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Baseline characteristics and disease phenotype in inflammatory bowel disease results of a paediatric IBD cohort

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Abstract

Background and Aims: Predicting short-term relapses and long-term prognosis is of outmost importance in paediatric inflammatory bowel disease. Our aim was to investigate the short-term disease outcome and medication during the first year in a paediatric incident cohort from Hungary. In addition, association laboratory markers and disease activity indices with short-term disease outcome and medication were analysed.

Methods: From January 1, 2008 to December 31, 2010 demographic data and clinical characteristics of newly diagnosed paediatric inflammatory bowel disease patients younger than 18 years of age were prospectively recorded.

Results: A total of 420 patients were identified [Crohn's disease: 266; ulcerative colitis 124]. Initially, 48% (124/256) of Crohn's disease patients had moderate to severe disease (PCDAI>31), and this rate decreased to 2.1% at one-year follow-up. Proportion of ulcerative colitis patients with moderate to severe disease (PUCAI>35) at diagnosis declined from 57.5% (69/120) to 6.8% at one-year follow-up. Terminal ileal involvement correlated with higher initial CRP (p=0.021) and initial PCDAI (p=0.026). In ulcerative colitis, elevated CRP (p=0.002) was associated with disease extension. CRP and PCDAI at diagnosis were associated with the need for immunomodulators at one year in children with Crohn's disease. Initial CRP was also associated with the need for immunomodulators in patients with ulcerative colitis at one-year follow-up.

Conclusions: At diagnosis half of the patients with inflammatory bowel disease had moderate to severe disease and this rate decreased to less than 10% after one year. Initial CRP and PCDAI were related to the need for aggressive therapy in Crohn's disease.

Key Words: pediatric inflammatory bowel disease, epidemiology, therapy, disease activity index, CRP, follow-up

What is known

- Predicting short-and long-term prognosis would be essential in the management of IBD
- Some studies described, that initial CRP is associated with short-and long-term disease course.
- Relationship of pediatric IBD acitivity indeces and prognosis has not been investigated.

What is new

- Initially half of the patients had moderate to severe disease, this rate decreased to less than 10% after one year.
- Initially elevated CRP was associated with the need of immunomodulator at one year in CD and UC.
- PCDAI at baseline was associated with the need of aggressive therapy.

Introduction

A marker for prediction of disease progression and relapses would be beneficial in the management of paediatric IBD (inflammatory bowel disease). The ideal marker should be noninvasive, and could reliably identify patients at risk for relapse and for surgical interventions, who need initially more aggressive treatment.

Recently, numerous laboratory markers have been evaluated for diagnostic and differential diagnostic purposes, for assessment of disease activity, risk of complications, and for prediction of relapse with some success (1). Essential laboratory parameters: CRP, erythrocyte sedimentation rate (ESR), platelet count, and albumin have been described to correlate with disease activity in both UC and CD. It is also widely reported that CD is associated with a stronger response of laboratory markers, while only severe UC tends to present with abnormal laboratory markers (1).

CRP has been shown to be a good marker for evaluating disease course in a number of diseases (e.g. cardiovascular diseases), and some studies investigated its role in IBD. Consigny et al analysed a number of biological markers (complete blood count, CRP, ESR, etc.) of short-term relapse (2). Seventy-one adults with CD in remission were followed up and biological markers were checked every six weeks. Two markers were described to predict relapse: CRP >20 mg/L and ESR >15 mm. The negative predictive value was 97%. Furthermore, a Hungarian study (not nationwide study, adult patients) showed that positive (higher than 10 mg/L) high-sensitivity CRP (hs-CRP) at diagnosis is a predictor of short- and medium-term clinical relapses during follow-up (3). Kiss et al analysed data of 260 adult CD patients, and found that elevated hs-CRP at diagnosis was associated with subsequent need for azathioprine and infliximab (IFX). In addition, elevated hs-CRP at diagnosis was an independent predictor for relapse at 12-months in patients who were in clinical remission.

