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Inflammatory Bowel Disease in Children and Adolescents – a Retrospective Study of 13 Years of Records Investigating Potential Prognostic Factors

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ABSTRACT

Purpose: *To assess the landscape of management of pediatric inflammatory bowel disease (IBD) patients in Greece and investigate possible prognostic factors for the disease outcome.*

Methods: *The medical records of all IBD patients who visited the gastroenterology divisions of two university pediatric clinics as in- or outpatients over 13 years were examined.*

Results: *Twenty-seven females and 25 males were included in the study. Ulcerative colitis (UC) was diagnosed in 46% of cases, Crohn's Disease (CD) in 33% and unclassified IBD (IBD-U) remained the diagnosis in 21%. The CRP level was elevated in 68% of cases at diagnosis, whereas only 27.4% of patients had ESR levels and platelet counts within the age-adjusted normal range. No parameter derived from patient history, physical examination or laboratory and imaging was found to influence the time to diagnosis. Abdominal pain and lack of diarrhea at the time of diagnosis were significantly associated with the need for biologic therapy during the disease course in CD. Consistent with the "step-up" approach the treating physicians practiced, an increased number of relapses correlated with the addition of biologics in the treatment of both CD and UC patients (P=.03 and P=.002, respectively).*

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Conclusion: *It is the first time that clinical data regarding IBD pediatric patients in Greece were reviewed. Some clinical and imaging factors were associated with more aggressive disease, an increased need for biological treatment and frequent hospitalizations for IBD flares. Moreover, it was observed that the clinical features of IBD in Greek children were similar to those in other countries.*

Keywords: inflammatory bowel disease, prognostic factors, Crohn's disease, ulcerative colitis, pediatric, adolescents.

INTRODUCTION

Inflammatory bowel diseases (IBDs) are a group of disorders characterized by chronic inflammation of the intestinal tract. The main types of IBD are Crohn's disease (CD) and ulcerative colitis (UC), although some patients' condition fails to fulfill the published criteria for either type; these patients are diagnosed with unclassified inflammatory bowel disease (IBD-U) (1, 2).

The incidence of IBD in children and adolescents has increased in the last decade, both in developed and developing countries. Recent studies suggest that childhood-onset IBD comprises 25% of all IBD cases (3, 4).

The underlying mechanisms of the disease are quite complicated. Several genetic loci have been observed to play a role in the pathogenesis of the disease. It can roughly be stated that an abnormal immune state leads to inflammation in the intestine and disease progression (1).

The clinical appearance of IBD in children and adolescents may depend, among else, on the affected part of the gastrointestinal tract. Diarrhea and rectal bleeding are associated with an inflamed colon, whereas affected terminal ileum with or without jejunum involvement is characterized by more vague symptomatology comprised of fever, abdominal pain and weight loss (5). Extra-intestinal symptoms such as erythema nodosum, arthritis, and uveitis appear in less than one third of children (2). Some noticeable differences between childhood-onset and adult-onset IBD are reported throughout the literature. For example, childhood-onset UC tends to appear as pancolitis, in contrast with the more localized character of adult-onset UC (6). Apart from the standard clinical picture, untreated pediatric IBD patients, and especially CD patients, are led to a failure to thrive, as the intestinal tract plays a major role in human growth (6, 7).

The diagnosis is "ruled in" by observing the aforementioned symptomatology and is confirmed through the findings of colonoscopy, imaging modalities and histopathological examination (2, 8). Stool examination is also helpful to differentiate IBD from infectious diarrhea. Genetic testing of specific mutations could also have a role in the diagnostic algorithm (1).

The non-invasive management of the disease encompasses a wide range of pharmaceuticals (5-ASA, steroids, immunosuppressants and dietary supplements specifically developed for IBD), in addition to specific antibodies (anti-TNF, etc). Treatment with biologic factors has brought a reduction of relapses and a measurable increase in patients' quality of life. Nonetheless, surgery is still unavoidable in certain cases (2, 9).

