Journal of Pediatric Gastroenterology and Nutrition, Publish Ahead of Print

DOI :10.1097/MPG.0000000000003335

Clinical Features and Outcomes of Paediatric Patients with Isolated Colonic Crohn's Disease

Tal David Berger[1,2], Huey Miin Lee[3], Lavenya Ramasamy Padmanaban[3], Eytan Wine[4], Anat Yerushalmy-Feler[2,5], Iva Hojsak[6], Denis Kazeka[7], Daniela Elena Serban[8], Dotan Yogev[9], Oren Ledder[9], Paolo Lionetti[10], Luca Scarallo[10], Marco Gasparetto[11], Nicholas M Croft[11,12], Erasmo Miele[13], Annamaria Staiano[13], Joseph Meredith[14], Marina Aloi[15], Patrizia Alvisi[16], Darja Urlep[17], Batia Weiss[1,2], Mikkel Malham[18], Manar Matar[2,19], Víctor Manuel Navas-López[20], Claudio Romano[21], Valeria Dipasquale[21], Lorenzo Norsa[22], Kaija-Leena Kolho[23], Raanan Shamir[2,19] and Dror S Shouval[2,19] on behalf of the Paediatric IBD Porto Group of ESPGHAN.

[1]Pediatric Gastroenterology Unit, Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Ramat Gan, Israel;

[2]Sackler Faculty of Medicine, Tel- Aviv University, Tel-Aviv, Israel;

[3]Paediatric Liver, GI & Nutrition Centre and Mowat Labs, King's College Hospital NHS Foundation Trust, London, UK;

[4]Edmonton Pediatric IBD Clinic, University of Alberta, Edmonton, Canada;

[5]Pediatric Gastroenterology Unit, Dana-Dwek Children's Hospital, Tel Aviv Sourasky Medical Center, Tel-Aviv, Israel;

[6]Children's Hospital Zagreb, University of Zagreb School of Medicine, University of J. J. Strossmayer School of Medicine Osijek, Croatia;

[7]Department of Paediatrics, University Hospital Motol, Prague, Czech Republic;

[8]2nd Clinic of Pediatrics, "Iuliu Hatieganu" University of Medicine and Pharmacy, Emergency Clinical Hospital for Children, Cluj-Napoca, Romania;

[9]Juliet Keidan Institute of Paediatric Gastroenterology and Nutrition, Shaare Zedek Medical Center, affiliated to the Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel;

[10]Department Neurofarba, University of Florence, Meyer Children Hospital, Florence, Italy;

[11]The Royal London Children's Hospital, Barts' Health NHS Trust, London;

[12]Barts and the London School of Medicine, Queen Mary University of London, London, UK;

[13]Department of Translational Medical Science, Section of Pediatrics, University of Naples "Federico II", Naples, Italy;

[14]Department of Paediatric Gastroenterology and Nutrition, Royal Hospital for Sick Children, Edinburgh, UK;

[15]Pediatric Gastroenterology and Liver Unit, Sapienza University of Rome, Rome, Italy;

[16]Pediatric Unit, Maggiore Hospital, Bologna, Italy;

[17]Department of Gastroenterology Hepatology and Nutrition, Children's Hospital University Medical Centre Ljubljana, Ljubljana, Slovenia;

[18]The pediatric Department, Copenhagen University Hospital, Hvidovre, and The Pediatric Department, Holbaek Hospital, Denmark;

[19]Institute of Gastroenterology, Nutrition and Liver Diseases, Schneider Children's Medical Center of Israel, Petach Tikva, Israel;

[20]Pediatric Gastroenterology and Nutrition Unit. Hospital Regional Universitario de Málaga; Spain;

[21]Pediatric Gastroenterology and Cystic Fibrosis Unit, Department of Human Pathology in Adulthood and Childhood "G. Barresi", University of Messina, Messina, Italy;

[22]Paediatric Hepatology Gastroenterology and Transplantation, Papa Giovanni XXIII Hospital, Bergamo, Italy;

[23]Paediatric Gastroenterology of the Children's Hospital, University of Helsinki, Helsinki, Finland.

Corresponding Author: Dror S. Shouval, MD MMSc

Institute of Gastroenterology, Nutrition and Liver Diseases, Schneider Children's Medical Center of Israel, 14 Kaplan st, Petah Tikva 4920235, Israel

Tel: +972-3-9253673

Fax: +972-3-9253104

Email: dror.shouval@gmail.com

Author contribution:

- TB – data collection, data analysis, drafting of manuscript.
- HML, LRP, EW, AYF, IH, DK, DES, DY, OL, PL, LS, MG, NMC, EM, AS, JM, MA, PA, DU, BW, MiM, MaM, VMNL, CR, VD, LN, KLK, RS – data collection, manuscript editing, review of final manuscript
- DSS – study design, data collection, data analysis, writing of manuscript.

Funding: none.

Abstract

Objectives: Adult studies suggest that patients with isolated colonic Crohn's disease (L2 CD) exhibit unique characteristics differentiating them from patients with ileo-caecal (L1) CD and ulcerative colitis (UC). We aimed to characterize clinical features and outcomes of paediatric patients with L2.

Methods: Retrospective data was collected through the Porto IBD group of ESPGHAN on paediatric patients with L2, L1 or UC at different time-points. Outcome measures included time to 1st flare, hospital admissions, initiation of anti-TNFα drug, stricture and surgery.

