# Disease location as a predictor for clinical outcomes in Paediatric Crohn's Disease.

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Background & aims Disease location is a known predictor of adverse outcomes in paediatric Crohn's Disease, but data on clinical medium- and long-term outcomes are lacking. This study aims to evaluate disease location as a predictor of biochemical remission, disease severity, medication use, growth and adverse outcomes in paediatric Crohn's.

Methods 396 participants with paediatric Crohn's Disease were included and prospectively reviewed at set time points. Clinical data was calculated into disease activity scores and combined with laboratory results to compose the primary outcome.

Results 24.5% of participants had isolated ileal disease, 17.4% had isolated colonic disease and 58.1% had ileocolonic disease at baseline. Isolated ileal disease was associated with longer median time to diagnosis (209 ± 260 days) and more complicated disease at baseline. Ileocolonic disease was associated with higher prevalence of upper gastrointestinal disease, higher inflammation markers and lower albumin. Isolated ileal disease was associated with less achievement of biochemical remission within one year follow up, but not with sustained biochemical remission at one year follow up. Multivariate analysis showed no association between disease location (HR 0.45; 95%CI 0.20-1.01; p=0.053) and time to biochemical remission or time to biological treatment (HR 1.37; 95%CI 0.98-1.90; p=0.062).

Conclusion In paediatric Crohn's Disease, ileal involvement is associated with less biochemical remission within one year and unfavourable disease characteristics at baseline. Further research is needed to establish the relationship between disease location and prolonged biochemical remission.

## INTRODUCTION

Paediatric Inflammatory Bowel Disease (PIBD), is characterized by a complex and only partially unravelled pathogenesis[1,2] and significant heterogeneity in presentation in disease course[3]. Evidence-based knowledge on prognostic factors is required to develop personalized patient management strategies.

In paediatric Crohn's disease (CD), one of the hypothesized predictors is disease location as per the Paris Classification.[4] Literature regarding adults with CD identified ileal involvement as a risk factor for complicated disease behaviour and surgery[5], and a potential predictor of treatment responsiveness to biologics[6].

Because PIBD is thought to be etiologically distinct from adult IBD[4,7,8], these results require validation. In paediatric studies, including the systematic review from the PIBDAhead program, ileal location is associated with a higher risk of stricturing complications and may be a risk factor for penetrating complications[9-13] and surgery[11-14]. However, the heterogeneity of the methodology, mainly retrospective design and conflicting results of the studies impair the reported associations.

In light of the STRIDE-II consensus statements[15], the predictive qualities of disease location should not only be investigated as a predictor of complicated disease course, but must also be assessed in relation to intermediate and long-term treatment targets, ranging from clinical remission and normalization of biomarkers to endoscopic mucosal healing. Associations between disease location and disease severity and relapse in paediatric CD have been observed in several mainly retrospective, single center studies[11,14,16-19]. However, these studies did not assess biochemical markers like C-reactive protein (CRP) and faecal calprotectin (FCP) which are better correlated with endoscopic activity[15,20]. Progression to biological therapy as an indicator of unfavourable disease course has only been investigated in relation to disease location in two single-center retrospective studies[14,19]. Adequately sized prospective multicenter studies are needed to determine the role of disease location as a prognostic factor in pediatric CD.

Using real-world data from an international inception cohort[21], this study aims to investigate the value of disease location in predicting clinical outcome and complicated disease course, and response to treatment in paediatric CD. Ileal disease location is hypothesized to be a predictor of more severe disease course, and its predictive role in response to treatment will be determined.

## METHODS

*Study setting and participants*

The PIBD-SETQuality inception cohort study is an observational prospective study resulting from international Asian-European collaboration. Details of this study have previously been described[21]. In brief, patients <18 years old with a confirmed diagnosis of IBD based on the revised Porto criteria[22] were prospectively enrolled at 25 centers from 2017 onwards. The intended follow up period is 20 years after initial diagnosis. Participants from the PIBD-SETQuality inception cohort were eligible for this study if they were diagnosed with CD or IBD-unclassified (IBD-U) favouring CD, with available information about disease location at baseline. Participants with isolated upper gastrointestinal disease and without ileal or colonic involvement were not eligible.

*Data collection*

Data was collected in concordance with regular PIBD follow up visits at diagnosis (baseline), and after 4 weeks, 3 months, 6 months, one year, 18 months, 2 years and annually thereafter. At baseline, data on

family history, environmental factors, and demographics were collected. Time to diagnosis was calculated by subtracting the date the patient was reported to be 'last well' and the date of diagnosis. At every follow up visit, research staff documented clinical data including the participants' history, physical examination, the presence of extra-intestinal manifestations (EIMs) and/or perianal disease. Data on dosage and timing of induction and maintenance therapies were recorded, as well as clinical response to, side effects of and adjustments in the treatment regimen. Laboratory, imaging, and endoscopy results including Simple Endoscopic Score for Crohn's Disease (SES-CD) were collected. Every visit the disease activity was scored by the weighted Pediatric Crohn's Disease Activity Index-scores (wPCDAI)[23], the physician's global assessment (PGA) and the Mucosal Inflammation Non-invasive Index For Pediatric Crohn's Disease (MINI)[24]. Adverse events, including hospitalizations, ER visits, and surgery, were recorded. The Paris Classification was completed at baseline and annually thereafter. All data was collected in a secured electronic database, REDCap.

*Outcome measures*

The primary outcome of this study is sustained biochemical remission at one year follow up. Biochemical remission is defined as a combination of 1) clinical remission defined as weighted Paediatric Crohn's Disease Activity Index (wPCDAI) <12.5 as validated in paediatric cohorts[25] or a Physician's Global Assessment of disease activity scored as 'None'; and 2) CRP levels <5 mg/l. Sustained biochemical remission is defined as biochemical remission at three months, six months and one year follow up.

Secondary outcomes include biochemical remission rates, time to biochemical remission, relapse, sustained corticosteroid-free remission, corticosteroid-free remission rates, biological therapy use, immunomodulatory therapy use, growth, surgery, extra-intestinal manifestations and development of complicated disease and/or perianal disease.