Unveiling a correlation between certain clinical as well as laboratory parameters and the increased number and severity of relapses would greatly assist with treatment decisions. This was the aim of our study.

MATERIALS AND METHODS

The study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving research study participants were approved by the hospital's research committee. Written informed consent was obtained from all patients. In the cases of underage patients, consent from legal guardians was obtained.

We retrospectively reviewed the medical records of all patients who were diagnosed with IBD under the age of 18 years in the gastroenterology divisions of two university pediatric clinics. Data from the records of an internal medicine clinic have been also included, children

from the age of 14 onwards needing referral to an adult gastroenterologist in Greece. The medical records mainly contained data about patient hospitalizations and biologic drug injection visits, and were dated from 2004 through 2017.

Telephone inquiries were additionally made to children's parents to acquire data that were missing from the medical records, with a focus on retrieving data that they could corroborate from their own written records, thus not subject to memory biases.

The diagnosis of UC, CD or IBD-U were made by experienced pediatric gastroenterologists based on patients' clinical picture, colonoscopy, imaging, and histopathological findings. The latter three have been also used to determine which anatomic parts of the colon were affected by the disease.

Through the medical records and phone conversations, we sought to record patient information, age at onset as well as time to diagnosis. Symptoms at onset were also recorded, as were the results of any imaging or endoscopic procedure, to map the involvement of different parts of the colon and the terminal ileum to the disease. If present, the existence of strictures and/or fistulas has been also noted. The therapeutic regimen used to induce remission was recorded too, in addition to all additional flares for which patients were hospitalized.

Differences in the means of ordinal and scale variables were investigated for statistical significance with the t-test in case they were normally distributed, whereas the Mann-Whitney U test was used when they were not. Examining the difference in frequency between groups, the chi-square test was conducted. Finally, when trying to detect a correlation between scale and/or ordinal variables, Spearman's rho was utilized.

RESULTS

Demographic data-Follow-up time

In total, 52 patients with IBD were recorded, 48% of whom were males. Table 1 contains the demographic data of CD, UC and IBD-U patients; CD patients experienced 99.76 flares *per* 100 person-years (SD= 105.31), whereas UC patients 58.35 flares *per* 100 person-years (SD= 56.62). This difference was not found to be statistically significant (U=140, P=.352). The number of flares significantly correlated with the duration of follow-up in both CD (r_s=.598, P=.019) and UC patients (r_s=.605, P=.019) (Figure 1).

Clinical presentation at diagnosis

A detailed report of the frequency of each symptom at disease presentation can be found in Table 2. Investigating any potential correlation between the clinical presentation of IBD and the time to final diagnosis, no specific symptom (or lack) was found to significantly delay the diagnosis of CD. The absence of hematochezia at UC onset seems to delay the diagnosis, but no definitive statements can be made because of the small sample size.

Regarding gender and differences in disease symptomatology, female UC patients were significantly more likely than males to present with the perianal disease (χ^2=5.000, P=.025).

	CD (n=17)	SD	UC (n=24)	SD	IBD-U (n=11)	SD	p-value[1]
Age at onset, years	12.1	3.4	8.3	4.3	9.8	4.6	0.011
Sex, male (%)	47.1%	NA	54.2%	NA	36%	NA	0.664
Symptom onset to diagnosis, months	4.3	4.7	5.4	9.7	3.8	1.1	0.760
No. of IBD flares	1.9	2.0	2.4	2.7	1.1	1.3	0.563
Follow-up duration, months	37.3	35.5	46.9	40.6	22.9	22.7	0.793

CD=Crohn's disease, UC=ulcerative colitis, SD=standard deviation, IBD=inflammatory bowel disease, IBD-U=unclassified IBD.
[1]This is the p-value for the difference between means CD and UC means.