Disease activity indices (PCDAI and PUCAI) as noninvasive tools for follow-up have also been developed (4),(5). Although some clinical trials applied these indices (6),(7), there are only a limited number of reports available with activity indices in a population-based paediatric IBD cohort (8),(9).

Despite the increasing number of epidemiological studies conducted in paediatric IBD, until now prospective assessment of activity indices at diagnosis and during the first year of the disease from a nationwide study is missing. The relationship between laboratory parameters, disease activity indices and disease phenotype (location, age, familiarity) and their role in short-term and long-term outcome has not been established. Therefore, our primary aim was to investigate the association between disease activity indices, laboratory parameters, disease phenotype and short-term outcomes in the Hungarian Pediatric IBD Registry (HUPIR).

Methods

The associations among baseline characteristics, initial disease activity indices, laboratory parameters, and disease phenotype of newly diagnosed paediatric IBD patients were assessed. In addition, the relationship between outcome at one-year follow-up (disease activity indices, surgery, immunosuppressive and biological therapy) and initial parameters, as baseline disease activity indices, disease location, phenotype, laboratory parameters were also investigated. We analysed retrospectively the data of patients recorded from the 1st of January 2008 to 31st of December 2010 (36 months) recorded in the Hungarian Pediatric IBD Registry (HUPIR).

HUPIR was founded by the Hungarian Pediatric Gastroenterology Society in 2007. Twenty-seven institutes participate (4 academic centers in Hungary, 17 tertiary hospitals, where paediatric gastroenterology is present, 4 secondary hospitals with paediatric gastroenterologists, the rest were paediatric gastroenterology outpatient offices) in this prospective registry to

ensure a nationwide coverage (10). Private paediatric gastroenterology offices with endoscopy are not available in Hungary. Furthermore, coordinators are in contact with the main adult IBD centers to find adolescents diagnosed in adult centers.

Questionnaires are filled out by gastroenterologists who made the IBD diagnosis. Newly diagnosed IBD patients younger than 18 years are reported. Exclusion criteria were: age at diagnosis older than 18 years, missing information on ileocolonoscopy and ileocolonic histology, and a diagnostic workup without endoscopic, histologic, and radiologic abnormalities. Coordinators contact monthly the centers via email or phone calls to ask about newly diagnosed patients and actual follow-up data. The questionnaires are collected via email and double-checked by the leader of coordinators (KEM) and the leader of the HUPIR registry (GV). Age, gender, weight, height, presenting symptoms, concomitant diseases, extraintestinal manifestations (EIM), familiarity (first-degree), and complications are recorded. Furthermore, characteristics of diagnostic procedures including laboratory findings, endoscopy, radiology, histology, disease activity index, surgical interventions, and initial treatment are documented. Data are obtained anonymously. Every child is re-evaluated at 3 months and 12 months after diagnosis and followed-up yearly. Confirmation of diagnosis, current medical therapy as well as previous surgical interventions are reported by physicians at yearly follow up. Disease activity indices and anthropometric data are also requested on the follow-up survey.

The diagnosis of IBD is based on the Porto criteria (11). Disease activity at baseline is determined using validated multi-item disease activity indices, PUCAI and PCDAI (4, 5). Location and phenotype of disease are based on the Paris classification criteria (12). The site of the disease is evaluated only for those patients who underwent a complete bowel investigation (colonoscopy and esophagogastroduodenoscopy and/or small and large bowel were visualized for CD; large bowel was visualized up to the cecum for UC). Therapeutic strategy in paediatric IBD in Hungary is based on international guidelines.

The age- and gender-specific demographical data for calculating incidence were obtained from the Hungarian Central Statistical Office. The population, a total of 10.04 million, is predominantly white in Hungary. In 2009, 1.8 million of the inhabitants were <18 years old.

