*Journal of Crohn's and Colitis*, 2020, 71–78
doi:10.1093/ecco-jcc/jjz111
Advance Access publication June 3, 2019
Original Article

Original Article

# Complicated Disease and Response to Initial Therapy Predicts Early Surgery in Paediatric Crohn's Disease: Results From the Porto Group GROWTH Study

**Arie Levine,[a] Neil Chanchlani,[b,*] Seamus Hussey,[c] Tomer Ziv-Baran,[d] Johanna C. Escher,[e] Jorge Amil Dias,[f] Gabor Veres,[g] Sibylle Koletzko,[h] Dan Turner,[i] Kaija-Leena Kolho,[j] Anders Paerregaard,[k] Annamaria Staiano,[l] Paolo Lionetti,[m] Federica Nuti,[n,o] Malgorata Sladek,[p] Ron Shaoul,[q] Isabella Lazowska-Prezeorek,[r] Javier Martin de Carpi,[s] Rotem Sigall Boneh,[a] Tamar Pfeffer Gik,[a] Noa Cohen-Dolev,[a] Richard K. Russell,[t] on behalf of the Porto Group of ESPGHAN**

[a]Paediatric Gastroenterology and Nutrition Unit, Tel Aviv University, Edith Wolfson Medical Center, 62 HaLohamim Street, 58100 Holon, Israel [b]Exeter IBD Pharmacogenetics, RILD building, Royal Devon and Exeter NHS Foundation Trust, Exeter, UK [c]National Children's Research Centre, Crumlin; Department of Paediatrics, UCD and RCSI, Dublin, Ireland [d]School of Public Health, Sackler Faculty of Medicine, Tel Aviv University, Tel-Aviv, Israel [e]Erasmus MC-Sophia Children's Hospital, Pediatric Gastroenterology, Rotterdam, Netherlands [f]Pediatric Gastroenterology Unit, Centro Hospitalar de São João, Porto, Portugal [g]Pediatric Institute, University of Debrecen, Hungary [h]Ludwig Maximilians-Universität München, Dr. von Hauner Children's Hospital, Munich, Germany [i]Shaare Zedek Medical Center, The Hebrew University of Jerusalem, Israel [j]University of Tampere, Tampere, Finland and Children's Hospital, Helsinki, Finland [k]Department of Paediatrics 460, Hvidovre University Hospital, Denmark [l]Department of Translational Medical Science, Section of Pediatrics, University of Naples 'Federico II' [m]University of Florence-Meyer Hospital, Florence, Italy [n]Intermediate Pediatric Care Unit, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy [o]Pediatric Gastroenterology and Hepatology Unit, Sapienza University Rome, Italy [p]Jagiellonian University Medical College, Krakow, Poland [q]Rambam Medical Center, Haifa, Israel [r]Department of Pediatric Gastroenterology and Nutrition, Medical University of Warsaw, Poland [s]Department of Pediatric Gastroenterology, Hepatology and Nutritiom, Hospital Sant Joan de Déu, Barcelona, Spain [t]Department of Paediatric Gastroenterology, Royal Hospital for Children, 1345 Govan Road, Glasgow G51 4TF, UK

Corresponding author: Richard K. Russell, Department of Paediatric Gastroenterology, Royal Hospital for Children, 1345 Govan Road, Glasgow G51 4TF, UK. E-mail: richardrussell@nhs.net

## Abstract

**Introduction:** The ability to predict risk for poor outcomes in Crohn's disease [CD] would enable early treatment intensification. We aimed to identify children with CD with complications at baseline and throughout the study period who are at risk for surgery 2 years from diagnosis.

**Methods:** Newly diagnosed children with CD were enrolled into a prospective, multicentre inception cohort. Disease characteristics and serological markers were obtained at baseline and week 12 thereafter. Outcome data including disease activity, therapies, complications and need

for surgery were collected until the end of 104 weeks. A chi-square automatic interaction detection [CHAID] algorithm was used to develop a prediction model for early surgery.
**Results:** Of 285 children enrolled, 31 [10.9%] required surgery within 2 years. Multivariate analysis identified stricturing disease at baseline (odds ratio [OR] 5.26, 95% confidence interval [CI] 2.02–13.67 [$p = 0.001$]), and Paediatric Crohn's Disease Activity Index [PCDAI] >10 at week 12 (OR 1.06, 95% CI 1.02–1.10 [$p = 0.005$]) as key predictors for early surgery. CHAID demonstrated that absence of strictures at diagnosis [7.6%], corticosteroid-free remission at week 12 [4.1%] and early immunomodulator therapy [0.8%] were associated with the lowest risk of surgery, while stricturing disease at diagnosis [27.1%, $p < 0.001$] or elevated PCDAI at week 12 [16.7%, $p = 0.014$] had an increased risk of surgery at follow-up. Anti-OmpC status further stratified high-risk patients.
**Discussion:** A risk algorithm using clinical and serological variables at diagnosis and week 12 can categorize patients into high- and low-risk groups from diagnosis.

