Biologics Delay Progression of Crohn's Disease, but Not Early Surgery, in Children

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BACKGROUND & AIMS: Up to 30% of patients with Crohn's disease (CD) require surgery within the first 5 years from diagnosis. We investigated the recent risk of bowel surgery in an inception cohort of pediatric patients with CD and whether early use of biologics (tumor necrosis factor antagonists) alters later disease course.

METHODS: We collected data from the Pediatric Inflammatory Bowel Disease Collaborative Research Group registry on 1442 children (age, ≤16 y) diagnosed with CD from January 2002 through December 2014. Data were collected at diagnosis, 30 days following diagnosis, and then quarterly and during hospitalizations for up to 12 years. Our primary aim was to determine the 10-year risk for surgery in children with CD. Our secondary aim was to determine whether early use of biologics (<3 mo of diagnosis) affected risk of disease progression.

RESULTS: The 10-year risk of first bowel surgery was 26%. The 5-year risk of bowel surgery did not change from 2002 through 2014, and remained between 13% and 14%. Most surgeries occurred within 3 years from diagnosis. The only predictor of surgery was disease behavior at diagnosis. CD with inflammatory behavior had the lowest risk of surgery compared to stricturing disease, penetrating disease, or both. We associated slowing of disease progression to stricturing or penetrating disease (but not surgery) with early use of biologics, but this effect only became evident after 5 years of disease. Our results indicate that biologics slow disease progression over time (hazard ratio, 0.85; 95% CI, 0.76–0.95).

CONCLUSIONS: In an analysis of data from a registry of pediatric patients with CD, we found that among those with significant and progressing disease at or shortly after presentation,

early surgery is difficult to prevent, even with early use of biologics. Early use of biologics (<3 mo of diagnosis) can delay later disease progression to stricturing and/or penetrating disease, but this affect could become evident only years after initial management decisions are made.

Crohn's disease (CD) is a chronic, frequently progressive inflammatory disorder characterized by an exaggerated mucosal immune response of the gastrointestinal system in a genetically susceptible individual.[1] CD and ulcerative colitis are the 2 major clinical phenotypes and affect approximately 1 in 200 people in the Western world, with an increasing prevalence in developing countries.[2–4] More than 50% of children are expected to develop complicated disease behavior (stricturing and/or penetrating behavior) by 5 years after diagnosis. Disease progression is worse in children compared with adults.[5]

The impact of medical management on disease progression and on surgical rates remains controversial.[6–26]

We previously reported, using data from this same patient registry, that the 5-year risk of bowel surgery in pediatric CD was 13.8%.[27] Retrospective pediatric studies have reported the 5-year risk of surgery to be between 14.2% and 34%.[28–30]

Our primary goal was to determine the 10-year surgical risk in children with CD. Our secondary goal was to determine if the early use of biologics (anti–tumor necrosis factor [TNF]α) influenced the risk of disease progression.

Materials and Methods

Study Population

The Pediatric Inflammatory Bowel Disease Collaborative Research Group registry was established by 26 North American pediatric inflammatory bowel disease (IBD) centers in 2002 to study the contemporary natural history of IBD. Newly diagnosed children 16 years of age and younger were enrolled. Patients were managed according to the practice of their individual physician. Uniform data were collected at diagnosis, 30 days after diagnosis, and then quarterly and during hospitalizations. Between January 2002 and December 2014, the registry enrolled 2116 pediatric IBD patients. The 1442 CD patients (68% of the total) constitute the study population of this report.

Outcomes

The outcomes of interest were time from diagnosis to (a) first intestinal surgery and (b) time to progression to stricturing and/or penetrating disease.