Time to biochemical remission was defined as days from diagnosis to the date of the day of the blood draw from the visit biochemical remission as defined above was achieved. Relapse was defined as wPCDAI > 12.5 after initial achievement of clinical remission within one year after diagnosis. Time to relapse was calculated as time from diagnosis until the visit the first relapse was recorded. Corticosteroid-free remission (CSFR) was defined as 1) clinical remission as defined above; 2) no current corticosteroid use or previous corticosteroid use from three months after diagnosis onwards; 3) no previous or current immunomodulatory therapy or biological therapy. Sustained CSFR was defined as CSFR three months, six months and one year follow up. MINI medians and change from baseline were assessed at one year follow up.

The use of any biological therapy and immunomodulatory therapy was evaluated at one year follow up. Subsequently, in the group of participants who could be analysed for this outcome, the proportions of early biological or immunomodulatory drug use, i.e. within three months was assessed. Time to biological therapy was calculated as days from diagnosis until the start date of the first biologic agent participants received.

Growth was assessed by calculating height and weight measures into WHO Growth Indicators using the zscorer R package: An Anthropometric z-score Calculator.[26] For assessing linear growth mass-to-linear height ratios, the height-for-age Z-scores and BMI-for-age Z-scores were calculated for those 5 years and older. The change in Z-score (ΔZ) between baseline and one year after diagnosis was evaluated.

The rates of IBD-related luminal surgery, EIMs, new complicated of disease and new perianal disease were evaluated at end of follow up. Time to surgery was calculated in days from diagnosis to admission due to lacking surgery date. EIMs recorded included IBD-associated arthropathy, pancreatitis, skin disease including erythema nodosum and pyoderma gangrenosum, auto-immune hepatitis, primary sclerosing cholangitis or other IBD-associated liver disease, iritis or uveitis. New complicated disease was defined as new stricturing and/or penetrating luminal disease in participants with inflammatory (B1) disease at baseline, confirmed using imaging performed after 90 days from diagnosis until end of follow up. New perianal disease was defined as new ulceration, fistula(s) or abscess(es) after 90 days from diagnosis until end of follow up in patients without perianal disease at diagnosis.

*Description of variables*

Disease location was scored by the treating physicians and categorized into isolated ileal disease (L1), isolated colonic disease (L2) and ileocolonic disease (L3) as per the Paris classification[4]. If the Paris classification was missing at baseline, it was completed using the available endoscopy, imaging and clinical data, using the criteria listed in Appendix 1. In brief, endoscopy was required to assess the presence of colonic inflammation. Ileal inflammation was assessed by endoscopy or imaging results, such as magnetic resonance enterography (MRE), small bowel ultrasound, wireless capsule endoscopy or abdominal computed tomography scan. When the ileum could not be intubated during colonoscopy and no imaging results were available, we considered disease location as missing. In case of discrepancies between radiologic and endoscopic assessment of the ileum, full reports were retrieved. To differentiate isolated ileal disease with limited caecal disease from ileocolonic disease with only right colonic involvement, we evaluated the SES-CD score of the ascending colon. Mild inflammation according to global assessment and <50% affected surface was regarded as limited caecal inflammation, higher SES-CD scores were regarded as colonic involvement. Any ulcerative inflammation of the stomach, oesophagus or duodenum during endoscopy, was scored as upper gastrointestinal involvement (L4a as per Paris classification). Non-ulcerative isolated mild-to-moderate inflammation of the oesophagus, stomach and/or duodenum was regarded as non-specific oesophagitis, gastritis and duodenitis respectively, and did not classify as upper gastrointestinal disease (L4a). Stricturing (B2) and/or penetrating (B3) disease determined with endoscopic

or radiographic assessment. When missing, disease behaviour was scored as inflammatory. In concordance with the Paris Classification, perianal ulceration, fistula(e) and/or abscess(es) was classified as present perianal disease (P).

*Statistical analyses*

All statistical analyses were performed using IBM SPSS Statistics for Windows version 28.0.1.0 or R studio. Continuous data was presented as median and interquartile range (IQR) for abnormally distributed data, and as mean and standard deviation (SD) for normally distributed data. One-way ANOVA or Kruskal-Wallis tests were used to compare continuous variables at baseline and continuous outcomes at follow up between groups of disease location. Paired Sample T-tests were used to assessed change in continuous outcomes from baseline. Categorical variables were presented as frequencies and percentages and compared at baseline and follow up using the Fisher's Exact test or Pearson chi-square analysis where appropriate. Binominal logistic regression was performed to assess the association between dichotomized disease location and the likelihood of the binary primary and secondary outcomes at follow up, resulting in Odds Ratio's (OR) with 95% confidence intervals (95%CI) to describe the relationship between the predictor and outcome.

Cumulative probabilities of biochemical remission were estimated by plotting Kaplan-Meier curves stratified by disease location, and comparing the curves using the log-rank analysis. Identical procedures were performed to assess time to biological and time to relapse.

In the Cox Proportional Hazards Model, baseline variables potentially correlated with disease location and hypothesized predictors of time to remission, relapse and biologicals were assessed in a univariate analysis. If a p-value below 0.15 was found in the univariate analysis, the predictor was included in the multivariate analysis. The model was tested for Proportional Hazards Assumption. The association between the predictors and the outcome was presented as hazard ratio's (HR) and 95%CI with a HR greater than one reflecting shorter time to event. All analyses were 2-sided and the α-level was 0.05.

## RESULTS

*Study population*

Between January 2017 and 19 September 2022, 429 children with CD were enrolled in the PIBD-SETQuality inception cohort. After manually completing the Paris Classification for 87 participants, baseline information on disease location was available for 402 participants. Of the 27 participants with missing disease location at baseline, in 8 participants the ileum was not intubated during colonoscopy and not assessed with MRE or VCEA, and the remaining 21 had missing results on their endoscopy forms. 6 participants were excluded because there was no colonic or ileal involvement, resulting in 396 participants included in the study. 62.4% of participants (n=247) met the Porto criteria[22] for diagnosing IBD. Upper endoscopy was missing in 7.1% (n=28), and appropriate imaging, i.e. magnetic resonance enterography or wireless capsule endoscopy, in 35.9% (n=142).

