DOI: 10.53469/jcmp.2024.06(08).46

Clinical Characteristics and Related Factors of Pediatric Crohn's Disease with Perianal Disease

Hongding Wang, Dongmei Wei, Shenglan Ning, Jiani Pan, Zhongqin Jin*

**Correspondence Author, Jinzhongqin628@126.com*

Abstract: ***Objective:*** ***Perianal Lesions are among the most serious complications of Crohn disease in pediatric. our objective was to analyze the chinical characteristics of crohn's disease with perianal disease in children. And explore the influencing factors of perianal crohn's disease.*** ***Methods:*** ***A retrospective analysis was conducted on the children, who were diagnosed with Crohn's disease (CD) from April 2019 to April 2023. According to the American gastroenterological association technical review criteria (2003 edition), they were divided into two groups: the perianal lesion (PD) group (n=38) and non- perianal lesion group(n=41). The two groups were compared in terms of clinical characteristics, laboratory test results, Pediatric Crohn's Disease Activity Index (PCDAI)scores and treatment.*** ***Results:*** ***The incidence of crohn's disease with perianal disease was 48.1% (38/79). The mean age of the perianal lesion group was10.78±3.69 years, and 78% were males. Among the perianal lesion group, the most common types are anal fistula and perianal abscess, accounting for 36.8%and44.7%.The level of C-reactive protein(CRP), gender and PCDAI scores in the PD group was significantly higher than that in the non-PD group, and the difference between the groups was statistically significant (P<0.05), whlie other serological indexes was not statistically significant (P>0.05).*** ***Conclusion:*** ***Male children with CD are more likely to be complicated with perianal lesions. When young children, especially boys, have perforation, fistula and other deep penetrating lesions, crohn's disease screening may be considered. The disease activity index of PD crohn's disease in children showed moderate-severe inflammatory changes. Among the perianal lesion group, there is a high proportion of children with the use of biological agents.***

Keywords: Clinical Characteristics, Crohn's Disease, Perianal lesion**.**

1. Introduction

The incidence rate of Crohn's disease is on the rise worldwide, especially among children and adolescents [1]. Data shows that one quarter of Crohn's disease patients worldwide have perianal lesions, with 18% of cases presenting as penetrating lesions of fistulas and abscesses [2]. The cumulative incidence rate of perianal Crohn's disease increases with the course of the disease. In a population-based study, the probability of any type of perianal lesions occurring 10 and 20 years after diagnosis was 29.5% and 42.7%, respectively. In particular, the probability of anal fistula occurring 10 and 20 years after diagnosis was 16.9% and 28.3%, respectively. 17.2% of patients developed perianal lesions 6 months before Crohn's disease diagnosis, 26.9% of patients developed perianal lesions 6 months before Crohn's disease diagnosis to 6 months after diagnosis, and the remaining 55.9% of patients first developed perianal diseases 6 months after Crohn's disease diagnosis [3]. A study on children with Crohn's disease showed that despite receiving the best treatment, up to one-third of pediatric patients still experience complications related to Crohn's disease, including anal fistula, stenosis, or perianal abscess [4]. Conversely, perianal lesions may also be the first manifestation of Crohn's disease. Studies have shown that the prevalence of perianal diseases in newly diagnosed children with Crohn's disease ranges from 8% to 26% [5-7]. In a large multicenter prospective database cohort containing over 6600 pediatric Crohn's disease patients, 21% reported perianal disease, with an estimated probability of 4%, 9%, 17%, and 26% at 2 months, 1 year, 3 years, and 5 years after diagnosis [4]. Perianal Lesions are a common complication of CD. The objective of this study to analyze the clinical characteristics of Crohn's disease complicated with perianal lesions in children, And provide reference for the diagnosis and treatment of children with CD.

2. Methods

2.1 Patients and Methods

This study used a retrospective analysis to select children diagnosed with Crohn's disease between April 2019 and April 2023 in Children's hosptital of Soochow University. Strictly follow the diagnostic standards of the Expert Consensus on the Diagnosis and Treatment of Inflammatory Bowel Disease in Children (2019 Edition) and the Modified Porto Standard for the Diagnosis of Inflammatory Bowel Disease in Children and Adolescents (2014 Edition) of the European Association of Pediatric Gastroenterology, Hepatology, and Nutrition. All included cases were diagnosed with CD. Exclude cases of ulcerative colitis, intestinal tuberculosis, Behcet's disease, eosinophilic enteritis, lymphoma, severe liver and kidney disease, other infectious bowel diseases, tumors, etc. A total of 79 cases of CD were screened using inclusion and exclusion criteria, and ultimately included in the study.

