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Alimentary Tract

Histologic findings at diagnosis as predictive markers of clinical outcome in pediatric ulcerative colitis ☆

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ABSTRACT

Background: The role of histological inflammation at diagnosis as a possible prognostic factor for disease course has not been investigated.
Aims: To assess whether histologic findings at diagnosis could predict clinical outcomes and evaluate the association between clinical, biochemical, endoscopic, and histological findings.
Methods: Prospective single-center study including pediatric UC patients with a minimum follow-up of 12 months. The association between histological activity (Nancy Index, Robarts Histopathology Index, and Geboes Score) and 12-month clinical outcomes was evaluated. Secondarily, we assessed the correlation between histological scores and endoscopic and inflammatory markers at the diagnosis. Inter-observer agreement for histologic and endoscopic scores was also evaluated.
Results: Forty-nine UC patients were included. No association was found between 1-year clinical relapse and the three histological indices at diagnosis ($p > 0.05$). Good concordance was found among the three histological scores ($p < 0.001$), and between all histological and endoscopic indices ($p < 0.05$). No correlation was found between histologic scores and serum inflammatory markers. Inter-observer agreement was good for eMayo, Nancy and Robarts score ($k = 0.71$, $k = 0.74$ and $k = 0.68$, respectively) and moderate for Geboes ($k = 0.46$).
Conclusions: Histological findings at diagnosis cannot be used as a predictor of the disease course. The three histological scores used in routine clinical practice show an overall good correlation and reliability.
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1. Introduction

Ulcerative colitis (UC) is a chronic relapsing inflammatory bowel disease (IBD) with multifactorial etiology. Approximately 25 % of UC cases are diagnosed in childhood [1]. In children, the disease is usually more complex than in adults: the extension is usually pancolonic (70 % vs 40 %), the course is more aggressive, and the risk of acute severe colitis (ASC) and colectomy is higher [2,3,4]. These findings, together with the need to minimize the side effects of steroids and improve growth, have led to greater and earlier use of biological agents than in adult patients [5]. The expanding milieu of pharmacological agents, along with their high costs for health systems, highlighted the need to identify predictors of disease course, which might enable tailored treatment since diagnosis.

According to the latest European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) Revised Porto Criteria of 2014, histologic evaluation has the only function to establish the right diagnosis [6], while the initial treatment decision is based on clinical and endoscopic findings [7]. However, the degree of endoscopic inflammation does not always reflect the histological picture. For instance, microscopic inflammation persists in up to 40 % of cases of apparent mucosal healing (MH) on endoscopy [8].

According to the STRIDE program, during follow-up, the therapeutic approach is based on the "treat to target" strategy and mainly relies on clinical symptoms and mucosal evaluation, while histologic remission is not a formal target of medical therapy, but it is considered an "*adjunct to endoscopic remission to represent a*

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deeper level of healing" [9]. In fact, histological remission seems to correlate with long-term clinical remission, better clinical outcomes, and a lower risk of intestinal dysplasia, even though significant data are lacking [10,11]. Multiple scoring systems have been developed to objectively assess histological activity. Among these, the Nancy index (NI), Robarts Histopathology index (RHI), and Geboes score (GS) are the most widely used, but none has been validated in pediatric patients with UC [12–14]. The evaluation of histological activity and the presence of specific histologic features at diagnosis in treatment-naïve patients, as a possible predictive factor of the disease course and, hence, as a tool to drive therapeutic choices, have never been investigated.

The primary aim of this study was to assess the association between histological activity at diagnosis and clinical outcomes at 12-month follow-up. As secondary aims, we assessed the correlations between histology and endoscopic activity and between histological activity and inflammatory markers, all at the time of diagnosis; the correlation between histological activity at diagnosis and clinical outcomes at 6 months; the association between the combined endoscopic and histologic scores and clinical outcome at 1 year. Additionally, we investigated the inter-observer agreement for the histological and endoscopic scores.