Results: Three hundred patients were included: 102 L1, 94 L2 and 104 UC. Rates of hematochezia at presentation were 14.7%, 44.7% and 95.2%, while rates of fever were 12.7%, 26.6% and 2.9%, for patients with L1, L2 and UC, respectively ($P<0.001$ for all comparisons). Skip lesions were identified in 65% of patients with L2, and granulomas in 36%, similar to L1 patients. Rates of ASCA and pANCA positivity nificantlysig differed between the three groups: 25.4% and 16.7% for patients with L2, compared with 55.2% and 2.3%, and 1.8% and 52.9% for patients with L1 and UC, respectively. Response rates to exclusive enteral nutrition were comparable between L1 and L2 (78.3-82.4%), as was the response to oral steroids (70.4-76.5%) in the three groups. While times to 1st flare and admission were similar between groups, patients with L1 were commenced on anti-TNFα earlier. Moreover, stricturing phenotype and need for colectomy were very rare in patients with L2.

Conclusions: Significant differences are observed in the clinical presentation and outcomes of paediatric patients with L2, compared to patients with L1 and UC.

Keywords: IBD, Crohn's disease, ulcerative colitis, isolated colonic Crohn's, ASCA, pANCA, pediatric

What is Known

- Isolated colonic inflammation is an uncommon presentation of patients with Crohn's disease (CD)
- Adult studies suggest that patients with isolated colonic CD exhibit unique clinical and genetic characteristics.

What is Knew

- The clinical features of paediatric patients with isolated colonic CD are in between those of patients with ulcerative colitis (UC) and ileal CD
- Response rates to exclusive enteral nutrition in patients with isolated colonic CD are high, and are similar to those in patients with ileal CD
- Half of the patients with isolated colonic CD are treated with an anti-TNFα agent within three years after the diagnosis
- Development of colonic strictures and need for colectomy are rare in patients with colonic CD within three years after diagnosis

Introduction

Differentiation between CD and ulcerative colitis (UC) is based on a combination of clinical manifestations along with endoscopic, histologic and radiologic features. Most patients with CD exhibit inflammation of the terminal ileum (with or without cecal involvement), defined as L1[1, 2], or inflammation involving the terminal ileum and colon, defined as L3. Isolated colonic inflammation (L2) is identified in a minority of patients with CD: In adults, 18.1%-28.3% of patients exhibit an L2 phenotype[3-6], while studies in the paediatric age range showed that 5.1%-24.4% of patients with CD present with isolated colonic disease[7-9].

In recent years it became apparent that patients with L2 CD have unique genetic, demographic and clinical features, in comparison with patients with L1 CD or patients with UC[10-13]. Moreover, response to therapy may also differ between these groups[14], emphasizing the importance of reaching an accurate diagnosis. Based on these observations, the possibility of calling isolated colonic CD as "the third IBD", aside from ileal-predominant CD and UC, has been raised[10-12].

One key aspect in defining patients with isolated colonic CD is obtaining an accurate diagnosis, especially in children, given relatively high rates of atypical UC phenotypes, including rectal sparing, caceal patch, skip lesions and gastritis[15]. Data on the clinical course of children with isolated colonic CD have not been evaluated in depth. We present a multi-center study that aimed to characterize the clinical features at diagnosis and during follow-up of a large cohort of paediatric patients with L2 CD, and compare them to patients with L1 CD and UC followed at the same centers.

Methods

Study design

This multi-center, retrospective study on behalf of the Paediatric IBD Porto Group of ESPGHAN and its IBD special interest group was conducted in 21 paediatric gastroenterology centers across Europe, Israel and Canada. The study was approved by the Institutional Review Board at each site. Patients between the ages of 6.0-17.9 years diagnosed with either L1 CD, L2 CD or UC between January 1st, 2014 to December 31st, 2017 were identified. Patients with L1 CD exhibited inflammation limited to the terminal ileum, with or without caecal involvement. The diagnosis of isolated colonic CD was established based on endoscopic assessment, and all patients exhibited inflammation confined only to the colon, with normal endoscopic inspection of the terminal ileum. Patients with UC were identified based on standard criteria[2].

Data collection

Data were collected using a detailed case report form related to four different time points, including time of diagnosis, end of induction phase (typically after 12-16 weeks), 1-year post diagnosis and 3-years post diagnosis (or at last encounter). The case report form included demographic characteristics, clinical features, anthropomorphic indices, laboratory work-up, endoscopic data, severity scores, medication utilization and response. Disease

outcomes were defined as time to first flare, hospitalization, initiation of an anti-TNFα drug, stricture development and surgical intervention (small bowel resection or colectomy).

Statistical Analyses

Categorical variables were summarized as frequency and percentage. Continuous variables were evaluated for normal distribution using histogram and Q-Q plot. Normally distributed continuous variables were reported as mean±standard deviation and skewed variables as median (interquartile range, IQR). Categorical variables were compared between groups using chi square test Fischer exact test. Continuous variables were compared using analysis of variance (ANOVA), independent sample t-test, Kruskal-Wallis test or Mann-Whitney test. Kaplan meier curves were used to describe incidence during the follow-up period. Log-rank test was used for comparisons among groups. All statistical tests were two-sided and $P<0.05$ was considered statistically significant. * Signifies $P<0.05$, ** $P<0.01$ and *** $P<0.001$. SPSS statistics was used for all statistical analyses (IBM SPSS statistical, version 24, IBM corporation, Armonk, NY, USA 2016).

