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Original Research Articles - Clinical

Clusters of Disease Activity and Early Risk Factors of Clinical Course of Pediatric Crohn's Disease

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Background: This study aimed to define clusters of disease activity and prognostic factors of disease course in a well-characterized cohort of children with Crohn's disease (CD).

Methods: All patients from the SIGENP IBD (Italian Society of Pediatric Gastroenterology Hepatology and Nutrition Inflammatory Bowel Disease) registry with a 5-year follow-up and 6-monthly evaluation were included. Active disease was defined for each semester as follows: clinical activity (weighted Pediatric Crohn's Disease Activity Index ≥12.5 or Mucosal Inflammation Noninvasive Index ≥8) and active disease on endoscopy (Simple Endoscopic Score for Crohn's Disease >3 or fecal calprotectin >250 µg/g) or imaging. Formula-based clusters were generated based on previously published patterns in adults.

Results: Data from 332 patients were analyzed. A total of 105 (32%) experienced a quiescent disease course; 49 (15%) and 31 (9%) a moderate-to-severe chronically active and chronic intermittent disease, respectively; 104 (31%) and 43 (13%) had active disease in the first 2 years after diagnosis and remission thereafter and vice versa, respectively. Surgery at diagnosis was significantly associated with a quiescent course (odds ratio [OR], 10.05; 95% confidence interval [CI], 3.05-25.22; *P*=.0005), while growth impairment at the diagnosis and active disease requiring corticosteroids at 6 months were inversely related to the quiescent group (OR, 0.48; 95% CI, 0.27-0.81; *P*= .007; and OR, 0.35; 95% CI, 0.16-0.71; *P*= .005, respectively). Perianal involvement at diagnosis and moderate–severe activity at 6 months correlated with disease progression (OR, 3.85; 95% CI, 1.20-12.85; *P*=.02).

Conclusions: During the first 5 years of follow-up, one-third of children with CD experience a quiescent course. However, another one-third have a moderate-to-severe disease course. Surgery at the diagnosis is related to a quiescent course, while growth impairment and lack of response to induction therapy correlate with more severe disease activity during follow-up.

Lay Summary

We aimed to define clusters of disease activity and prognostic factors of disease course in pediatric Crohn's disease. One-third of patients have a quiescent course; however, half of them have an active disease by the end of the 5-year follow-up.

Key Words: cluster, Crohn's disease, prognostic risk factors, children

Introduction

Pediatric Crohn's disease (CD) is a complex condition to diagnose and treat due to its heterogeneous clinical manifestations. Children with CD often present with extensive intestinal involvement and complicated disease behaviors, requiring early use of immunomodulators and/or biological therapy.[1] Despite advancements in therapy, CD can negatively impact long-term outcomes such as growth, pubertal development, and bone mineral density, leading to psychological and emotional effects, especially in adolescents.[2-5] Therefore, it is crucial to identify patients who will have a severe disease course and related risk variables already at diagnosis. Although several studies have attempted to pinpoint prognostic factors of

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Key Messages

What is already known?

- Pediatric Crohn's disease is characterized by heterogeneous clinical manifestations and an unpredictable disease course.

What is new here?

- About one-third of children with Crohn's disease experience a quiescent course during a 5-year follow-up, while half of them still have an active disease by the end of the follow-up. Early surgery is related to a mild disease course, while growth failure and lack of response to induction therapy are related to a worse prognosis.

How can this study help patient care?

- Identifying early prognostic risk factors for disease courses can help clinicians adjust therapeutic strategies based on early risk stratification.

disease course in both children and adults, in real-life practice each patient's disease course remains somewhat unpredictable.[6-8] This can make it challenging to decide on a tailored treatment strategy early at the diagnosis. In 2021, Wintjens et al[9] reported data from a cohort of 432 adult patients with CD, divided into 6 clusters of activity in a 10-year follow-up. About one-third of patients had a quiescent disease course, of whom 89% never received immunomodulators or biologics. Surgery at the diagnosis and higher age were positively associated with the quiescent course. Conversely, an ileocolonic location, smoking, and the need for steroids within 6 months from the diagnosis were related to a worse prognosis.[9] Data on specific disease patterns in pediatric CD are lacking. Thus, this study aimed to define clusters of disease activity in pediatric CD based on clinical, laboratory, endoscopic, and therapeutic findings. As a secondary outcome, we sought to identify early prognostic risk factors for disease courses based on clinical and laboratory variables at diagnosis and in the first 6 months of follow-up.