**Key Words:** Crohn, Crohn's Disease inflammatory bowel disease, child; relapse, surgery, complications, serological markers

## 1. Introduction

Children and young people with Crohn's disease [CD] often have more extensive disease, increased disease activity and a higher rate of complications compared with adult-onset CD.[1] Treatment goals in paediatric CD have traditionally focused on relieving symptoms, optimizing growth and improving quality of life, while minimizing drug toxicity. More recently, mucosal healing became a specific treatment target to alleviate the risk of complications.[2] The historical lifetime risk of surgery is approximately 80%,[3] with around 20% of children with CD requiring surgery within 5 years of diagnosis.[4] Complications that may lead to surgery include fibrostricturing disease with obstructive symptoms, complicated perianal disease and internal penetrating disease, as well as treatment-refractory inflammation.[4–7]

Those diagnosed with ileal CD and older children are more likely to experience severe/extensive or stricturing/penetrating CD and have an increased risk for bowel surgery.[8]

A systematic review and meta-analysis including 21 632 patients with CD found that thiopurine use was associated with a 40% decreased risk of surgical resection compared to those not exposed to thiopurines.[9] The majority of studies included adults and no risk stratification for paediatric CD was sufficiently explored.

In this study, we aimed to explore the clinical, biochemical and treatment-related factors leading to early surgical interventions and develop a risk algorithm in a prospective multicentre inception cohort of children with CD. We hypothesized that those with severe or persistent inflammation despite therapy and patients with complicated disease behaviour at onset would have the highest risk of surgery within 2 years of follow-up.

## 2. Material and Methods

Details on the GROWTH CD [Growth, Relapse and Outcomes With Therapy] study have been previously described [clinicialtrials.gov identifier: NCT00711945].[10–12] In brief, this was a prospectively established cohort from the Paediatric IBD Porto Group of the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition [ESPGHAN], which consisted of newly diagnosed untreated children aged 4–17 years with CD from 17 sites in Europe and Israel [Supplementary Table 1], in order to develop predictors for early adverse outcomes. The study was designed to assess predictors at baseline and week 12. Previous work from this cohort examined the association between induction of first remission on treatment outcomes, including relapse, growth retardation, non-inflammatory behaviour and complicated disease behaviour.[10–12] Participants must have been diagnosed with new-onset CD by a combination of clinical, laboratory, endoscopic and histological criteria, and be treatment naïve.[13] Participants who received medical or surgical intervention before enrolment, who had a diagnosis of IBD unclassified, or those with inadequate follow-up were excluded.

The present study evaluated children between 2010–2013 at seven scheduled visits from disease onset: baseline visit before treatment introduction and at 8, 12, 26, 52, 78 and 104 weeks thereafter. All centres obtained ethical approval and informed consent. All patients underwent gastroscopy, colonoscopy and small bowel imaging at diagnosis.

Disease extent was categorized according to the Paris classification.[14] Data collected at visits included history, medications, physical examination, anthropometrics, Paediatric Crohn's Disease Activity Index [PCDAI], physicians global assessment of disease activity,[15] faecal calprotectin and serology, including antibody measurements and C-reactive protein [CRP]. Aliquots of serum were obtained at weeks 0, 12 and 52 for serological and other biomarkers. Serological anti-OmpC, ASCA [IgA] and CBir1 markers were performed by Prometheus at baseline and week 12 while blinded to patient data. Consistent with previous literature, cut-off values for antibody measurement by enzyme-linked immunosorbent assay (ELISA [ELISA units/mL, EU/mL]) indicating antibody positivity were: anti OmpC >5.3, ASCA IgA > 9.2 and CBir1 >35.5.[16,17] Any patient undergoing relapse had a relapse form filled out.

Active disease was defined as PCDAI >10 and mild to moderate disease was defined as PCDAI >10 and <40. Normal values were considered as CRP < 0.5 mg/dL [<5 mg/L], faecal calprotectin <50 µg/g and albumin 3.5–5.5 g/dL. Data were remotely monitored, and queries were resolved by the research coordinators [TP-G, NC-D and RS-B].

### 2.1. Definition of immunosuppression

Patients were managed at the discretion of the treating physician, but general treatment rules were suggested. To maintain an objective definition of clinical remission, all patients requiring steroids were to be tapered by week 11 in order to establish corticosteroid-free

remission at week 12.[11] Patients may have commenced standardized doses of immunomodulator [IMM] therapy, azathioprine [2–2.5 mg/kg/day], mercaptopurine [1–1.5 mg/kg/day] or methotrexate [15 mg/m$^2$/week, maximum 25 mg] according to the physician's discretion. Early IMM was defined as IMM started within 8 weeks from commencement of induction therapy. Use of infliximab with a loading dose of 5 mg/kg at weeks 0, 2 and 6 was also allowed. Surgical treatment was decided by the treating physician.

### 2.2. Definition of surgery

Surgery was defined as any surgical intervention for treating complications of CD, including intestinal resection, stricturoplasty, drainage of internal or peri-anal abscess, fistulectomy and surgery related to perforation.[18] We defined surgery within 2 years from diagnosis, our follow-up period, as early and use the term 'early surgery' herein.

Baseline complications were defined as stricturing, penetrating or active perianal fistula and/or abscess present at the time of diagnosis. New complications were defined as stricture, penetrating disease, perianal abscess and/or draining fistula that were not present at the time of diagnosis and developed during the follow-up period.

### 2.3. Developing predictors for outcomes

We studied baseline *and* week 12 variables as predictors. The usual week 12 visit was chosen assuming that patients who do not respond to initial medical therapy and/or are steroid-dependent may have worse clinical outcomes during the follow-up period.