Results

Baseline Patients' characteristics

Data on 300 patients were collected from 21 centers, including 102 subjects with L1 CD, 94 subjects with L2 CD and 104 subjects with UC. Gender distribution was similar in the three cohorts. There was no difference in age at the time of diagnosis between L1 CD, L2 CD and UC, including children aged 6.0-9.9 years (Supplemental Table 1, http://links.lww.com/MPG/C553).

Presenting clinical manifestations, shown in **Figure 1**, demonstrated different features among the groups. Abdominal pain and diarrhea were common in all groups. Despite exhibiting colonic inflammation, bloody stools were documented in only 42/94 (44.7%) of patients with L2 CD, compared with 99/104 (95.2%) in patients with UC, but still more than in L1 CD patients (15/102, 14.7%, $P<0.001$ for comparisons between L1-L2, L2-UC and L1-UC). Perianal disease rates were similar in both groups of patients with CD, reaching around 15%. Interestingly, fever rates were highest in L2 CD (25/94, 26.6%), compared with L1 (13/102, 12.7%) and UC (3/104, 2.9%) groups, respectively (L1-L2, $P<0.05$; L2-UC, $P<0.001$; L1-UC, $P<0.01$). Erythema nodosum was identified in 4 patients, all of them from the L2 CD group, and uveitis in a single patient from the L1 CD group. There were no cases presenting with pyoderma gangrenosum.

Laboratory data at diagnosis showed similar hemoglobin and hematocrit levels in the three groups (**Figure 2B-C**). Moreover, rates of anemia, determined based on standard values for age and gender[16], were also comparable: 64/100 (64.0%), 60/93 (64.5%) and 59/98 (60.2%), in patients with L1 CD, L2 CD and UC, respectively. Albumin levels were significantly lower for patients with L1 CD and L2 CD vs. patients with UC (3.7±0.6 and 3.7±0.6 vs. 3.9±0.5, $P=0.007$ and $P=0.02$, respectively, **Figure 2D**). Moreover, inflammatory indices, including ESR and CRP were similar between L1 and L2 CD patients, but significantly higher compared to patients with UC (**Figure 2E-F**).

In the L2 CD group, 15/59 (25.4%) had positive ASCA serology, in comparison with 32/58 (55.2%) and 1/56 (1.8%) among patients with L1 CD and UC, respectively (P<0.001 for comparisons between L1-UC and, L2-UC; P=0.001 for comparison L1-L2). In addition, pANCA was positive in 8/48 (16.7%) of patients with L2 CD, compared with 1/43 (2.3%) and 27/51 (52.9%) of patients with L1 CD and UC, respectively (P<0.001 for comparisons between L1-UC and L2-UC; P=0.02 for comparison L1-L2). Positive ASCA serology alongside negative pANCA serology, previously shown to be a good discriminator between L2 CD and UC[17], was found in 27/41 (65.9%), 14/43 (32.6%) and 1/43 (2.3%) of patients with L1 CD, L2 CD and UC, respectively (P<0.001 for comparisons between L1-UC and L2-UC; P=0.002 for comparison L1-L2).

Assessment of disease activity at the time of diagnosis

Comparable median PCDAI scores were observed for patients with L1 CD and L2 CD, with values of 25 (IQR 17.5-37.5) and 27.5 (IQR 20.0-40.0), respectively, while the median PUCAI score for patients with UC was 40 (IQR 30-55). Most patients with L1 CD or L2 CD had mild clinical disease activity; inflammation among the majority of patients with UC was assessed as moderate (Supplemental Figure 1, http://links.lww.com/MPG/C548). Median calprotectin values at diagnosis were comparable (**Figure 2G**): 662 (IQR 300-1416), 580 (319-1157) and 1008 μg/g stool (400-2255) among patients with L1 CD, L2 CD and UC, respectively.

In the majority of patients with L2 CD, inflammation was characterized as skip lesions (59/91, 64.8%). Most patients within this group had inflammation in the left colon (84/94, 89.4%), with lower rates in the transverse and right colon (79/94, 84.0% and 69/94, 73.4%), respectively. In contrast, 10 patients (9.6%) with UC demonstrated inflammation limited to the rectum (E1 phenotype), 16 patients exhibited left-sided colitis (E2 phenotype) and 78 patients (79.0%) had either extensive colitis or pancolitis (E3/E4 phenotype). Granulomas were identified in a similar proportion of patients with L1 and L2 CD (30/92, 32.6% and 33/91, 36.3%, respectively) vs. none of the patients with UC.

Induction therapies and rates of response to specific interventions

Figure 2A displays the proportion of medications chosen for remission induction in patients from the three groups. Exclusive enteral nutrition (EEN) was used in 47/94 (50%) of patients in the L2 CD group, compared with 73/102 (71.6%) in the L1 CD group (P=0.002). Rates of oral steroids therapy were comparable in the L2 CD and UC groups (42/94, 44.7% vs. 54/104, 51.9%), but significantly higher for both compared to patients with L1 CD (28/102, 27.5%, P=0.01 for L2 vs. L1, and P<0.001 for UC vs. L1). The rates of anti-TNFα used for induction of remission were slightly higher for patients with CD vs. UC, but not significantly different.

To assess response to induction therapy, data was collected from each patient at a mean time of 3.3±0.8, 3.2±0.7 and 3.3±0.8 months after diagnosis in the L1 CD, L2 CD and UC groups, respectively. The median PCDAI scores at the end of induction were 0 (IQR 0-5) and 2.5 (0-7.5) in the L1 CD and L2 CD groups, respectively, and the median PUCAI score was 0 (0-5) in the UC group (see also Supplemental Figure 2,

http://links.lww.com/MPG/C549). Blood tests showed similar hemoglobin, hematocrit and albumin levels in the three groups (**Figure 2B-D**). Inflammatory markers were slightly elevated in CD vs. UC at the end of induction (**Figure 2E-F**). Median calprotectin values were also similar between groups, and were significantly lower than results at the time of diagnosis (**Figure 2G**).

