



# Comparison of the extent of pediatric inflammatory bowel disease based on endo-colonoscopy and histological findings

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## Abstract

**Introduction:** Paris classification for the extent of inflammatory bowel disease (IBD) in children is based solely on macroscopic findings obtained via endo-colonoscopy. However, in some cases histologic findings may indicate more severe cases.

**Objectives:** The aim of the present study was to compare the extent of pediatric IBD based on endo-colonoscopy and pathological findings.

**Methods:** Data on 67 hospitalizations were collected from 51 children with IBD who had been admitted to the children's medical center of Tehran. All subjects underwent endoscopy or colonoscopy and had a histological report.

**Results:** Comparison of the endoscopic and histological findings in ulcerative colitis showed that, in 37% of cases, gastric involvement was reported in histology, while these cases were reported normal in endoscopy. In colonoscopy, the transverse colon was more involved, as compared with the results of histology, while in other parts of the colon, the histological involvement showed more severe findings. Considering Paris classification, in 25% of cases, the extent of the disease was higher in colonoscopy, and in 16% of cases, it was higher in histology. Of all children with Crohn's disease, gastric involvement in 20% of cases and esophageal and duodenal involvement in 13% of cases were more reported in histology than in endoscopy. In the ascending colon, descending colon, and rectosigmoid, histological involvement was more than that observed in colonoscopy. Considering Paris classification, in 5% of cases, the extent of the disease was higher in colonoscopy, and in 9% of cases, it was higher in histology.

**Conclusion:** Concurrent use of histological findings and endoscopic findings may help to better determine the severity and extent of the disease and facilitate the process of treatment.

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## Introduction

Inflammatory bowel disease (IBD) is characterized by chronic inflammation of the gastrointestinal mucosa, and it is classically divided into two types of Crohn's disease and ulcerative colitis. Crohn's disease can involve every part of the gastrointestinal tract, but in a discontinuous fashion; the inflammation mainly affects the entire wall of gastrointestinal tract and may cause granulomas. In ulcerative colitis, the involvement begins in rectum and spreads continuously upward, and the inflammation is often superficial. However, in some cases, the pattern of involvement does not follow the above cases, which is called unclassified IBD. Numerous studies have shown that 25% of IBD cases occur in children under 18 years of age (1). However, its incidence seems to be increasing, especially

## Key point

Numerous studies have shown that 25% of IBD cases occur in children under 18 years of age. Paris classification IBD in children is based solely on macroscopic findings obtained via endo-colonoscopy. In some pediatric IBD cases, histologic findings may indicate more severe cases than endo-colonoscopy findings. Therefore, concurrent use of histological and endo-colonoscopy findings may help to better determine the severity and extent of the disease and facilitate the process of treatment.

in children (2).

Due to the increasing incidence of IBD in children, it is of great importance to develop criteria to achieve rapid, accurate and definitive diagnosis in this group of patients (3,4). On the other hand, it is important to evaluate the severity and extent of the disease to make a good plan for treatment

(5). Although Paris classification (6) is conducted to assess the extent of pediatric IBD for diagnosis and follow-up of patients (7), it is based solely on macroscopic findings and does not use histological findings. However, determining the extent of the disease using histological findings may also be helpful in making good decisions on treatment and assessing the progress of the disease (8,9).

Various studies in adults have shown that microscopic disease is more common than macroscopic disease (10), especially after treatment. Some studies on pediatric IBD have also reported that endoscopic and histological findings in IBD may not be fully consistent, and in some cases, histological findings are more severe than endoscopic findings (9,11,12).

Mucosal healing is considered as part of the therapeutic goal in these patients (13,14), which may not be visible and evaluable in endo-colonoscopy and can only be verified using histological examination on specimens. The use of Paris classification, which does not include histological criteria, may lead to inaccurate determination of the extent of the disease, making problems in following up the treatment process. Therefore, it is necessary to study the consistency between histological and endo-colonoscopy findings in these patients. When the histological disease is more widespread, histological criteria can be conducted for the diagnosis and follow-up of patients.

## Objectives

The aim of the present study was to compare the extent of pediatric IBD based on endo-colonoscopy and pathological findings.