We analysed the data of patients recorded from the 1st of January 2008 to 31st of December 2010 (36 months). Disease activity indices, laboratory parameters (iron, CRP, platelets and hematocrit) and disease phenotype (age, gender, familial disease, extraintestinal manifestation, location, and behaviour) were recorded. Furthermore, association between initial activity indices, laboratory parameters and the later need for immunomodulators, biologicals, and bowel resection at one-year were assessed. CRP higher than 10 mg/L and platelets higher than 450 G/L were regarded as elevated. Iron level was regarded abnormal if it was lower than 7 micromoles/L. Abnormal hematocrit meant lower than 34%.

The study was approved by the National Ethical Committee.

Statistics

Our data did not follow Gaussian distribution based on Kolmogorov-Smirnov test. Therefore data are expressed as median and interquartile range, and nonparametric tests were used. Univariate comparisons were applied among different subgroups (gender, age groups according to Paris Classification, familial disease, extraintestinal manifestation, involvement of terminal ileum and upper gastrointestinal involvement) with regard to laboratory parameters and activity indices. Laboratory parameters were categorized as those with normal and abnormal values (see above). Disease activity indeces were categorzied as recommended in the literature (4, 13). Mann-Whitney test was applied for binomial comparisons. Association between more than two groups of categorical data was evaluated by Chi square test. To assess the relationship between paired activity indices at diagnosis and at one-year, Wilcoxon rank sum test was applied. We

performed ROC (Receiver operator characteristic curve) analysis to identify the best cut-off for continous variables.

A $p<0.05$ was considered as significant. Statistical analyses were performed using the SPSS® statistical package, version 17.0 (SPSS Inc., Chicago, IL, USA) for Windows®.

Results

A total of 421 children with IBD were diagnosed between January 1, 2008 and December 31, 2010 in Hungary. Two hundred and sixty-six had CD (63.2%), the number of UC cases was 124 (29.4%); and 31 patients (7.4%) were classified as having inflammatory bowel disease type unclassified (IBD-U). Demographic and clinical characteristics of patients are shown in Table 1. One-hundred and three UC patients (83%) and 240 CD (90.2%) patients had available data regarding disease activity, therapy and surgery at first year follow-up.

Disease activity at diagnosis and at one-year follow-up

Disease activity indices were available in 96.4% patients (376 of 390 UC and CD patients) at diagnosis and in 93.5% (343 of 376 CD and UC patients) at one-year follow-up. Of these, 124 of 256 patients with CD (48%) and 67 of 120 children with UC (57.3%) had moderate to severe disease at onset (PCDAI >31, PUCAI >=35). Younger CD patients (A1a) experienced lower disease activity at diagnosis than patients older than 10 years (A1b) (median PCDAI 20 vs. 32.5, p=0.007).

The proportion of CD patients with severe disease at diagnosis decreased from 48% to from 2.1% (5/240) at one-year follow-up. Rate of UC patients with moderate to severe disease activity declined from 55% to 7.8% (Figure 1)

Initial laboratory parameters

CRP, hematocrit, platelet count and iron level were documented in 411 children (97.6%) with IBD (laboratory parameters are presented in Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/MPG/A506).

CRP was higher than 10 mg/L in 177 children with CD (67.3%) at diagnosis. CRP level in girls was significantly lower than in boys (p=0.015) in CD. The difference in CRP between genders was significant only in children older than 10 years (A1b) (47.5 vs. 28.3 mg/L), while CRP level was comparable in male and female patients younger than 10 years (A1a) (34.5 vs. 37.5 mg/L, p=NS.

Location according to Paris Classification at diagnosis and association with initial disease activity and laboratory markers

A total of 243 (91.4%) CD patients were eligible for determination of disease location according to Paris Classification. L1 location (isolated terminal ileal±cecal disease) was seen at presentation in 10% (n=25), isolated colonic disease (L2) in 22% (n=55), and ileocolonic (L3) in 66% (n=163) (details of disease location of the recorded CD patients are shown in Supplemental Table 2, Supplemental Digital Content 2, http://links.lww.com/MPG/A507). The proportion of patients with inflammatory phenotype (B1, B1p) was 82%. Seven percent of CD patients had growth retardation.