Methods

This is a retrospective, multicenter study involving pediatric patients affected with CD enrolled in the prospective SIGENP IBD (Italian Society of Pediatric Gastroenterology Hepatology and Nutrition Inflammatory Bowel Disease) registry, started on January 1, 2009. The study end date is considered as the date of the last visit before March 30, 2022. The methodology of the SIGENP IBD registry has been previously reported in detail.[10] Written consent was obtained from all patients and parents, and the study was approved by regional Ethics Committees, according to the rules of SIGENP IBD registry (Coordinating center approval, Sapienza University, Umberto I Hospital n. 4654). Eligible subjects included CD patients <18 years of age, with a 6-month follow-up during the first 5 years after diagnosis. All patients were enrolled at the diagnosis of CD. Patients with a shorter follow-up or incomplete data were excluded. According to Porto criteria, the diagnosis of IBD was based on clinical history, physical examination, endoscopic and histologic findings, and imaging.[11] Data collected for this study included demographic features (age, sex), family history for IBD, disease location and behavior according to the Paris classification,[12] therapy at diagnosis, and follow-up. Disease activity was defined by the weighted Pediatric Crohn's Disease Activity Index (wPCDAI).[13] Laboratory data included erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), platelet count, hemoglobin, albumin, and fecal calprotectin (FC), recorded at diagnosis and every 6 months throughout the follow-up. ESR was considered abnormal for values >20 mm/h, CRP >0.6 mg/dL, platelet count >400 × 10^9/L, hemoglobin <10 g/dL, albumin <3.5 g/dL, and FC >250 µg/g. Endoscopic and/or imaging evaluations (magnetic resonance enterography, ultrasonography) were recorded at diagnosis and follow-up, when available. The endoscopic activity was defined by the Simple Endoscopic Score for Crohn's Disease (SES-CD).[14] Mucosal healing was defined as SES-CD <3. When endoscopy was not available, FC <250 µg/g or Mucosal Inflammation Noninvasive Index (MINI) <8 were used as surrogate markers of mucosal healing. The MINI is a clinical-laboratory score based on 3 main items (frequency and characteristics of stool, FC, ESR, and CRP), with an overall score ranging from −3 to a maximum of 25 points.[15] A bowel wall thickness >3mm with signs of active inflammation on magnetic resonance enterography or ultrasonography (ie, the presence of an abnormal stratification, hypervascularization, mesenteric inflammatory fat, abscesses, or fistulas) was considered an active disease, regardless of the location.[16]

Treatment escalation was defined as the need for additional medical therapy based on a lack of sustained response/remission with the use of the previous maintenance drug: immunomodulators (azathioprine/6-mercaptopurine or methotrexate), biological therapies (anti-tumor necrosis factor α [anti-TNFα], vedolizumab, and ustekinumab), 5-aminosalicylic acid, or partial enteral nutrition.

Surgical procedures (bowel resection) were assessed at each time point. Disease progression was defined as a switch of CD phenotype from B1 to B2 or B3 or B2/B3 (12).

The previous variables were assessed on a 6-monthly basis during a 60-month follow-up. A disease flare was defined by the presence of 1 or more of these criteria at each semester: clinical activity (wPCDAI ≥12.5 or MINI ≥8) and/or SES-CD >3 or FC >250 µg/g and/or active disease at imaging methods.

Definition of Clusters

The disease course was defined by the number of semesters with a flare during the first 5 years of follow-up. Then, based on the disease course, patients were classified into 1 of 5 previously identified disease activity clusters[9]: cluster A, active to remission (≥2 semesters of activity in the first 2 years, <2 semesters from 25-60 months); cluster B, remission to active (<2 semesters of activity in the first 2 years, ≥2 semesters from 25-60 months); cluster C, moderate–severe chronically active (≥1 semester of activity/year); cluster D, chronic intermittent (≥1 semester of activity every 2 years or an irregular chronic–intermittent, inactive–active–inactive, or vice versa pattern); and cluster E, quiescent (<2 semesters of activity on the entire 5-year follow-up).

Statistical Methods

All data were summarized and expressed as mean ± SD or median and interquartile range (IQR) for continuous variables. Categorical data were expressed as frequencies

and percentages. Differences between groups, if any, were assessed by Student's *t* test. For qualitative variables, Fisher's correction chi-square statistical test was applied. The different clusters of patients in this population were identified based on previously published known patterns of disease activity in adults by considering either the presence or absence of disease recurrence for each 6-month follow-up.[9] The cumulative risk of surgical resection was calculated on the entire cohort of patients by assessing surgery-free survival using the Kaplan-Meier method. Univariate analysis was performed by simple logistic regression of variables detected at diagnosis and 6-month follow-up predicting quiescent course (cluster E), disease progression, and surgery. Multiple logistic regression was then performed using the significant variables in univariate. The odds ratio (OR), 95% confidence interval (CI), and *P* value were calculated in each analysis. A *P* value <.05 was considered statistically significant. GraphPad statistical software (GraphPad Instat 3.1 and Prism 8.4.2; GraphPad Software) was used to perform all statistical tests.