## Patients and Methods

### Study design

This retrospective study was conducted in 2020 in the Children's Medical Center, Tehran, Iran. Children aged 1-18 years old, who were hospitalized with a definitive diagnosis of IBD during 2018-19, underwent endoscopy or colonoscopy, and had available histologic reports were enrolled into the study. Data were collected on 51 patients with 67 cases of hospitalizations. Using a form, data on patients including age, gender, type of disease, endoscopic and colonoscopy findings, as well as histological findings of examination on biopsy specimens (collected from different parts of the gastrointestinal tract) were recorded and the extent of the disease was determined based on Paris classification. Endoscopic findings on upper gastrointestinal tract included erythema, erosion, inflammation, prolapse, and nodularity. On the other hand, colonoscopy findings included erythema and edema, reduced or disappearing vascular pattern, mucosal fragility, aphthous ulcers, exudate, erosion, fisher, fistula, and other items (polyps, pseudopolyps, granularity, nodular lesions and bleeding). Histological diagnoses were also based on inflammatory findings of the mucosa (esophagitis, gastritis, duodenitis, colitis, cryptitis, crypt abscesses and

granulomas), structural changes (destruction, branching or atrophy of the crypts), epithelial abnormalities and its superficial irregularities (metaplasia, mucin depletion, and regenerative changes). The extent of the disease was evaluated using endo-colonoscopy and histological findings and the results were compared with each other.

### Statistical analysis

SPSS 25 statistical software was applied for data analysis. Qualitative variables were described using frequency and percentage and quantitative variables were described using mean and standard deviation. *P* value < 0.05 was regarded as statistically significant.

## Results

Of 51 children with IBD, 25 patients (49%) were male and 26 patients (51%) were female with the mean age (SD) of  $9 \pm 4$  years. Of all participants, 27 children (53%) were diagnosed with ulcerative colitis, 16 children (31%) with Crohn's disease, and 8 children (16%) with unclassified IBD. The studied children were hospitalized for 67 cases, and endoscopy and colonoscopy, were performed in 39 (58%) and 60 cases (90%), respectively.

### Ulcerative colitis

Of all patients, 27 children with ulcerative colitis were hospitalized 36 times, and endoscopy and colonoscopy were performed in 16 and 32 cases, respectively. Due to the severity of the disease in different areas of the colon, the entire colon was visible in only eight cases of colonoscopy. In 12 cases up to hepatic flexion and in five cases up to splenic flexion were visible. In seven cases, only the rectosigmoid were visible. **Table 1** presents the frequency of involvement of different parts of the gastrointestinal tract in endoscopy and colonoscopy and the histological result of biopsy, as well as the similarity between endo-colonoscopy findings and the results of histology in patients with ulcerative colitis. Comparison of the endoscopic and histological findings showed that, in 37% of cases, gastric involvement was reported in histology, while these cases were reported normal in endoscopy. The comparison between colonoscopy and histological findings also showed that the colonoscopy indicated more involvement in the transverse colon, while histological involvement was more severe in other parts of the colon. **Figure 1** compares Paris classification in patients with ulcerative colitis based on colonoscopy findings alone and together with histological findings. Considering Paris classification, the extent of the disease was higher in colonoscopy and histology in 25% and 16% of cases, respectively.

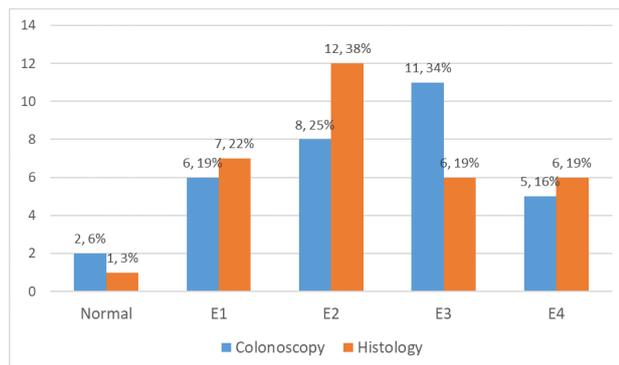
### Crohn's disease

Of all subjects, 16 children with ulcerative colitis were hospitalized 22 times, and endoscopy and colonoscopy were performed in 15 and 21 cases, respectively. Due to the severity of the disease in different areas of the colon, the

**Table 1.** Frequency of endo-colonoscopy and histological involvement and their similarity in different parts of the gastrointestinal tract in patients with ulcerative colitis