We next aimed to assess response to specific therapeutic regimens for remission induction, focusing on steroids and EEN. Since many patients received a combination of medications, and due to the retrospective nature of this study, we determined that if the subjects were on steroids+EEN (with or without antibiotics), they would be regarded as being treated with steroids, if with EEN+mesalazine (with or without antibiotics) they would be regarded as being treated with EEN, and if anti-TNFα was used with either EEN or steroids, they would not be included in the EEN and steroids analyses. Similar response assessments were not possible for patients solely being treated with mesalazine, antibiotics or anti-TNFα due to the small number of patients. Response to EEN was overall excellent in both CD groups, as demonstrated in **Figure 3A**, with 78.3-82.4% remission and 15.7-21.7% exhibiting mild disease activity, based on the PCDAI scores. In addition, response to steroids was similar among patients with L1 CD, L2 CD and UC, ranging from 70.4%-76.5% (**Figure 3B**).

Maintenance regimens used over time

We next looked at maintenance regimens at end of induction **(Supplemental Figure 3A,** http://links.lww.com/MPG/C550) and at 1-year post diagnosis (Supplemental Figure 3B, http://links.lww.com/MPG/C550). Rates of thiopurine utilization as a maintenance regimen were 53/91 (58.2%) and 46/83 (55.4%) at the end of induction, in L1 CD and L2 CD groups, respectively, which were significantly higher than in the UC group (27/92, 29%, P<0.001 for both comparisons). Similarly, usage of methotrexate was also significantly higher in L1 CD (8/91, 8.8%) and L2 CD (13/83, 15.7%), compared with UC (2/92, P=0.04 and P=0.001, respectively). In contrast, mesalazine utilization was significantly more common among patients with UC (69/92, 75.0%), compared to patients with L1 CD (13/91, 14.3%) and L2 CD (30/83, 36.1%), respectively (P<0.001 for all comparisons). By the end of induction, already 18.1-23.1% of patients with CD were on anti-TNFα drugs, compared with 8.7% of patients with UC (P=0.008 for L1 CD vs. UC comparison).

At one-year post-diagnosis, most patients in the three groups were in clinical remission. The median PCDAI scores of L1 CD and L2 CD were 0 (IQR 0-5) and 2.5 (IQR 0-7.5), respectively, and the PUCAI score of patients with UC was 0 (IQR 0-5, see also Supplemental Figure 4, http://links.lww.com/MPG/C551). Most patients with CD who were started on thiopurines after diagnosis were still on this drug (Supplemental Figure 3B, http://links.lww.com/MPG/C550), while the rates of thiopurine utilization in UC increased to 35.0%. In addition, the percentage of patients on anti-TNFα increased to 41.6%, 26.3% and 22.3% in the L1 CD, L2 CD and UC groups, respectively.

Clinical outcomes of patients

We next assessed clinical outcomes of patients from the three groups. Time to first flare (**Figure 4A**) and time to first admission (**Figure 4B**) were similar among groups, with about 30-40% of patients having an additional flare and 20% of patients being hospitalized, within one year after diagnosis. Time to treatment with an anti-TNFα drug was significantly shorter in patients with L1 CD, compared with UC (**Figure 4C**, P=0.02), but not significantly different to patients with L2 CD. Overall, after two years, the trends in the three groups were similar. Three years after diagnosis, the rates of patients using an anti-TNFα drug were 55.4%, 50.2% and 39.3% in the L1 CD, L2 CD and UC groups, respectively. Finally, only 2.3% of the patients with L2 CD and none of the patients with UC developed colonic strictures, within 36 months after diagnosis, compared to 13.1% of patients with L1 CD (**Figure 4D**). Moreover, by 36 months only 1.1% and 2.6% of patients with L2 CD and UC required surgery (colectomy), compared with 13.5% of patients with L1 CD (**Figure 4E**).

Anthropomorphic trajectories during follow-up

Since IBD can have a marked impact on growth in paediatric patients, we assessed anthropomorphic features at the time of diagnosis and growth trajectories over time in each group. As demonstrated in Supplemental Figure 5A, http://links.lww.com/MPG/C552, at the time of diagnosis Z scores for weight were significantly lower for patients with L1 CD and L2 CD, vs patients with UC, however by one year from diagnosis these differences resolved. Interestingly, Z scores for height were comparable among the three groups at the time of diagnosis and during follow-up (Supplemental Figure 5B, http://links.lww.com/MPG/C552).

Discussion

We present a comprehensive analysis of the clinical features and outcomes of paediatric patients with isolated colonic CD, followed in over 20 medical centers, and thus providing a large real-life cohort. Moreover, in order to determine whether these features of patients with L2 CD were unique, we compared them to both patients with L1 CD and those with UC. The presenting clinical features of patients with L2 CD place them in between patients with L1 CD and UC. Rates of perianal disease, fever, fatigue and arthritis were similar to L1 CD, and significantly higher than UC. Interestingly, although inflammation in L2 patients is confined to the colon, hematochezia was significantly less frequent than in patients with UC. In addition, CRP levels in both groups of CD were significantly higher than in the UC group. Nevertheless, calprotectin values were comparable. Adult studies identified several different clinical characteristics that differentiate the L2 CD group from other IBD sub-types, including female predominance[10], higher rates of extra-intestinal manifestations[18] and older age at presentation[13, 17] (though some studies in pediatric CD showed increased colonic involvement at younger ages[19]).

