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Disease activity patterns in the first 5 years after diagnosis in children with ulcerative colitis: a population-based study

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Marina Aloi, M.D., Ph.D., designed the study, wrote the manuscript and approved the version to be published.

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Erasmo Miele, M.D., Claudio Romano, M.D., Camilla Giobbi, M.D., collected the data and made the statistical analysis.

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ABSTRACT

The aim of this study was to define clusters of activity in a population-based cohort during the first 5 years after diagnosis and to identify early prognostic risk factors.

PATIENTS AND METHODS: All UC patients from SIGENP IBD registry with a complete follow-up of at least 5 years were included. Active disease was defined every six months in the presence of at least 1 of the following: clinical activity (PUCAI≥35); endoscopic activity (Mayo≥1); fecal calprotectin >250 mcg/g; hospitalization; surgery; treatment escalation. Formula-based clusters were generated based on four published questionnaire-based activity patterns in adults' plus one additional cluster.

RESULTS: 226 patients were identified. Forty-two (19%) had a moderate-severe chronically active disease, 31(14%) chronic-intermittent, 75 (33%) quiescent, 54 (24%) an active disease in the first 2 years after the diagnosis, then sustained remission, and 24 (11%) a remission in the first 2 years then an active disease. A mild disease onset along with a lower clinical severity not requiring the use of corticosteroids at 6 months were related with a quiescent disease course in the next follow-up [logistic model AUC 0.86 (95% CI 0.78-0.94); PPV 67%; NPV 70%]. Eight % of patients needed surgery, none in the quiescent group (p=0.04).

CONCLUSIONS: More than one-third of children with UC present a chronically active or intermittent course during the first 5 years of follow-up. A significant group of patients has an active disease in the first 2 years then a sustained remission. Interestingly, after initial treatment one-third of patients have a well-controlled disease throughout.

Keywords: clusters; natural history; ulcerative colitis

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BACKGROUND AND AIMS

Ulcerative colitis (UC) is a chronic relapsing inflammatory bowel disorder of unknown origin belonging to the inflammatory bowel diseases (IBD). Several data suggest pediatric UC to be more extensive and severe than adult-onset disease and to require more aggressive treatment[1-3]. Nevertheless, the clinical picture at the diagnosis is extremely heterogeneous, and the subsequent disease course may be difficult to predict, ranging from a quiescent disease to a chronic refractory disease, or to severely acute flares leading to surgery[1]. Previous studies in children with UC report higher rates of acute severe colitis and colectomy (28% and 30% respectively), compared to adult UC (15% and 10-17% respectively)[2,4-7] during follow-up, although only sparse reports on clinical course and disease prediction have been published so far. Data derived from population-based cohorts of pediatric-onset UC show that most patients present colonic extension overtime and about two-thirds of children present with pancolitis[2].

However, most of those studies were conducted before the era of biological therapies and describe the disease course based on pre-determined outcomes, like colectomy rate and hospitalization, not taking into account the impact of the disease on patients' daily life.

A better understanding of the natural disease course of chronic diseases is crucial to improve patient management, assess the effectiveness of treatments, and provide predictors for patient' prognosis.

Thus, the primary aim of the present study was to define distinct clinical activity patterns of UC in a well-characterized population-based cohort of children followed for the first 5 years after diagnosis. As a secondary outcome, we tried to identify

early prognostic risk factors for disease course on the basis of clinical and laboratory data at diagnosis and in first 6 months. Finally, we sought to correlate the outcome of the study with the Paris classification in order to assess the relationship between different subgroups of disease and disease outcome.