TABLE 1. Demographic and follow-up data of ulcerative colitis and Crohn's disease patients

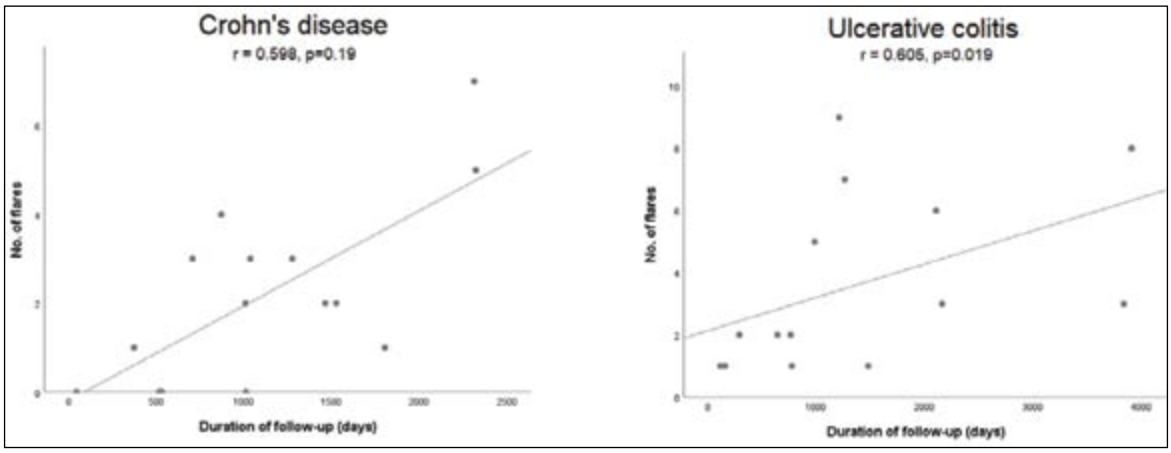

FIGURE 1. Graph displaying the correlation between the duration of follow-up and the number of relapses in CD and UC patients. CD=Crohn's disease, UC=ulcerative colitis

CD patients who presented with abdominal pain suffered more flares on average (mean=2.789, SD=2.22) than those who did not (mean=1, SD= 1.53), but the difference was not detected as statistically significant (U=16.0, P=.09). No other symptom was found to predict an increased number of flares at a statistically significant level for neither UC nor CD.

Patients that remained in the IBD-U group throughout follow-up were more likely to present with skin manifestations (χ^2=12.66, P<.001). They also experienced fewer flares (mean=0.80, SD=1.03) than patients with a UC or CD diagnosis, (mean=2.2, SD=2.41) but the difference didn't prove statistically significant in our sample population (U=132.5, P=.077) (Figure 2).

Diagnostic procedures

Although in all cases IBD was diagnosed with colonoscopy, the complete procedure reports were procured for the colonoscopies of only 31 out of the 52 patients, performed close to the time of diagnosis (12 UC, 12 CD, and seven IBD-U cases). Of them, only two revealed completely normal intestinal lumen, both microscopically and macroscopically.

Colonoscopies performed on patients ultimately diagnosed with CD revealed colitis in 100% of cases (n=12) and ileitis in 41.2% (n=7). CD patients who presented with ileum involvement were older at disease onset (mean age=13.94 years, SD=34.13) than those without (mean age=9.56 years, SD=33.01). This difference was detected as statistically significant

Signs and symptoms	CD (n=16)	UC (n=20)	IBD-U (n=9)	p-value
Diarrhoea	68.8%	90%	77.8%	0.109
Abdominal pain	56.3%	30%	22.2%	0.112
Mucous diarrhea	31.3%	30%	33.3%	0.936
Hematochezia	25%	80%	55.6%	*0.001*
Perianal disease	25%	20%	33.3%	0.720
Fever	37.5%	30%	22.2%	0.635
Arthralgia	6.3%	5%	11.1%	0.871
Anemia	12.6%	10%	44.4%	0.813
Iron deficiency	6.3%	15%	22.2%	0.106
Skin disorders	6.3%	0%	44.4%	0.257