We also found significant differences in ASCA and pANCA seropositivity among the three groups, similar to data from adult studies[10, 20-22]. It is possible that these differences may result, in part, from distinct microbial, viral and fungal communities in each disease subtype, influenced by location of inflammation. In support, several studies demonstrated that mucosa-associated microbiome profiles of patients with L2 CD differ significantly from

those of patients with L1 CD[23-25], and are in fact generally closer to those of healthy controls[10]. Whether these differences are influenced by unique genetic variants, (e.g. *NOD2*, *ATG16L1)*, predisposing to a specific sub-type of CD, is not well understood.

We showed that most patients with L2 CD were on an immunomodulator by the end of induction, with similar rates one year after diagnosis. However, the rates of escalation to an anti-TNFα drug increased steadily, up to 22.5%, 31.4% and 50.2% at 12, 24 and 36 months after diagnosis, respectively. Although the time to initiation of anti-TNFα was shorter in L1 CD, the rates after 2-3 years were comparable between the groups. Importantly, patients with L2 CD rarely developed colonic stricture or required intestinal resection surgery. Adult studies also documented significantly lower risk of requirement for surgery in L2 vs. L1 CD (22-33% vs. 75-90% within 10 years of diagnosis)[17, 26].

Response rates to EEN and steroids used as first line therapies for remission induction after diagnosis were excellent. Given the retrospective nature of our study, and due to utilization of different combinations for inducing remission, we limited our analyses to patients that were treated with EEN alone or with steroids, demonstrating similar clinical efficacy among all groups. It is very likely that this generated a bias in data analysis, by possibly assessing patients with a milder disease who responded to a single intervention. Two previous studies showed that EEN was less effective in patients with isolated colonic CD than in patients with ileal or ileo-colonic disease[27, 28], though a different study in paediatric patients showed similar efficacy[29]. More broadly, a recent meta-analysis demonstrated that response rates of adult patients with isolated colonic CD to biologics were significantly higher than patients with ileal disease[11]. Prospective rigorous studies, specifically in paediatric patients, are required to determine the effects of different medical and dietary interventions in patients with L2 CD.

Complementing differences in clinical phenotypes among the groups are observations noted in genome-wide association studies: A study including more than 34,000 adult IBD patients demonstrate that genetic determinates can distinguish between ileal CD, isolated colonic CD and UC, suggesting that genetics can at least in part affect disease location and phenotype[13]. Specific variants within *IL23R*[17] and *HLA-DRB1*01:03*[30] have been shown to be specifically associated with isolated colonic CD (and not with ileal CD). How and why do these variants confer risk for colonic disease is not understood, to date. However, these data support new ideas to classify colonic CD as a separate entity of IBD[10-12].

Our study has several limitations. First, this was a multi-center study conducted in different countries across Europe and Canada. In addition, we did not include patients with ileo-colonic CD (L3) in this study. Finally, the diagnosis of L2 CD was based on physician's assessment, and it is possible that some patients that were identified as having isolated colonic CD in fact exhibit ileo-colonic CD, atypical UC or IBD-U. We were unable to follow the PIBD classes criteria developed by Birimberg-Schwartz[31] et al (and its modified version by Ledder[32] et al) in order to accurately classify paediatric patients into different IBD phenotype (including colonic CD vs. UC vs. atypical UC vs. IBD-U). These criteria are based on 19 items divided into 3 tiers, and require detailed phenotyping of each patient, including clinical, endoscopic, histologic and imaging data. As an example, in our study data on ASCA

and pANCA serologies was available for 53.8%-62.8% and 42.2%-51.1% of the patients, respectively. Nevertheless, this is the largest cohort published to date of paediatric patients with isolated colonic CD, with detailed phenotyping at time of diagnosis, and data on short- and long-term outcomes. The comparison of this group of patients to subjects with L1 CD and UC identified unique features that may distinguish L2 CD from other IBD phenotypes, thus supporting similar observations identified in adult studies.

In conclusion, we demonstrated significant differences in the presenting features and course of paediatric patients with isolated colonic CD, in comparison to patients with ileal CD and UC. Interestingly, patients with L2 CD rarely develop colonic strictures or require intestinal surgery within 3 years from the time of diagnosis, in contrast to patients with L1 CD. Similar to adult studies, our data suggest that L2 CD lays in between L1 CD and UC. Additional prospective studies, utilizing detailed protocols to accurately define patients with isolated colonic CD, are required to determine their response to nutritional and medical interventions and assess short- and long-term complications.

References

1. Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol 2005;19 Suppl A:5A-36A.
2. Levine A, Griffiths A, Markowitz J, et al. Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. Inflamm Bowel Dis 2011;17:1314-21.
3. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med 2010;362:1383-95.
4. Panes J, Lopez-Sanroman A, Bermejo F, et al. Early azathioprine therapy is no more effective than placebo for newly diagnosed Crohn's disease. Gastroenterology 2013;145:766-74 e1.
5. Feagan BG, Sandborn WJ, Gasink C, et al. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. N Engl J Med 2016;375:1946-1960.
6. Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med 2013;369:711-21.
7. Cohen-Dolev N, Sladek M, Hussey S, et al. Differences in Outcomes Over Time With Exclusive Enteral Nutrition Compared With Steroids in Children With Mild to Moderate Crohn's Disease: Results From the GROWTH CD Study. J Crohns Colitis 2018;12:306-312.