Results

Demographic Data

During the inclusion period, 1019 children diagnosed with CD were enrolled in the registry. Of these, 687 were excluded (median age 13.1 years [IQR; 8.3-16.2 years]): 435 due to a follow-up <5 years, 189 due to lack of exhaustive data at each time point, and 63 due to a lack of each semester evaluation. Thus, 332 patients were enrolled in this study (142 [43%] females, median age 12 years [IQR, 8-14 years]). At diagnosis, 17 (5%) patients presented with severe disease activity, and 73 (22%), 192 (58%), and 50 (15%) with moderate, mild, and no clinical activity, respectively. Thirty-nine (12%) had an ileal location, 51 (15%) had a colonic disease, 144 (44%) had an ileocolonic disease, 21 (6%) had an isolated small bowel involvement, and 77 (23%) had a panenteric disease. Sixty-five (20%) children presented with perianal involvement at the diagnosis. An inflammatory phenotype (B1) was present in 253 (76%) patients at the diagnosis, stricturing (B2) in 44 (13%), penetrating (B3) in 32 (10%), and B2/B3 in 3 (1%). The baseline characteristics of the population are shown in Table 1.

Clusters of Disease Activity and Clinical Outcomes

A total of 104 (31%) had active disease in the first 2 years, then substantial remission (cluster A), 43 (13%) were classified as cluster B (remission to active), 49 (15%) had a moderate–severe chronically active disease course (cluster C), and 31 (9%) were chronic-intermittent (cluster D) and 105 (32%) were quiescent (cluster E). Overall, 123 (37%) experienced a mostly active disease course at the end of follow-up. The disease patterns in the entire cohort are shown in Figure 1. No significant differences in age, location, and behavior at diagnosis were found. Cluster E (the quiescent pattern) was compared with all other clusters (Supplementary Table 1). Growth impairment at disease onset was significantly more frequent in clusters A and D compared with cluster E (*P*= .008 and *P*= .04, respectively), and persistent high ESR at 6 months from diagnosis was significantly related to cluster C than cluster E (*P*= .01). On the other hand, a significantly higher rate of patients with a quiescent disease course underwent surgery at the diagnosis than in cluster A (*P*= .01), without any differences between other clusters.

In the univariate logistic regression analysis, a moderate–severe disease onset (wPCDAI >40), along with growth impairment at the diagnosis and persistently active disease at 6 months (ESR >20 mm/h and wPCDAI >40) requiring corticosteroids were inversely related to a quiescent disease course in the subsequent follow-up. Surgery at diagnosis was strongly related to the quiescent course (OR, 10.05; 95% CI, 3.05-25.22; *P*=0005). In a multivariable logistic regression model, clinically moderate–severe disease onset and the need for surgery at diagnosis maintained statistical significance (OR, 0.17; 95% CI, 0.06-0.43; *P* = .0005; and OR, 11.28; 95% CI, 1.44-25.00; *P*= .04, respectively; area under the curve [AUC], 0.76; 95% CI, 0.68-0.84; positive predictive value of 57% and negative predictive value [NPV] of 80%) (Table 2).

At maximum follow-up, 60 (18%) patients presented disease progression (10% in cluster A, 28% in B, 40% in C, 24% in D, and 8% in E), with a statistically significant difference between clusters C and E (*P* < .001). Fifty-three percent of patients progressed from inflammatory to stricturing disease, 33% to penetrating, and 14% to combined B2/B3. In multiple logistic regression analysis, perianal involvement at diagnosis and persistently active disease (ESR >20 mm/h and wPCDAI >40) correlated with disease progression at follow-up (AUC, 0.69; 95% CI, 0.59-0.79; NPV = 78%) (Table 3).

Medications

In the first year after diagnosis, the use of corticosteroids significantly decreased, while the use of biologics increased in the entire patient cohort. This trend remained stable over the medium and long term (Supplementary Figure 1). At the end of the follow-up, 139 (42%) patients were on biologic therapy, 93 (28%) were on immunomodulators, 67 (20%) were on 5-aminosalicylic acid, and 33 (10%) required systemic steroids. None of the patients were on partial enteral nutrition. Among those on biologics, 115 (35%) were receiving anti-TNFα, 15 (5%) ustekinumab, and 9 (3%) vedolizumab. No patients had discontinued medical treatment. At 5 years, there was a significant increase in the use of immunomodulators and biologics in clusters E and B, respectively (*P*= .0002 and *P* < .0001, respectively), compared with the others. No significant differences were found for other treatments according to disease clusters (Figure 2).