Description of Variables

Day 0 was defined as the date of initial diagnosis. The study end date for patients who had a CD-related surgery was the date of the first bowel surgery. The patients who did not have surgery had a study end date defined by the last quarter of follow-up evaluation, which also was used to censor values in time-to-event analyses. Bowel surgery was defined as intestinal resection with primary anastomosis or diverting ostomy (including subtotal and total colectomy) or strictureplasty. Other surgical procedures such as abdominal or perianal abscess drainage, or fistulotomy, were excluded. Family history of IBD was defined as having an affected mother, father, or sibling. Disease location was recorded within 30 days of diagnosis. The presence of endoscopic, histologic, or radiologic disease was recorded for the esophagus, gastroduodenum, jejunum, ileum, right colon, transverse colon, left colon, and for disease of the sigmoid colon and/or rectum. Disease location was classified as esophagus to jejunum, ileum to right colon, and transverse colon to rectum. Disease behavior was recorded at baseline, 30 days after diagnosis, and then quarterly. Disease behavior was defined as nonstricturing, nonpenetrating (inflammatory) disease (B1), stricturing (B2), and penetrating disease (B3). If a patient had a missing disease behavior for a particular quarter, the previous quarter's disease behavior was carried forward. Disease progression was defined as change from inflammatory only to either stricturing or penetrating or both. Regarding treatments, use of biologics was considered "early" if patients were started during the first quarter after diagnosis and completed their induction phase.[20] Immunomodulator use was defined if the use of 6-mercaptopurine, azathioprine, or methotrexate was documented for more than 1 quarter.

Statistical Methods

The Kaplan–Meier method was used to estimate survival functions with 95% CIs for first bowel surgery, first nonbowel surgery, and all first CD-related surgery. The Wilcoxon weighting of the chi-square statistic was used when comparing subsets of patients (weighting by changing sample size over time). The family wise α value was maintained at .05 across multiple comparisons using a Tukey adjustment of the raw P values. Proportional hazards (Cox) regression with time-varying covariates was used to model time-to-event outcomes with time-varying covariates. Disease severity was dummy coded

Table 1. Characteristics of the 1442 Patients With CD Diagnosed Between 2002 and 2014

Patient characteristics (N = 1442)

Age		
<6 y	56	3.90%
>6 y	1386	96.10%
Male sex	850	59%
Race		
Caucasian	1240	86.00%
African American	120	8.30%
Hispanic	24	1.70%
Asian	14	1.00%
Other	41	2.80%
Duration of follow-up period, y	Median, 4.7	Range, 1–12
Disease behavior at diagnosis		
B1, inflammatory	1291	89.50%
B2, stricturing	51	3.50%
B3, penetrating	27	1.90%
B2 and B3, stricturing and penetrating	11	0.70%
Timing of patients enrolled		
Enrolled before 2008	913	63.60%
Enrolled after 2008	529	36.70%

as stricturing or penetrating disease relative to inflammatory disease. Age was treated as continuous. All statistical analyses were performed using SAS version 9.4 (The SAS Institute, Inc, Cary, NC).

The protocol for the Pediatric Inflammatory Bowel Disease Collaborative Research Group registry was approved by the institutional review boards of all participating institutions, and informed consent/assent was obtained at the time of enrollment in the registry.

Results

Demographics

Demographics and disease characteristics for the 1442 CD patients enrolled in our study are shown in Table 1.

Risk of Crohn's Disease–Related Bowel Surgery

The Kaplan–Meier estimated risk of CD-related bowel surgery was 4% at 1 year, 13% at 5 years, and 26% at 10 years (Figure 1A). A total of 241 subjects underwent any type of surgery, 171 of these had bowel-related surgery (Table 2).

Figure 1B shows the monthly occurrence of the 171 bowel surgeries since the diagnosis. Two patients (1%) underwent bowel resection at diagnosis and were not included in our analyses, 66% of first bowel surgeries occurred within 36 months from diagnosis and the remaining 33% occurred over the last 84 months of the study.