CD=Crohn's disease, UC=ulcerative colitis, IBD-U=unclassified inflammatory bowel disease

TABLE 2. Frequency of symptoms and comorbidities of inflammatory bowel disease patients at diagnosis

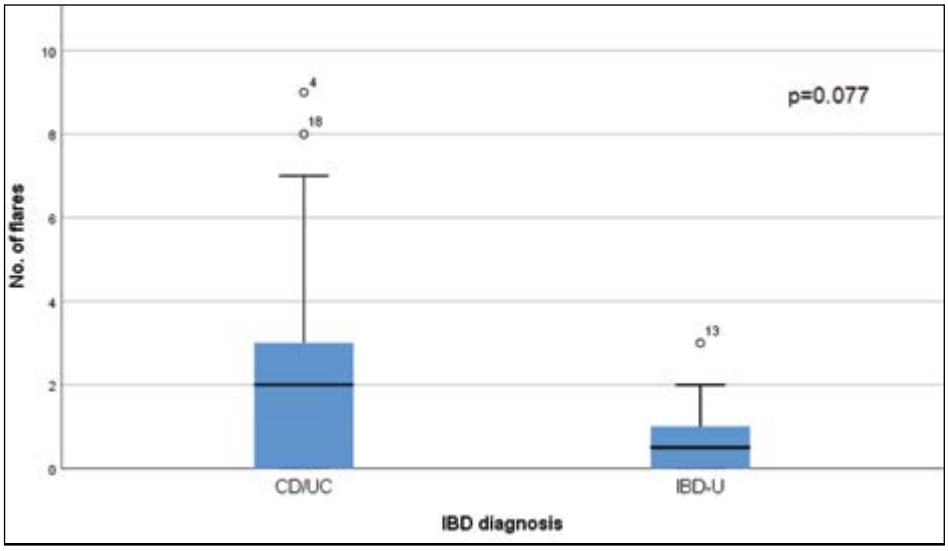

FIGURE 2.
Boxplot chart displaying the number of flares of UC and CD patients. CD=Crohn's disease, UC=ulcerative colitis, IBD=inflammatory bowel disease, IBD-U= undifferentiated IBD.

Biomarkers	CD (n=7)	UC (n=8)	IBD total
CRP (>5 mg/dL)	6 (85.7%)	5 (45.5%)	17 (68.0%)
ESR (>18 mm/h)	6 (85.7%)	6 (75%)	19 (82.6%)
PLT (>350× 10^9/L)	6 (85.7%)	7 (87.5%)	19 (82.6%)

UC=ulcerative colitis, CD=Crohn's disease, IBD=inflammatory bowel disease, CRP=C-reactive protein, ESR=erythrocyte sedimentation rate, PLT=platelet count

TABLE 3. Frequency of abnormal laboratory values in inflammatory bowel disease patients at the time of diagnosis, n (%)

(U=2.00, P=.033). CD patients with ileitis were also significantly less likely to present with hematochezia (χ^2=7.22 P=.007). Granulomas were detected in biopsy specimens in 33% of CD cases (n=4).

Regarding UC cases, 50% (n=6) of colonoscopies performed at diagnosis revealed pancolitis, and one patient suffered from backwash ileitis. No patient-related parameters seemed to predict the existence of pancolitis at disease onset. A rectal-sparing phenotype was observed in 16.7% (n=2) of colonoscopies performed on UC patients.

Laboratory findings

Utilizing reference ranges of <5 mg/dL for CRP, <18 mm/h for ESR and <350×109/L for platelet count, the frequency of abnormal laboratory values at the time of diagnosis was calculated (Table 3).

CRP and ESR levels correlated significantly in UC patients (rs=.850, P=.007) but not in CD patients (rs=.286, P=.535). The existence of fever in UC patients positively correlated with increased CRP levels (U=1.0 P=.01) and platelet counts (U=0, P=.021).

Therapy

The medications that were part of the initial treatment of the disease can be found in Table 4, and those used throughout the disease are presented in Table 5.