*Associations with disease phenotype at diagnosis*

Table 1 displays the baseline characteristics of the included participants. The observed percentages for the disease location were 24.5%, 17.4%, and 58.1% for L1, L2 and L3, respectively. The participants for whom the Paris Classification was manually completed based on REDCap data there were no statistically significant differences in prevalence of disease location (p=0.424, Pearson $\chi 2$) proximal upper gastrointestinal tract involvement (L4a) (p=0.149, Pearson $\chi 2$) and inflammatory behaviour at baseline (B1, p=0.219, Pearson $\chi 2$) compared to the participants for whom the Paris Classification was assessed by a physician. There was a lower proportion of perianal disease (p=0.002, Pearson $\chi 2$) in the manually assessed group.

The median follow up was 17.6 months (IQR 18.3). The cohort showed male predominance (62.4%) which was most pronounced in the group with ileocolonic disease. The majority had inflammatory disease (B1) at baseline (88.7%), which occurred the most frequent in the colonic disease group (98.5%) and was least frequent in the ileal disease group (82.3%). In the group with ileocolonic disease at baseline, higher proportions of proximal and distal upper gastrointestinal tract involvement was observed. The mean BMI-for-age Z-scores were significantly lower in this group (mean -1.14 ± 1.37 SD, p=<0.001). At baseline, the group with ileocolonic disease had statistically significantly higher levels of inflammatory markers, i.e. ESR, CRP and white blood cell counts, and lower levels of albumin. FCP levels did not significantly differ.

The group with colonic disease had the least males (50.7%). Although the median at age diagnosis did not differ between groups, a higher proportion of children with very early onset (VEO) IBD was observed in the group with isolated colonic disease (8.7%). Isolated ileal disease was associated with a statistically significant longer time to diagnosis (median 209 days ± 201 IQR, p=0.023) and higher prevalence of stricturing disease (12.5% vs . 1.5% in the isolated colonic group and 6.1% in the ileocolonic group). Although the proportion of participants with perianal disease was numerically lower in this group (14.9% in the isolated ileal group vs. 22.1% and 24.8% in the isolated colonic and ileocolonic group, respectively), these results were not statistically significant.

223 participants (56.3%) were started on exclusive enteral nutrition as their induction therapy, 71 participants (17.9%) received biological therapy, 65 (16.4%) received corticosteroids and 11 (2.8%) received aminosalicylic acids. There was a statistically significant difference in distribution (Table 2).

*Disease Location at Diagnosis and sustained biochemical remission at one year follow up*

338 participants could be analysed for the primary outcome. At one year follow up, 39 participants had achieved biochemical remission since baseline and 9 participants had been in sustained biochemical remission since 3 months. In binary logistic regression, disease location was

**Table 1. Characteristics of entire cohort and disease location subgroups at baseline**

| | Overall (n=396) | L1 (n=97, 24.5%) | L2 (n=69, 17.4%) | L3 (n=230, 58.1%) | p-value |
|---|---|---|---|---|---|
| **Male** *n (%)* | 247 (62.4) | 57 (58.8) | 35 (50.7) | 155 (67.4) | **0.030**[a] |
| **Age at diagnosis in years** *median ± IQR* | 13.8 ± 3.8 | 14.1 ± 4.3 | 13.7 ± 5.3 | 13.5 ± 3.5 | 0.401[c] |
| VEO-IBD *n (%)* | 9 (2.3) | 1 (1.0) | 6 (8.7) | 2 (0.9) | **0.002**[b] |
| **Ethnicity** *n (%)* | | | | | 0.984[b] |
| White | 240 (68.6) | 60 (67.4) | 42 (66.7) | 138 (69.7) | |
| Asian | 44 (12.6) | 11 (12.4) | 9 (14.3) | 24 (12.1) | |
| Black | 11 (3.1) | 4 (4.5) | 2 (3.2) | 5 (2.5) | |
| Hispanic | 1 (0.3) | - | - | 1 (0.5) | |
| Mixed or Other | 54 (15.4) | 14 (15.7) | 10 (15.9) | 30 (15.2) | |
| **Family history of IBD** 1st degree *n (%)* | 77 (19.5) | 21 (22.1) | 15 (21.7) | 41 (17.8) | 0.614[a] |
| **IBD-U favouring CD** *n (%)* | 14 (3.5) | 0 (0) | 6 (8.2) | 7 (3.2) | **0.008**[b] |
| **Time to diagnosis in days** *median ± IQR* | 153 ± 201 | 209 ± 260 | 120 ± 146 | 148 ± 199 | **0.023**[c] |
| **Upper gastrointestinal tract disease*** *n (%)* | | | | | |
| None | 184 (47.9) | 57 (50.0) | 41 (61.2) | 86 (38.7) | **0.003**[b] |
| L4a | 171 (44.5) | 32 (33.7) | 23 (34.3) | 116 (52.3) | |
| L4b | 25 (6.5) | 6 (6.3) | 3 (4.5) | 16 (7.2) | |
| L4ab | 4 (1.0) | 0 (0) | 0 (0) | 4 (1.8) | |
| **Behaviour*** *n (%)* | | | | | **0.047**[b] |
| B1 | 377 (88.7) | 79 (82.3) | 66 (98.5) | 202 (88.6) | |
| B2 | 27 (6.9) | 12 (12.5) | 1 (1.5) | 14 (6.1) | |
| B3 | 18 (4.7) | 4 (4.2) | 0 (0) | 9 (3.9) | |
| B2B3 | 4 (1.0) | 1 (1.0) | - | 3 (1.3) | |
| **Perianal disease*** *n (%)* | 85 (21.9) | 14 (14.9) | 15 (22.1) | 56 (24.8) | 0.150[a] |
| **Z-Scores** | | | | | |
| Height-for-age *mean ± SD* | -0.07 ± 1.18 | 0.03 ± 1.23 | 0.20 ± 1.00 | -0.19 ± 1.19 | 0.067[d] |
| BMI-for-age *mean ± SD* | -0.87 ± 1.50 | -0.52 ± 1.51 | -0.51 ± 1.72 | -1.14 ± 1.37 | **<0.001**[d] |
| **EIM** *n (%)* | 40 (10.2) | 9 (9.5) | 8 (11.6) | 23 (10.0) | 0.895[b] |
| **Laboratory findings** | | | | | |
| Hb, *mmol/l mean ± SD* | 7.0 ± 1.0 | 7.2 ± 1.0 | 7.0 ± 1.2 | 7.0 ± 1.0 | 0.514[d] |
| ESR *mm/h median ± IQR* | 31.0 ± 31.0 | 26.5 ± 25.5 | 33 ± 51 | 34 ± 28 | **0.023**[c] |
| CRP *mg/l median ± IQR* | 19.0 ± 40.6 | 14 ± 30.7 | 14.5 ± 24.6 | 24 ± 43 | **<0.001**[c] |
| WBC count *x10^9 median ± IQR* | 8.6 ± 3.8 | 8.1 ± 3.6 | 8.5 ± 5.2 | 9.1 ± 4.0 | **0.016**[c] |
| ASAT *U/l median ± IQR* | 19 ± 10 | 21 ± 12 | 23 ± 12 | 18 ± 8 | **0.003**[c] |
| ALAT *U/l median ± IQR* | 11 ± 8 | 13 ± 8 | 13 ± 11 | 11 ± 8 | **0.007**[c] |
| Albumin, *g/l mean ± SD* | 35.6 ± 6.6 | 36.9 ± 6.4 | 36.1 ± 7.2 | 34.9 ± 6.4 | **0.049**[d] |
| **FCP** *mcg/g median ± IQR* | 1451 ± 1861 | 982 ± 1655 | 1766 ± 2518 | 1505 ± 1765 | 0.224[c] |
| **MINI** *median ± IQR* | 17 ± 6 | 14 ± 7 | 18 ± 8 | 17 ± 4 | 0.104[c] |
| **wPCDAI** *median ± IQR* | 45 ± 32 | 43 ± 25 | 51.3 ± 41.8 | 45 ± 33 | 0.162[c] |