Specific Risks for Surgery

Patients with stricturing and/or penetrating disease behavior at diagnosis were at a significantly higher risk of surgery over time ($P = .001$) (Figure 1C). Table 3 shows the risk of surgery for subsets of patients based on age, sex, and disease behavior. Overall, our analyses show that over time neither age of the patient ($P = .05$), disease location at diagnosis ($P = .8$), year of diagnosis ($P = .6$), nor presence of perianal disease ($P = .4$) predict differences in the risk of surgery. There was also no difference in the 5-year risk of surgery between patients who entered the study between 2002 and 2007 and those enrolled between 2008 and 2014 (Figure 2A), despite an increased use of biologics (Figure 2B) and the earlier initiation of biologics (Figure 2C).

No significant effects on disease progression were identified for nonbiologic treatments.

### Impact of Treatment on Disease Progression

Among patients who received a biologic agent at any time during the study (including the first 3 months), the risk of disease progression to stricturing or penetrating disease was statistically significantly reduced by biologic use as analyzed by proportional hazards (Cox) regression with biologic use as a time-varying covariate (hazard ratio, 0.85; 95% CI, 0.76–0.95; $P = .005$). No significant effect on surgery was found.

We examined the impact of biologics on disease progression in children with inflammatory (B1) disease. Of the 1291 patients with B1 disease at diagnosis, 145 patients had been started by their pediatric gastroenterologists on biologics within the first 3 months after diagnosis. Analyses (Figure 3A) of those who were treated early showed that disease progression from B1 to B2 or B3 after 5 years was decreased when compared with those not receiving early biologics ($P < .005$). No statistically significant effect was found on progression to surgery. We could not show a significant impact on any outcome in those groups in which the biologics were started after the first 3 months.

Interestingly, Figure 3B shows that patients with B1 disease, exposed to biologics in the first quarter of their disease, seemed more likely to have early surgery than those with B1 disease who were not started on biologics.