2. Materials and methods

2.1. Patients

This was a prospective, single-center study conducted in the Pediatric Gastroenterology and Liver Unit of Sapienza University of Rome between January 2018 and January 2021. Eligible patients were children aged between 6 and 18 years of age newly diagnosed with UC. Patients with other comorbidities and those taking concurrent medications were excluded from this study.

2.2. Endoscopic assessment

Ulcerative colitis was diagnosed, in line with the current ESPGHAN Revised Porto Criteria of 2014 [6], by ileocolonoscopy under general anesthesia with mucosal biopsies for histologic confirmation. Disease location and behavior were defined according to the Paris Classification [15] as follows: E1 isolated rectal disease, E2 descending and sigmoid colon and rectum, E3 extensive colitis before the hepatic flexure, and E4 pancolitis. The endoscopies were performed by a single endoscopist (G.C.). The endoscopic Mayo score (eMayo) was used to grade disease activity (0, normal or inactive; 1, mild; 2, moderate; 3, severe) [16–18]. Endoscopic images were then assessed by a second endoscopist (S.O.), who independently graded the inflammation using the Mayo score.

2.3. Histological assessment

Biopsies were obtained from all colonic segments. Histological activity was then assessed by a pathologist (C.G.), who was unaware of the endoscopic and clinical activity scores, using the Nancy Index, Robarts Histopathology Index, and Geboes Score [12–14]. A second pathologist (F.A.) independently reviewed the histological slides, grading the inflammation using the same scores. Each score was calculated on the sample with the most severe involvement. Histological activity was graded according to Nancy as quiescent (NI 0–1), mild (NI 2), moderate (NI 3), and severe (NI 4). As for RHI and GS, quiescent disease was defined as RHI 0–3 and GS 0–6; mild disease as RHI 4–9 and GS 7–12; moderate-severe disease as $\geq$ 9 and $\geq$ 12, respectively [19]. Appendix 1 reports the histological scores details.

2.4. Clinical and laboratory assessment

The Pediatric Ulcerative Colitis Activity Index (PUCAI) was used to score disease activity (<10, clinical remission; 10–34, mild disease activity; 35–64, moderate disease; 65–85, severe) [20]. Laboratory data included erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fecal calprotectin (FC), albumin, and hemoglobin (Hb). Fecal calprotectin stools were collected within 2 days of the three visits (diagnosis and the two follow-up visits) and measured using enzyme-linked immunosorbent assay (ELISA) as the gold standard. The normal ranges for CRP level and ESR were $<$ 0.5 mg/dl and <25 mm/h, respectively. FC $<$ 250 µg/g was considered a surrogate marker of MH [21–23].

2.5. Study design

Data were recorded at baseline, 6 months, and 1-year follow-up. At baseline, the following data were included: demographic (age, sex), clinical (age at diagnosis, disease location, disease behavior, clinical disease activity), biological (serum Hb, ESR, CRP, FC), endoscopic (Mayo score) and histologic (NI, RHI, GS).

At 6 and 12 months, major clinical outcomes [episodes of acute severe colitis (ASC), disease relapses defined as PUCAI $>$ 35 or FC $>$ 250, need for surgery, need for therapy escalation, and need for steroids] were recorded for each patient.

Ethical consideration. The Human Ethics Committee of Sapienza of Rome approved the protocol in accordance with the Declaration of Helsinki (6th revision, 2008). Written informed consent was obtained from each of the subjects and their parents prior to enrollment in the study.