a =Pearson's Chi Square test; b=Fisher's Exact test; c = Kruskal-Wallis test; d = one-way ANOVA; *According to the Paris classification. EIM = extra-intestinal manifestations; FCP = faecal calprotectin; wPCDAI= weighted Pediatric Crohn's Disease Activity Index ; MINI = Mucosal Inflammation Non-invasive Index

dichotomized and the group with isolated ileal disease (indicator) was compared with the group with colonic or ileocolonic disease. Isolated ileal disease was associated with lower biochemical remission rates within one year from diagnosis (OR 0.33; 95% CI 0.12-0.90; p=0.03) but not with sustained biochemical remission (OR 0.38; 95%CI 0.04-2.73; p=0.309) at one year follow up (Table 3).

*Disease Location at Diagnosis and other Clinical Outcomes at one year Follow up*

Table 3 summarizes the prevalences of the other outcomes in participants compared by disease location at baseline. Higher proportions of relapse were observed in the ileocolonic disease group, although this was not statistically significant (p=0.078). Disease location was not associated with (sustained) corticosteroid-free remission rates. There was statistically significant change in MINI and BMI-for-age Z-scores from baseline, without any statistically significant differences between disease location subgroups.

Ileocolonic disease was associated with higher rates of biological therapy use at three months (OR 2.28; 1.71-4.67 95%CI p<0.001) and one year (OR 2.34; 95%CI 1.42-3.93; p<0.001) follow up. 49.6% of participants with ileocolonic disease received biological therapy within 3 months and 75.2% within one year after diagnosis.

Lower surgery rates in the isolated colonic disease group were near-significant (p=0.051). The rates of EIMs at end of follow up were numerically higher in the isolated colonic disease group albeit without statistical significance (p=0.087).

**Table 2: Type of induction therapy per disease location at baseline**

| | Overall (n=396) | L1 (n=98) | L2 (n=70) | L3 (n=230) | p-value |
|---|---|---|---|---|---|
| **Type of induction therapy** *n (%)* | | | | | **0.001[a]** |
| **None** | 26 (6.6) | 6 (6.2) | 4 (5.8) | 16 (7.0) | |
| **EEN** | 223 (56.3) | 58 (59.8) | 35 (50.7) | 130 (56.5) | |
| **Biologicals** | 71 (17.9) | 11 (11.3) | 6 (8.7) | 54 (17.9) | |
| **Corticosteroids** | 65 (16.4) | 20 (20.6) | 18 (26.1) | 27 (11.7) | |
| **Aminosalicylic acids** | 11 (2.8) | 2 (2.1) | 6 (8.7) | 3 (1.3) | |

EEN = exclusive enteral nutrition; a = Fishers' Exact Test;

*Survival Analyses for Clinical Outcomes According to Disease Location at Diagnosis*

Survival analysis of time to biochemical remission, relapse and start biological therapy according to disease location are illustrated as Kaplan-Meier curves (Figure 1a-d). Biochemical remission occurred in 54 participants (mean time to biochemical remission 52.9 months). Disease location affected the time to biochemical remission (log rank p=0.045). The longest time to biochemical remission was observed in the group with isolated ileal disease (mean time to biochemical remission 55.5 months).

A Cox Proportional Hazards Model (Table 4) to predict time to biochemical remission was constructed, with baseline variables including demographic factors, other components of the Paris Classifications and variables statistically significantly associated with disease location at baseline. In multivariate analysis, both isolated ileal disease (HR 0.45; 95%CI 0.20-1.01; p=0.053) and days to diagnosis >120 days (HR 0.62; 95%CI 0.36-1.07; p=0.088) showed a trend towards statistical significance for independently predicting time to biochemical remission.