### 2.4. Statistical methods

Categorical variables were described using frequency and percentage. Normally distributed continuous variables were described as the mean and standard deviation and skewed variables were expressed as the median and interquartile range [IQR]. An independent samples *t*-test and Mann–Whitney tests were used to compare continuous variables. In cases where calprotectin or CRP were missing, the last observation was carried forward. Categorical variables were compared using a chi-square test or Fisher's exact test. Multivariate logistic regression was used to identify independent predictors of the studied outcome.[19] All the predictors were included in the logistic regression, and a backward stepwise [likelihood ratio] method was used for variable selection [$p > 0.1$ was used as criteria for removal]. The chi-square automatic interaction detection [CHAID] algorithm was used to identify predictors and cut-offs for continuous exposure variables in predicting surgical outcome.[20] For conservative analysis, patients with absent serological markers undergoing surgery had those imputed as negative. Risk associated with incidence of surgery was defined as low [<5%], intermediate [5–15%] and high [≥15.1%]. All statistical tests were two tailed. A value of $p < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS [IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0]

## 3. Results

### 3.1. Study population

Of 348 children enrolled, 285 [82%] had valid baseline and long-term follow-up visits to be included in the final analysis [Figure 1, Table 1]. In total, 63 children were excluded, before statistical analyses, due to: lack of appropriate imaging [$n = 13$], incomplete follow-up/withdrawn [$n = 38$] or data issues [$n = 12$].

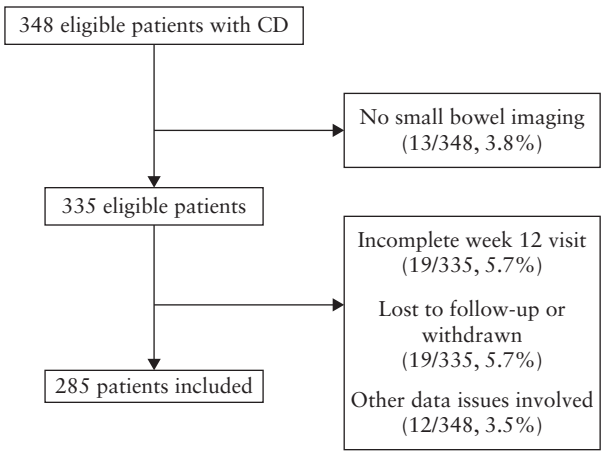


**Figure 1.** Patient flow chart. Legend: CD = Crohn's disease

Forty-four [16%] children had panenteric disease. The majority [81.8%] of children had non-stricturing or penetrating disease, six [2.1%] had both stricturing and penetrating disease, and five [1.8%] had both perianal and complicated disease combined at baseline.

Fifteen [5.3%] children were treated with infliximab by week 12. Children treated with mesalamine or antibiotics [median PCDAI 30, IQR 20–40] had significantly milder disease than children treated with exclusive enteral nutrition [EEN], corticosteroids or anti-tumour necrosis factor [anti-TNF] therapy [$p = 0.009$]. There were no significant differences in median PCDAI between the three latter groups.

### 3.2. Complications and surgery

At baseline, 58 [20.4%] children presented with complicated disease behaviour or active perianal disease and ten [3.5%] had two different complications at diagnosis. The most common complications at presentation were strictures [B2 or B2B3] in 16 [5.6%], followed by enteric fistula [B3] in two [0.7%] children. Perianal fistula or abscess were present in 15 [5.3%] children.

During the follow-up period, 43 [15.1%] children developed complications. The most common new complications were strictures in 12 [4.2%], perianal fistula or abscess in nine [3.1%], and penetrating disease in two [0.7%] children. We identified 31 [10.9%] children requiring surgery during follow-up. Two children had multiple surgeries at different time points, both for perianal disease and for intestinal strictures. At week 12, 18 [58.1%] of the children who underwent surgery were in steroid-free remission compared with 186 [74%] of the others [$p = 0.08$].

Thirty-three surgical procedures were performed in the 31 patients. The most common reason for surgery was stricture in 14 [4.9%], medically refractory disease without complications in nine [3.2%], perianal disease in six [2.1%], and combination of stricturing and penetrating disease in two [0.7%] children. Fifty per cent of patients with B2 or B2B3 diagnosed at presentation or during follow-up required surgery within first 2 years.

### 3.3. Associated factors for early surgery

#### 3.3.1. Baseline

Stricturing disease was significantly associated with surgery at 2 years of follow-up (B2 35.5% [11/31] in the surgical group vs