Clinical presentation and initial treatment

Investigating potential correlations between the patients' clinical picture at diagnosis and the pharmacological therapy used to induce remission, CD patients presenting with rectum involvement were significantly more likely to require corticosteroids to induce remission (χ^2=4.41, P=.036). Semi-elemental diet (Modulen IBD ®) was significantly more likely to be included in the therapeutic plan of CD patients who presented with fever (χ^2=5, P=.025) and those with Crohn's ileitis (χ^2=4.44, P=.035), whereas it was less likely to be prescribed in CD patients with diarrhoea (χ^2=11.25, P=.001).

There was a tendency for UC patients with elevated CRP levels to require corticosteroids to

Medication	CD (n=15)	UC (n=19)	IBD-U (n=8)	IBD total (n=42) (%)
5-ASA per os	12 (80.0%)	17 (89.4%)	7 (87.5%)	36 (85.7%)
5-ASA enemas	0	3 (15.8%)	1 (12.5%)	4 (9.5%)
Corticosteroids	8 (53.3%)	11 (57.9%)	8 (100%)	27 (64.3%)
Semi-elemental diet	6 (40.0%)	7 (36.8%)	5 (62.5%)	18 (42.9%)
Metronidazol	1 (6.7%)	1 (5.6%)	2 (25%)	4 (9.5%)
6-MP / AZA	0	3 (15.8%)	1 (12.5%)	3 (7.1%)
MTX	0	1 (5.3%)	0	1 (1.9%)
Biologic	3 (20.0%)	1 (5.3%)	1 (12.5%)	5 (11.9%)

UC=ulcerative colitis, CD=Crohn's disease, IBD=inflammatory bowel disease, IBD-U=unclassified IBD, 5-ASA=5-aminosalicylic acid, 6-MP=6-mercaptopurine, AZA=azathioprine, MTX=methotrexate

TABLE 4. Frequency of medication prescribed at diagnosis

Medication	CD (n=17) (%)	UC (n=23) (%)	IBD total (n=48) (%)
6-MP/AZA/MTX	9 (52.9%)	13 (56.5%)	25 (52.1%)
Biologic therapy	9 (52.9%)	11 (47.8%)	22 (45.8%)
PO iron supplementation	5 (29.4%)	6 (26.1%)	13 (25.0%)
IV iron therapy	2 (11.8%)	3 (13.0%)	5 (10.4%)

UC=ulcerative colitis, CD=Crohn's disease, IBD=inflammatory bowel disease, 6-MP=6-mercaptopurine, AZA=azathioprine, MTX=methotrexate, PO=per os.

TABLE 5. Frequency of symptoms and comorbidities of inflammatory bowel disease patients at diagnosis

induce remission at diagnosis, but the difference was not detected as statistically significant (U=34.50, P=.086). 5ASA enemas were significantly more likely to be administered to UC patients with perianal disease at diagnosis (χ^2=4.11, P=.043).

Clinical and laboratory parameters predicting disease course

To discover clinical and laboratory parameters at disease onset that can predict disease course and severity, the following results are reported.

Regarding CD cases, neither gender nor age at disease onset predicted the necessity of biologic therapy to induce remission. Perianal manifestations at disease onset positively correlated with the need to prescribe *per* os iron supplements for follow-up in CD patients (χ^2=4.75, P=.03). Abdominal pain at diagnosis positively correlated with the inclusion of biologic therapy for the disease in CD patients (Figure 3). This correlation was detected as statistically significant (χ^2=8.90, P=.003). CD patients who presented with diarrhoea were significantly less likely to need biologics for the disease (χ^2=5.66, P=.017).

CRP and ESR levels at disease onset appeared to predict biologic use over the disease's course in UC, but statistical significance was not detected (U=5.5, P=.082 for CRP; U=1, P=.051 for ESR). Age, gender, the existence of pancolitis, laboratory, and endoscopic parameters were tested and none predicted the need of resorting to biologic or immunosuppressive therapy to induce and maintain remission in UC patients.