2.6. Statistical analysis

All data were summarized and expressed as mean and standard deviation (SD) for continuous variables. Categorical data were expressed as frequencies and percentages. Comparison of the groups was performed using the Student's *t*-test for unpaired data in a two-group comparison. A chi-square test with Fisher's correction was used to evaluate the differences for categorical variables wherever needed. A two-tailed *p*-value $<$ 0.05 was considered significant. The strength of the correlation of continuous and categorical variables was measured with Spearman's correlation coefficient. Multivariate Cox regression was used to identify the association between the three histological scores (independent variables) and clinical outcomes (dependent variable) at 1 year. Survival curve analyses were performed using the Kaplan–Meier method and the log-rank test. Multiple logistic regression analysis for endoscopic and histologic predictors of clinical outcome was performed. Inter-observer agreement between the two pathologists and the two endoscopists was calculated and quantified using Cohen's Kappa (κ) statistic, interpreting the results as follows: values $\leq$ 0 indicating no agreement; 0.01–0.20 as none to slight, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as substantial or good, and 0.81–1.00 as almost perfect agreement [24].

All statistical analyses were performed using the IBM SPSS Statistics package (version 23.0 for Windows, IBM Armonk, New York, USA).

3. Results

3.1. Patients' baseline and follow-up characteristics

The flowchart of the study is shown in Fig. 1. One hundred fourteen patients with suspected IBD were investigated, 53 of them met the inclusion criteria. One patient refused to sign the informed consent, and 3 patients were lost to follow-up. Therefore, 49 UC

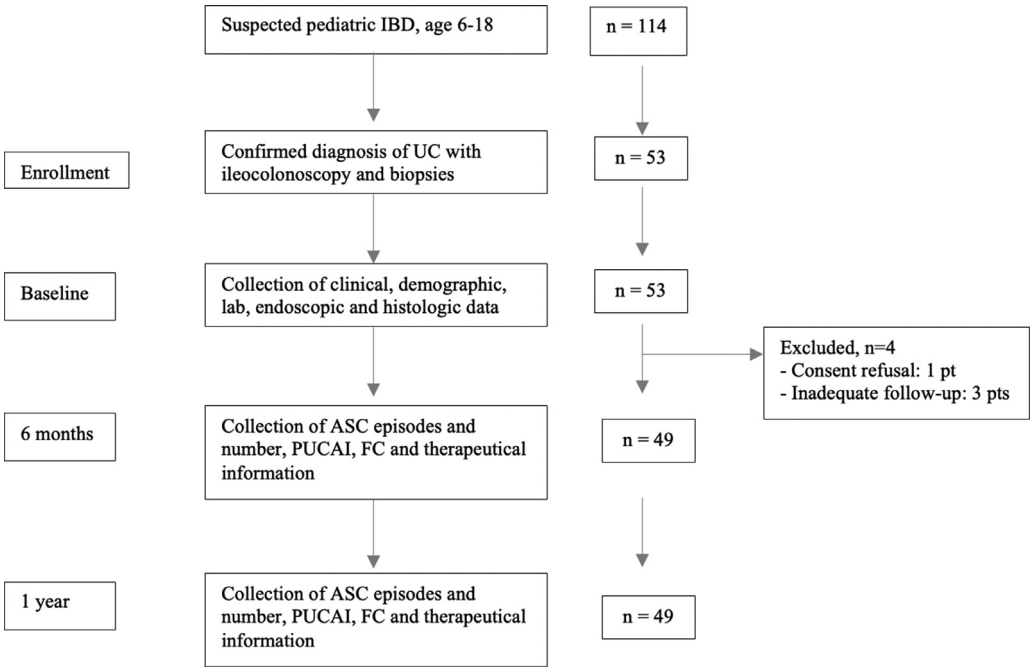

Fig. 1. Study flowchart.

Table 1
Demographic, clinical and laboratory characteristics of 49 patients with UC at the diagnosis.