2.2 Grouping

After screening with inclusion and exclusion criteria, eligible patients will be identified. According to the technical review criteria of the American Gastrointestinal Association (AGA) in 2003, children are divided into perianal lesions group and non perianal lesions group.

2.3 Data Collection

All patient information is comprehensive complete, collect the general information, perianal lesions, laboratory tests, imaging tests, pediatric Crohn's disease activity index and treatment through the hospital's electronic medical record system.

2.4 Statistical Analyses

Statistical analyses were performed using SPSS version 25.0 statistical package.

The normality of the distribution of numerical data was evaluated with the Kolmogo-rov–Smirnov test. Data were expressed as mean ± standard deviation for normal distribution, and as median and Interquartile range for non-normal distribution. In numerical data that were not distributed normally, Wilcoxon signed-rank test was used to compare differences between two related samples and Mann–Whitney U test between two independent groups. In numerical data that were distributed normally, the Student's t test was used. Chi-square test was used to compare differences between frequencies. A p value of less than 0.05 was considered statistically significant.

3. Results

3.1 Characteristics of the Participants

There were a total of 79 enrolled cases in this study. There are 48 males and 31 females, with a male to female ratio of 1.54:1. There were a total of 38 cases (48.1%) in the perianal lesion group, with a male to female ratio of 3.75:1. Comparing the general information between the two groups, it was found that the average initial diagnosis age of the perianal lesion group was (10.78 ± 3.69) years old, which was lower than that of the non perianal lesion group (11.187 ± 3.26) years old, with no statistically significant difference. In addition, the gender composition difference between the two groups was statistically significant (p=0.002) (see Tables 1 and 1, Figures 1 to 2 for details).

Table 1: Comparison of General Information between Two Groups

Group	Age(year)
perianal lesion group	10.78±3.69
non- perianal lesion group	11.187±3.26
t	-0.518
p	0.649

Table 2: Comparison of General Information between Two Groups

Group	Gender	
	female	male
perianal lesion group	8	30
non- perianal lesion group	23	18
χ^2	Fisher	
P	0.002	

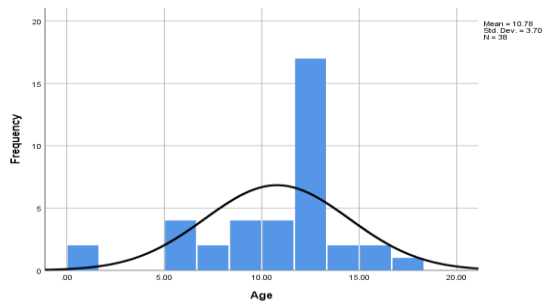

Figure 1: Age distribution of confirmed cases of Crohn's disease in 38 children with perianal lesions

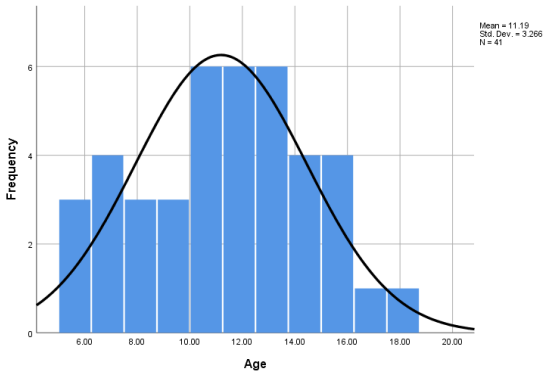

Figure 2: Age distribution of confirmed cases of Crohn's disease in 41 children

3.2 Perianal Lesions

Among 79 children with CD, 38 cases (48.1%) were complicated with perianal lesions, including 14 cases of anal fistula, 17 cases of perianal abscess, 6 cases of skin growths, and 1 case of perineal fistula (see Figure3)