Place	Involvement frequency			Similarity		
	Endo-colonoscopy	Histology	Both similar (normal or involved)	Only endo-colonoscopy	Only histology	
Endoscopy <sup>a</sup>	Esophagus	6 (38%)	6 (38%)	12 (74%)	2 (13%)	2 (13%)
	Stomach	9 (55%)	15 (94%)	10 (63%)	0 (0%)	6 (37%)
	Duodenum	3 (19%)	3 (19%)	14 (88%)	1 (6%)	1 (6%)
Colonoscopy <sup>a</sup>	Terminal ileum <sup>b</sup>	1 (13%)	1 (13%)	6 (74%)	1 (13%)	1 (13%)
	Ascending colon <sup>b</sup>	5 (63%)	6 (75%)	5 (62%)	1 (13%)	2 (25%)
	Transverse colon <sup>c</sup>	16 (80%)	12 (60%)	12 (60%)	6 (30%)	2 (10%)
	Descending colon <sup>d</sup>	22 (88%)	24 (96%)	21 (84%)	1 (4%)	3 (12%)
	Retosigmoid <sup>e</sup>	27 (84%)	30 (94%)	27 (84%)	1 (3%)	4 (13%)

<sup>a</sup> Out of 36 hospitalizations, endoscopy was performed in 16 cases and colonoscopy in 32 cases; <sup>b</sup> Terminal ileum and ascending colon were visible in 8 cases; <sup>c</sup> Transverse colon was visible in 20 cases; <sup>d</sup> Descending colon was visible in 25 cases; <sup>e</sup> Rectosigmoid was visible in 32 cases.

**Figure 1.** Comparison of Paris classification in the extent of involvement in patients with ulcerative colitis

entire colon was visible in only five cases of colonoscopy. In two cases up to hepatic flexion and in nine cases up to splenic flexion were visible. In five cases, only the rectosigmoid were visible. Table 2 presents the frequency of involvement of different parts of the gastrointestinal tract in endoscopy and colonoscopy, the histological result of their biopsy, as well as the similarity between endo-colonoscopy findings and the results of histology in patients with Crohn's disease. Comparison of the endoscopic and histological findings showed that, in 20% of cases, gastric involvement was reported in histology, while these cases were reported

normal in endoscopy. On the other hand, the involvement of the esophagus and duodenum was reported in 13% of cases in endoscopy, while these cases were reported normal in histology. The comparison between colonoscopy and histological findings in each section also showed that in the ascending colon, descending colon and rectosigmoid, histological involvement was more than colonoscopy. Figure 2 compares Paris classification in patients with Crohn's disease based on endo-colonoscopy findings alone and together with histological findings. Concerning Paris classification, the extent of the disease was higher in in colonoscopy and histology in 5% and 9% of cases, respectively.

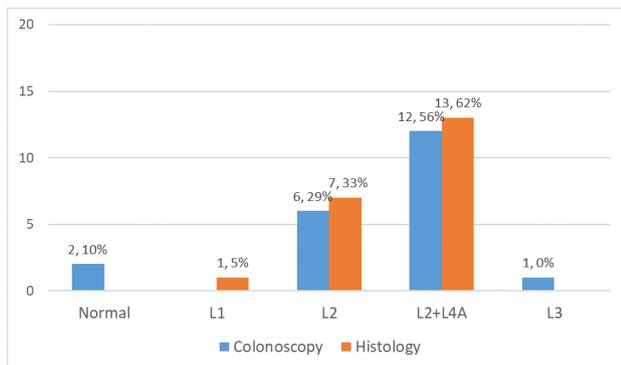
#### Unclassified IBD

Of all patients, eight children with unclassified IBD were hospitalized 9 times, and endoscopy and colonoscopy were performed in eight and seven cases, respectively. Due to the severity of the disease in different areas of the colon, the entire colon was visible in only two cases of colonoscopy. In three cases up to hepatic flexion and in one case up to splenic flexion were visible. In one case, only the rectosigmoid were visible. Table 3 presents the frequency of involvement of different parts of the gastrointestinal tract in endoscopy and colonoscopy, the histological result of their biopsy, as well as the similarity between

**Table 2.** Frequency of endo-colonoscopy and histological involvement and their similarity in different parts of the gastrointestinal tract in patients with Crohn's disease