PATIENTS AND METHODS

Patients population

Data from all patients with a confirmed diagnosis of UC, prospectively recorded in the Italian Society for Pediatric Gastroenterology, Hepatology and Nutrition (SIGENP) registry from January 1, 2009, to June 1, 2018 (data retrieval date) were retrospectively collected. The study end date was defined as the date of the most recent clinic visit before June 1, 2018. The methodology of the SIGENP IBD registry has been previously described in detail[8]. This is a longitudinal, prospective registry including pediatric patients with a diagnosis of IBD made after January 1, 2009. According to the registry general rules, patient's data are recorded by each participating center every 6 months from the diagnosis, although data collection at least every 12 months is also accepted. Written consent was obtained by all patients and parents and the study was approved by regional Ethics Committees. Eligible subjects included all patients under 18 years of age diagnosed with UC, a minimum follow-up of 5 years, at least a 6-monthly evaluation during the first 5 years after diagnosis defining ability to validly assign cluster. Patients with shorter follow-up or incomplete data were excluded. Diagnosis of UC was made according to Porto criteria and was based on clinical history, physical examination, endoscopic, histological and radiological findings[9]. Data collected for this study included demographic features (age, sex), disease location according to Paris classification[10],

therapy at diagnosis and concomitant treatment at follow-up. Disease activity at diagnosis and during follow-up was defined by the Pediatric Ulcerative Colitis Activity Index (PUCAI)[11]. Clinical remission was defined as a PUCAI below 10. Laboratory tests included C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR), platelet count (PLT), hemoglobin (Hb), albumin, and fecal calprotectin (FC), which were recorded at diagnosis and every six months during follow up. CRP was considered abnormal for values >0.6mg/dL; ESR >20 mm/h; PLT >400x10^9/L; Hb< 10 mg/dl; albumin <3.5 g/dl. Endoscopic evaluation was available at the diagnosis and at different time points at follow-up. Mucosal healing (MH) was assessed every 6 months by endoscopy or by FC for patients with no endoscopy available. The degree of endoscopic activity was determined using the Mayo score[12] as follows: 0, normal or inactive; 1, mild (erythema, absent vascular pattern, mild friability); 2, moderate (marked erythema, absent vascular pattern, friability, erosions); and 3, severe (spontaneous bleeding, ulceration). Patients were classified based on the maximum Mayo score recorded in any area of the colon. MH was defined as a value of 0 in Mayo score. A cut-off level of FC of 250 microg/g was used as a surrogate marker of MH in patients with no endoscopic reassessment available[13]. Treatment escalation was defined as the need for additional medical therapy based on lack of sustained response/remission with the use of the previous maintenance agent (mesalamine, sulfasalazine, immunomodulators, infliximab). Disease extension was defined as the involvement, during follow-up, of at least one additional colonic segment.

Since diagnosis, a disease flare was defined for each semester (half-year) by the presence of one or more of the following criteria:

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- PUCAI> 34 or its increase ≥ than 10 compared to the previous, and/or

- need for surgery, and/or

- need for hospitalization, and/or

- need for treatment escalation, and/or

- Mayo score ≥1 or FC>250 mcg/g

Disease activity patterns

The course of the disease was determined by the number of flares and periods of inactive disease for each semester during the follow-up period. Disease course was then classified into one of 4 disease activity patterns; these 4 activity patterns were derived from a previous publication that used questionnaires to assess disease activity[14], namely:

- Cluster A: active to remission. Two or more semesters of activity in the first 24 months, < 2 semesters of activity from 25 to 60 months.
- Cluster B: remission to active. Less than 2 semesters of activity in the first 24 months, >2 semesters of activity from 25 to 60 months.
- Cluster C: moderate-severe chronically active. One or more semesters of activity per year.
- Cluster D: chronic intermittent. One or more semesters of activity every 2 years or an irregular chronic-intermittent, inactive-active-inactive or vice-versa pattern

A new pattern subgroup was defined based on the major patterns seen for

each patient in succession:

- Cluster E: quiescent. Less than 2 semesters of activity in total.

Disease activity at six-monthly intervals for each patient was readily classified into one of the 5 major pattern groups as defined above (see supplementary figure S1). The first evaluation was made at 6 months after the diagnosis, disease activity at the diagnosis was not considered to assign clusters. Patients requiring colectomy in the first semester were considered as belonging to the worst clinical cluster (cluster C).