8. Kugathasan S, Denson LA, Walters TD, et al. Prediction of complicated disease course for children newly diagnosed with Crohn's disease: a multicentre inception cohort study. Lancet 2017;389:1710-1718.
9. Assa A, Matar M, Turner D, et al. Proactive Monitoring of Adalimumab Trough Concentration Associated With Increased Clinical Remission in Children With Crohn's Disease Compared With Reactive Monitoring. Gastroenterology 2019;157:985-996 e2.
10. Subramanian S, Ekbom A, Rhodes JM. Recent advances in clinical practice: a systematic review of isolated colonic Crohn's disease: the third IBD? Gut 2017;66:362-381.
11. Dulai PS, Singh S, Vande Casteele N, et al. Should We Divide Crohn's Disease Into Ileum-Dominant and Isolated Colonic Diseases? Clin Gastroenterol Hepatol 2019;17:2634-2643.
12. Atreya R, Siegmund B. Location is important: differentiation between ileal and colonic Crohn's disease. Nat Rev Gastroenterol Hepatol 2021.
13. Cleynen I, Boucher G, Jostins L, et al. Inherited determinants of Crohn's disease and ulcerative colitis phenotypes: a genetic association study. Lancet 2016;387:156-67.
14. Dulai PS, Jairath V, Zou G, et al. Early Combined Immunosuppression May Be More Effective for Reducing Complications in Isolated Colonic- vs Ileal-Dominant Crohn Disease. Inflamm Bowel Dis 2021;27:639-646.
15. 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;19:370-7.
16. Wang M. Iron Deficiency and Other Types of Anemia in Infants and Children. Am Fam Physician 2016;93:270-8.
17. Cleynen I, Gonzalez JR, Figueroa C, et al. Genetic factors conferring an increased susceptibility to develop Crohn's disease also influence disease phenotype: results from the IBDchip European Project. Gut 2013;62:1556-65.
18. Vavricka SR, Schoepfer A, Scharl M, et al. Extraintestinal Manifestations of Inflammatory Bowel Disease. Inflamm Bowel Dis 2015;21:1982-92.
19. Meinzer U, Idestrom M, Alberti C, et al. Ileal involvement is age dependent in pediatric Crohn's disease. Inflamm Bowel Dis 2005;11:639-44.
20. Elkadri AA, Stempak JM, Walters TD, et al. Serum antibodies associated with complex inflammatory bowel disease. Inflamm Bowel Dis 2013;19:1499-505.
21. Linskens RK, Mallant-Hent RC, Groothuismink ZM, et al. Evaluation of serological markers to differentiate between ulcerative colitis and Crohn's disease: pANCA, ASCA and agglutinating antibodies to anaerobic coccoid rods. Eur J Gastroenterol Hepatol 2002;14:1013-8.

22. Zholudev A, Zurakowski D, Young W, et al. Serologic testing with ANCA, ASCA, and anti-OmpC in children and young adults with Crohn's disease and ulcerative colitis: diagnostic value and correlation with disease phenotype. Am J Gastroenterol 2004;99:2235-41.

23. Baumgart M, Dogan B, Rishniw M, et al. Culture independent analysis of ileal mucosa reveals a selective increase in invasive Escherichia coli of novel phylogeny relative to depletion of Clostridiales in Crohn's disease involving the ileum. ISME J 2007;1:403-18.

24. Willing BP, Dicksved J, Halfvarson J, et al. A pyrosequencing study in twins shows that gastrointestinal microbial profiles vary with inflammatory bowel disease phenotypes. Gastroenterology 2010;139:1844-1854 e1.

25. Willing B, Halfvarson J, Dicksved J, et al. Twin studies reveal specific imbalances in the mucosa-associated microbiota of patients with ileal Crohn's disease. Inflamm Bowel Dis 2009;15:653-60.

26. Hancock L, Beckly J, Geremia A, et al. Clinical and molecular characteristics of isolated colonic Crohn's disease. Inflamm Bowel Dis 2008;14:1667-77.

27. Xu Y, Guo Z, Cao L, et al. Isolated colonic Crohn's disease is associated with a reduced response to exclusive enteral nutrition compared to ileal or ileocolonic disease. Clin Nutr 2019;38:1629-1635.

28. Afzal NA, Davies S, Paintin M, et al. Colonic Crohn's disease in children does not respond well to treatment with enteral nutrition if the ileum is not involved. Dig Dis Sci 2005;50:1471-5.

29. Buchanan E, Gaunt WW, Cardigan T, et al. The use of exclusive enteral nutrition for induction of remission in children with Crohn's disease demonstrates that disease phenotype does not influence clinical remission. Aliment Pharmacol Ther 2009;30:501-7.

30. Ahmad T, Armuzzi A, Bunce M, et al. The molecular classification of the clinical manifestations of Crohn's disease. Gastroenterology 2002;122:854-66.

31. Birimberg-Schwartz L, Zucker DM, Akriv A, et al. Development and Validation of Diagnostic Criteria for IBD Subtypes Including IBD-unclassified in Children: a Multicentre Study From the Pediatric IBD Porto Group of ESPGHAN. J Crohns Colitis 2017;11:1078-1084.

32. Ledder O, Sonnino M, Birimberg-Schwartz L, et al. Appraisal of the PIBD-classes criteria: a multicenter validation. J Crohns Colitis 2020.

Legend to Figures

Figure 1: Clinical features at time of diagnosis. Figure displays rates of different presenting clinical features.