Predictably, biologic use throughout the disease course significantly correlated with the number of relapses both in CD (U=14, P=.03) and UC patients (U=13.5 P=.002). An increased amount of relapses also significantly correlated

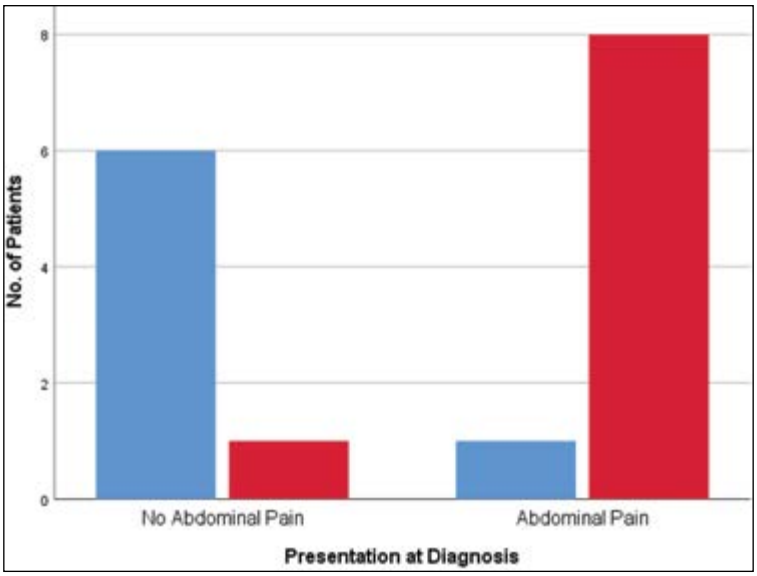

FIGURE 3.
Bar chart of abdominal pain at diagnosis related to the use of biologic therapy in CD patients. CD=Crohn's disease

with the necessity of *per* os iron supplements in CD cases (U=6.5, P=.011).

DISCUSSION

Crohn's disease

CD patients comprised 33% of all IBD patients. The most frequent complaint that brought patients and their parents to the physician was diarrhea (68.8%), closely followed by abdominal pain (56.3%). Only two of the 16 total patients (12.5%) presented with extra-intestinal manifestation, arthritis, and skin manifestations, respectively. These observations are consistent with those made in other studies (10, 11).

Virtually all colonoscopies performed on CD patients at the time of diagnosis revealed colitis, whereas ileal involvement was observed in 41.2% which is equivalent to studies performed on the Mediterranean population (10).

Granulomas were detected in four out of the 12 CD cases for whom biopsy data were available. Regarding initial therapy, a little more than half of the CD patients required corticosteroids to induce remission. Throughout the disease, 52.9% of patients required therapy with biologics.

Looking at the data collected for patients suffering from CD, neither age at onset nor gender predicts the need for biologic therapy during the disease. Abdominal pain (P=.003) and the lack of diarrhea (P=.017) appear to predict the need for biologic therapy in CD, hinting at a more aggressive disease phenotype. Unfortunately, none of the other demographic, clinical, endoscopic or laboratory parameters available at diagnosis seem to have similar predictive value.

Likewise, no information that is available to the physician at diagnosis proved capable of detecting patients that are at risk for an increased amount of relapses. Finally, no parameters were found to correlate with the development of a perianal disease.

Ulcerative colitis

Forty-six percent (46%) of patients have been eventually diagnosed with UC, which, as previously discussed, was consistent with findings of other studies that underline the increase of UC in the pediatric population (5, 10, 12). On the other hand, our finding that UC patients were on average significantly younger than CD patients at disease onset was not in total agreement with other studies (6). A study including Mediterranean patients found the opposite (5).