Statistical Methods

The follow-up of all patients was analyzed as patients-semesters. Disease activity patterns of overall patients and the absolute number of patterns at the end of the first 5 years of follow-up were classified according to the above pattern definitions and were expressed as frequencies. All data were summarized and displayed as mean±SD for the continuous variables. Continuous variables were compared by using the Student t test for normal variables or the Wilcoxon rank sum test for not normally distributed ones, and categorical data by using Chi square tests with Fisher's correction, as needed. Cumulative rates of colectomy were calculated for the whole cohort using the Kaplan-Meier method. A stepwise multiple logistic regression analysis was used to identify early clinical and laboratory predictors of surgery at the end of follow—up (dependent variable) and to determine the odds ratio (OR) and 95% confidence intervals (CI). Independent variables included in the regression model were age, disease location, PUCAI, FC, acute severe colitis and need for steroid therapy, at the diagnosis. Multiple logistic regression analysis for

clinical and laboratory predictors at the diagnosis and at 6-month follow-up [PUCAI, disease location (E4), need for CS, ASC, FC, CRP) of quiescent disease course was performed. Multicollinearity among variables was also evaluated in the multivariable model[15]. A p value of 0.05 or less was considered as statistically significant. GraphPad Prism and Instat software (GraphPad Instat 3.1 and Prism 8.4.2, San Diego, CA) were used to perform all statistical analyses.

RESULTS

Demographic data

At the retrieval date, 631 patients with a diagnosis of UC were enrolled in the registry. Of these, 405 were excluded: [median age 12.4 years (IQR 7.8-17.1); 136 (34%) adolescents]: 220 (54%) due to a follow-up < 5 years, 159 (39%) for a lack of half-yearly evaluations, 26 (6%) because of incomplete clinical/laboratory data. Thus, 226 patients were enrolled for this study [(122 females (53%), median age 11 years (IQR 7-13)].

At diagnosis, 32 patients (13%) had a severe disease (PUCAI≥65) and 77 (33%) presented with a moderate activity (PUCAI 35-64). One hundred twenty-seven (53%) had pancolitis (E4), 29 (13%) extensive colitis (E3), 24 (14%) left-sided colitis (E2) and 36 (16%) proctitis (E1).

The baseline clinical characteristics of the population are shown in table 1.

Clusters of disease activity and clinical outcomes

The disease course was classified as moderate-severe chronically active (cluster C) in 19% of patients (n=42), chronic-intermittent (cluster D) in 14% (n=31), while 33% (n=75) had a quiescent course (cluster E). Fifty-four patients (24%) were classified as cluster A (active to remission) and 24 (11%) as cluster B (remission to active).

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Figure 1 shows the disease patterns in the entire cohort. One-hundred seventy-seven (78%) patients experienced at least one disease relapse after the diagnosis and 29 (13%) at least one episode of acute severe colitis (ASC), mainly in cluster C (70%; p<0.005 vs all other clusters).

Fifty-four patients (24%) presented disease extension during the 5-year follow-up, with no significant differences based on the activity group.

No significant differences in the disease course were found based on age at the diagnosis (<10 versus >10 years), disease severity and location at the diagnosis according to Paris classification.

Acute severe colitis at the diagnosis was significantly more frequent in cluster A and C compared to cluster E (p=0.01 and p=0.04, respectively), higher CRP (p=0.007) and platelet count (p=0.05) at the diagnosis significantly differentiated cluster C to E, while the need for corticosteroids at 6 months was significantly higher in cluster A and D, compared to cluster E (p=0,01 and p=0.03 respectively) (table 2, supplementary). A mild disease onset without an episode of acute severe colitis, along with lower disease activity (PUCAI<45), not requiring the use of CS, at 6 months, were related to a quiescent disease course in the next follow-up (cluster E). The multivariable logistic regression model showed good discriminant power with AUC of 0.86 (95% CI 0.78-0.94), PPV 79%, NPV 70% (table 2).

We then evaluated clusters of disease activity based on clinical criteria only (PUCAI, need for treatment escalation, hospitalization, and surgery) and we did not find any significant difference compared to disease activity patterns defined including endoscopic activity and FC. We only found a slight increase in the number of patients with a quiescent course [cluster E, n=84 (37%)], and a reduction of patients

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in cluster C [(n=38 (17%)] and D [n=26 (11,5%)].

Further analysis of the main clinical outcomes in patients excluded from our study due to the lack of half-yearly evaluations has been made. No significant differences were found for the main clinical outcomes (table 3, supplementary).