Discussion

The long-term effect of current IBD therapies, especially biologics, in children is not clear.[25,26] Recently Kugathasan et al[20] showed that children enrolled in the Risk Stratification and Identification of Immunogenic and Microbial Markers of Rapid Disease Progression in Children with Crohn's (RISK)[20] cohort, who received early (within the first 3 months from diagnosis) anti-TNFα therapy, showed a reduction in penetrating disease but
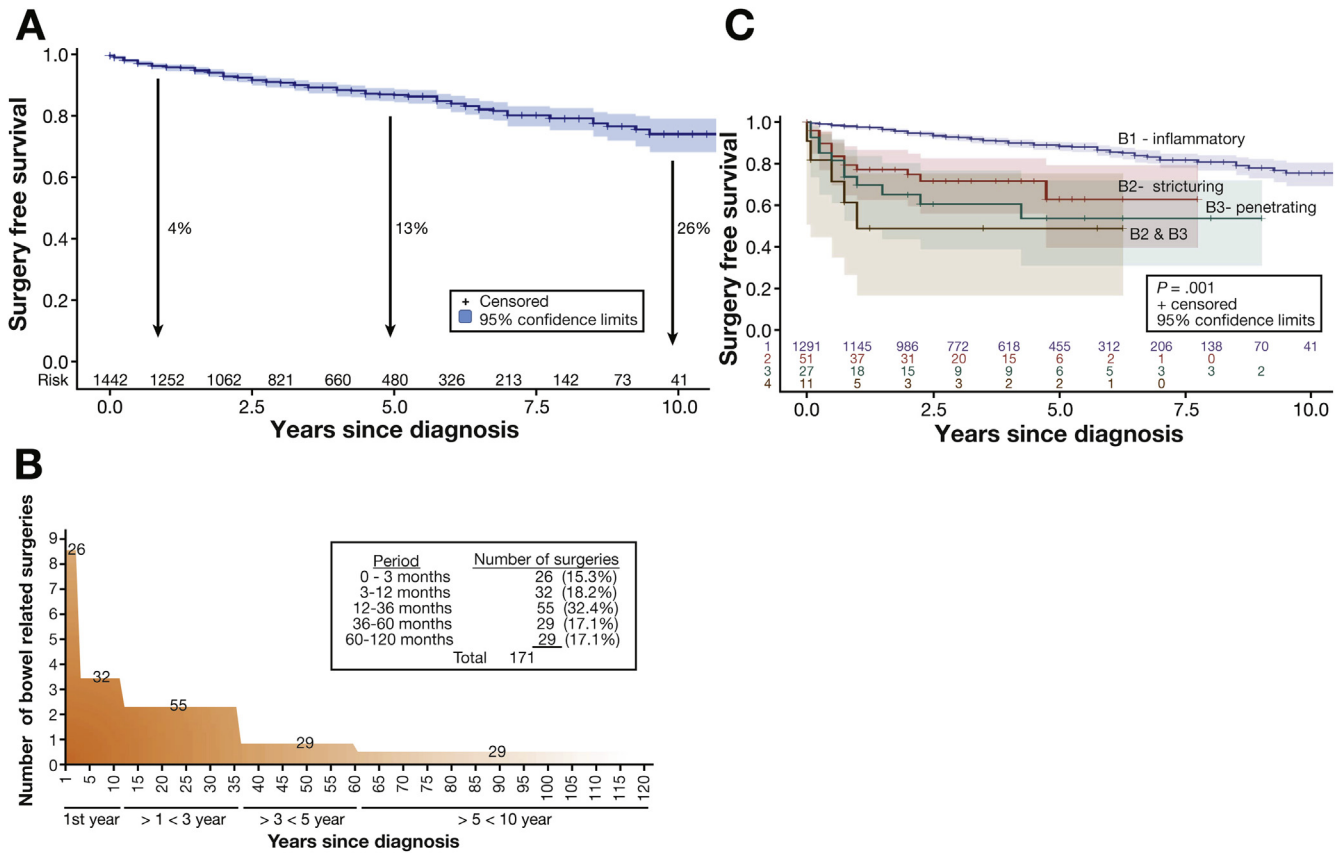
Figure 1. (*A*) Cumulative incidence of CD bowel-related surgery over 10 years. The x-axis represents the years since the diagnosis. The y-axis represents surgery-free survival. (*B*) Occurrences of bowel surgery since the diagnosis. The x-axis represents each month (and longer time periods) since the diagnosis. The y-axis represents the average number of surgeries performed per month in each time period (as recorded in the legend box). (*C*) Cumulative incidence of bowel surgery stratified by disease behavior at diagnosis. B1, inflammatory; B2, stricturing; B3, penetrating; B2 and B3, both stricturing and penetrating.

not stricturing disease within their first 4 years after diagnosis. Our study was not able to show an effect on disease progression within a timeframe similar to that of the RISK study. We were, however, able to show an overall effect on disease progression after 5 years. The difference reflects the differences in study populations. The RISK study[20] included only children who were still classified as having inflammatory (B1) disease at 90 days after diagnosis, excluding children with disease progression within 3 months of diagnosis. We included

those children. By including many children in whom early disease progression already had taken place, we lessened our ability to show an early effect on their group as a whole. More than 15% of our cohort already had their first bowel-related surgery in the first 90 days after diagnosis (Figure 1*B*).

Table 2. First Bowel Surgery: 171 Patients

Ileocecal resection	74
Segmental resection and anastomosis of small bowel	62
Segmental resection and anastomosis of large bowel	15
Ostomy of small bowel	18
Ostomy of large bowel	11
Strictureplasty	3
Colectomy with ostomy	1
Colectomy with IPAA	1

NOTE. Table does not include patients who had surgery related to intravenous access devices appendectomy, anal examination under anesthesia, washout of fistula, local abscess drainage, G-tube insertion, and so forth. Table may include more than 1 procedure at first surgery (ie, resection + ostomy). IPAA, ileal pouch–anal anastomosis.