Time to start of biological therapy differed between groups of disease location (p<0.001). The cumulative incidence of biological therapy during follow up was 67.8% and mean time to biological therapy was 13.5 months for the entire group, 9.6 months for the group with ileocolonic disease and 18.5 months for the group with isolated ileal disease. When corrected for other baseline variables (Table 5), ileocolonic disease location at baseline did not achieve statistical significance (HR 0.72 95% 0.49-1.06; p=0.091). Perianal disease at baseline was the only statistically

**Table 3: secondary outcomes at 3 months and one year follow up**

| | Overall | L1 | L2 | L3 | p-value | Ind. | OR (95% CI) | p-value |
|---|---|---|---|---|---|---|---|---|
| Clinical outcomes at one year follow up | | | | | | | | |
| Had biochemical remission *n (%)* | 39 (20.3) | 5 (9.6) | 8 (25.0) | 26 (20.3) | 0.065[a] | L1 | 0.33 (0.12-0.90) | 0.030[b] |
| Sustained biochemical remission *n (%)* | 9 (2.7) | 1 (1.1) | 3 (5.2) | 5 (2.6) | 0.330[a] | L1 | 0.38 (0.04-2.73) | 0.309[b] |
| Had corticosteroid-free remission *n (%)* | 222 (85.7) | 63 (88.7) | 33 (76.7) | 126 (86.9) | 0.204[c] | L2 | 0.47 (0.21-1.06) | 0.070[b] |
| Sustained corticosteroid-free remission *n (%)* | 59 (22.4) | 17 (24.6) | 10 (21.3) | 32 (21.8) | 0.899[c] | L2 | 0.92 (0.43-1.99) | 0.834[b] |
| Relapse *n (%)* | 85 (36.5) | 25 (37.9) | 9 (23.7) | 51 (39.5) | 0.119[a] | L2 | 0.49 (0.22-1.08) | 0.078[b] |
| MINI *median ± IQR* | 5 ± 10* | 5 ± 8* | 6 ± 15* | 4.5 ± 21* | 0.622[e] | | N/a | |
| ΔMINI *mean ± SD* | -11.5 ± 7.4 | -11.6 ± 5.7 | -15.5 ± 8.2 | -10.6 ± 7.9 | 0.314[d] | | N/a | |
| Height-for-age Z-score *mean ± SD* | -0.08±1.11 | -0.12±1.14 | 0.06±1.12 | -0.11±1.10 | 0.376 | | N/a | |
| BMI-for-age Z-score *mean ± SD* | 0.12±1.18 | 0.31±1.16 | 0.46±1.14 | -0.05±1.16 | **0.031[d]** | | N/a | |
| ΔBMI-for-age *mean ± SD* | 1.06 ± 1.00* | 1.01 ± 1.03* | 0.93 ± 1.14* | 1.11 ± 1.09* | 0.667[d] | | N/a | |
| Medication use at one year follow up | | | | | | | | |
| Biological therapy *n (%)* | 186 (66.9) | 41 (56.2) | 27 (56.3) | 118 (75.2) | 0.004[c] | L3 | 2.34 (1.42-3.93) | <0.001[b] |
| Within 3 months *n (%)* | 119 (42.8) | 19 (26.0) | 16 (33.3) | 84 (53.5) | <0.001[c] | L3 | 2.28 (1.71-4.67) | <0.001[b] |
| Immunomodulatory therapy *n (%)* | 233 (83.8) | 61 (83.6) | 42 (87.5) | 130 (82.8) | 0.792[c] | L2 | 1.43 (0.57-3.59) | 0.448[b] |
| Within 3 months *n (%)* | 191 (68.7) | 47 (64.4) | 33 (68.8) | 111 (70.7) | 0.640[c] | L2 | 0.99 (0.51-1.96) | 0.904[b] |
| Complicated disease at end of follow up | | | | | | | | |
| New complicated disease *n (%)* | 13 (3.3) | 6 (6.2) | 1 (1.4) | 6 (2.6) | 0.202[a] | L2 | 0.39 (0.05-3.02) | 0.364[b] |
| New perianal disease *n (%)* | 15 (3.8) | 2 (2.1) | 4 (5.8) | 9 (3.9) | 0.405[a] | L2 | 1.77 (0.55-5.73) | 0.342[b] |
| EIMs *n (%)* | 74 (18.7) | 15 (15.6) | 18 (26.1) | 41 (17.8) | 0.217[c] | L2 | 1.70 (0.93-3.13) | 0.087[b] |
| Surgery *n (%)* | 21 (5.3) | 9 (9.3) | 1 (1.4) | 11 (4.8) | 0.090[a] | L1 | 2.45 (1.00-6.00) | 0.051[b] |

a= Fisher's Exact test; b = binary logistic regression; c =Chi-Square test; d=One-Way Anova; e= Kruskal-Waliis test ;
*Statistically significant from baseline (paired T-test); Ind. = indicator category in dichotomization of the variable for binary logistic regression. wPCDAI= weighted Pediatric Crohn's Disease Activity Index ; MINI = Mucosal Inflammation Non-invasive Index; EIM = extra-intestinal manifestations;

significant independent predictor of shorter time to biological therapy in multivariate analysis (HR 2.68; 95%CI 1.88-3.81; p<0.001). Disease location did not predict mean time to relapse (overall 34.8 months, cumulative incidence 33.7%), or mean time to surgery (overall 59.5 months, cumulative incidence 5.3%).

## DISCUSSION

This was the first study to assess disease location as a predictor of an outcome combining clinical remission and low biomarkers. In this multicentre international cohort study, analysis of 396 participants diagnosed with paediatric CD demonstrated that isolated ileal disease location as per the Paris Classification was associated with a lower chance of achieving biochemical remission within one year from diagnosis. Additionally, ileal disease was found to be associated with longer time to biochemical remission, although statistical significance of this association did not sustain in multivariate Cox Regression analysis.