**Table 1.** Demographic and treatment induction and maintenance therapy [by week 12] details of cohort at baseline.

| | Received surgery | Did not receive surgery | Entire cohort | *p*-value |
|---|---|---|---|---|
| Age [years] [IQR] *n* = 285 | 14.0 [11.0–14.5] | 13.0 [11.0–13.0] | 13.0 [11.0–13.0] | 0.741 |
| Sex [%], *n* = 285 total, *n* = 254 did not receive surgery | | | | |
| Male | 16/31 [51.6] | 155/254 [61.0] | 171 [60] | 0.313 |
| Behaviour [%] | | | | |
| B1–Non-stricturing, non-penetrating | 18/31 [58.1] | 215/254 [84.6] | 233/285 [81.8] | <0.001 |
| B2–Stricturing | 11/31 [35.5] | 31/254 [12.2] | 42/285 [14.7] | 0.001 |
| B3–Penetrating | 0 [0] | 4/254 [1.6] | 4/285 [1.4] | >0.999 |
| B2+B3 | 2/31 [6.5] | 4/254 [1.6] | 6/285 [2.1] | 0.130 |
| Perianal | 3/31 [9.7] | 9/254 [3.5] | 12/285 [4.2] | 0.130 |
| Location [%] | | | | |
| L1–Distal 1/3 ileum ± limited caecal disease | 10/31 [32.2] | 52/250 [20.8] | 62/281 [22.1] | 0.133 |
| L2–Colonic | 3/31 [9.7] | 17/250 [6.8] | 20/281 [7.1] | 0.471 |
| L3–Ileocolonic | 18/31 [58.1] | 174/250 [69.6] | 192/281 [68.3] | 0.242 |
| L4–Isolated disease | 0 [0] | 7/250 [2.8] | 7/281 [2.5] | >0.999 |
| L4 Involvement | | | | |
| No L4 involvement | 16/31 [51.6] | 81/250 [32.4] | 97/281 [34.5] | 0.029 |
| L4a–Upper disease proximal to ligament of Treitz | 10/31 [32.3] | 112/250 [44.8] | 122/281 [43.5] | 0.209 |
| L4b–Upper disease distal to ligament of Treitz and proximal to distal 1/3 ileum | 4 /31 [12.9] | 25/250 [10] | 29/281 [10.3] | 0.541 |
| L4a+b | 1/31 [3.2] | 32/250 [12.8] | 33/281 [11.7] | 0.146 |
| First induction therapy | | | | |
| Exclusive enteral nutrition | 10/31 [32.3] | 79/254 [31.1] | 89/285 [31.2] | 1 |
| Corticosteroids | 5/31 [16.1] | 85/254 [33.5] | 90/285 [31.6] | 0.06 |
| Anti-TNF | 1/31 [3.2] | 7/254 [2.8] | 8/285 [2.8] | 1 |
| Other [mesalamine, antibiotics or no therapy] | 15/31 [48.4] | 83/254 [32.7] | 98/285 [3.2] | 0.108 |
| Maintenance therapy | | | | |
| Immunomodulators* | 22/31 [71.0] | 183/254 [72.0] | 205/285 [71.9] | 1 |
| Anti-TNF * | 3/31 [9.7] | 12/254 [4.7] | 15/285 [5.3] | 0.215 |
| Other [mesalamine, or no therapy] | 7/31 [22.6] | 66/254 [26.0] | 73/285 [25.6] | 0.829 |

Abbreviations: IQR, interquartile range; TNF, tumour necrosis factor.

Patients receiving concomitant mesalamine or antibiotics prior to or with anti TNF/steroids/etc. at diagnosis were still considered primary anti-TNF/steroid/EEN therapy.

*One person received both immunomodulator and anti-TNF therapy as maintenance.

12.2% [31/254] in the non-surgical group, $p = 0.002$). Active perianal disease at disease onset was not associated with need for surgery [$p = 0.13$]. Calprotectin as a continuous variable [$p = 0.88$], albumin [$p = 0.88$] and the presence of antibodies, individual or combined, were not predictive of surgery at 2 years [Table 2].

### 3.3.2. Week 12

Low albumin and high PCDAI (16.7% [5/30] in the surgical group vs 5.8% [14/243] in the non-surgical group, $p = 0.044$) predicted surgery at 2 years while calprotectin, whether as a continuous [$p = 0.789$] or binary [>250 mg/dL] variable [$p = 0.377$], did not.

Serological markers were available for 211 patients at baseline or week 12 for anti-OmpC, and for 201 patients for ASCA and CBir. The presence of anti-OmpC and CBir antibodies at baseline or 12 weeks were not predictive of early surgery. Week 12 ASCA IgA levels were higher (85.7% [18/21] in the surgical group vs 55.1% [86/156] in the non-surgical group, $p = 0.008$). The sum of all antibodies [$p = 0.418$] at baseline was not predictive [Table 2]. As serological tests were only available for 70–75% of all patients, these results should be interpreted with caution.

### 3.3.3. Multivariate analysis

At baseline, disease behaviour, PCDAI and CRP, combined with PCDAI at week 12, were all significant predictors for surgery [Table 3]. Those with stricturing [B2] disease were significantly more likely (odds ratio [OR] 5.26, 95% confidence interval [CI] 2.02–13.67, $p = 0.001$) to require surgery than those without stricturing or penetrating disease. Those with stricturing and penetrating disease were 10.3 times [95% CI 1.43–74.12, $p = 0.021$] more likely to require surgery than those without.

A higher CRP at baseline was associated with a lower risk for surgery at 2 years of follow-up (OR 0.82 [95% CI 0.70–0.98, $p = 0.025$]), and higher PCDAI at week 12 [OR 1.06, 95% CI 1.02–1.10, $p = 0.005$] was a significant risk factor for surgery. CRP and calprotectin at week 12 were not predictive.

### 3.3.4. CHAID algorithm

Modelling a stratified clinical risk prediction tool for this cohort of patients using CHAID [Figure 2] demonstrated that stricturing disease at diagnosis and active disease at week 12 were the strongest determinants for high-risk patients requiring early surgery. For all patients with a stricture at diagnosis, the risk was 27.1% compared to 7.6% of patients without B2 or B2B3 classification [$p < 0.001$]. Patients without stricturing disease and PCDAI > 10 at week 12 had a 16.7% risk for early surgery, whereas patients without stricturing disease and a PCDAI <10 at week 12 had a 4.1% risk for early surgery [$p = 0.014$].