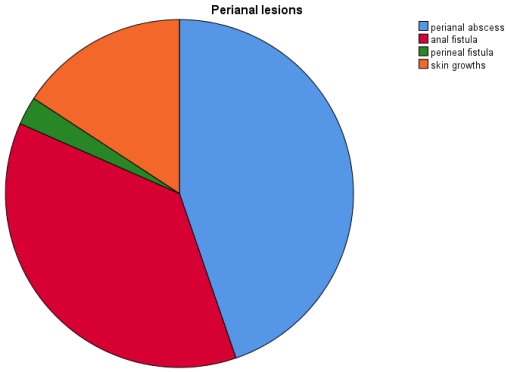

Figure 3: Distribution of lesion types in the perianal lesion group

3.2 Laboratory Indicators

The two groups of laboratory data indicators are complete, and the PCDIA score and CRP at admission are higher than those of the group without perianal lesions, with statistical significance (P<0.05). There was no statistically significant difference in the comparison of WBC, ESR, ALB, and NLR types between the two groups (P>0.05) (see Table 4 and Table 4)

Table 3: Comparison of serological indicators between two groups

Group	WBC	CRP	ESR	ALB
perianal lesion group	10.47± 3.68	31.21 (11.50-79.72)	26.50 (9-42.75)	40.17± 5.43
non- perianal lesion group	8.448± 2.88	18.64 (0.83-58.01)	17 (5-39)	40.23± 5.69
z/t	2.75	-2.002	-1.562	-0.48
P	0.352	0.045	0.118	0.886

Table 4: Comparison of serological indicators between two groups

Group	NLR	PCDIA
perianal lesion group	1.638±0.48	28.75(17.50-37.50)
non- perianal lesion group	1.59±0.334	17.50(10-28.75)
z/t	0.472	-2.664
P	0.340	0.008

The WBC, ALB, and NLR indicators follow a normal distribution, with a median of x ± S in the table; The CRP,

ESR, and PCDIA indicators have a non normal distribution, and the median in the table is within the interquartile range.

3.3 Comparison of Different Activity Periods

The WBC, CRP, and ESR of the moderate to severe group were significantly higher than those of the remission group ($p<0.005$), while the ALB of the moderate to severe group was significantly lower than that of the remission group ($p<0.005$). The WBC, CRP, and ESR of the moderate to severe group were significantly higher than those of the mild group ($p<0.005$), while the ALB of the moderate to severe group was significantly lower than that of the mild group ($p<0.005$). The WBC and ESR of the mild group were significantly higher than those of the remission group ($p<0.005$), while the ALB of the mild group was significantly lower than that of the remission group ($p<0.005$). There was no difference in NLR between the remission group, mild group, and moderate to severe group ($p>0.005$) (see Table 5)

Table 5: comparison of different activity periods

Group	Parameter	N#	Median	P
remission group	WBC	14	6.82±1.97	0.025*
	NLR	14	1.68 (1.44-1.99)	0.716*
	CRP	14	1.50 (0.56-4.20)	0.055*
	ESR	14	4 (1-7.75)	0.005*
	ALB	14	45.50±3.53	0.003*
mild group	WBC	38	9±3.40	0.003γ
	NLR	38	1.60 (1.45-1.80)	0.081γ
	CRP	38	19.50 (3.95-77.87)	0.017γ
	ESR	38	14.50 (6-30.5)	0.000γ
	ALB	14	41.15±5.14	0.000γ
moderate to severe group	WBC	27	11.35±2.91	0.000α
	NLR	27	1.46 (1.33-1.55)	0.093α
	CRP	27	55.51 (30.06-105.01)	0.000α
	ESR	27	40 (33-52)	0.000α
	ALB	14	36.10±3.75	0.000α

Comparisons of * remission vs mild, αremission vs moderate to severe, γmild vs moderate to severe

3.4 IFX Treatment for Two Groups of Pediatric Patients

57.8% (22/38) of patients with perianal lesions received infliximab induced remission treatment; 31.7% (13/41) of children with non perianal lesions were treated with nfliximab induced remission. The proportion of IFX induced remission and treatment in children with perianal lesions was higher in the non pfCD group ($P>0.005$) (see Table 6).