Place	Involvement frequency			Similarity		
	Endo-colonoscopy	Histology	Both similar (normal or involved)	Only endo-colonoscopy	Only histology	
Endoscopy <sup>a</sup>	Esophagus	9 (60%)	8 (53%)	12 (80%)	2 (13%)	1 (7%)
	Stomach	12 (80%)	15 (100%)	12 (80%)	0 (0%)	3 (20%)
	Duodenum	5 (33%)	4 (27%)	12 (80%)	2 (13%)	1 (7%)
Colonoscopy <sup>a</sup>	Terminal ileum <sup>b</sup>	1 (20%)	1 (20%)	5 (100%)	0 (0%)	0 (0%)
	Ascending colon <sup>b</sup>	3 (60%)	5 (100%)	3 (60%)	0 (0%)	2 (40%)
	Transverse colon <sup>c</sup>	5 (71%)	5 (71%)	5 (71%)	1 (14%)	1 (14%)
	Descending colon <sup>d</sup>	13 (81%)	16 (100%)	13 (81%)	0 (0%)	3 (19%)
	Retosigmoid <sup>e</sup>	18 (86%)	20 (95%)	17 (81%)	1 (5%)	3 (14%)

<sup>a</sup> Out of 22 hospitalizations, endoscopy was performed in 15 cases and colonoscopy in 21 cases; <sup>b</sup> Terminal ileum and ascending colon were visible in 8 cases; <sup>c</sup> Transverse colon was visible in 5 cases; <sup>d</sup> Descending colon was visible in 16 cases; <sup>e</sup> Rectosigmoid was visible in 21 cases.



**Figure 2.** Comparison of Paris classification in the extent of involvement in patients with Crohn's disease.

endo-colonoscopy findings and the results of histology in patients with unclassified IBD. Concerning the similarity between endoscopic and histological findings, histological involvement of the stomach was higher in 25% of cases, while involvement of the duodenum in endoscopy was higher in 25% of cases. The comparison between colonoscopy and histological findings in each part also showed that in most parts, colonoscopy involvement was more than that observed in histology.

**Discussion**

The findings of the present study showed that in some cases the histological findings in biopsy specimens collected via endo-colonoscopy from children with IBD were more severe than the findings observed in endo-colonoscopy. In addition, in many cases, gastric involvement was more observed in histology than in endoscopy.

Paris classification for determining the severity of IBD in children is based on endoscopic and colonoscopy findings (6) and does not include histological findings. Our study showed that in some cases, histological findings are more comprehensive than endoscopic or colonoscopy findings and the use of histological findings in this classification may help to better determine the severity of the disease. Moreover, according to the study of Ashton

et al, who conducted two studies on both diagnosis and follow-ups, histological findings were more important than endoscopic findings and they must be conducted along with endoscopic findings to determine the extent and severity of the disease (12,15). Based on the study by Fernandes et al, on Crohn's disease, when combining microscopic findings with endoscopic findings, the extent of the disease varies and further studies are needed (16).

We did not find another study comparing histological and endoscopic findings in pediatric IBD. However, our study also showed that in some cases the histological findings were more severe than the endo-colonoscopy findings. As a result, it seems that the use of microscopic findings along with macroscopic findings can help to determine the severity, extent and classification of IBD in children, which in turn can help to choose a better treatment and follow-up plan for patients. However, more extensive studies in this area are recommended.

On the other hand, previous studies have reported gastric involvement in a significant number of patients with ulcerative colitis. Ashton et al reported endoscopic gastric involvement in 40% of patients and histological involvement in 66.7% of patients (12). Tobin et al also reported that patients with ulcerative colitis had gastritis in 69% of cases and duodenitis in 23% of cases (17). Our study also showed that in children with ulcerative colitis, the stomach was involved in endoscopy in more than half of cases and in histology, it was observed in almost all the cases. In Crohn's disease, gastric involvement was present in endoscopy in 80% of cases and in histology, it was observed in all cases. Ashton et al reported gastric involvement in endoscopy and histology of 42.9% and 85.9% of patients, respectively (12). In addition, gastric involvement was reported to a high extent in the follow-up of patients (15,18). In our study, gastric involvement was present in nearly two-thirds of patients with unclassified IBD. In all the three disease groups, gastric involvement was more visible in histology than in endoscopy. Although this involvement may not be specific to the disease and may be attributed to side effects of medications, apparently

**Table 3.** Frequency of endo-colonoscopy and histological involvement and their similarity in different parts of the gastrointestinal tract in patients with unclassified inflammatory bowel disease