Eighteen patients were diagnosed with primary sclerosing cholangitis (PSC) at follow-up (8%). Most of them were in cluster E [10 (13% of patients in cluster E)], while none was in cluster C (p=0.01). Four (7%) were in cluster A, 3 (1%) in cluster B and 1(3%) in cluster D.

Medications

Figure 2 shows therapeutic treatments during the 5-year follow-up. At 12 months, there was a significant drop in the use of CS and 5-ASA (p=0.0001), which was maintained for the next follow-up. No significant differences were found for other therapies (i.e., immunomodulators, biologics). At the end of follow-up, 11% of patients were under steroids, 46% 5-ASA, 15% under sulfasalazine, 17% immunomodulators and 14% infliximab. No patient was off therapy. No significant differences were found both at diagnosis and at 5-year follow-up according to disease clusters (Figure 3a and b).

Surgery

During the 5 years, 18 patients (8%) underwent colectomy, most of them (89%) during the first 2 years after diagnosis. No patient in the quiescent group (cluster E) required surgery, while 6 were in cluster C (14%; p=0.001). Figure 4 a and b shows the survival free from colectomy in the cohort of included patients and the percentage and numbers of colectomies for each disease cluster.

Logistic regression analysis of clinical and laboratory risk factors for colectomy at the

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diagnosis showed higher PUCAI, acute severe colitis and E4 location to be significantly associated with colectomy risk at follow-up (p=0.006, 0.002, 0.039 respectively). Only PUCAI and disease location (E4) maintained significance at multiple regression analysis (table 3), with good discriminant power, AUC 0,83 (95% CI 0,73-0,93), PPV 93%, NPV 92%. Age, need for systemic steroids, other disease locations and FC at diagnosis did not significantly influence the risk of surgery.

DISCUSSION

This is the first population-based cohort study aiming to define the patterns of disease course of pediatric UC. Our results give several insights about the natural history of UC and show that a relatively high percentage of children have a "benign" disease course or an active disease in the first 2 years after the diagnosis, followed by a sustained clinical and laboratory remission (more than 50%). On the other hand, about 1/3 of patients had a persistently active or a chronic-intermittent activity for the entire follow-up.

Previous studies described the natural history of pediatric UC in terms of disease extension, number of hospitalizations and surgery[1,2]. Based on those data, pediatric UC seems to be more aggressive and extensive than the adult counterpart, with higher rates of disease extension overtime, and a surgical rate of 14-20% after 5 years and up to 40% at 10-year follow-up[16-18].

Although these parameters are objective, they aren't ideal to evaluate the real impact of the disease on patients' daily life and give only little information about the disease activity course. Our patterns of activity allow to describe the evolution of pediatric UC in the first 5 years after the diagnosis. Previous data in adults, based on

questionnaire-generated disease activity curves, reported more than 50% of patients to be in clinical remission in a 5-year follow-up, with only 9% of them with a chronically active disease[14]. Similar results were reported in the IBSEN study, in which half of patients were relapse-free during the 5 years of follow-up[19]. Compared to those data, in our large cohort of children, only 1/3 of patients maintained a sustained clinical remission after the first relapse at the diagnosis. These results seem thus to confirm a higher severity of pediatric UC than the adult-onset disease, with a higher percentage of patients with persistently active disease, although it is worth noting that no previous studies used criteria for defining disease activity as stringent as ours. Nevertheless, at the same time, a significant rate of children have a quiescent disease course after the diagnosis.

We tried to evaluate therapeutic approaches based on different disease clusters. Interestingly, we did not find any significant difference according to clusters both at the diagnosis and at final follow-up. One could speculate that therapies are decided already at the diagnosis or soon after and maintained once remission has been achieved, also in those patients with a mild disease course. Indeed, during follow-up, there was no significant difference in terms of therapeutic strategy based on disease activity, although a significantly lower use of CS and 5-ASA was found in all groups. Strikingly, no patient was out of therapy at the end of follow-up, also in the cluster of quiescent disease. These data differ from previous population-based studies in adults showing 40-50% of patients to be without any therapy in the long-term[14,19,20].