The STRIDE-II Systematic Review & Meta-Analysis[15] emphasized that endoscopic healing is associated with favourable long term outcomes and should be pursued in PIBD management. Non-invasive biomarkers in combination with clinical symptoms have been proven to correlate with endoscopic healing. In this light the chosen outcome biochemical remission is both a clinically relevant outcome with potential prospective value.

Sassine et al.[17] conducted a retrospective, single center cohort study to investigate predictors of time to clinical remission based on PCDAI in 654 patients diagnosed paediatric CD. In multivariate linear regression models, upper gastro-intestinal tract involvement was associated with longer time to clinical remission. These findings demonstrate the impact of phenotype on clinical outcomes but do not compare to this study, since biomarkers were not taken into account and lower gastrointestinal tract disease was not separately assessed.

Even though the findings might suggest better clinical outcomes at one year follow up, the MINI did not differ between groups of disease location. However, since FCP was not routinely tested during follow up, a lot of missing values for FCP accounted for a large number of missing values for the MINI. This impeded investigating the association with disease location.

An interesting finding is that in ileocolonic disease was found to be associated with statistically significantly more biological therapy use within three months and one year from diagnosis. Shorter time to biological therapy was observed in the group with ileocolonic disease, but its predictive value was not proven in multivariate analysis (HR =1.37; 95%CI 0.98-1.90; p=0.062). The high rates of biological therapy use within one year and three months are unparalleled in current literature. This reflects the recent conclusion from the RISK-study that early anti-TNF use is associated with favourable clinical outcomes[27] which has since been incorporated in the PIBD treatment guidelines[28]. Perianal disease at diagnosis was the only statistically significant predictor of shorter time to biological therapy (HR 2.68; 95% CI 1.88-3.81; p<0.001). This is not surprising, since perianal disease at diagnosis is an

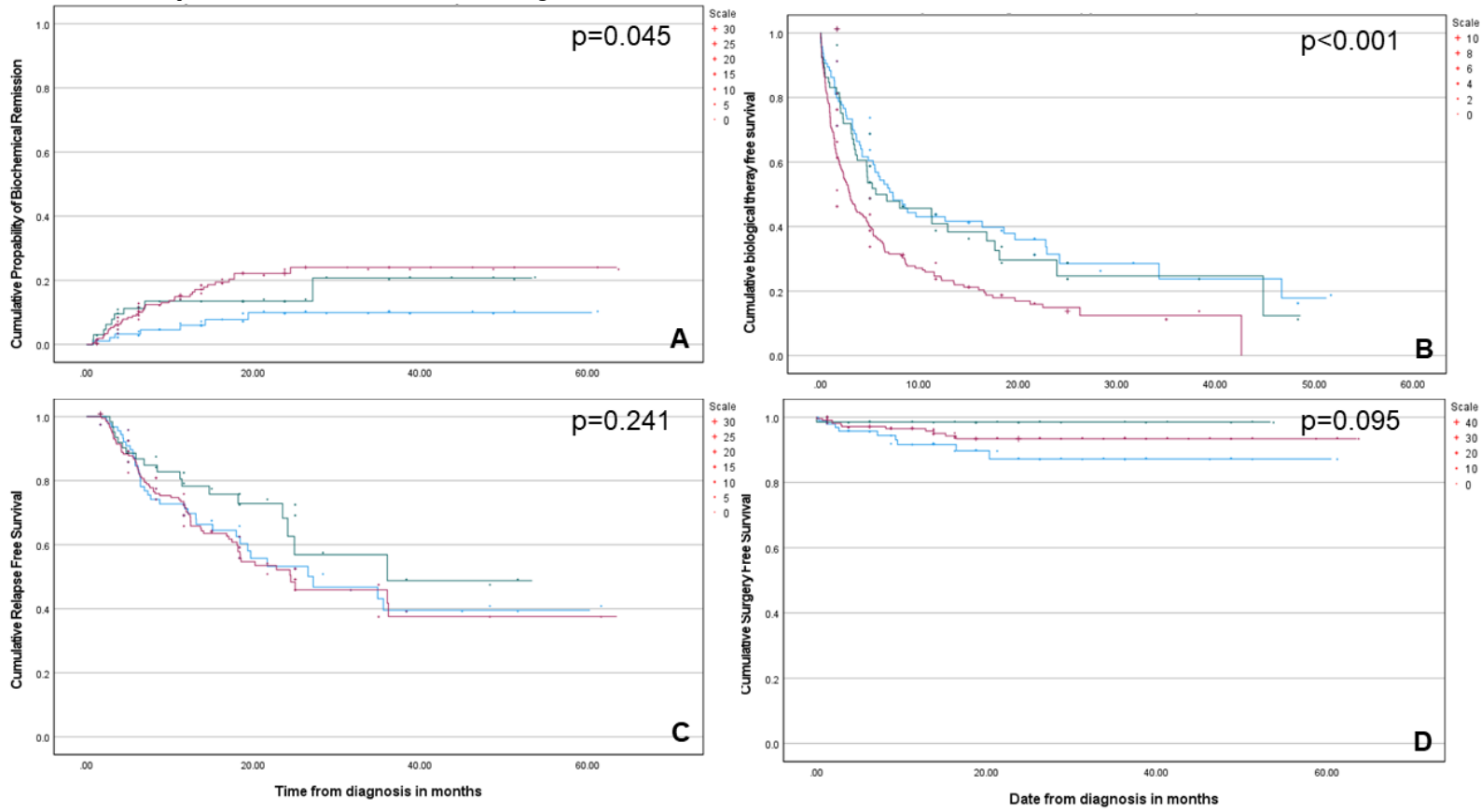


**Figure 1: Kaplan-Meier estimates of a. time to biochemical remission; b. time to biological therapy; c. time to relapse; d. time to surgery; Blue = L1; Green = L2; Red = L3.**

indication to start with up-front anti-TNF therapy in the latest and previous PIBD management guidelines.[28,29] The latest guideline also recommends up-front anti-TNF therapy in patients with extensive disease, i.e. ileocolonic disease with upper gastrointestinal tract involvement, which might contribute to an association found between ileocolonic disease and biological therapy use.