Surgery

During the 5-year follow-up, 73 (22%) children underwent bowel resection. A total of 43% of these surgeries occurred within the first 6 months after diagnosis. Among the quiescent group (cluster E), 11 (11%) patients required surgery at diagnosis, with 9 more during the follow-up. A significantly higher proportion of patients in cluster C (33%) needed surgery than all other clusters (*P*= .04). Figure 3 shows the surgery-free survival rate in the entire cohort and the distribution by disease clusters. The logistic regression model showed that stricturing or penetrating phenotype at disease onset (OR, 3.04; 95% CI, 1.54-5.93; *P*= .001; OR, 9.24; 95% CI, 4.36-20.48; *P* < .001) along with perianal involvement (OR, 6.63; 95% CI,3.65-12.19; *P* < .0001) and anti-TNFα use at diagnosis (OR, 3.15; 95% CI, 1.61-6.09; *P*= .0007) were significantly related to surgery risk at 5-year follow-up. Among these factors, only

Table 1. Baseline characteristics of 332 children with CD (N = 332).

Female	142 (43)
Age, y	12 (8-14)
A1a (<10 y at CD onset)	97 (29)
wPCDAI at diagnosis	27 ± 14
<12.5 (remission)	50 (15)
12.5-40 (mild)	192 (58)
40-57.5 (moderate)	73 (22)
≥57.5 (severe)	17 (5)
CRP, mg/dL	2.3 ± 0.55
FC, µg/g	760 ± 518
ESR, mm/h	42 ± 20
CD location at diagnosis	
L1	39 (12)
L2	51 (15)
L3	144 (44)
L4a	77 (23)
L4b	21 (6)
Perianal disease at diagnosis	65 (20)
Behavior at diagnosis	
B1	253 (76)
B2	44 (13)
B3	32 (10)
B2/B3	3 (1)
Therapy at diagnosis	
CS	153 (46)
5-ASA	113 (34)
IFX	37 (11)
ADA	6 (2)
AZA	154 (46)
MTX	6 (2)
EEN	132 (40)

Values are n (%), median (interquartile range), or mean ± SD.
Abbreviations: 5-ASA, 5-aminosalicylic acid; ADA, adalimumab; AZA, azathioprine; CD, Crohn's disease; CRP, C-reactive protein; CS, corticosteroids; EEN, exclusive enteral nutrition; ESR, erythrocyte sedimentation rate; FC, fecal calprotectin; IFX, infliximab; MTX, methotrexate; wPCDAI, weighted Pediatric Crohn's Disease Activity Index.

disease phenotype and perianal involvement maintained statistical significance on multiple regression analysis (AUC, 0.76; 95% CI, 0.69-0.83; NPV 82%; positive predictive value 61%) (Table 4). Age, disease location, growth impairment, need for systemic steroids, and exclusive enteral nutrition did not significantly influence the risk of surgery.

Discussion

To the best of our knowledge, this is the first cohort study identifying patterns of clinical activity and early risk factors for disease courses in pediatric CD.

Our data show that around one-third of pediatric patients experience a mild long-term disease course after an initial activity phase. However, 37% have an active disease during the entire follow-up, either persistently active, chronically intermittent, or persistently active after an initial remission. Our data are consistent with previously published data in adults over 10 years of follow-up,[9,17-19] although we found a higher percentage of children with a persistently active disease course. Solberg et al[19] recently reported similar results in a cohort of adult patients with CD. In this study, the authors identified 4 disease patterns by submitting questionnaires to enrolled patients. Forty percent of them reported a quiescent or mild disease course at follow-up. This finding is higher than our cohort, although the method based on a patient survey could have determined biases in defining active disease. It is worth noting that comparing pediatric and adult outcomes does not account for significant differences between the 2 groups. Chronic active disease can have a negative impact on a child's growth, pubertal development, and psychological well-being, which may be irreversible.[20-24] Moreover, the need for continuous medical therapies to control a persistently active disease is a significant concern. In our study, we found that most children with a quiescent disease course were on immunomodulators or biologics. Interestingly, in a similar study by Wintjens et al,[9] about 90% of adult patients with the same disease course never used immunosuppressives or biologics.

Additionally, our study revealed that immunomodulators are widely used to sustain remission in pediatric CD. This finding is consistent with other data showing that this class of drugs is commonly used as the maintenance therapy in pediatric CD and UC, even in the biologic era.[25-30]

As a secondary outcome, we analyzed several variables at diagnosis and in the first 6 months after diagnosis to identify predictive factors of the disease course.