The low-risk model was defined by three main variables: absence of stricturing disease at diagnosis, steroid-free clinical remission by week 12 and use of early immunosuppression. If PCDAI is <10 at week 12 and the patient has received immunosuppression by

**Table 2.** Risk factors for early surgery, univariate analysis of exposure at baseline.

| | Received surgery | Did not receive surgery | Entire cohort | *p*-value |
|---|---|---|---|---|
| Clinical response | | | | |
| PCDAI ≥10 week 0 | 30/31 [96.8] | 244/254 [96.1] | 274/285 [96.1] | >0.999 |
| PCDAI week 0 [median][IQR] *n* = 285 total, *n* = 31 received surgery, *n* = 254 did not receive surgery | 37.5 [27.5–45.0] | 33.8 [22.5–42.5] | 35.0 [25.0–45.0] | 0.131 |
| PCDAI ≥10 week 12 | 17/31 [54.8] | 86/252 [34.1] | 103/283 [36.4] | 0.024 |
| Biochemical parameters | | | | |
| CRP >5 week 0 | 4/31 [12.9] | 69/252 [27.4] | 73/283 [25.8] | 0.082 |
| CRP week 0 [mg/kg][median][IQR] *n* = 283 total, *n* = 31 received surgery, *n* = 252 did not receive surgery | 2.3 [0.9–4.0] | 2.6 [0.8–5.3] | 2.6 [0.8–5.1] | 0.358 |
| CRP >5 week 12 | 0/31 | 5/245 [2.0] | 5/276 [1.81] | >0.999 |
| Low albumin [%] week 0 | 13/31 [41.9] | 103/254 [40.6] | 116/285 [40.7] | 0.882 |
| Low albumin [%] week 12 | 3/31 [9.7] | 14/239 [5.9] | 17/270 [6.3] | 0.376 |
| Calprotectin [%] week 0 | | | | 0.377 |
| <250 | 1/16 [6.3] | 31/184 [16.8] | 32/200 [16.0] | 0.477 |
| 250–399 | 1/16 [6.3] | 7/184 [3.9] | 8/200 [4.0] | 0.493 |
| >400 | 14/16 [87.4] | 146/184 [79.3] | 160/200 [80.0] | 0.744 |
| Calprotectin week 0 [mg/dL] [median][IQR] *n* = 200 total, *n* = 16 received surgery, *n* = 169 did not receive surgery | 1800 [678–1862] | 1800 [551–1800] | 1800 [596–1800] | 0.878 |
| Calprotectin >250 week 12 | 18/29 [62.1] | 149/246 [60.1] | 167/277 [60.3] | 0.3770 |
| Antibody status | | | | |
| All antibodies [sum] | | | | 0.418 |
| 0 | 5/24 [20.8] | 50/178 [28.1] | 55/202 [27.2] | |
| 1 | 8/24 [33.3] | 70/178 [39.3] | 78/202 [38.6] | |
| 2 | 8/24 [33.3] | 49/178 [27.5] | 57/202 [28.2] | |
| 3 | 3/24 [12.6] | 9/178 [5.1] | 12/202 [5.9] | |
| Positive anti-OmpC antibody | 20/24 [83.3] | 116/187 [62.0] | 136/211 [64.5] | 0.118 |
| Positive ASCA IgA antibody | 19/24 [79.2] | 111/177 [62.7] | 130/201 [64.7] | 0.114 |
| Positive CBir antibody | 10/24 [41.7] | 56/177 [31.6] | 66/201 [32.8] | 0.326 |

Abbreviations: PCDAI, Paediatric Crohn's Disease Activity Index; IQR, interquartile range; CRP, C-reactive protein.

**Table 3.** Risk factors for early surgery, multivariate analysis of exposure

| *n* = 253 | Odds ratio [OR] | 95% Confidence interval | *p*-value |
|---|---|---|---|
| At baseline | | | |
| Disease behaviour | | | 0.002 |
| Paris B1 | 1.00 [reference] | | |
| Paris B2 | 5.26 | 2.02–13.67 | 0.001 |
| Paris B3 | NA [none received surgery] | | |
| Paris B2 + 3 | 10.30 | 1.43–74.12 | 0.021 |
| PCDAI | 1.03 | 1.001–1.07 | 0.047 |
| CRP | 0.82 | 0.70–0.98 | 0.025 |
| At week 12 | | | |
| PCDAI | 1.06 | 1.02–1.10 | 0.005 |

Thirty-two patients with missing variables at week 0 or 12 were excluded from the analysis.

week 12, he or she has a lower chance of requiring surgery at 2-year follow-up compared to those that have not received immunosuppression [0.8% vs 11.5%, $p < 0.008$].

Among serological predictors, only anti-OmpC as a continuous variable, with a lower cutoff than found in the Prometheus kit, added to the model. High-risk patients with no stricturing disease, who have active disease at week 12 despite therapy, and positive anti-OmpC status had a significantly elevated need for surgery than those who are anti-OmpC-negative [38.1% vs 6.7%, $p = 0.027$]. In this high-risk cohort, the risk for surgery with measured negative anti-OmpC was 4.5%, for patients with positive anti-OmpC was 38.1% and for those with missing data was 8.7%. Because surgical outcomes for patients with missing data were intermediate between the negative and positive groups, we imputed all missing anti-OmpC as negative to remain conservative. ASCA or other antibodies did not add to this model. An association between both B2 phenotype and anti-OmpC-positive status and risk of surgery was not significant during testing.

## 4. Discussion

Based on a prospective international inception cohort of 285 patients, we were able to develop a risk-stratified algorithm for predicting early surgery in patients diagnosed with paediatric CD. Using a combination of factors from baseline and after induction of remission, including disease behaviour phenotype, use of immunosuppression therapy, and PCDAI at 12 weeks, patients can be categorized into low- and high-risk groups for surgery within 2 years of follow-up.

While this study validated some associated risk factors, others we hypothesized to be predictive, such as panenteric disease, perianal disease and elevated inflammatory markers, were not predictive of surgical outcome. While perianal disease is not registered as a complication using the Paris classification for behaviour, it is a unique poor outcome that may lead to surgery and early top-down therapy; it was important to analyse this without classification bias. Low albumin and high PCDAI at week 12 was a predictive combined variable in the univariate analysis but did not remain significant in the multivariate analysis.