Variable	n (%)
Age, year (**mean** ± SD)	10,25 ± 4
Gender (F) n (%)	20 (40,8 %)
Disease location n (%)	
E1	7 (14,3 %)
E2	8 (16,3 %)
E3	8 (16,3 %)
E4	26 (53,1 %)
Growth retardation (G1) n (%)	0
Acute severe colitis (S1) (PUCAI ≥ 65) n (%)	7 (14,2 %)
PUCAI (mean ± SD) n, (%)	46,6 ± 15,8
Remission	0
Mild	11 (22 %)
Moderate	31 (63 %)
Severe	7 (14 %)
Lab data (mean ± SD)	
ESR (mm/h)	47,7 ± 30,0
CRP (mg/dL)	0,753 ± 1,36
Albumin (g/L)	43,5 ± 6,4
Fecal Calprotectin (μg/g)	2928,6 ± 12,656,2
Hb (g/dL)	12 ± 2
Need of systemic steroids n (%)	19 (38,7 %)
Starting therapy (n,%)	
Mesalamine	42 (85,7 %)
Azathioprine	5 (10,2 %)
Sulphasalazine	11 (22,4 %)
Infliximab	6 (12,2 %)
Extraintestinal manifestations, n (%)	
Sclerosing cholangitis	5 (10,2 %)
Arthritis	2 (4 %)
Weight loss	12 (24,4 %)

PUCAI, pediatric ulcerative colitis activity index; ESR, erythrocyte sedimentation rate; CRP, c-reactive protein; Hb, hemoglobin.

patients completed the study and were included in the final analysis. Table 1 presents the demographic, biological, and clinical data of the study participants. The histological activity scores and endoscopic disease activity are presented in Table 2. At diagnosis, most patients had moderate clinical disease activity 31 (63 %), 11 (23 %) mild, and 7 (14 %) severe colitis.

Table 2
Endoscopic and histologic findings at the diagnosis.

Mayo endoscopic score	
0/1	4 (8,2 %)
2	41 (83,6 %)
3	4 (8,2 %)
Activity score (Robarts histopathology Index) n (%)	
Mild	10 (20 %)
Moderate - Severe	39 (80 %)
Activity score (Nancy Index), n (%)	
Mild	5 (10,2 %)
Moderate	9 (18,4 %)
Severe	35 (71,4 %)
Activity score (Goebes score), n (%)	
Mild	2 (4 %)
Moderate-Severe	47 (95 %)

During the first 6 months, 29 (59 %) patients had a favorable clinical course without any relapse, 20 (41 %) had at least one disease flare and 5 (10 %) experienced an episode of ASC. At one year, the percentage of patients with a favorable course decreased to 19 (39 %), 30 (61 %) had at least one relapse, and 8 (16 %) had an episode of ASC.

3.2. Primary outcome

No significant association was found between the three histological indices at diagnosis and major clinical outcomes at 1 year (Table 4).

3.3. Secondary outcomes

No significant association was found between the three histological indices at diagnosis and major clinical outcomes at 6 months (Table 3).

There were no differences over time for each clinical outcome between patients with a moderate-severe histologic score and those with mild histological inflammation at diagnosis, considering all the histologic scores (log-rank > 0.05) (Fig. 2).

As for the concordance between the three scores, excellent concordance was found between NI and GS (rs: 0.909, $p < 0.001$),

Table 3
Cox regression analysis between histological scores and clinical outcomes at 6 months.

	Nancy Index		Geboes Score		Robarts Histopathology Index	
	Hazard ratio (95 % CI)	p-value	Hazard ratio (95 % CI)	p-value	Hazard ratio (95 % CI)	p-value
Relapse	0,7 (0,1–3,7)	0,7	1,0 (0,7–1,5)	0,84	1,0 (0,9–1,2)	0,4
ASC	2,7 (0,0–9,6)	0,96	1,3 (0,5–3,6)	0,5	1,0 (0,8–1,2)	0,7
Steroids	1,3 (0,5–10,7)	0,8	0,99 (0,6–1,5)	0,96	0,9 (0,8–1,1)	0,9
Treatment escalation	0,2 (0,04–2)	0,2	1,1 (0,6–1,7)	0,64	0,13 (0,9–1,3)	0,05
PUCAI>35 or FC>250 mcg/g	1,4 (0,2–8,5)	0,7	0,8 (0,6–1,2)	0,47	1,1 (0,9–1,2)	0,1

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

Table 4
Cox regression analysis between histological scores and clinical outcomes at 1 year.