Table 3. Risk of Surgery by Demographics of CD

| Kaplan–Meier estimated surgery rate	Time since diagnosis, y			
Risk of bowel surgery	1	5	10	Significance
Age at diagnosis				NS
<6 y	3.80%	13%	21.60%	
>6 y	4%	13%	26.90%	
Sex				NS
Males	3%	12.50%	20%	
Females	5%	14%	32%	
Disease behavior at diagnosis				P < .001
B1	2.50%	11.50%	24.50%	
B2	2.50%	37%	—	
B3	30%	46%	46%	
B2 and B3	50%	51%	–	
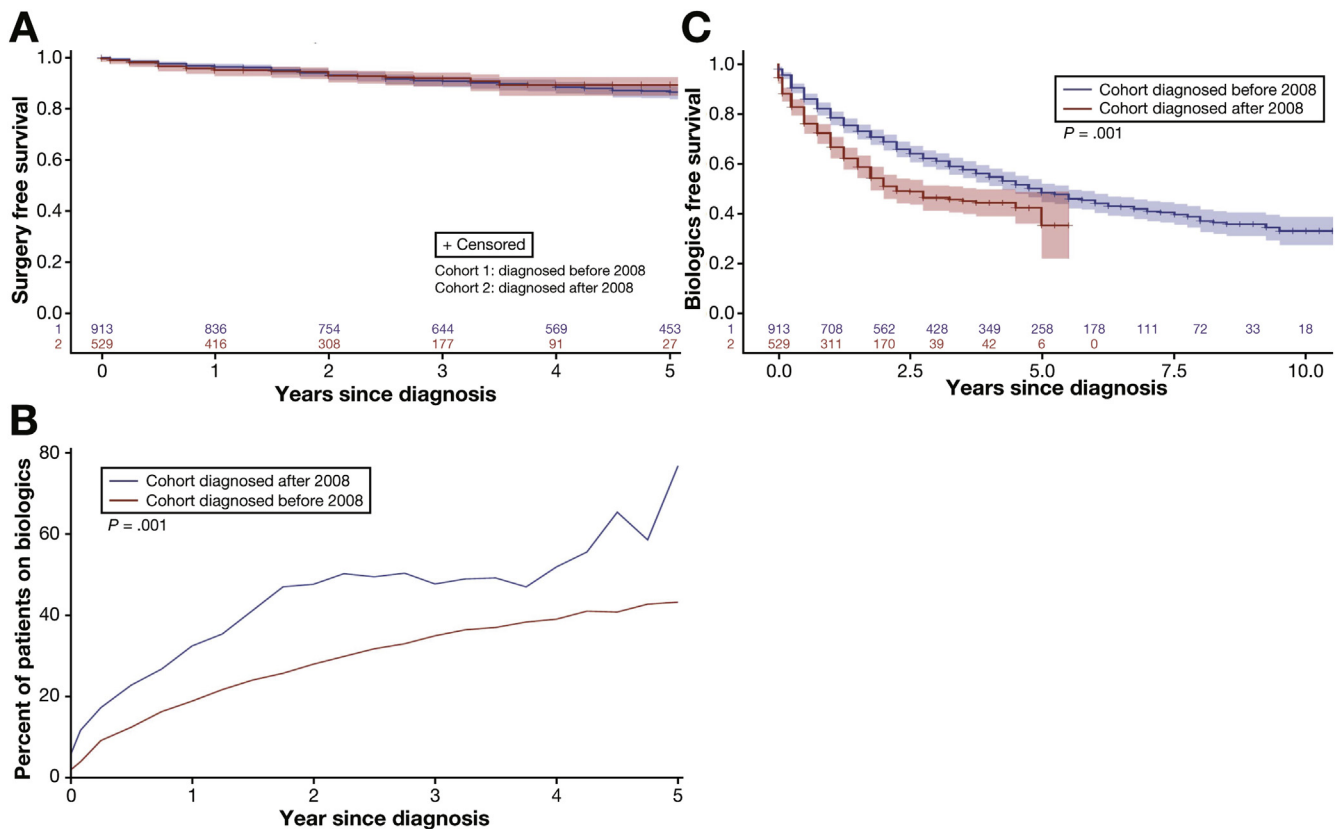
Figure 2. (*A*) Cumulative incidence of bowel surgery stratified by year of diagnosis (diagnosed before 2008 to after 2008). The x-axis shows the years since the diagnosis, and the y-axis shows surgery-free survival. The 5-year surgery-free survival curves of both groups overlap, indicating no change in risk of surgery from 2002 to 2014. (*B*) Percentage of patients on biologics at any given time stratified by year of diagnosis (diagnosed before 2008 or after 2008). The x-axis shows the years since the diagnosis, and the y-axis shows the percentage of patients on biologics. This confirms the increasing use of biologics. (*C*) Time to initiation of biologics stratified by year of diagnosis (diagnosed before 2008 vs after 2008). The x-axis shows the years since the diagnosis, and the y-axis shows biologics-free survival. This confirms the increasing early use of biologics.