Figure 1

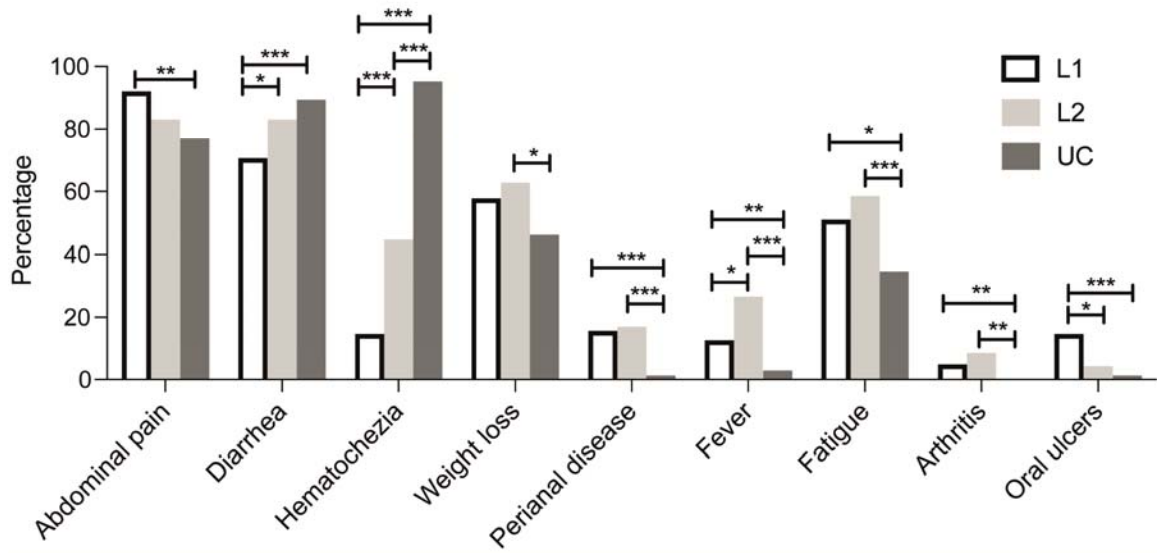

Figure 2: Induction regimen preferences and laboratory tests at diagnosis and end of induction. (**A**) Rates of different interventions used for induction of remission after diagnosis. Next, figure depicts violin plots of (**B**) hemoglobin, (**C**) hematocrit, (**D**) albumin, (**E**) ESR, (**F**) CRP and (**G**) faecal calprotectin values of each of the three studied groups at the time of diagnosis and at the end of induction. EEN, exclusive enteral nutrition; ESR, erythrocyte sedimentation rate. CRP, C-reactive protein.