Growth impairment at diagnosis and persistently active disease 6 months after diagnosis were associated with a more aggressive disease course. These results are in keeping with previous data by Ziv-Baran et al.[31] In their study, an early response to remission-inducing therapies correlated with a lower risk of disease recurrence and complications in the medium term, much more than the disease severity at the diagnosis. A more recent pediatric study also supports this finding, showing that clinical and laboratory response to exclusive enteral nutrition as induction therapy in CD is related to favorable long-term outcomes and a lower risk of recurrence.[32]

We also assessed the early risk factors of disease progression from noncomplicated to complicated disease behaviors in the entire cohort of patients. Perianal disease at diagnosis and persistently active disease 6 months after diagnosis were related to a high risk of disease progression. This is consistent with data highlighting the role of perianal disease at onset as a risk factor for disease progression.[33-35] Recently, a systematic review analyzing prognostic risk factors in CD identified small bowel disease location, elevated levels of anti-*Saccharomyces cerevisiae* antibodies, and polymorphisms in the NOD2/CARD15 genes as prognostic factors of a worse prognosis in pediatric CD.[6] Our research did not include an autoantibodies profile and genetic evaluation because they were unavailable in most patients.

We found a 5-year surgical rate of 22%. These data align with previously published reports ranging from 13% to 35%.[36,37] It is worth noting that a relatively high number of patients underwent surgery within the first 6 months of their diagnosis. We also found that early surgery was related to a quiescent course at follow-up, a finding that was also reported by Wintjens et al[9] in adults with CD. It is also interesting that the randomized, prospective, open-label LIR!C (Laparoscopic ileocaecal resection versus infliximab for

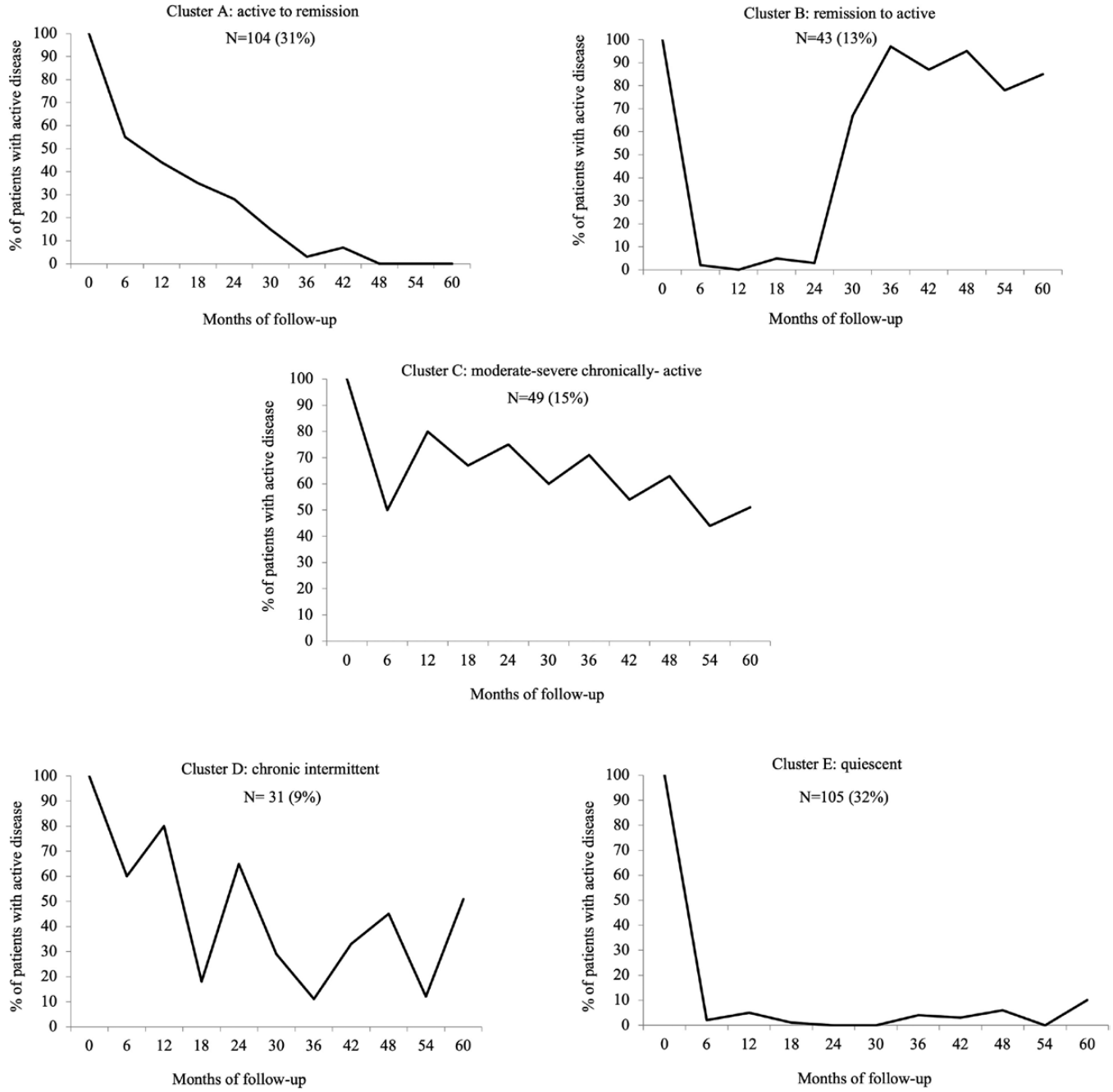


Figure 1. Clusters of disease activity in a cohort of 332 children with Crohn's disease.