The vast majority of patients did not need any systemic steroids at the end of the follow-up, though 78% of children experienced at least one disease relapse during the 5-year period, which is in line with the previous studies[17,21].

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We found a lower rate of ASC, compared to previous pediatric studies[4,22]. Most patients presented an episode of acute colitis early at the diagnosis and then kept a chronically-active disease at follow-up.

Interestingly, a mild disease onset, without episodes of acute severe colitis, along with lower disease activity not requiring CS at 6 months, were associated with a quiescent disease course in the next follow-up.

There are only a few studies evaluating variables able to identify children with different disease courses. Very recently, the PROTECT multicenter inception cohort study reported independent predictors of 12-month CS-free remission in 400 children newly-diagnosed with UC. Lower baseline clinical severity, higher baseline hemoglobin, and Week 4 clinical remission, predicted 12-month clinical remission[23]. In our study, we sought to determine early predictors of a "benign" disease course at a 5-year follow-up, we thought this result could help physicians to identify already in the first months after the diagnosis those patients with a mild disease course and adapt the therapeutic strategy according.

Another important result of our study is that only 8% of patients underwent colectomy during the 5-year follow-up period. This figure is in keeping with a recent study published by Martinelli et al in a population of 111 children with UC, showing a cumulative colectomy risk of 8% at 5 years and 16% at 10 years of follow-up[24].

Previously, data from the EPIMAD registry in France reported a significantly higher rate of colectomy in pediatric UC (24% at 5 years)[2]. Similar figures were observed in other pediatric cohorts[25-27]. It is worth noting that those studies were performed before the widespread use of biologics in children with UC, thus one could speculate that our lower surgical rate could be related to different treatment strategies, with

higher use of immunomodulators or biologics early at the diagnosis, although we did not find any significant differences in terms of treatments in the different clusters .

Most colectomies were performed in the first 2 years after diagnosis, while only a very few patients needed surgery thereafter. These data are in line with previously reported result in the pediatric population[17].

Previous studies mainly evaluated disease outcomes in terms of colectomy risk during follow-up. An extensive disease and an episode of acute severe colitis at the diagnosis along with steroid refractoriness were reported as predictors of the surgical risk in the majority of them[4,24].

In the present study, a pancolitis and higher PUCAI at the diagnosis were related to colectomy risk during follow-up. Interestingly, most patients undergoing colectomy had a persistently-active disease at follow-up, while no patient in the quiescent group needed surgery. Based on those results, patients with a pancolitis and severe symptoms at the diagnosis should be considered at high risk for surgery at follow-up and possibly treated with more aggressive treatments early after the diagnosis.

Interestingly, we found a significantly higher percentage of PSC in patients with a quiescent disease course compared to those with a persistently active disease. These data are in keeping with previous studies reporting a milder UC course in children with PSC[28,29]

The strengths of our study are the large number of patients evaluated with stringent criteria for follow-up and a strict definition of disease activity, based not only on clinical symptoms, evaluated through PUCAI score, but also on inflammatory activity, assessed by FC and, when available, endoscopy. Moreover, only patients with complete data for each semester were enrolled in the study. These strict criteria

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allowed us to precisely define any disease relapse during the entire follow-up period. Our study has some weaknesses. First, it is a retrospective analysis of prospectively collected registry data, therefore several patients were excluded due to incomplete follow-up or data. Second, we cannot exclude possible bias in patients' selection, as all children were followed-up in tertiary referral centers for pediatric IBD, although in Italy all children are followed in pediatric IBD Units, and, thus, we believe our study approximating a population-based study. Moreover, as our inclusion criteria were very stringent, a significant percentage of patients from the entire cohort were excluded, increasing the risk of bias related to patient selection. For this reason, we carried out an analysis of those patients excluded due to the absence of a six-monthly evaluation, which in theory could have been those with a milder clinical course. We did not find any significant difference in the major clinical outcomes in this group compared to those who were selected, so we could speculate that our cohort reflects the real course of pediatric UC.