The 5-year risk of surgery in our prospective cohort was 13%, and the 10-year risk was 26% (Figure 1*A*). This is identical to a recent single-center retrospective study in children published by an Israeli group.[28] However, the risk is lower than all other published pediatric and adult studies.[29,30] The difference may be related to this being a true inception cohort of patients, or to the era of diagnosis. The surgical rates are less when compared with most of the population-based cohorts in adults, suggesting that the risk of surgery may be different in pediatric Crohn's disease compared with adult-onset Crohn's disease. However, the 5-year risk of surgery did not change significantly when comparing cohorts diagnosed between 2002 and 2007 (13.8%)[27] and 2008 and 2014 (13%) (Figure 2*A*). This is true despite the documented earlier and increasingly frequent use of biologics over the course of the study (Figure 2*B* and *C*).

Disease behavior (inflammatory vs stricturing vs penetrating) at diagnosis was the best predictor of surgery (Figure 1*C*). None of the other disease characteristics at diagnosis such as disease location, sex, age at onset, year of diagnosis, or center from which patient was recruited predicted surgery.

Although several studies have shown that disease location does not predict the risk of surgery,[31–33] a recent study by Cleynen et al,[14] one of the larger genotype-phenotype correlation studies of IBD, showed that the risk of surgery was low in colonic disease compared with those with ileocolonic/ileal disease.