CD patients with terminal ileum involvement had higher PCDAI (p=0.026). Terminal ileum involvement was associated more often with elevated CRP (p=0.021). Elevated CRP was significantly more frequent in CD patients with upper gastrointestinal involvement (p=0.030) and with stricturing and fistulizing phenotype (B2, B3 or B2B3) (p=0.01). Upper gastrointestinal involvement in CD was associated with increased platelet count (p<0.001).

Decreased iron concentration (lower than 7 micromoles/L) was more characteristic in patients with complicated behaviour (B2, B3 or B2B3) (p=0.006).

Fifty-seven percent of UC patients (n=69) had pancolitis (E4) and 5% had proctitis (E1). (details of disease location of the recorded UC patients are shown in Supplemental Table 3, Supplemental Digital Content 3, http://links.lww.com/MPG/A508). Elevated initial CRP was related to disease extent (p=0.002) at diagnosis. Abnormal iron level was also associated with location in patients with UC (p=0.004). PUCAI tended to be higher in more extensive disease, though this tendency was not significant (p=0.086).

Association between initial disease activity, laboratory parameters and medical therapy

Initial therapy and management at one year are presented in Table 2. Thirty-one percent (75/240) of CD children were treated with azathioprine initially, and this proportion increased to 51.7% by the end of the first year of disease. Induction therapy was often completed in CD patients with antibiotics (29%). Exclusive enteral nutrition was applied in a few centers only (10 CD patients). Cumulative incidence of intestinal resection (small bowel resection or/with partial colectomy) was 4.2% (10/240) at one year.

Initial PCDAI and elevated CRP at diagnosis was associated with azathioprine use at one year (PCDAI: OR: 2.3 95% CI 1.33-3.96, p=0.01, AUC_{PDCAI}:0.585, cut-off: 30, CRP: OR: 2.6, 95% CI 1.48-4.49, p=0.0007, AUC_{CRP}: 0.636, cut-off: 20). Elevated CRP at diagnosis was also associated with the administration of IFX at 12 months in children with CD (CRP: OR: 2.98, 95% CI: 0.38-23.25, p=0.297). CD patients receiving IFX at one year had higher PCDAI at diagnosis ($X(2)=16.54$, $p<0.001$).

Initial immunomodulator use was 3.2% (n=4) in UC. IFX was not available in paediatric UC during this period. No UC patients underwent surgery during the first year of disease course.

Initial PUCAI was not related to treatment strategies in UC, in contrast, elevated CRP and platelets were associated with subsequent use of azathioprine (CRP: OR: 6.2, 95% CI 2.3 - 16.4, p=0.003, AUC_{CRP}:0.663, cut-off: 18, and Platelet: OR: 0.43, 95% CI 0.17-1.07, p=0.073, AUC_{PLT}:0.651, cut-off: 400) (Figure 2). Abnormal iron levels was also more frequent at diagnosis in patients receiving azathioprine at one year (iron: p=0.018).

Discussion

This is the first nationwide paediatric incident cohort study reporting activity indices for IBD (PCDAI, PUCAI) at diagnosis and one-year later. Furthermore, we evaluated the relationship between initial laboratory parameters and disease characteristics based on the database of HUPIR. The association of laboratory findings and short-term disease outcome (surgery, disease activity) were analyzed. In addition, associations of disease activity indices with disease phenotype and short-term disease outcome were investigated.

Our study demonstrated that half of the newly diagnosed IBD patients had moderate to severe disease at diagnosis, and this proportion decreased to tenth of children by the end of the first year, which may be due to the therapy. PCDAI and elevated CRP at diagnosis were correlated to the need of azathioprine at one-year follow-up. In contrast, PUCAI did not show similar association, however all of the analyzed laboratory parameters were associated with the subsequent need for azathioprine. Furthermore, we found that CD patients younger than 10 years had lower PCDAI. As in adult studies, Crohn colitis was associated with lower disease activity and with less frequently elevated CRP (14). Complicated disease behaviour was also related to abnormal laboratory results (CRP, iron levels). In this cohort, UC patients with pancolitis had more frequently elevated CRP and lower iron levels. Finally, higher CRP was also more characteristic in UC children with EIM.