	Nancy Index		Geboes Score		Robarts Histopathology Index	
	Hazard ratio (95 % CI)	p-value	Hazard ratio (95 % CI)	p-value	Hazard ratio (95 % CI)	p-value
Relapse	0,9 (0,6–1,5)	0,8	1 (0,9- 1,1)	0,9	1 (0,9- 1)	0,6
ASC	2,0 (0,2- 18,0)	0,5	1,6 (0,8- 3,2)	0,1	1 (0,9–1,1)	0,6
Steroids	0,7 (0,3–1,5)	0,4	0,9 (0,7–1,1)	0,6	0,9 (0,9–1)	0,5
Treatment escalation	1,0 (0,6–1,7)	0,8	1,0 (0,8–1,9)	0,6	1,0 (0,9–1,0)	0,3
PUCAI >35 or FC>250 mcg/g	1,0 (0,5–1,7)	1,0	0,9 (0,8– 1,1)	0,8	0,9 (0,9–1)	0,9

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

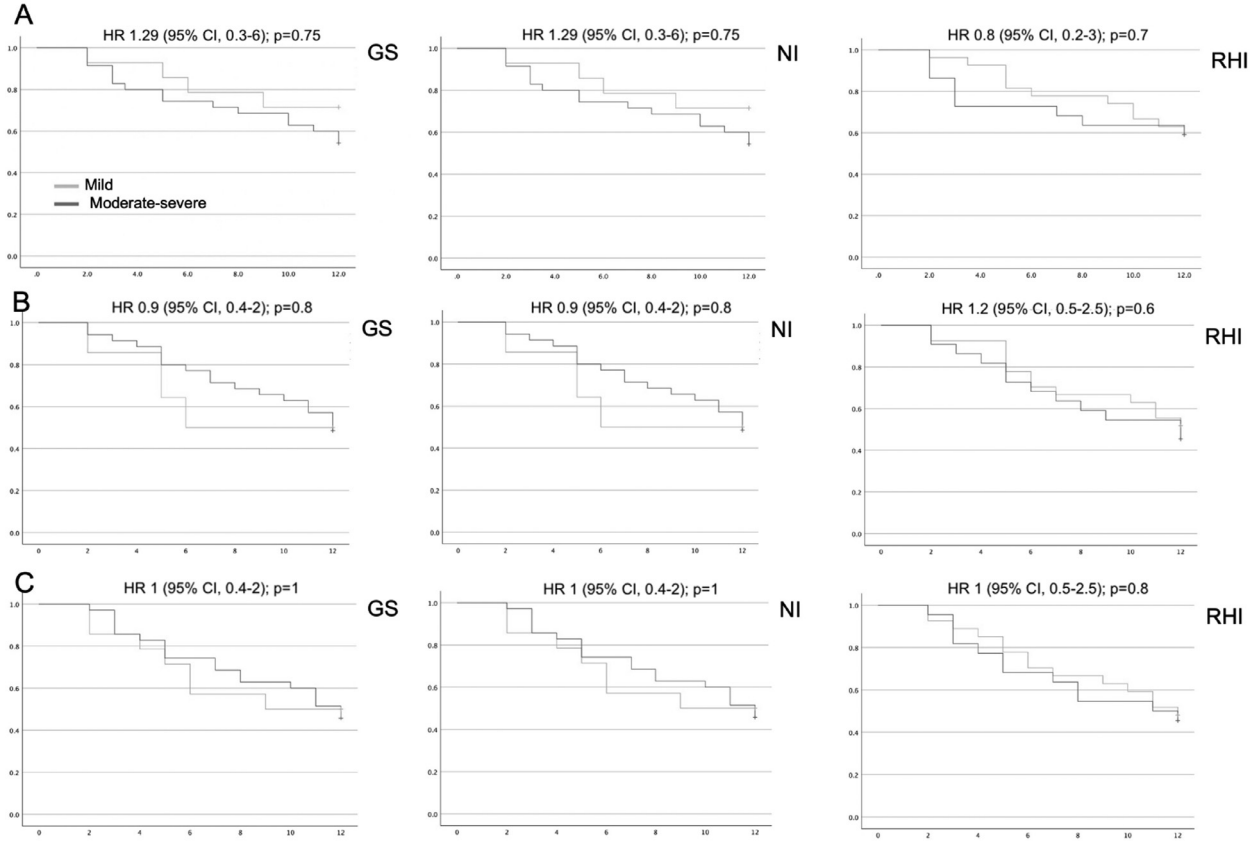

Fig. 2. Kaplan Meier estimate of survival by histological score. (A) Steroid-free survival in mild and moderate-severe. (B) Step-up therapy-free survival in mild and moderate-severe. (C) PUCAI > 35 and/or FC > 250 free survival in mild and moderate-severe. GS, Geboes score; NI, Nancy Index; RHI, Robarts Histologic Score.

moderate between NI and RHI (rs: 0.791, $p < 0.001$), and moderate between GS and RHI (rs: 0.737, $p < 0.001$) (Table 5). A moderate correlation was found between all histological scores and the endoscopic index (NI-Mayo, rs = 0.391; GS-Mayo, rs = 0.312; RHI-Mayo, rs = 0.328, $p < 0.05$).

Finally, no correlation was found between histological scores and serum inflammatory markers (VES, PCR, and FC) at diagnosis ($p > 0.05$) (Supplementary Table 1).

The multivariate logistic regression model showed no association between the combined endoscopic and histological scores and clinical relapse at 1 year follow-up (Supplementary Table 2).

The eMayo score showed good inter-rater reliability for endoscopic activity, with a k value of 0.71 (95 % CI 0.38 to 0.94)

Histopathological assessment demonstrated varying levels of inter-observer agreement: good for the Nancy and Robarts Histopathology Indexes [k = 0.74 (95 % confidence interval, CI:

0.54–0.91) and $k = 0.68$ (95 % confidence interval, CI: 0.52–0.83), respectively] and moderate for the Geboes Score [$k = 0.46$ (95 % confidence interval, CI: 0.3–0.61)].