Place	Involvement frequency		Similarity			
	Endo-colonoscopy	Histology	Both similar (normal or involved)	Only endo-colonoscopy	Only histology	
Endoscopy <sup>a</sup>	Esophagus	4 (50%)	3 (38%)	7 (88%)	1 (12%)	0 (0%)
	Stomach	3 (38%)	5 (63%)	6 (75%)	0 (0%)	2 (25%)
	Duodenum	3 (38%)	1 (12%)	6 (75%)	2 (25%)	0 (0%)
Colonoscopy <sup>a</sup>	Terminal ileum <sup>b</sup>	0 (0%)	0 (0%)	2 (100%)	0 (0%)	0 (0%)
	Ascending colon <sup>b</sup>	1 (50%)	0 (0%)	1 (50%)	1 (50%)	0 (0%)
	Transverse colon <sup>c</sup>	5 (100%)	3 (60%)	3 (60%)	2 (40%)	0 (0%)
	Descending colon <sup>d</sup>	6 (100%)	4 (67%)	4 (67%)	2 (33%)	0 (0%)
	Retosigmoid <sup>e</sup>	6 (86%)	6 (86%)	5 (72%)	1 (14%)	1 (14%)

<sup>a</sup> Out of 9 hospitalizations, endoscopy was performed in 8 cases and colonoscopy in 7 cases; <sup>b</sup> Terminal ileum and ascending colon were visible in 2 cases; <sup>c</sup> Transverse colon was visible in 5 cases; <sup>d</sup> Descending colon was visible in 6 cases; <sup>e</sup> Rectosigmoid was visible in 7 cases.

gastric involvement in all patients with IBD should be properly evaluated and treated, if necessary.

Overall, the findings of the present study showed that in some cases, histological findings in endoscopic/colonoscopy biopsy specimens of children with IBD are more severe than those observed in endoscopy/colonoscopy. Therefore, it is recommended to take samples from healthy or seemingly healthy areas and label them properly in endoscopy/colonoscopy of the patients to undergo histological examination. Since, in all three groups of diseases, gastric involvement in histology was more visible than the involvement in endoscopy, it is recommended for all patients with IBD, to examine stomach separately and perform appropriate treatments, if necessary.

### Conclusion

The findings of the present study on pediatric IBD showed that in some cases the histological findings were more severe than those observed in endo-colonoscopy. Although Paris classification is based solely on endo-colonoscopy findings to determine the severity of ulcerative colitis and Crohn's disease, the concurrent use of histological findings and endoscopic findings may help to better determine disease severity and facilitate its treatment.

### Limitations of the study

One of the limitations of this study was the small sample size, which can be managed via conducting more extensive, multicenter and prospective studies. Such studies can further investigate the use of histological findings on current indices and classifications for determining the severity and extent of the disease at the time of diagnosis and in subsequent follow-ups. As another limitation of our study, due to the severity of the disease, in some cases it was not possible to conduct a complete colonoscopy. In such cases, Paris classification is based on the findings on different parts that underwent colonoscopy, which may underestimate the severity of the disease, especially in Crohn's disease.

### Authors' contribution

All authors passed four criteria for authorship contribution based on recommendations of the International Committee of Medical Journal Editors. AA, FF and HA designed the protocol of study. AA developed the protocol and performed it. Critical revision of the manuscript for important intellectual content was performed by all. Analysis of data performed by AA. All authors read and approved the final paper.

### Ethical issues

The study was approved by the ethics committee of the pediatric medical center of Tehran University of Medical Sciences with the registration code of IR.TUMS.CHMC.REC.1398.085. This study was extracted from M.D thesis of Ali Asgari at this university (Thesis #9711364004). Accordingly, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

### Conflicts of interest

There is no conflict of interest among authors.