Active disease reflected by higher disease activity scores at diagnosis, including PCDAI, has been reported to be a significant

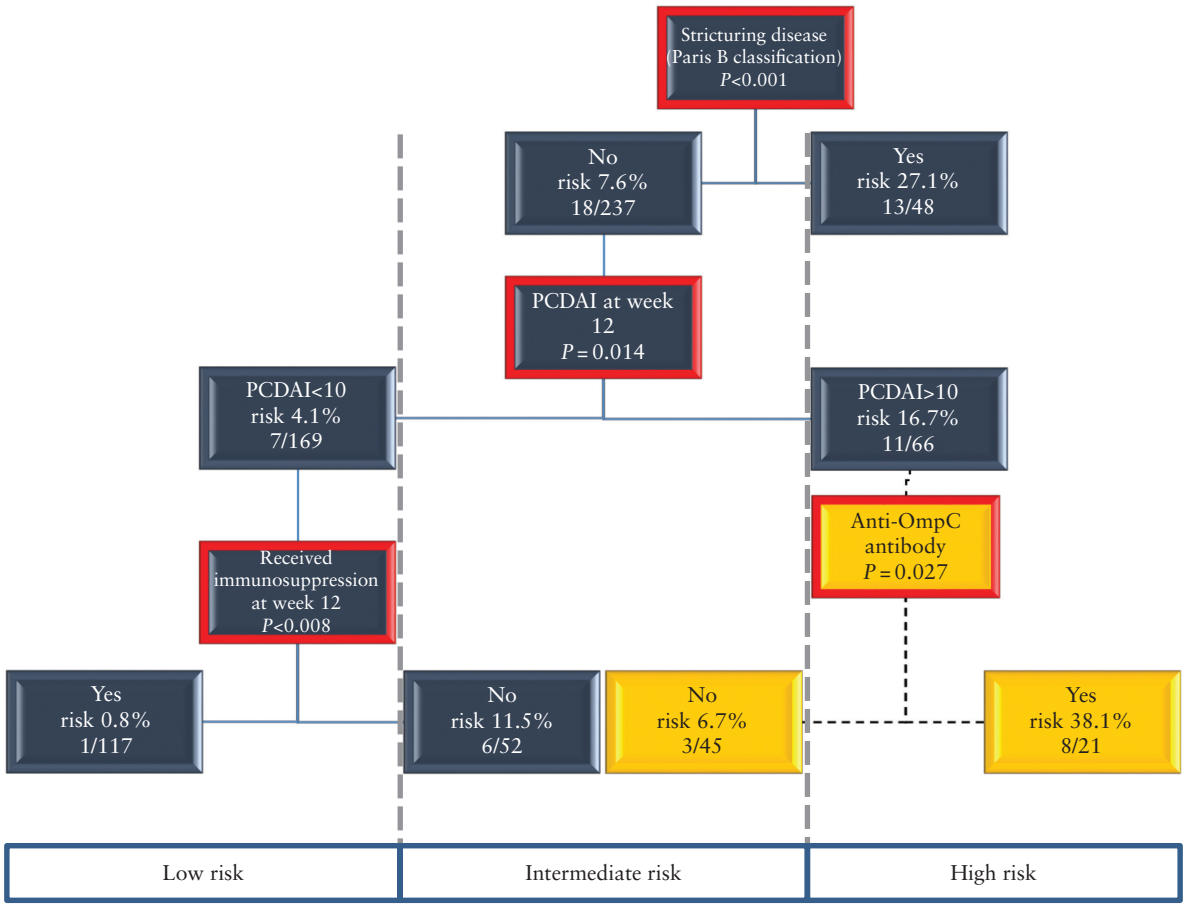


**Figure 2.** Risk-stratified CHAID algorithm. Legend: Boxes with *p*-values, outlined in red, compare the subsequent groups against each other. Boxes with percentages represent the risk of surgery at 2 years of follow-up. Risk is defined as low [≤4.9%], intermediate [5.0–15.0%] and high [≥15.1%], and is separated by the dashed line. Anti-OmpC antibody [cut off of ≥5.3] is marked differently as it was measured only in 211/285 patients. Three patients undergoing surgery were missing anti-OmpC status.

independent predictor for surgical intervention.[21] However, no studies have incorporated disease activity scores in combination with disease behaviour and serology at baseline and follow-up in a multivariate analysis. Studies have traditionally sought prognostic factors at diagnosis, but recent studies are now demonstrating that post-induction variables may be better in this regard than baseline factors, as has been demonstrated in paediatric ulcerative colitis.[22]

Our finding that even mildly elevated PCDAI scores at 3 months were associated with an increased risk of surgery are novel, suggesting that active disease post-induction, even with mild symptoms, may be a prognostic indicator for a complicated disease course.

Multiple studies have looked at the associations of antibacterial or antiglycan antibody status and the risk for surgery. The strongest association between antibody presence and risk of surgery has been identified for positive ASCA while anti-OmpC has been associated specifically with penetrating disease, which often requires surgical interventions.[6,21,23] However, the evidence remains mixed, particularly when incorporated into multivariate analysis.[16,24]

Anti-OmpC was not an independent predictor of outcomes in our study, but when associated with disease that does not respond to initial medial therapy, it appeared to have additive value. Within the CHAID algorithm, anti-OmpC status was a statistically significant modifying predictor of surgery [$p$ = 0.03] when analysed for patients with B1 phenotype, in combination with active disease despite therapy. This observation requires further validation because anti-OmpC was missing for about 25% of patients. ASCA was predictive of complications when pooling complications at diagnosis with new complications [data not shown]. At week 12, about 85% of children receiving surgery were ASCA-positive compared to 55% who did not receive surgery [$p$ = 0.008], and therefore, here as in other studies, it is helpful in determining risk for surgery.