Our study presents disease activity indices at diagnosis and one year later. In a retrospective study from Western Slovenia 53% of children with CD (39/73) and 8% of children with UC (3/35) had severe disease activity (PCDAI>31, UCAI>16) (9). The only study that reported both PUCAI and PCDAI is a population-based incident cohort from South-Eastern Norway in 39 paediatric'onset CD and 19 UC patients (8). The median PCDAI was 25 and median PUCAI was 35, as in this report. These results are in concordance with earlier findings, where more than 70% of children had moderate to severe disease at diagnosis based on clinical symptoms (15) or physician global assessment (PGA) (16). In previous studies, Dubner et al evaluated bone mineral density and structure in a smaller cohort of CD patients, and described that median PCDAI decreased from 36 (at diagnosis) to 5 (12 months after diagnosis) (17), respectively. The proportion of patients with moderate to severe disease activity was 5% 12 months after diagnosis in the paper of Pfefferkorn et al, who analyzed growth outcome in children with CD (18). Taken together, our results are remarkable and unique because these activity indices represent a common paediatric IBD population (not only highly specialized IBD centres). In addition, this is the first study related to PCDAI and PUCAI at diagnosis and at one-year of follow-up in a nationwide incident cohort. Studies on development of PUCAI have not been found in the literature.

At the time of data collection there was no available guideline regarding management of paediatric IBD in Hungary. Initially published trials showed oral 5ASA to be an effective treatment for active ileal, ileocolic or colonic CD. As a consequence, mesalazine became a popular treatment with limited toxicity for mild disease (19). Comparing with other reports the use of 5-ASA was not more frequent in Hungary than other countries at that time (20, 21).

The relationship between disease activity indices and prognosis has not yet been investigated. Initially higher PCDAI was associated with subsequent azathioprine. PCDAI includes items that are not sensitive for rapid changes (perirectal disease, EIM, height velocity)

(22). However, these parameters are associated with poor prognosis. PCDAI may be related to disease course because it includes parameters that change slowly. In contrast, PUCAI was not related to short-term disease course that may reflect the difference between these two tools. PUCAI consists of clinical signs purely and does not contain laboratory tests or other less responsive items. In conclusion, the combination of rapidly and slowly responsive items seems to be effective in predicting disease course.

Laboratory parameters correlate with disease activity, but their value in the evaluation of disease course has not been established in paediatric IBD. In the present study initially increased CRP was associated with the need for azathioprine and IFX at one year. This finding supports earlier results that demonstrated a role of CRP in predicting relapses (2),(23) and short-term disease course (3),(24). The IBSEN study group described that CRP is a long-term predictor of surgery in subgroups of patients with either UC or CD (25). Based on these results CRP is probably a factor that contributes to the relationship of PCDAI and disease course.

There is much less data on the value of laboratory markers in assessing disease course of UC. In a Korean study 256 adult patients with UC were followed for five years after diagnosis: hemoglobin lower than 10.5 g/dL was an independent predictor of relapses (26). Bitton et al aimed to assess whether clinical, biological, and histologic parameters in quiescent UC predict time to clinical relapse. Seventy-four patients with clinically and endoscopically determined inactive UC were followed up for one year. Younger age, multiple previous relapses and basal plasmacytosis on rectal biopsy specimens were independent predictors of earlier relapse, but laboratory parameters could not predict relapses reliably (27).

Moreover, we demonstrated relationship between location and CRP. Previous reports showed that ileal disease is associated with elevated CRP (28),(29). It is of interest, that children with ileocolonic CD had higher CRP than patients with no ileal involvement or ulcerative colitis (28),(29, 30). It seems that its involvement is related to higher levels of CRP.