This study demonstrated significantly lower mean BMI-for-age Z-scores at diagnosis and one year follow up in the group with ileocolonic disease. This contrasts previous findings. De Greef et al.[16] found no such association. Vesseur et al.[30] evaluated 261 patients with paediatric Crohn's disease from the French EPIMAD registry and found disease location not to be associated with BMI Z-scores at diagnosis or follow up. Possibly, the larger sample size of this study enabled demonstration of this association for the first time.

Similar to the study by Riciuttio et al.[12] a longer time to diagnosis was found in participants with isolated ileal disease location. A higher prevalence of stricturing disease at baseline was also observed in this group. However, independent association between time to diagnosis and stricturing disease at baseline was not precluded.

The investigated cohort was characterized by a high proportion of ileocolonic disease (58.1%) and inflammatory behaviour (88.7%) similar to previous European[31,32] and North-American cohorts[27,33]. The baseline prevalence of perianal disease in this cohort was high compared to previously reported (2-17%)[27,32-35], possibly reflecting over-reporting perianal fissures and skin tags as perianal disease. In concordance with earlier studies, disease location was not found to be a predictor of perianal disease in this cohort. The prevalence of EIMs at diagnosis (10.2% for the overall cohort) was strikingly lower than those found in previous EIM-focused studies.[36-37] In this study, aphtous stomatitis was not specifically listed in the form used to extra-intestinal manifestations, which might explain this difference.

Surprisingly, in this study we failed to demonstrate statistically significant association (p=0.051) between disease location and surgery. The median follow up of 17.6 months found in this study is substantially lower than the average follow up in the studies that have previously reported on this association[13]. This has resulted in very low absolute risks of surgery in our cohort, impeding statistical significance. Therefore, there is no reason to believe that our findings contrast previous reports. The same reasoning also applies to the development of complicated disease.

The prospective design and large sample size are the major strengths of this cohort. Furthermore, we established robust baseline data by manually completing the missing data for the Paris Classification. The risk of reporter bias was minimalized because the primary outcome was composed of standardized disease activity scores and an objective and widely used biomarker. Real-world data was collected at frequent standardized follow up visits. This detailed clinical data provides detailed insight in the disease course of paediatric CD patients around the globe.

A limitation of the study was the low median follow up. It was however unlikely that this introduced any selection bias because loss-to-follow up is not likely to be related to either disease location or the outcome. Data on perianal disease was collected in two forms and many discrepancies were found between those forms and the baseline Paris Classification, in a way that both over- and underreporting of perianal disease

**Table 4. Cox Regression Proportional Hazards Model for predicting time to biochemical remission**

| Variables at baseline | Time to biochemical remission | | | |
|---|---|---|---|---|
| | Univariate *HR 95%CI* | P-value | Multivariate *HR 95%CI* | P-value |
| Isolated ileal disease | 0.39 [0.18-0.87] | 0.021 | 0.45 [0.20-1.01] | 0.053 |
| Age at diagnosis >13 years | 0.40 [0.80-1.36] | 0.404 | | |
| Male gender | 1.08 [0.63-1.87] | 0.774 | | |
| White ethnicity | 0.75 [0.42-1.34] | 0.335 | | |
| Upper gastrointestinal tract involvement | 1.62 [0.93-2.82] | 0.091 | 1.42 [0.81-2.48] | 0.227 |
| Penetrating and/or stricturing disease | 1.24 [0.56-2.75] | 0.592 | | |
| Perianal disease | 1.50 [0.83-2.73] | 0.183 | | |
| EIMs | 1.58 [0.67-3.07] | 0.295 | | |
| BMI Z-score <-1.0 at diagnosis | 1.15 [0.65-2.06] | 0.629 | | |
| Days to diagnosis > 120 days | 0.58 [0.34-1.00] | 0.048 | 0.62 [0.36-1.07] | 0.088 |
| MINI≥11 | 0.80 [0.27-2.40] | 0.686 | | |
| wPCDAI>40 | 0.84 [0.48-1.44] | 0.524 | | |
| FCP >300mcg/l | 0.70 [0.16-3.02] | 0.633 | | |
| ESR>20mm/h | 1.62 [0.80-3.28] | 0.162 | | |
| CRP >7.5mg/l | 0.89 [0.49-1.60] | 0.690 | | |
| Albumin <31g/L | 1.34 [0.74-2.42] | 0.337 | | |
| Biological induction therapy | 0.91 [0.44-1.86] | 0.789 | | |
| EEN induction therapy | 1.34 [0.76-2.34] | 0.304 | | |
| Corticosteroid induction therapy | 0.79 [0.37-1.68] | 0.540 | | |

HR = Hazard Ratio; EIMs = extra-intestinal manifestations; MINI = mucosal inflammation non-invasive index; wPCDAI = weighted paediatric Crohn's Disease Activity Index; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; FCP = faecal calprotectin. *A hazard ratio > 1 reflects shorter time to biochemical remission.*

could have occurred. Because FCP was not measured on standardized time points, this could have led to bias because FCP is less frequently measured in participants in remission.

Because the presence or absence of biochemical remission must be established using the laboratory results and clinical data from a set time point, the follow up visit, it only provides a snapshot of biochemical remission status at the time of the visit. To evaluate biochemical remission over time, sustained biochemical remission was therefore chosen as the primary outcome. If participants achieved biochemical remission in between visits but were not in biochemical remission at the time of visit, this could have led to underestimation of the results. This risk is small in the first year of follow up in which frequent visits occur but is higher after 2 years of follow up. The estimation of time to remission also becomes less reliable. Thus, outcome time to biochemical remission becomes less informative after 2 years of follow up because increased visit interval makes it hard to establish exact time to event, and the found association might have been underestimated.

In conclusion, isolated ileal involvement is associated with less frequent achievement of biochemical remission within one year and might be associated with shorter time to biochemical remission. However, since no association was found for sustained biochemical remission, the predictive value of disease location in predicting long-term biochemical remission was not demonstrated. Furthermore, ileal involvement and especially ileocolonic disease is associated with unfavourable characteristics at baseline, but disease location was not associated with overall severe disease activity according to the MINI. Insufficient follow up time prevented demonstration of the association between disease location and surgery rates and rates of development of complicated disease.

