 (19)	62 (18)	15 (77)	0.127
UC in a 1st Degree Relative	38 (9.3)	29 (8.3)	9 (16)	0.072
Crohn's Disease	38 (9.3)	31 (8.9)	7 (12)	0.414
Colectomy	11 (2.7)	8 (2.3)	3 (5.3)	0.200
Medication History				
Acetylsalicylic Acid	149 (37)	125 (36)	24 (42)	0.361
6-Mercaptopurine	138 (34)	120 (34)	18 (32)	0.678
Azathioprine	59 (15)	48 (14)	11 (19)	0.271
Azulfidine	145 (36)	124 (36)	21 (37)	0.848
Methotrexate	13 (3.2)	9 (2.6)	4 (7.0)	0.078

Demographics	Total N=406 (%)	No Surgery N=349 (%)	Surgery N=57 (%)	P-value
Infliximab	33 (8.1)	27 (7.7)	6 (11)	0.475
Steroids	312 (77)	263 (75)	49 (86)	0.078
Calcineurin Inhibitors				
Cyclosporine	23 (5.7)	11 (3.2)	12 (21)	<0.001
Tacrolimus	11 (2.7)	5 (1.4)	6 (11)	<0.001

Table 2

Clinical Parameters Predictive of Colectomy Two Years after Diagnosis and Overall Risk of Colectomy

	Colectomy at Two Years			Overall Colectomy		
	HR	**P-Value**	**99% CI**	**HR**	**P-Value**	**99% CI**
Serum albumin < 3.5 g/dL	2.77	0.213	0.34–22.92	6.05	<0.001	2.15–17.04
Serum ESR >20 mm/h	0.39	0.121	0.08–1.87	0.36	0.073	0.09–1.55
Hemoglobin <10 g/dL	1.17	0.868	0.10–13.76	0.41	0.389	0.03–6.01
Serum CRP >5.0 mg/dL	2.49	0.200	0.397–15.67	2.75	0.045	0.75–10.15
1st Degree Relative with UC	1.44	0.205	0.69–3.01	1.81	<0.001	1.25–2.61
Family History of Crohn's Disease	1.30	0.556	0.41–4.13	1.58	0.141	0.71–3.51
Age at Diagnosis	1.00	0.912	0.92–1.08	0.99	0.837	0.87–1.13
Male Gender	0.98	0.959	0.19–5.05	0.91	0.827	0.30–2.78
Caucasian	0.96	0.902	0.39–2.34	1.14	0.620	0.57–2.29
Weight Loss at Diagnosis	4.01	<0.001	1.82–8.83	2.55	0.001	1.21–5.35
Medical Therapy						
Acetylsalicylic Acid	1.41	0.445	0.44–4.45	0.94	0.811	0.50–1.79
6-Mercaptopurine	0.21	0.005	0.05–0.88	0.39	0.022	0.14–1.12
Azathioprine	0.06	<0.001	0.01–0.27	0.59	0.170	0.22–1.58
Azulfidine	0.76	0.510	0.27–2.19	0.67	0.170	0.32–1.41
Methotrexate*	-	-	-	1.09	0.897	0.21–5.75
Infliximab	4.30	0.142	0.33–55.69	1.53	0.368	0.45–5.24
Steroids	0.94	0.934	0.16–5.55	1.41	0.570	0.29–6.95
Calcineurin Inhibitors						
Cyclosporine	20.94	<0.001	8.49–51.67	6.11	<0.001	3.90–9.57
Tacrolimus	3.62	<0.001	2.08–6.34	3.66	<0.001	1.60–8.39

HR – Hazard Ratio

CI – Confidence Interval

*Unable to evaluate risk of colectomy two years after diagnosis due to low number of events

Table 3

Two-year and Overall Colectomy Rates of Significant Clinical Predictors

		2-Year Colectomy Rate	Overall Colectomy Rate
Albumin < 3.5mg/dL	+	12.2%	24.4%
	−	6.9%	12.9%
Family History of UC	+	7.8%	19.5%
	−	7.3%	12.8%
Weight Loss at Diagnosis	+	14.0%	27.9%
	−	6.6%	12.4%
Cyclosporine	+	34.8%	52.2%
	−	5.7%	11.8%
Tacrolimus	+	18.2%	54.6%
	−	7.1%	12.9%