The increased level of CRP may be due to the more intensified cytokine production of the Peyer's patches. The number of Peyer's patches increases during childhood and reaches a peak in late adolescence, then it starts to regress (31). This observation may be the link between the lower CRP levels in Crohn colitis.

Of note, the observation that younger patients have lower PCDAI, have not been reported yet. The explanation for that is may be the location of the disease. Children under 10 years have mostly colonic localization, and patients with isolated colonic localization have usually lower PCDAI, as previously discussed. Children under 10 years have mostly colonic localization but this fact did not explain the lower PCDAI in this subgroup.

Although this is the first population-wide study describing the activity indices at diagnosis and at one-year follow-up, it has some limitations. First of all, this is a post hoc analysis of prospectively collected data. Furthermore, it is of note that, medication utilization during the 1 year of disease course was relatively subjective before the era of published international guidelines. In addition, activity indices and follow-up data were not available for every patient. Detailed information regarding relapses, steroid-dependency are not collected, that would allow to analyze more precisely the relationship of the disease course and activity indices, laboratory parameters.

In summary, this is the first study that disease activity indices are presented in a paediatric incident cohort and their relationship with 1st year disease course is analyzed. Based on these results half of the children had moderate to severe disease activity (PCDAI, PUCAI) at diagnosis and after one year of therapy only one tenth of children had moderate to severe disease activity. The association of PCDAI with ileal localization and age indicates that PCDAI differs in distinct phenotypes in CD. Initial CRP level correlated positively with the need for azathioprine at one year of follow-up in patients with CD and UC.

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Figure and Table Legends

Figure 1 Disease activity indices at diagnosis and one-year follow-up in ulcerative colitis and Crohn's disease.

Figure 2 Receiver operator characteristic (ROC) curve analysis used to estimate the best cut off-point of CRP able to discriminate between UC patients who required immunomodulator treatment at one-year follow-up

Table 1 Demographic and clinical characteristics of paediatric patients with inflammatory bowel disease diagnosed between 2008-2010 in Hungarian Pediatric IBD Registry (HUPIR).

Table 2 Initial therapy and therapy at one-year follow-up in paediatric patients with inflammatory bowel disease.

Figure 1

Figure 1 Disease activity indices at diagnosis and one-year follow-up in ulcerative colitis and Crohn's disease.