The PIBD-SETQuality cohort will continue its follow up, which means the already robust real-world data from this cohort will only grow to be more valuable over time. Further research should focus on the association between phenotype and clinical outcomes correlated with endoscopic healing, using standardized assessment of important biomarkers (FCP, CRP).

**Table 5. Cox Regression Proportional Hazards Model for predicting time to biological treatment**

| **Baseline characteristics** | **Time to biological treatment** | | | |
|---|---|---|---|---|
| | **Univariate *HR 95%CI*** | **P-value** | **Multivariate *HR 95%CI*** | **P-value** |
| Ileocolonic disease | 1.70 [1.32-2.18] | <0.001 | 1.37 [0.98-1.90] | 0.062 |
| Age at diagnosis >13 years | 1.12 [0.88-1.44] | 0.351 | | |
| White ethnicity | 1.18 [0.90-1.57] | 0.221 | | |
| Male gender | 0.83 [0.65-1.07] | 0.155 | | |
| Penetrating and/or stricturing disease behaviour | 1.67 [1.17-2.38] | 0.005 | 1.47 [0.92-2.34] | 0.108 |
| Upper gastro-intestinal tract involvement | 1.30 [1.02-1.66] | 0.037 | 1.19 [0.87-1.64] | 0.272 |
| Perianal disease | 2.51 [1.90-3.31] | <0.001 | **2.71 [1.91-3.88]** | **<0.001** |
| EIMs | 1.30 [0.89-1.91] | 0.173 | | |
| BMI Z-score <-1.0 | 1.32 [1.02-1.71] | 0.036 | 1.14 [0.81-1.59] | 0.458 |
| Days to diagnosis>120 days | 0.93 [0.72-1.18] | 0.535 | | |
| MINI≥11 | 1.43 [0.83-2.45] | 0.194 | | |
| wPCDAI>40 | 1.36 [1.05-1.75] | 0.019 | 1.11 [0.75-1.64] | 0.594 |
| FCP>300mcg/l | 0.90 [0.52-1.57] | 0.901 | | |
| ESR>20mm/h | 1.61 [1.20-2.18] | 0.009 | 1.14 [0.78-1.70] | 0.512 |
| CRP >7.5mg/l | 1.70 [1.13-2.30] | <0.001 | 1.38 [0.91-2.09] | 0.127 |
| Albumin <31g/L | 1.57 [1.20-2.07] | 0.001 | 1.35 [0.90-2.04] | 0.156 |

HR = Hazard Ratio; EIMs = extra-intestinal manifestations; MINI = mucosal inflammation noninvasive index; wPCDAI = weighted paediatric Crohn's Disease Activity Index; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein. *A hazard ratio > 1 reflects shorter time to biological treatment.*

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# APPENDIX

| Disease location | Must meet following requirements on endoscopy and/or imaging[i]*: |
|---|---|
| Isolated ileal disease +- limited caecal disease (L1) | 1. (Macroscopically) abnormal ileum according to endoscopic and/or MRE assessment.**<br>2. Endoscopy shows macroscopically normal right colon OR<br>Endoscopy shows macroscopically abnormal right colon limited to mild inflammation according to global assessment and <50% affected surface during endoscopy AND no evidence of colonic involvement on MRE.<br>3. Endoscopy shows macroscopically normal rectum, transverse and left colon at endoscopic assessment. |
| Isolated colonic disease (L2) | 1. Endoscopy shows macroscopically abnormal rectum, right colon, transverse colon, or left colon.<br>2. (Macroscopically) normal ileum according to endoscopic and/or MRE assessment.** |
| Ileocolonic disease (L3) | 1. Macroscopically abnormal ileum according to endoscopic and/or MRE assessment.**<br>2. Endoscopy shows macroscopically abnormal right colon minimally scored as moderate inflammation on global assessment, and/or macroscopically abnormal left colon, transverse colon, rectum. |
| Upper GI disease | Must meet following requirements on endoscopy and/or imaging*: |
| No upper gastrointestinal disease (L4()) | Gastroscopy shows macroscopically normal oesophagus, stomach and duodenum OR<br>The stomach, oesophagus, and/or duodenum are mildly or moderately inflamed according to Global Assessment during gastroscopy, without ulceration***. |
| Proximal upper gastrointestinal disease (L4a) | Gastroscopy shows severe inflammation or ulceration in the oesophagus, stomach and/or duodenum. |
| Distal upper gastrointestinal disease (L4b) | Jejunal or proximal ileal involvement is specifically described in MRE or other radiological reports |
| Behaviour | Must meet following requirements on endoscopy and/or imaging*: |
| Non-stricturing, non-penetrating disease (B1) | No evidence of stricturing or penetrating luminal disease during endoscopy and/or MRE. |
| Stricturing disease (B2)<br>Penetrating disease (B3)<br>Stricturing and penetrating disease (B2B3) | Evidence of stricturing disease and/or penetrating luminal disease on radiological assessment and/or endoscopy. |
| Perianal disease | Must meet following requirements stated in endoscopy report or clinical data*: |
| Perianal disease (P) | 1. Reported peri-anal ulcers, fistula(s) and/or abscess(es). |

i; imaging includes: magnetic resonance enterography, small bowel ultrasound, wireless capsule endoscopy or abdominal computed tomography scan

*If macroscopic involvement is seen on endoscopy OR imaging, the bowel section was scored as 'involved' . If no endoscopy was performed, colonic involvement could not be assessed, and therefore disease location could not be completed.

**If the ileum was not intubated, small bowel wall enhancement on imaging was interpreted as ileal disease. If no small bowel wall enhancement was present on imaging and the ileum was not endoscopically assessed, ileal involvement was precluded. If the ileum was endoscopically nor radiologically assessed, disease location could not be completed.

***The components 'Ulcerated Surface' and 'Size of Ulcers' are both scored as 0.