terminal ileitis in Crohn's disease) trial, conducted in 143 adults with limited ileocecal disease and who have failed conventional therapy, demonstrated that ileocecal resection could be considered a valid alternative to infliximab therapy in terms of long-term quality of life.[38] The significance of early surgery as a predictor of a mild disease course is noteworthy because it suggests that in certain pediatric CD patients, a limited bowel resection early on after diagnosis may improve their long-term outcomes and potentially reduce the impact of medical therapies.

In line with other data, we found the inflammatory phenotype to be inversely correlated with the surgical risk, while complicated phenotypes along with perianal disease at diagnosis were related to increased surgical risk.[39-42]

We did not find any significant difference in age and disease location. This finding contradicts a recent meta-analysis that found that older children with an isolated ileal location are at a higher risk of surgery.[6]

Interestingly, in the univariate analysis, anti-TNFα use at diagnosis and at 6 months significantly correlated with the surgical risk, although this result was not maintained in the multivariate analysis. This result is somewhat in line with the results of the RISK study (Risk Stratification and Identification of Immunogenetic and Microbial Markers of Rapid Disease Progression in Children with Crohn's Disease), showing that early anti-TNF therapy is not associated with a reduction of fibrostenotic complications (while it reduces the risk of penetrating phenotypes).[43]

Table 2. Univariate and multivariate analysis of early variables related to a quiescent disease course (cluster E).

	Univariate			Multivariate		
	OR	95% CI	*P*	OR	95% CI	*P*
wPCDAI >40 at diagnosis	0.15	0.06-0.31	**<.0001**[a]	0.17	0.06-0.43	**.0005**[a]
L2	1.12	0.61-1.99	.68			
G1	0.48	0.27-0.81	**.007**[a]	0.93	0.39-2.25	.87
B1	0.69	0.38-1.26	.21			
Age <6 y	1.45	0.68-2.96	.32			
Age <10 y	1.37	0.82-2.29	.23			
EEN at diagnosis	1.26	0.78-2.04	.34			
ESR >20 mm/h at diagnosis	1.11	0.53-2.45	.79			
Perianal disease	1.02	0.55-1.83	.95			
CS at diagnosis	1.03	0.64-1.54	.9			
Surgery at diagnosis	10.05	3.05-25.22	**.0005**[a]	11.28	1.44-25.00	**.04**[a]
wPCDAI >40 at 6 mo	0.21	0.06-0.54	**.004**[a]	0.39	0.08-1.42	.18
ESR >20 mm/h at 6 mo	0.42	0.22-0.79	**.007**[a]	0.55	0.25-1.19	.13
CS at 6 mo	0.36	0.16-0.71	**.005**[a]	0.03	0.35-2.06	.89
Surgery at 6 mo	0.7	0.19-2.06	.55			

Model characteristics were the following: area under the curve, 0.76; 95% CI, 0.68-0.84; $R^2 = 0.17$; positive predictive value = 57%; negative predictive value = 80%.
Abbreviations: CI, confidence interval; CS, corticosteroids; EEN, exclusive enteral nutrition; ESR, erythrocyte sedimentation rate; OR, odds ratio; wPCDAI, weighted Pediatric Crohn's Disease Activity Index.
[a]p<.05.