CONCLUSIONS

In conclusion, in this population-based cohort of children with UC, the prognosis during the first 5 years after diagnosis appears to be better than expected. A quarter of patients presented an active disease only in the first 2 years after the diagnosis and more than 1/3 a quiescent disease course during the entire follow-up. Mild disease onset and lower disease activity not requiring CS at the first follow-up predicted a quiescent disease course overtime. Children with these characteristics

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may be probably initially treated with “mild” therapies, before starting immunomodulators or biologics. Overall, the colectomy rate was low. Higher PUCAI and an extensive disease already at the diagnosis were related to greater surgical risk at follow-up. Therefore, based on the combination of all these criteria, physicians could adapt their initial therapeutic strategies to improve patients’ clinical outcomes. Further studies are warranted to determine predictive models of disease course in a longer follow-up and implement personalized medicine for pediatric UC.

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Table 1. Baseline clinical characteristics of a cohort of 226 children with UC.

	N = 226
Female, n (%)	122 (54%)
Median age, years (IQR)	11 (7-13)
A1a (< 10 years at the diagnosis), n (%)	86 (38%)
PUCAI at the diagnosis (mean±SD)	28±22
Disease activity at the diagnosis (PUCAI), n (%)	
<10 (remission)	31 (13%)
10-34 (mild)	86 (38%)
35-64 (moderate)	77 (33%)
≥65 (severe)	32 (13%)
CRP, mg/dl (mean ± SD)	3,12±1,52
Albumin, g/dl (mean ± SD)	4,06±0,66
FC, microg/g (mean ± SD)	465,9±356,2
Hb, mg/dl (mean ± SD)	11,2±2,01
ESR mm/h (mean ± SD)	31,34±25,44
Disease location, n (%)	
E1	36 (16%)
E2	34 (14%)
E3	29 (13%)
E4	127 (53%)
Therapy at the diagnosis,n (%)	
Corticosteroids	125 (55%)
5-ASA	145 (63%)
Infliximab	15 (6%)
Thiopurines	34 (15%)
Sulfasalazine	5 (2%)
methotrexate	6 (2%)

PUCAI, pediatric ulcerative colitis activity index; CRP, C-reactive protein; FC, fecal calprotectin; Hb, hemoglobin; ESR, erythrosedimentation rate; SD: standard deviation; IQR: interquartiles.

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Table 2. Univariate and multivariate logistic regression analysis of variables at the diagnosis and at 6-month related to a quiescent disease course (cluster E).

	OR	95% CI	p value	OR	95% CI	p value
PUCAI<45 at diagnosis	0,93	0,41 to 2,19	0,86			
E4	0,99	0,48 to 2,06	0,98			
ASC at diagnosis	0,03	0,001 to 0,16	**0,001**	0,04	0,002 to 0,33	**0,009**
CRP<0,6 mg/dl at diagnosis	1,06	0,44 to 2,66	0,90			
CS at diagnosis	0,98	0,48 to 2,00	0,96			
PUCAI<45 at 6 months	2,30	1,06 to 5,25	**0,039**	1,23	1,01 to 3,85	**0,04**
CRP <0,6 mg/dl at 6 months	1,73	0,50 to 7,80	0,42			
CS at 6 months	0,18	0,041 to 0,55	**0,007**	0,04	0,003 to 0,32	**0,006**
FC<250 mcg/g at 6 months	1,17	1,06 to 1,31	0,79			
Model characteristics						
AUC (95% CI)		0,86 (0,78 to 0,94)				
R^2		0,36				
PPV (%)		79,17				
NPV (%)		69,57				

PUCAI, pediatric ulcerative colitis activity index; ASC, acute severe colitis; CRP, C-reactive protein; CS, corticosteroids; FC, fecal calprotectin.

*No collinearity was found between variables (VIF>1).

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Table 3. Univariate and multivariate logistic regression analysis of variables at the diagnosis related to 5-year colectomy risk in all patients.