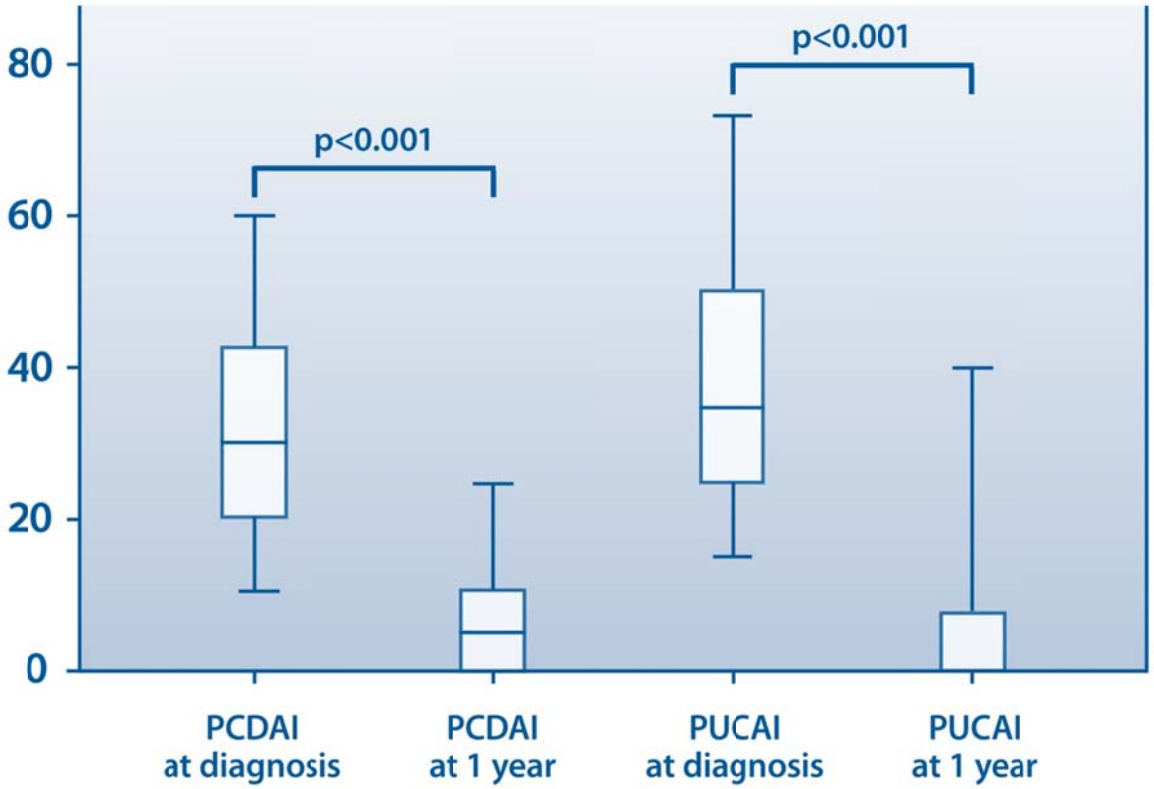

Figure 2

Figure 2 Receiver operator characteristic (ROC) curve analysis used to estimate the best cut off-point of CRP able to discriminate between UC patients who required immunomodulator treatment at one-year follow-up