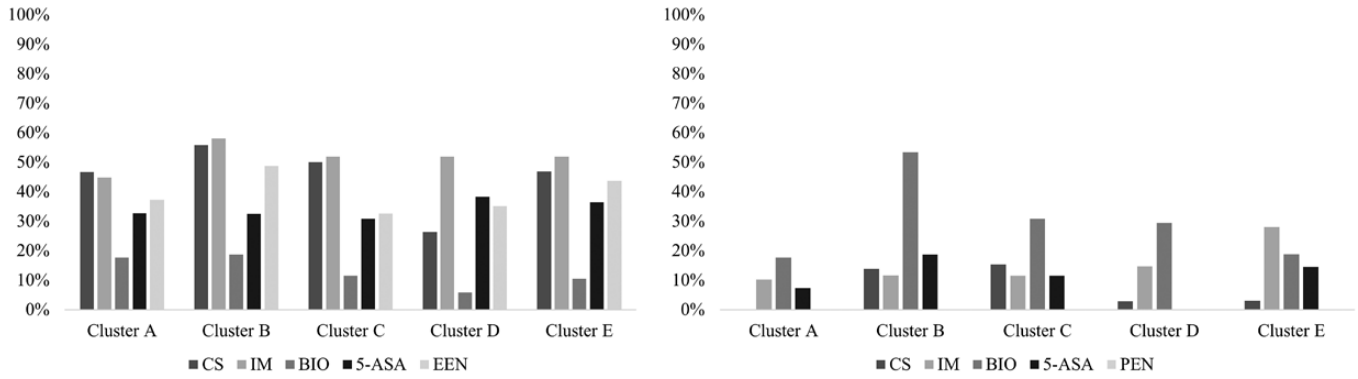
Table 3. Univariate and multivariate analysis of early variables related to disease progression in all patients.

	Univariate			Multivariate		
	OR	95% CI	*P*	OR	95% CI	*P*
wPCDAI >40 at diagnosis	1.94	0.98-3.76	**.05**[a]			
L2	0.78	0.39-1.46	.45			
G1	1.24	0.73-2.08	.42			
Age <6 y	0.44	0.07-1.60	.27			
Age <10 y	0.82	0.46-1.43	.5			
Age 10-17 y	1.18	0.68-2.09	.56			
ESR >20 mm/h at diagnosis	1.47	0.64-3.80	.39			
Perianal disease	1.84	1.01-3.30	**.04**[a]	2.55	1.05-6.07	**.03**[a]
EEN at diagnosis	1.16	0.69-1.93	.56			
CS at diagnosis	0.83	0.49-1.37	.46			
Anti-TNFα at diagnosis	1.33	0.64-2.63	.41			
wPCDAI >40 at 6 mo	3.21	1.28-7.96	**.01**[a]	3.85	1.20-12.55	**.02**[a]
ESR >20 mm/h at 6 mo	2.18	1.06-4.68	**.04**[a]	1.55	0.69-3.62	.29
CS at 6 mo	0.78	0.39-1.50	.48			
Anti-TNFα at 6 mo	1.64	0.91-2.89	**.09**[a]			

Model characteristics were the following: area under the curve, 0.69; 95% CI, 0.59-0.79; $R^2 = 0.08$; positive predictive value = 50%; negative predictive value = 77.85%.
Abbreviations: CI, confidence interval; CS, corticosteroids; EEN, exclusive enteral nutrition; ESR, erythrocyte sedimentation rate; OR, odds ratio; TNFα, tumor necrosis factor α; wPCDAI, weighted Pediatric Crohn's Disease Activity Index.
[a]p<.05.

One may speculate that patients with more severe disease at diagnosis who start anti-TNFα upfront may have a higher inflammatory burden and complicated diseases commonly requiring surgery during the disease course. The role of biological therapy as a risk factor for surgery remains unclear, with some studies suggesting a correlation and others showing opposite results.[42,44-46]

Our study has some notable strengths. First, we included a large cohort of pediatric patients and we used stringent criteria to evaluate the disease course. Second, we applied a



CS, corticosteroids; IM, immunomodulator; BIO, biologics; 5-ASA, 5-aminosalicylic acid; EEN, Exclusive Enteral Nutrition; PEN, Partial Enteral Nutrition.

Figure 2. Therapeutic strategies in each disease cluster at diagnosis (left) and the end of the 5-year follow-up (right).

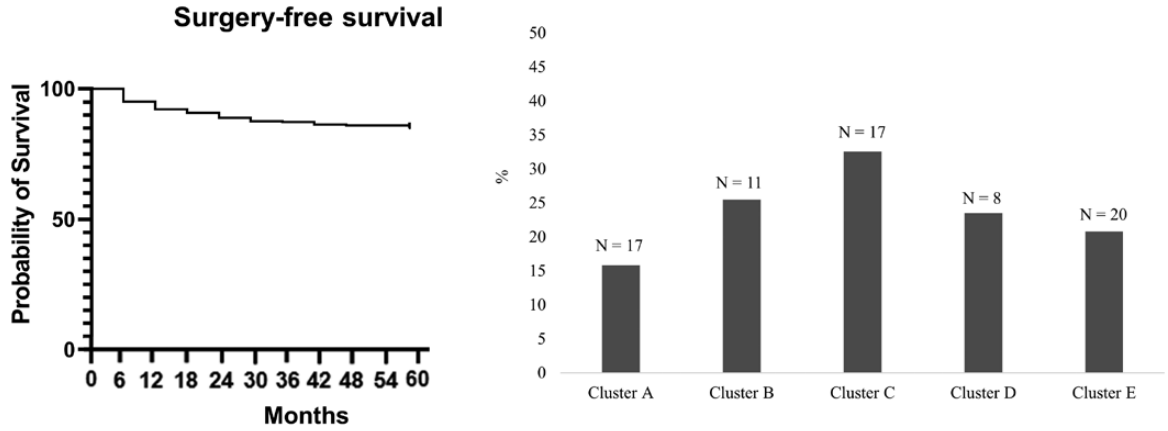


Figure 3. Surgery-free survival curve (left) and percentage and numbers of patients who underwent surgery for each disease cluster (right).