Choice of first therapy did not affect the overall risk for surgery in the cohort, although it seemed to have a reduced risk of surgery for low-risk patients. Use of immunomodulator treatment remains controversial. In one multi-centre study in France, the authors concluded that stricturing disease and treatment with corticosteroids were associated with an increased risk of surgery, whereas treatment with azathioprine was associated with a decreased risk.[25] One multi-centre study from the USA suggested that immunomodulator therapy at diagnosis did not alter the risk of surgery within 5 years of diagnosis.[26] In our cohort, the impact of immunomodulator use in isolation within the first 12 weeks was not a statistically significant predictor. However, there may be a subgroup that benefits and one that does not, as the CHAID analysis demonstrated; early immunomodulation may be of benefit in patients with lower risk presenting with inflammatory disease who are entering steroid-free clinical remission. Alternatively, it did not impact outcomes in patients with existing strictures or elevated PCDAI at week 12.

In one recently published prospective inception cohort study of paediatric patients with CD across 28 sites in North America, patients who received early TNF therapy were less likely to have penetrating complications but not stricturing complications.[6] In another North American registry study, stricturing or penetrating disease, but not surgery, was slowed as a result of early use of biologics, but this effect was only seen after 5 years of disease.[7] Data on anti-TNF therapy use in our cohort were not evaluated due to the small number of patients using this in the first few months of therapy, reflecting that this study was started in 2010 when anti-TNF was not readily available as a first-line therapy in some of the participating countries.

The strengths of our study included complete evaluation of all patients with upper and lower endoscopy as well as small bowel imaging, strict definitions of complications, and use of objective measures of disease response. We also chose to evaluate early surgery as opposed to need for surgery at any time point for the definition of risk. We included patients with existing complicated disease behaviour at diagnosis who are a high-risk group that may be excluded in studies when complications instead of surgery is the study end point. Additionally, the algorithm is clinically feasible and applicable in both ambulatory and tertiary settings.[27,28] A prospective validation cohort for this algorithm is now underway in the UK, the Netherlands and Israel [NL57248.078.16]. Study limitations include that only a few children had surgery [$n$ = 31], although this reflects the proportion of paediatric patients who develop complications requiring surgical intervention.[6] As data were collected from real-world clinical practice, there are differences in the use of exclusive enteral nutrition, corticosteroid and immunomodulation therapy, as per physician preference and institutional culture. Despite the prospective nature of the study, residual confounding may still be present, in the form of pre-diagnosis factors such as growth impairment secondary to delayed diagnosis. Lastly, this clinical risk prediction model has been developed in only one cohort, and needs external validation in a replication cohort.

Development of clinical risk prediction tools will aid physicians in providing treatment options for children and their families, better inform them of prognosis, and highlight where early intervention may help change the natural progression of the disease.

## Funding

This study was funded by grants from the A.L. Thrasher foundation and the Porto group of ESPGHAN. Serologies were kindly performed by Prometheus San Diego. The work of the IBD team in Glasgow is supported by the Catherine McEwan foundation. R.K.R. is supported by an NHS senior research fellowship.

## Conflict of Interest

R.K.R. supported/contracted research for Nestle Health Sciences, and consulting fees for Abbvie, Therakos, Celltrion, and Vifor. J.C.E. has received grants and served on advisory boards for MSD, Janssen and Abbvie. A.L. has received grants, honoraria, travel, licensed IP or served on advisory boards/DSMBs for Janssen, Abbvie, Takeda, Celgene and Nestle Health Science. In the last 3 years, D.T. received consultation fee, research grant, royalties or honorarium from Janssen, Pfizer, Ferring, AstraZeneca, Abbvie, Takeda, Boehringer Ingelheim, Biogen, Atlantic Health, Shire, Celgene and Lilly. R.S.B. has received speaker fees or consulted for Takeda and Nestle Health science. N.C. is supported by a Crohn's and Colitis UK research fellowship. T.F.G. and N.C.D. have no conflicts to declare.

## Author Contributions

The study protocol was conceived and designed by A.L. Analysis of data was performed by R.K.R., T.F.G., N.C., R.S.B. and T.Z.B. All the authors reviewed the final manuscript and, with the exception of N.C., T.Z.B., R.S.B. and N.C.B., enrolled patients. Data were collected and queried by R.S.B., N.C.D. and T.F.G. The draft manuscript was written by R.K.R., N.C., T.Z.B. and A.L.

## Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

## References

1. Pigneur B, Seksik P, Viola S, *et al*. Natural history of Crohn's disease: comparison between childhood- and adult-onset disease. *Inflamm Bowel Dis* 2010;**16**:953–61.
2. Ruemmele FM, Veres G, Kolho KL, *et al*.; European Crohn's and Colitis Organisation; European Society of Pediatric Gastroenterology, Hepatology and Nutrition. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. *J Crohns Colitis* 2014;**8**:1179–207.
3. Caprilli R, Gassull MA, Escher JC, *et al*.; European Crohn's and Colitis Organisation. European evidence based consensus on the diagnosis and management of Crohn's disease: special situations. *Gut* 2006;**55**[Suppl 1]:i36–58.
4. Blackburn SC, Wiskin AE, Barnes C, *et al*. Surgery for children with Crohn's disease: indications, complications and outcome. *Arch Dis Child* 2014;**99**:420–6.
5. Hansen LF, Jakobsen C, Paerregaard A, Qvist N, Wewer V. Surgery and postoperative recurrence in children with Crohn disease. *J Pediatr Gastroenterol Nutr* 2015;**60**:347–51.
6. Kugathasan S, Denson LA, Walters TD, *et al*. Prediction of complicated disease course for children newly diagnosed with Crohn's disease: a multicentre inception cohort study. *Lancet* 2017;**389**:1710–8.
7. Kerur B, Machan JT, Shapiro JM, *et al*. Biologics delay progression of Crohn's disease, but not early surgery, in children. *Clin Gastroenterol Hepatol* 2018;**16**:1467–73.
8. Van Limbergen J, Russell RK, Drummond HE, *et al*. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. *Gastroenterology* 2008;**135**:1114–22.
9. Chatu S, Subramanian V, Saxena S, Pollok RCG. The role of thiopurines in reducing the need for surgical resection in Crohn's disease: a systematic review and meta-analysis. *Am J Gastroenterol* 2014;**109**:23–34; quiz 35.
10. Cohen-Dolev N, Sladek M, Hussey S, *et al*. Differences in outcomes over time with exclusive enteral nutrition compared with steroids in children with mild to moderate crohn's disease: results from the GROWTH CD study. *J Crohn's Colitis* 2018;**12**:305–312.
11. Levine A, Turner D, Pfeffer Gik T, *et al*. Comparison of outcomes parameters for induction of remission in new onset pediatric Crohn's disease: evaluation of the porto IBD group "growth relapse and outcomes with therapy" (GROWTH CD) study. *Inflamm Bowel Dis* 2014;**20**:278–85.
12. Ziv-Baran T, Hussey S, Sladek M, *et al*. Response to treatment is more important than disease severity at diagnosis for prediction of early relapse in new-onset paediatric Crohn's disease. *Aliment Pharmacol Ther* 2018;**48**:1242–50.
13. Levine A, Koletzko S, Turner D, *et al*.; European Society of Pediatric Gastroenterology, Hepatology, and Nutrition. ESPGHAN revised porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. *J Pediatr Gastroenterol Nutr* 2014;**58**:795–806.

14. Levine A, Griffiths A, Markowitz J, *et al*. Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. *Inflamm Bowel Dis* 2011;**17**:1314–21.
15. Hyams J, Markowitz J, Otley A, *et al*.; Pediatric Inflammatory Bowel Disease Collaborative Research Group. Evaluation of the pediatric Crohn disease activity index: a prospective multicenter experience. *J Pediatr Gastroenterol Nutr* 2005;**41**:416–21.
16. Birimberg-Schwartz L, Wilson DC, Kolho KL, *et al*.; paediatric IBD Porto group of ESPGHAN. pANCA and ASCA in children with IBD-unclassified, Crohn's Colitis, and Ulcerative Colitis-A longitudinal report from the IBD Porto group of ESPGHAN. *Inflamm Bowel Dis* 2016;**22**:1908–14.
17. Mitsuyama K, Niwa M, Takedatsu H, *et al*. Antibody markers in the diagnosis of inflammatory bowel disease. *World J Gastroenterol* 2016;**22**:1304–10.
18. Amil-Dias J, Kolacek S, Turner D, *et al*.; IBD Working Group of ESPGHAN [IBD Porto Group]. Surgical management of crohn disease in children: guidelines from the paediatric IBD Porto group of ESPGHAN. *J Pediatr Gastroenterol Nutr* 2017;**64**:818–35.
19. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. *Am J Epidemiol* 2007;**165**:710–8.
20. Kass GV. An exploratory technique for investigating large quantities of categorical data. *Appl Stat* 1980;**29**:119.
21. Rinawi F, Assa A, Hartman C, *et al*. Incidence of bowel surgery and associated risk factors in pediatric-onset Crohn's disease. *Inflamm Bowel Dis* 2016;**22**:2917–23.
22. Schechter A, Griffiths C, Gana JC, *et al*. Early endoscopic, laboratory and clinical predictors of poor disease course in paediatric ulcerative colitis. *Gut* 2015;**64**:580–8.
23. Crocco S, Martelossi S, Giurici N, Villanacci V, Ventura A. Upper gastrointestinal involvement in paediatric onset Crohn's disease: prevalence and clinical implications. *J Crohns Colitis* 2012;**6**:51–5.
24. Ricciuto A, Aardoom M, Orlanski-Meyer E, *et al*. P283 Predicting outcomes in paediatric Crohn's disease: a systematic review. *J Crohns Colitis* 2018;**12**[suppl 1]:S244.
25. Vernier-Massouille G, Balde M, Salleron J, *et al*. Natural history of pediatric Crohn's disease: a population-based cohort study. *Gastroenterology* 2008;**135**:1106–13.
26. Schaefer ME, Machan JT, Kawatu D, *et al*. Factors that determine risk for surgery in pediatric patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2010;**8**:789–94.
27. Legaki E, Gazouli M. Influence of environmental factors in the development of inflammatory bowel diseases. *World J Gastrointest Pharmacol Ther* 2016;**7**:112–25.
28. Benchimol EI, Mack DR, Guttmann A, *et al*. Inflammatory bowel disease in immigrants to Canada and their children: a population-based cohort study. *Am J Gastroenterol* 2015;**110**:553–63.