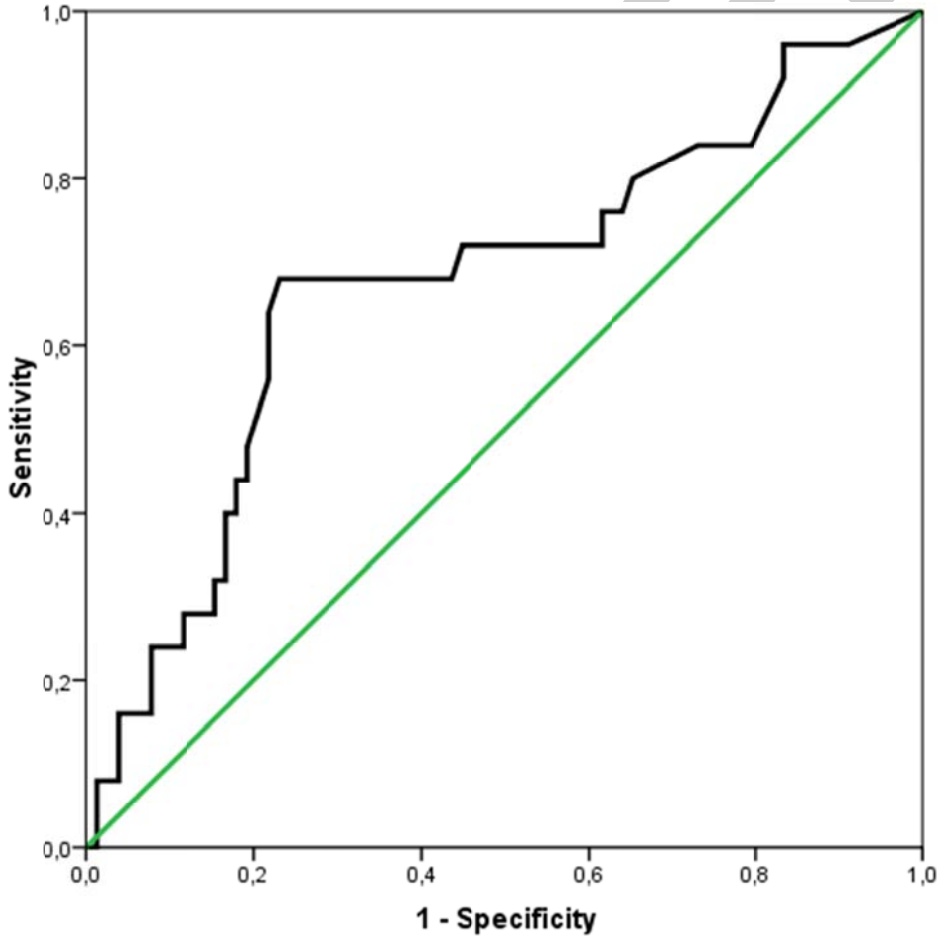

Table 1 Demographic and clinical characteristics of paediatric patients with inflammatory bowel disease diagnosed between 2008-2010 in Hungarian Pediatric IBD Registry (HUPIR).

	All IBD*	**Ulcerative colitis**	**Crohn's disease**	**IBD-U****
Number of patients (%)	421	124 (29.4%)	266 (63.2%)	31 (7.4%)
Gender				
Male	212 (50.4%)	52 (41.9%)	149 (56.1%)	11 (35.5%)
Female	209 (49.6%)	72 (58.1%)	117 (43.9%)	20 (64.5%)
Male:Female	1.01:1	1:1.4	1.3:1	1:1.8
Age***				
Median (±IQR, year)	13.9 (11.25-16)	13.5 (10.8-16)	14.2 (11.8-16.1)	12.4 (8.75-14.2)
A1a (0-<10 years)	70 (16.6%)	23 (18.5%)	38 (14.3%)	9 (29%)
A1b (10-<17 years)	309 (73.5%)	89 (71.8%)	199 (74.8%)	21 (67.7%)
A2 (17-<40 years)	42 (9.9%)	12 (9.7%)	29 (10.9%)	1 (3.3%)
Familial disease	52 (13.1%)	14 (11.3%)	35 (13.2%)	3 (9.6%)
Extraintestinal manifestations	63 (15%)	15 (12%)	47 (17.6%)	2 (6.5%)
Arthropathy	36 (57.1%)	8	28	0
PSC***	10 (15.8%)	6	3	1
Cutaneous	22 (35%)	2	19	1
Ocular	1 (1.6%)	0	1	0

PCDAI/PUCAI****				
PCDAI 0-10 PUCAI <10		2 (1.7%)	20 (7.8%)	
PCDAI 11-30 PUCAI 10-34		49 (40.8%)	112 (43.75%)	
PCDAI >31 PUCAI 35-64		54 (45%)	124 (48.4%)	
PUCAI >65		15 (12.5%)		

* IBD, inflammatory bowel disease
** IBD-U, inflammatory bowel disease type of unclassified
*** PSC, Primary sclerosing cholangitis
**** PCDAI, Pediatric Crohn's Disease Activity Indices;
PUCAI, Pediatric Ulcerative Colitis Activity Indices

Table 2 Initial therapy and therapy at one-year follow-up in paediatric patients with inflammatory bowel disease.

	Initial therapy	**Therapy at one-year follow-up**	**Significance (p)**
Ulcerative colitis (n=103)			
5-ASA (oral)	95 (92%)	81 (78.6%)	0.119
Corticosteroid (systemic)	67 (65%)	14 (13.5%)	<0.001
Azathioprine	4 (3.4%)	22 (21.3%)	<0.001
Antibiotics	30 (29%)	1 (0.9%)	<0.001
Crohn's disease (n=240)			
5-ASA (oral)	205 (86.1%)	188 (79%)	0.264
Corticosteroid (systemic)	180 (75.6%)	46 (19.3%)	<0.001
Azathioprine	75 (31.5%)	123 (51.7%)	<0.001
Antibiotics	81 (34%)	13 (5.4%)	<0.001
Infliximab	-	35 (14.5%)	<0.001