Table 4. Logistic regression of early predictive variables related to surgery risk.

	Univariate			Multivariate		
	OR	95% CI	*P*	OR	95% CI	*P*
wPCDAI >40 at diagnosis	1.47	0.75-2.79	.25			
L2	1.12	0.58-2.07	.73			
L3	0.86	0.51-1.47	.57			
G1	0.85	0.48-1.47	.55			
B1	0.19	0.10-0.35	**.001**[a]	0.85	0.29-2.48	.77
B2	3.04	1.54-5.93	**.001**[a]	3.68	1.21-10.89	**.01**[a]
B3	9.24	4.36-20.48	**<.001**[a]	4.28	1.38-13.78	**.012**[a]
EEN at diagnosis	1.07	0.63-1.81	.79			
ESR >20 mm/h at diagnosis	1.08	0.48-2.67	.86			
Perianal disease	6.63	3.65-12.19	**<.0001**[a]	2.99	1.29-6.77	**.008**[a]
CS at diagnosis	0.72	0.42-1.21	.22			
Anti-TNFα at diagnosis	3.15	1.61-6.09	**.0007**[a]	1.71	0.69-4.17	.24
wPCDAI >40 at 6 mo	0.96	0.38-2.19	.93			
ESR >20 mm/h at 6 mo	1.95	0.99-3.90	.053			
CS at 6 mo	0.47	0.21-0.97	.054			
Anti-TNFα at 6 mo	1.95	1.10-3.42	**.02**[a]	1.06	0.49-2.20	.89

Model characteristics were the following: area under the curve, 0.76; 95% CI, 0.69-0.83; $R^2 = 0.20$; positive predictive value = 61%; negative predictive value = 82%.
Abbreviations: CI, confidence interval; CS, corticosteroids; EEN, exclusive enteral nutrition; ESR, erythrocyte sedimentation rate; OR, odds ratio; TNFα, tumor necrosis factor α; wPCDAI, weighted Pediatric Crohn's Disease Activity Index.
[a]p<.05.

rigorous definition of disease activity, which was measured using clinical, laboratory, and multiparametric scores as well as endoscopic and/or imaging data. Last, we only included patients with complete data for each semester, which allowed us to accurately define disease recurrence during follow-up and cluster classification.

However, we are also aware of the weaknesses of our study. First, we collected retrospective data, which were, however, recorded prospectively in the SIGENP national registry for pediatric IBD. Second, due to our inclusion criteria and the need for strict follow-up, a significant proportion of patients from the entire cohort were excluded, which could increase selection bias. Nonetheless, we analyzed the portion of the excluded patients due to incomplete assessments and found no significant differences in the main outcomes analyzed. Therefore, we believe that our cohort reflects the real-life course of CD in children.

Conclusions

During a 5-year follow-up, about one-third of children with CD experience a quiescent course. However, nearly half of them still have an active disease by the end of the follow-up, with a persistently active or chronic-intermittent course or active after an initial remission. The severity of the disease at onset, growth impairment, and no response to induction therapy are associated with a more aggressive disease course. Conversely, early surgery is linked to a milder disease course. The 5-year surgical rate is 22%, with most surgeries occurring in the first 2 years of the disease. Complicated behaviors and the presence of perianal disease at the diagnosis increase the risk of bowel resection. Clinicians can adjust their therapeutic strategies based on an early risk stratification considering all these criteria to improve long-term disease outcomes.

Supplementary data

Supplementary data is available at *Inflammatory Bowel Diseases* online.

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Author Contribution

M.A. designed the study, wrote the manuscript, and approved the version to be published. M.D., S.R., and M.R. contributed to design and to write the manuscript. E.P., P.L., S.A., and P.A. contributed to design and write the manuscript. E.M., M.M., and G.Z. collected the data and made the statistical analysis. M.B. and M.C. contributed to collect the data and revised the article.

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Conflicts of Interest

None declared. All the authors declare no financial relationships with a commercial entity producing health-related products and or services related to this article. No honorarium, grant, or other form of payment was given to anyone to write and to produce the manuscript.

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