Our results reflect the natural progression of CD over 10 years. Our analysis shows that the use of biologics is associated with slowing disease progression from inflammatory to stricturing/penetrating (hazard ratio, 0.85; 95% CI, 0.76–0.95; $P = .005$). Our work extends the findings recently reported by Kugathasan et al,[20] that early anti-TNFα therapy was associated with a reduction in penetrating disease generally occurring within a 2-year period. They suggest that a specific ileal extracellular matrix protein gene signature present at diagnosis predicted stricturing disease in pediatric Crohn's disease. We suggest that their exclusion of patients with disease progression occurring in the first 90 days skews their study population toward a less severe group than we are reporting and toward a group more able to show response to early treatment. Most importantly, both reports support the positive impact of early therapy with biologics to prevent the
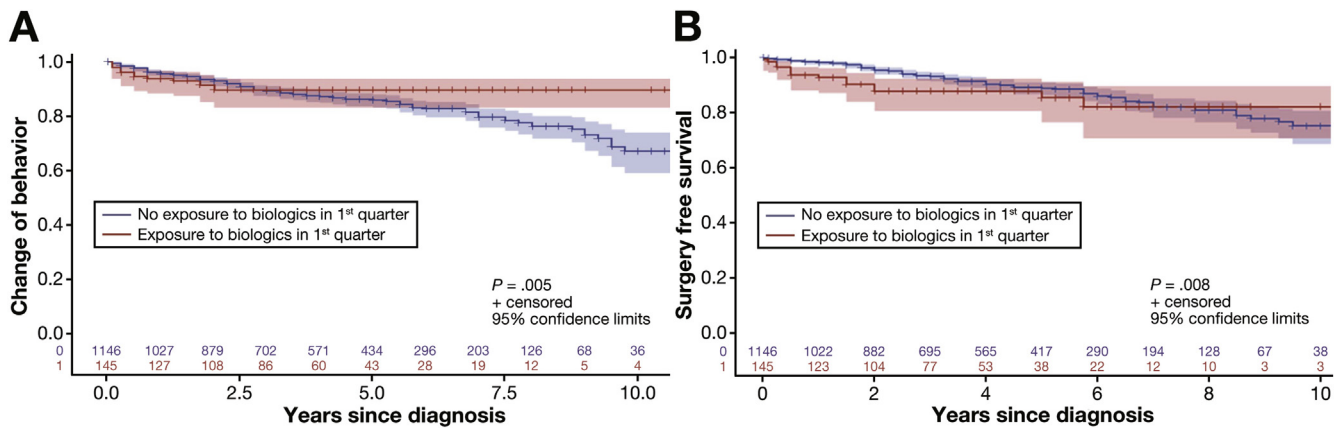
Figure 3. (*A*) Disease progression from inflammatory to stricturing and/or penetrating compared between the early initiation of biologics group (use of biologics in the first 3 months) and the no early exposure to biologics groups (did not receive biologics in the first 3 months). The x-axis show the follow-up period in years since the diagnosis, and the y-axis shows the proportion of patients without disease progression (ie, change of behavior from inflammatory to stricturing and/or penetrating.) (*B*) Cumulative risk of surgery among early initiation of biologics (within the first 3 months) compared with those who did not receive biologics in the first 3 months. The x-axis shows the years since the diagnosis, and the y-axis shows surgery-free survival. Note that those patients who received biologics within the first 3 months after diagnosis showed shorter surgery-free survival.

significant complications associated with disease progression.

It should be noted that we found that in the group receiving early biologics (n = 145), the risk of surgery appears to be increased paradoxically in the first 5 years after diagnosis (Figure 2*B*). This suggests that our practicing pediatric gastroenterologists may have selected the sicker patients to start biologics. If this is the case then this introduces a bias that strengthens our findings because it would be the sicker patients who are, in our study, experiencing the better long-term outcome (ie, less disease progression).

The strengths of our study include its long-term follow-up period, its large sample size, and being a true inception cohort (ie, inclusion of children within the first 30 days from diagnoses). These enable us to better assess temporal trends associated with the incidence of surgery. There were limitations, however, of the study. This study was started more than 15 years ago and conceived before our current ability to collect and process biological samples and to monitor anti-TNFα blood levels. As a registry-based study, disease location data were not universally available on follow-up evaluation, endoscopic and pathologic data were not collected uniformly, and variation in practice at different centers may have influenced the results. Even though details of the treatment were documented, we do not have information about whether therapeutic drug monitoring of biologics or immunomodulators were used to optimize these treatments during the study. Another important limitation was the decrease in the number of patients over time, similar to other prospective cohort studies. Some of these limitations also limit the analytic approaches available to us.

Overall, this study provides important information about temporal trends of surgical risk in pediatric Crohn's disease. The initial 5-year risk of surgery has not changed over the 12 years of our study despite the use of newer therapies. We believe that this may reflect significant subclinical and clinical disease progression before diagnosis and before current medications capable of altering disease course are used. However owing to limitation of the registry model, we could not prove that surgery would decrease with earlier or more aggressive biologic use.

Taken together, our work and the work of Kugathasan et al[20] present a picture consistent with the view that a critical factor in preventing bowel complications of IBD is starting effective treatment early, before the accumulation of significant bowel damage.

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