	OR	95% CI	p value	OR	95% CI	p value
PUCAI	1,06	1,03 to 1,10	**0,006**	1,07	0,01 to 1,12	**0,03**
Age	0,93	0,81 to 1,07	0,27			
ASC	9,88	2,18 to 42,07	**0,002**	4,02	0,63 to 24,67	0,11
CS	0,93	0,27 to 3,39	0,91			
FC	1,90	0,52 to 6,68	0,31			
E1	0,83	0,12 to 3,47	0,82			
E2	1,28	0,18 to 5,44	0,77			
E3	0,67	0,10 to 2,76	0,62			
E4	4,36	1,07 to 29,35	**0,039**	9,96	1,60 to 19,7	**0,04**
Model characteristics						
AUC (95% CI)		0,83 (0,73 to 0,93)				
R^2		0,16				
PPV (%)		93,25				
NPV (%)		92,75				

PUCAI, pediatric ulcerative colitis activity index; ASC, acute severe colitis; CS, corticosteroids; FC, fecal calprotectin.

*No collinearity was found between variables (VIF>1).

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LEGEND

Figure 1. Clusters of disease activity in a population of 226 children with UC.

Figure 2. Therapeutic treatment in the entire population of children with UC.CS: corticosteroids; 5-ASA: 5-aminosalicylic acid; SSZ: sulfasalazine; IM: immunomodulators; IFX: infliximab.

Figure 3. a) Therapy in the entire population of patients according to disease clusters at the diagnosis and at final follow-up **(b).** CS: corticosteroids; 5-ASA: 5-aminosalicylic acid; SSZ: sulfasalazine; IM: immunomodulators; IFX: infliximab.

Figure 4 a) Colectomy-free survival in the cohort of included patients and percentage and numbers of colectomies for each disease cluster **(b).**