By far, the most common complaints by UC patients at disease onset were diarrhea (90%) and blood in the stool (80%). IBD patients who presented with hematochezia were significantly more likely to be diagnosed with UC in our study sample (P=.001) (Figure 4), so our results reinforced the established observation that bloody diarrhea is highly indicative of UC. Whereas both genders were equally represented in the sample of UC patients, female UC patients were

significantly more likely to present with a perianal disease (P=.025).

Interestingly, 50% of colonoscopies performed on UC patients at diagnosis revealed pancolitis, a finding concordant with other studies, which point out the more aggressive disease phenotype of pediatric-onset UC in comparison to the adult one (6, 7, 10, 13).

A rectal sparing phenotype was detected in two patients, but the very small sample size precludes from any conclusions. It can only be confidently stated that its incidence in our sample is roughly consistent with that in other studies (14).

Among UC patients, 57.9% required corticosteroids to induce remission at diagnosis, whereas 56.5% needed immunosuppressants for the disease. Exactly half of UC patients eventually required biologic therapy to maintain remission. Unfortunately, no parameter available at diagnosis was found to predict either the necessitation of biologic therapy, immunosuppressants, or the number of relapses in UC patients.

There was a tendency for laboratory values at diagnosis (CRP, ESR, platelet count) to correlate with the need for corticosteroids to induce remission at diagnosis and for biologic therapy for the disease, both indications of more aggressive disease. Neither was detected as statistically significant. Even then, the actual clinical relevance would have remained doubtful, as this was not a randomized trial and the final choice of treatment could have been actually influenced by the laboratory values, and not vice versa. Finally, UC patients presenting with a perianal disease were significantly more likely to receive 5ASA in enemas form (P=.043), indicating that topical treatment was thought to be more effective in such cases.

Particular care was given during this study to confounding factors that could delay the diagnosis of IBD, as well as whether such a delay is linked to worse outcomes. The time from symptom onset to diagnosis observed in the patients of this study is relatively low compared to the results of an Italian study (10), which could be attributed to the high degree of suspicion for IBD exhibited in our clinics. In the end, no clinical, imaging or laboratory patient parameters could be associated with a delayed diagnosis. An increased delay between disease onset and diagnosis also did not seem to correlate with an increased number of relapses or the need for more aggressive therapy for the disease. This could indicate that, although a delayed diagnosis usually translates to increased disease severity at clinical presentation, the actual response of each patient to treatment and the therapeutic agents required to induce and maintain remission rely on other factors.