Table 6: IFX treatment in two groups of pediatric patients

Group	Number of users of IFX	
	with	without
perianal lesion group	22	16
non- perianal lesion group	13	28
t	2.396	
P	0.079	

3.5 Influence Factor

According to univariate analysis, gender, CRP, and PCDAI are related to the occurrence of perianal lesions. Using the occurrence of perianal lesions (perianal lesions=0, non perianal lesions=1) as the dependent variable and perianal lesions as the reference, three variables including gender, CRP, and PCDAI score were included for binary logistic regression analysis. The results of the logistic regression model show that gender and PCDAI score are risk factors for the occurrence of perianal lesions. Therefore, it can be inferred that males (OR=14.137, 95% CI: 3.459-57.774, p=0.000) and those with higher initial diagnosis scores (OR=1.078, 95% CI: 1.022-1.137, p=0.006) are more prone to perianal involvement. However, there was no significant difference in CRP levels in the model. (Table 7 and Table 8)

Table 7: Influence factor

Parameter	Variable Name	Assignment Description
Gender	X1	1= female, 2= male
CRP	X2	continuous variable
PCDIA	X3	continuous variable
With or without perianal lesion	Y	perianal lesion group =0, non- perianal lesion group =1

Table 8: Influence factor

Group		Univariate analysis		Mltivariate analys	
		OR(95%CI)	P	OR(95%CI)	p
Gender	(X1)	0.209 (0.077-0.564)	0.002	14.137 (3.459-57.774)	0.000
CRP	(X2)	0.994 (0.984-1.004)	0.229	1.008 (0.994-1.022)	0.245
PCDIA	(X3)	0.953 (0.916-0.991)	0.15	1.078 (1.022-1.137)	0.006

3.6 ROC Curve

We also calculated the prediction curve for active diseases in children with Crohn's disease combined with perianal lesions, with the highest AUC value of 0.807, indicating the best predictive performance of the model(see Figure 4).

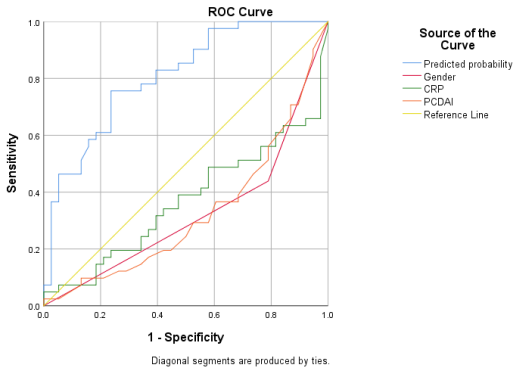

Figure 4: ROC Curve

4. Discussion

In the past 20 years, the global incidence rate of children's CD has increased significantly. Perianal disease (PD) is a unique type of CD with invasion and disability, which has been confirmed to increase the risk of hospitalization, surgical resection rate and the trend of chronic disability. At present, the mechanism of perianal lesions is not fully understood, including genetic polymorphisms, immune response disorders, and epithelial mesenchymal transition. More than 200 gene polymorphisms that may contribute to the occurrence of CD have been identified in genome-wide association studies. A study on IBD in Europe found that mutations in PRDM1,

NOD2, IL-23R, and ATG16L1 are associated with internal fistula, while polymorphism in PUS10 can prevent perianal diseases of CD [8]. In this study, perianal lesions accounted for 48.1% of children with CD, which is higher than reported in literature [9] and may be related to differences in race, age, and examination methods. In this study, all CD patients underwent perianal magnetic resonance imaging or perianal ultrasound examination at initial diagnosis, and the detection rate of perianal lesions was relatively high. The occurrence of perianal lesions has a significant gender bias, and a multicenter study has shown that male CD patients are more prone to perianal lesions [10], which is consistent with the conclusions of this study.

Widespread inflammatory burden and fistular disease are characteristics of perianal Crohn's disease in children. Compared with children without perianal disease, children with perianal disease have poorer clinical outcomes, greater inflammatory activity, more frequent involvement of the rectum and jejunum, higher incidence of inflammatory skin growths and perianal abscesses, and higher rates of colostomy [11]. In this study, the CRP of the perianal disease group was significantly higher than that of the non perianal disease group, and the difference between the two groups was statistically significant.