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Figure 1

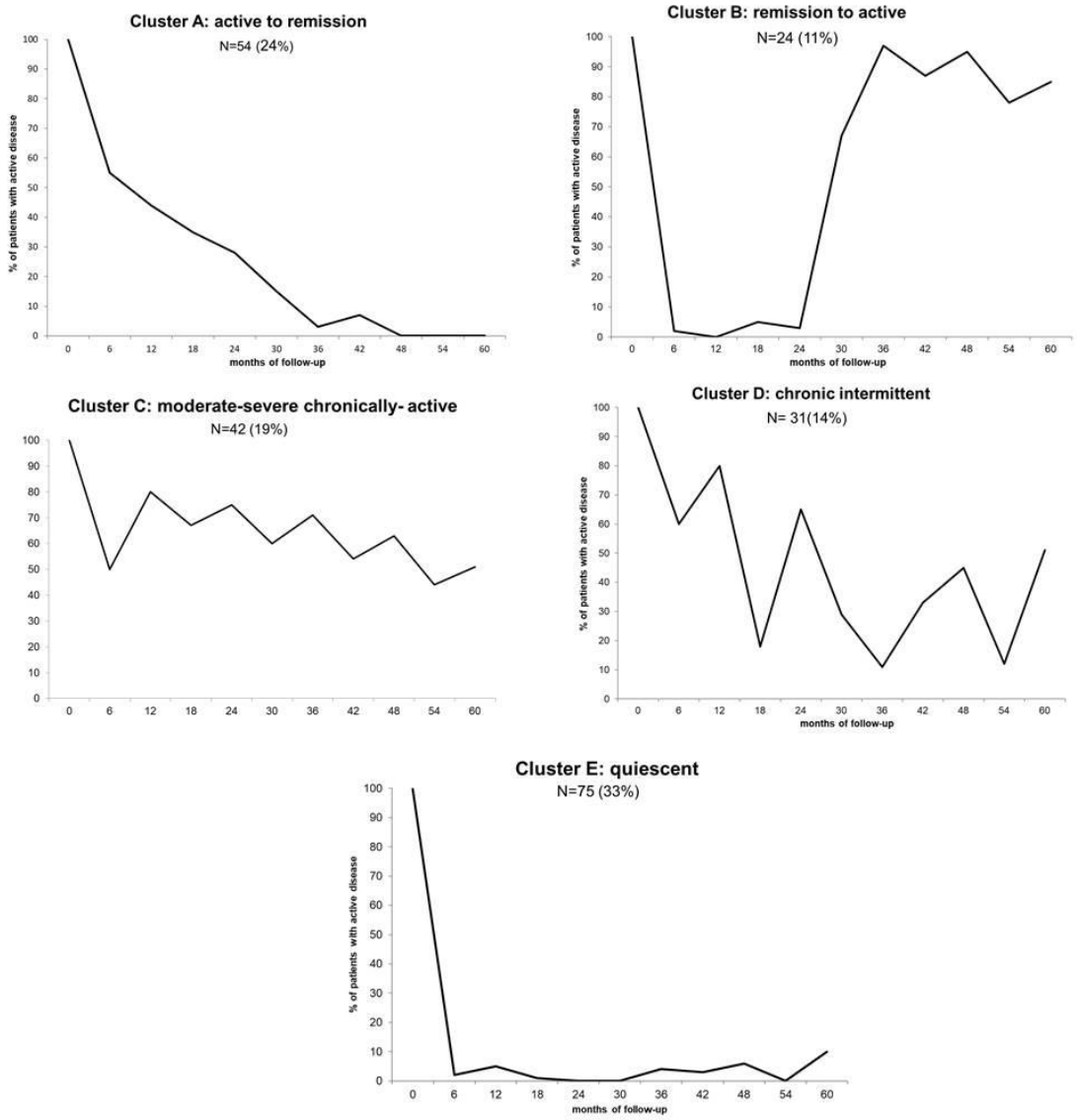

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Figure 2

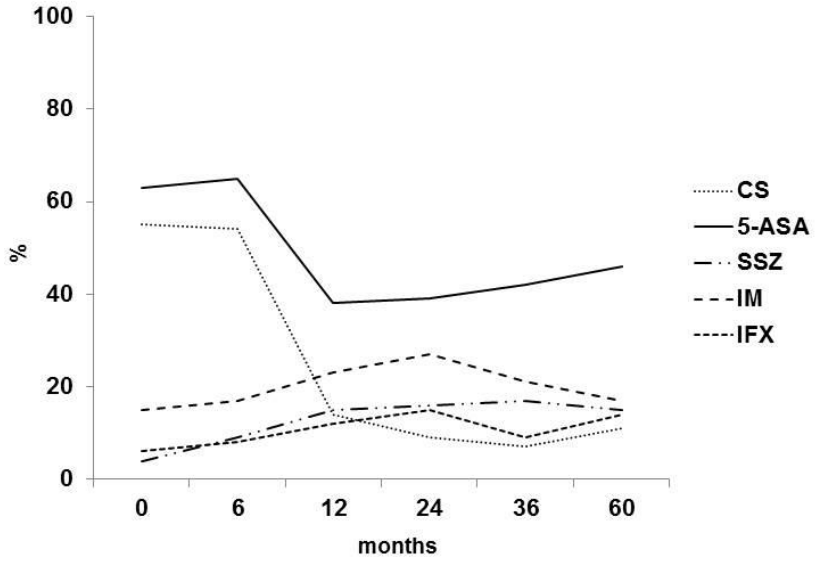

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Figure 3a and 3b

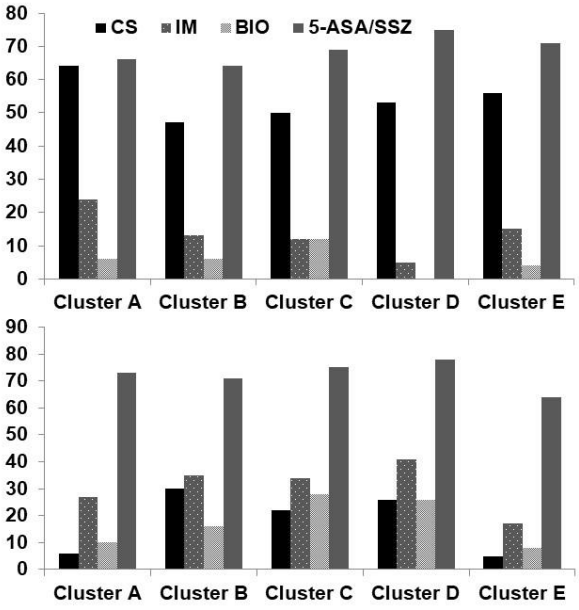

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Figure 4a and 4b