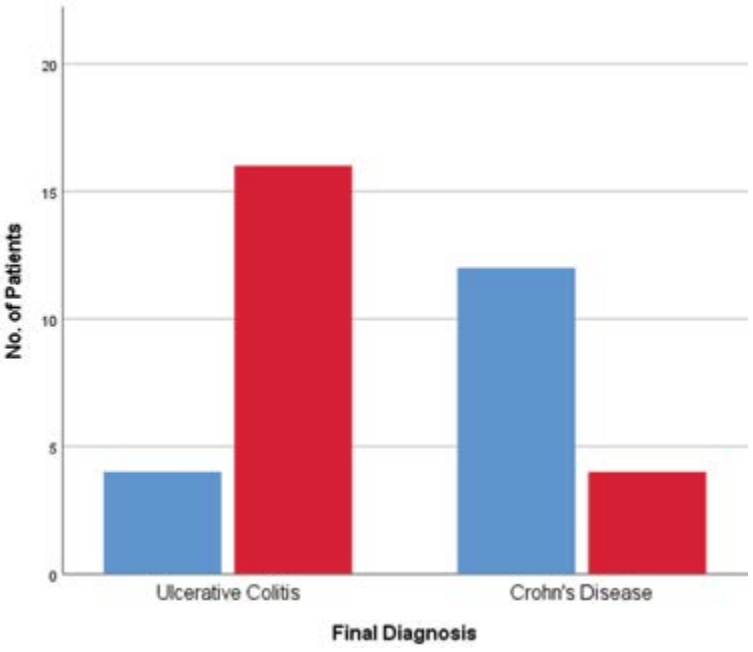

FIGURE 4.
Bar chart of final diagnosis by hematochezia at disease onset

CONCLUSIONS

In conclusion, our results paint a clear picture of IBD phenotype and therapy in Greek pediatric patients. Except for abdominal pain and lack of diarrhea correlating with early biologic use in CD patients, no other clinical or laboratory parameter was found to significantly predict disease course in pediatric IBD patients. Nonetheless, some trends could be observed, such as the tendency of patients with higher CRP and ESR values requiring biologic therapy to maintain remission. Because of this, our research team believes that further multi-center studies with larger sample sizes are required to accurately investigate and confirm these findings. ❑

Conflicts of interest: none declared.
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References

1. **Peloquin JM, Goel G, Villablanca EJ, et al.** Mechanisms of Pediatric Inflammatory Bowel Disease. *Annu Rev Immunol* [Internet] 2016;34:31-64. Available from: http://www.annualreviews.org/doi/10.1146/annurev-immunol-032414-112151.
2. **Lemberg DA, Day AS.** Crohn disease and ulcerative colitis in children: An update for 2014. *J Paediatr Child Health* 2015;51:266-270.
3. **Benchimol EI, Fortinsky KJ, Gozdyra P, et al.** Epidemiology of pediatric inflammatory bowel disease: A systematic review of international trends. *Inflamm Bowel Dis* 2011;17:423-439.
4. **Henderson P, Wilson DC.** The rising incidence of paediatric-onset inflammatory bowel disease. *Arch Dis Child* 2012;97:585-586.
5. **Cakir M, Unal F, Dinler G, et al.** Inflammatory bowel disease in Turkish children. *World J Pediatr* 2015;11:331-337.
6. **Griffiths AM.** Specificities of inflammatory bowel disease in childhood. *Best Pract Res Clin Gastroenterol* 2004;18:509-523.
7. **Hait E, Hait L, Bousvaros A, et al.** Pediatric inflammatory bowel disease: what children can teach adults. *Inflamm Bowel Dis* [Internet]. 2005;11:519-527. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15905698.
8. **Ogata H.** Advances in Endoscopy in *Inflammatory Bowel Disease* 2018;3-11. Available from: http://link.springer.com/10.1007/978-4-431-56018-0.
9. **Turner D, Levine A, Escher JC, et al.** Management of pediatric ulcerative colitis: Joint ECCO and ESPGHAN evidence-based consensus guidelines. *J Pediatr Gastroenterol Nutr* 2012;55:340-361.
10. **Castro M, Papadatou B, Baldassare M, et al.** Inflammatory bowel disease in children and adolescents in Italy: Data from the pediatric national IBD register (1996-2003). *Inflamm Bowel Dis* 2008;14:1246-1252.
11. **Rosen MJ, Dhawan A, Saeed SA, et al.** Inflammatory Bowel Disease in Children and Adolescents. *J Gastroenterol Nutr* [Internet] 2016;169:1053-1060. Available from: https://www-ncbi-nlm-nih-gov.eaccess.ub.tum.de/pmc/articles/PMC4702263/pdf/nihms-727007.pdf.
12. **Barnes EL, Kappelman MD.** Editorial: Increasing Incidence of Pediatric Inflammatory Bowel Disease in France: Implications for Etiology, Diagnosis, Prognosis, and Treatment. *Am J Gastroenterol* [Internet] 2018;113:273-275. Available from: http://www.nature.com/doifinder/10.1038/ajg.2017.431.
13. **Kelsen J, Baldassano RN.** Inflammatory bowel disease: The difference between children and adults. *Inflamm. Bowel Dis.* [Internet] 2008;14:S9-S11. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00054725-200810002-00005.
14. **Levine A, De Bie CI, Turner D, et al.** Atypical disease phenotypes in pediatric ulcerative colitis: 5-year analyses of the EUROKIDS registry. *Inflamm Bowel Dis* 2013;19:370-377.