A meta-analysis of 525adult and425 pediatric IBD patients showed that Asian CD patients were more likely to develop perianal diseases compared to white individuals [11]. Domestic studies have shown that the incidence of CD in children with perianal lesions is as high as 13.66%~62%. The incidence rate of early onset D perianal lesions is relatively high [12], and the incidence rate is higher among those with gene mutations, and the clinical manifestations are more serious. Perianal involvement in CD can occur at any stage of the disease process, and perianal lesions can appear as the first or only symptom in children with CD, and can also be detected during follow-up.In clinical practice, the diagnosis of perianal Crohn's disease requires comprehensive physical examination, endoscopic examination, pelvic MRI, and laboratory examination. Like adult Crohn's disease, pediatric Crohn's disease most commonly affects the distal ileum and colon, with a few patients affecting the rectum and proximal small intestine. Pelvic MRI is the gold standard for evaluating the anatomy, complexity, and activity of fistulas and abscesses in children and adults with Crohn's disease, with high accuracy [13]. In addition, MRI has no ionizing radiation and is more attractive in the diagnosis of pediatric diseases. As perianal lesions may be the first manifestation of this disease, Crohn's disease should always be considered when skin growths, cracks, perianal abscesses, or fistulas appear. If perianal disease occurs after the initial diagnosis of Crohn's disease, the progression of the disease should be reassessed through ileocolonoscopy, as accompanying intestinal inflammation and lesions (such as stenosis) are related to prognosis and treatment [14]. The efficacy and safety of Infliximab in adult and pediatric perianal diseases have been confirmed [15]. Infliximab is the first biologic proven to effectively promote and maintain CD related fistula closure, supported by a high-quality randomized controlled trial (RCT) with fistula closure as the primary endpoint. In a retrospective multicenter study of 50 pediatric patients with perianal Crohn's disease, Infliximab was effective and safe, as 72% of patients had completely closed fistulas within the first year of treatment, while 30% had recurrent fistulas [16]. In children, it is recommended to continue using Infliximab for at least 1 year after abscess drainage [17] The proportion of children with perianal lesions using IFX during the induction and relief treatment stage is higher than that in the non perianal lesion group, and the difference between the two is statistically significant.

In summary, the incidence of perianal lesions is higher in children with CD, with male children having a higher incidence. Children with CD complicated with perianal lesions often have more severe intestinal inflammation and higher disease activity index, which is highly valued by clinical physicians. Therefore, it is recommended to strengthen the frequency and meticulousness of physical examinations in the perianal area during the first visit, and to improve endoscopic and imaging assessments as early as possible for monitoring. Children with CD need close follow-up to pay attention to the occurrence of perianal lesions during the course of the disease.

This study has certain limitations. Due to limitations in retrospective analysis, there may be bias in the PCDAI score. In addition, the sample size of the study is relatively small. Future research should expand the sample size and conduct multicenter studies, focusing on identifying factors related to PD treatment response, in order to personalize treatment for children with PD.

References

[1] Amil-Dias J, Kolacek S, Turner D, Pærregaard A, Rintala R, Afzal NA, Karolewska-Bochenek K, Bronsky J, Chong S, Fell J, Hojsak I, Hugot JP, Koletzko S, Kumar D, Lazowska-Przeorek I, Lillehei C, Lionetti P, Martin-de-Carpi J, Pakarinen M, Ruemmele FM, Shaoul R, Spray C, Staiano A, Sugarman I, Wilson DC, Winter H, Kolho KL; 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 May;64(5):818-835.

[2] Schwartz DA, Loftus EV Jr, Tremaine WJ, Panaccione R, Harmsen WS, Zinsmeister AR, Sandborn WJ. The natural history of fistulizing Crohn's disease in Olmsted County, Minnesota. Gastroenterology. 2002 Apr; 122(4):875-80.

[3] Perianal Crohn Disease in a Large Multicenter Pediatric Collaborative. J Pediatr Gastroenterol Nutr. 2017 May; 64(5):e117-e124.

[4] Brückner A, Werkstetter KJ, de Laffolie J, Wendt C, Prell C, Weidenhausen T, Zimmer KP, Koletzko S; CEDATA-GPGE study group. Incidence and Risk Factors for Perianal Disease in Pediatric Crohn Disease Patients Followed in CEDATA-GPGE Registry. J Pediatr Gastroenterol Nutr. 2018 Jan;66(1):73-78.

[5] Singer AA, GadEglinton TW, Barclay ML, Gearry RB, Frizelle FA. The spectrum of perianal Crohn's disease in a population-based cohort. Dis Colon Rectum. 2012 Jul;55(7):773-7.