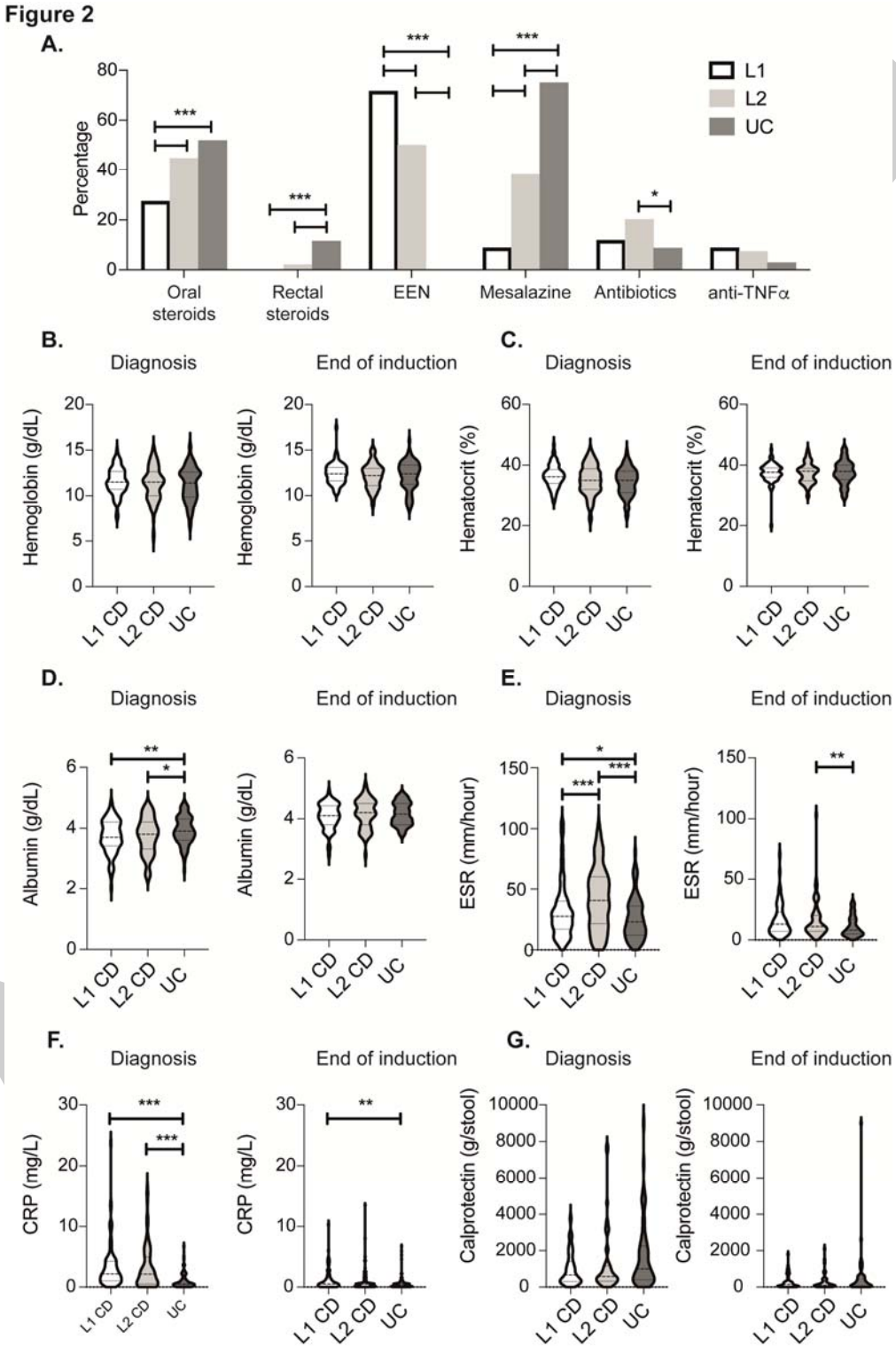

Figure 3: Response rates to different treatments used to induce remission. Figure displays pie charts of response to (**A**) EEN and to (**B**) oral steroids used to induce clinical remission at the time of diagnosis. Numbers of concomitant interventions used in each group are listed below the charts. EEN, exclusive enteral nutrition.

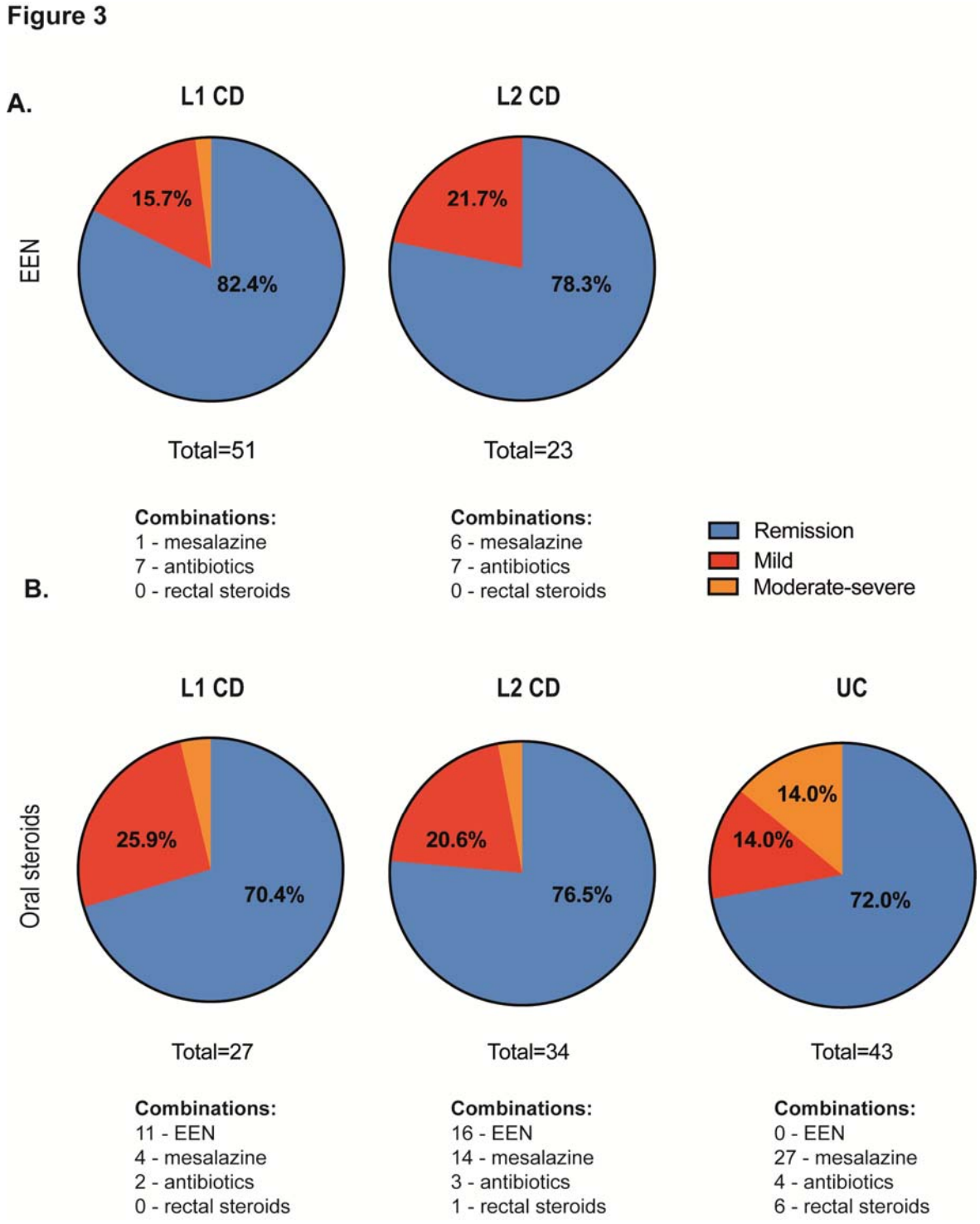

Figure 4: Clinical outcomes of patients. Kaplan Meier curves up to 3 years after diagnosis, including (**A**) time to first flare, (**B**) time to first admission, (**C**) time to initiation of an anti-TNFα medication, (**D**), time to stricture development and (**E**) time to first surgery (intestinal resection). Numbers at risk appear bellow each chart for each group.