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### References

1. Abraham BP, Mehta S, El-Serag HB. Natural history of pediatric-onset inflammatory bowel disease: a systematic review. *J Clin Gastroenterol.* 2012;46:581-9. doi:10.1097/MCG.0b013e318247c32f.
2. Kapoor A, Bhatia V, Sibal A. Pediatric Inflammatory Bowel Disease. *Indian Pediatr.* 2016;53:993-1002. doi:10.1007/s13312-016-0975-0.
3. Ashton JJ, Wiskin AE, Ennis S, Batra A, Afzal NA, Beattie RM. Rising incidence of paediatric inflammatory bowel disease (PIBD) in Wessex, Southern England. *Arch Dis Child.* 2014;99:659-64. doi: 10.1136/archdischild-2013-305419.
4. Henderson P, Hansen R, Cameron FL, Gerasimidis K, Rogers P, Bisset MW, et al. Rising incidence of pediatric inflammatory bowel disease in Scotland. *Inflamm Bowel Dis.* 2012;18:999-1005. doi:10.1002/ibd.21797.
5. Beattie RM. Enteral Nutrition as Primary Therapy in Childhood Crohn's Disease: Control of Intestinal Inflammation and Anabolic Response. *JPEN J Parenter Enteral Nutr.* 2005;29:S151-S59. doi:10.1177/01486071050290S4S151.
6. Levine A, Griffiths A, Markowitz J, Wilson DC, Turner D, Russell RK, et al. Pediatric modification of the Montreal classification for inflammatory bowel disease: The Paris classification. *Inflamm Bowel Dis.* 2011;17:1314-21. doi:10.1002/ibd.21493
7. de Bie CI, Paerregaard A, Kolacek S, Ruemmele FM, Koletzko S, Fell JME, et al. Disease Phenotype at Diagnosis in Pediatric Crohn's Disease: 5-year Analyses of the EUOKIDS Registry. *Inflamm Bowel Dis.* 2013;19:378-85. doi:10.1002/ibd.23008
8. Moum B, Ekbohm A, Vatn MH, Aadland E, Sauar J, Lygren I, et al. Clinical Course during the 1st Year after Diagnosis in Ulcerative Colitis and Crohn's Disease: Results of a Large, Prospective Population-based Study in Southeastern Norway, 1990-93. *Scand J Gastroenterol.* 1997;32:1005-12. doi: 10.3109/00365529709011217.
9. Raab Y, Bergström R, Ejerblad S, Graf W, Pählman L. Factors influencing recurrence in Crohn's disease: An analysis of a consecutive series of 353 patients treated with primary surgery. *Dis Colon Rectum.* 1996;39:918-25. doi: 10.1007/BF02053992.
10. Baars JE, Nuij VJAA, Oldenburg B, Kuipers EJ, van der Woude CJ. Majority of patients with inflammatory bowel disease in clinical remission have mucosal inflammation. *Inflamm Bowel Dis.* 2012;18:1634-40. doi:10.1002/ibd.21925.
11. Chong SK, Blackshaw AJ, Boyle S, Williams CB, Walker-Smith JA. Histological diagnosis of chronic inflammatory bowel disease in childhood. *Gut.* 1985;26:55-59. doi:10.1136/gut.26.1.55.
12. Ashton JJ, Coelho T, Ennis S, Vadgama B, Batra A, Afzal NA, et al. Endoscopic versus histological disease extent at presentation of paediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr.* 2016;62:246-51. doi: 10.1097/MPG.0000000000001032
13. Moum B, Ekbohm A, Vatn MH, Elgjo K. Change in the extent of colonoscopic and histological involvement in ulcerative colitis over time. *Am J Gastroenterol.* 1999;94:1564-69. doi: 10.1111/j.1572-0241.1999.01145.x.
14. Sankey EA, Dhillon AP, Anthony A, Wakefield AJ, Sim R, More L, et al. Early mucosal changes in Crohn's disease. *Gut.* 1993;34:375-81. doi: 10.1136/gut.34.3.375.

15. Ashton JJ, Bonduelle Q, Mossotto E, Coelho T, Batra A, Afzal NA, et al. Endoscopic and Histological Assessment of Paediatric Inflammatory Bowel Disease Over a 3-Year Follow-up Period. *J Pediatr Gastroenterol Nutr.* 2018;66:402-09. doi: 10.1097/MPG.0000000000001729
16. Fernandes MA, Verstraete SG, Garnett EA, Heyman MB. Addition of histology to the Paris classification of pediatric Crohn's disease alters classification of disease location. *J Pediatr Gastroenterol Nutr.* 2016;62:242. doi: 10.1097/MPG.0000000000000967.
17. Tobin JM, Sinha B, Ramani P, Saleh AR, Murphy MS. Upper gastrointestinal mucosal disease in pediatric Crohn disease and ulcerative colitis: a blinded, controlled study. *J Pediatr Gastroenterol Nutr.* 2001;32:443-8. doi:10.1097/00005176-200104000-00010.
18. Van Limbergen J, Russell RK, Drummond HE, Aldhous MC, Round NK, Nimmo ER, et al. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. *Gastroenterology* 2008;135:1114-22. doi:10.1053/j.gastro.2008.06.081.