[6] Adler J, Dong S, Eder SJ, Dombkowski KJ; ImproveCareNow Pediatric IBD Learning Health

System.epalli SK, Eder SJ, Adler J. Fistulizing Crohn's Disease Presenting After Surgery on a Perianal Lesion. Pediatrics. 2016 Mar;137(3):e20152878.

[7] Seemann NM, Elkadri A, Walters TD, Langer JC. The role of surgery for children with perianal Crohn's disease. J Pediatr Surg. 2015 Jan;50(1):140-3.

[8] Donnelly M, Ryan OK, Ryan ÉJ, Bass GA, Kelly ME, McNamara D, Whelan M, Neary PC, O'Riordan JM, Kavanagh DO. Comparison of Restorative Proctocolectomy with and Without Defunctioning Loop Ileostomy in Patients with Ulcerative Colitis: A Systematic Review and Meta-analysis. J Crohns Colitis. 2023 Jun 16;17(6):876-895.

[9] Eglinton TW, Roberts R, Pearson J, et al. Clinical and genetic risk factors for perianal Crohn's disease in a population-based cohort. Am J Gastroenterol. 2012;107(4):589-596.

[10] Assa A, Amitai M, Greer ML, Castro DA, Kuint RC, Martínez-León M, Herman-Sucharska I, Coppenrath E, Anupindi S, Towbin A, Moote D, Konen O, Pratt LT, Griffiths A, Turner D; ImageKids Study Group. Perianal Pediatric Crohn Disease Is Associated With a Distinct Phenotype and Greater Inflammatory Burden. J Pediatr Gastroenterol Nutr. 2017 Sep;65(3):293-298.

[11] Shi HY, Levy AN, Trivedi HD, Chan FKL, Ng SC, Ananthakrishnan AN. Ethnicity Influences Phenotype and Outcomes in Inflammatory Bowel Disease: A Systematic Review and Meta-analysis of Population - based Studies. Clin Gastroenterol Hepatol. 2018;16(2):190-197.e11.

[12] Mak WY, Mak OS, Lee CK, et al. Significant Medical and Surgical Morbidity in Perianal Crohn's Disease: Results from a Territory-Wide Study. J Crohns Colitis. 2018;12(12):1392-1398.

[13] Shenoy-Bhangle A, Nimkin K, Goldner D, Bradley WF, Israel EJ, Gee MS. MRI predictors of treatment response for perianal fistulizing Crohn disease in children and young adults. Pediatr Radiol. 2014 Jan;44(1):23-9.

[14] Gionchetti P, Dignass A, Danese S, Magro Dias FJ, Rogler G, Lakatos PL, Adamina M, Ardizzone S, Buskens CJ, Sebastian S, Laureti S, Sampietro GM, Vucelic B, van der Woude CJ, Barreiro-de Acosta M, Maaser C, Portela F, Vavricka SR, Gomollón F; ECCO. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 2: Surgical Management and Special Situations. J Crohns Colitis. 2017 Feb;11(2):135-149

[15] Crandall W, Hyams J, Kugathasan S, Griffiths A, Zrubek J, Olson A, Liu G, Heuschkel R, Markowitz J, Cohen S, Winter H, Veereman-Wauters G, Ferry G, Baldassano RN. Infliximab therapy in children with concurrent perianal Crohn disease: observations from REACH. J Pediatr Gastroenterol Nutr. 2009 Aug;49(2):183-90.

[16] Iwańczak BM, Ryżko J, Jankowski P, Sładek M, Wasilewska A, Szczepanik M, Sienkiewicz E, Szaflarska-Popławska A, Więcek S, Kwiecień J, Korczowski B, Maślana J. Induction and Maintenance Infliximab Therapy for the Treatment of Crohn's Disease with Perianal Fistulas in Children: Retrospective, Multicenter Study. Adv Clin Exp Med. 2016 May-Jun;25(3):523-30.

[17] Amil-Dias J, Kolacek S, Turner D, Pærregaard A, Rintala R, Afzal NA, Karolewska-Bochenek K, Bronsky J, Chong S, Fell J, Hojsak I, Hugot JP, Koletzko S, Kumar D, Lazowska-Przeorek I, Lillehei C, Lionetti P, Martin-de-Carpi J, Pakarinen M, Ruemmele FM, Shaoul R, Spray C, Staiano A, Sugarman I, Wilson DC, Winter H, Kolho KL; 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 May;64(5):818-835.