4. Discussion

In children with UC, therapeutic choices and follow-up are strictly influenced by the disease staging. Therefore, this step is of primary interest to the clinicians. Several studies have investigated the possible role of clinical, laboratory, endoscopic, and genetic factors as predictors of disease outcomes, with different results and poor reproducibility [25–27]. Currently, the therapeutic approach is mostly based on clinical and endoscopic activity [7,9]. This study aimed to investigate the role of histology as a possible predictor marker of prognosis to be used at diagnosis to guide treatment decisions in children with UC.

We did not find any association between the three validated histological activity scores at diagnosis and the disease course at one year. Hence, according to our results, these scores seem not useful for predicting clinical outcomes and cannot be used to drive therapeutic choices. This is in contrast with the prospective data reported by Zenlea in adults, which revealed a correlation between the GB score and clinical course in 179 patients. However, it is noteworthy that this study examined a different cohort of patients who were already diagnosed, under treatment, and in clinical remission [28].

Furthermore, in our study, histological scores did not correlate with serological and fecal inflammatory markers (CRP, ESR, and FC). Therefore, normalization of these biomarkers cannot be used as a surrogate indicator of histologic remission and should not be used as non-invasive markers of histological activity. The same finding was reported by Magro et al., however, in that study, an association between the presence of neutrophils in the epithelium and FC was found [29].

An important finding of our study was the good correlation between the 3 histological scores (GS, NI, RHI) in defining disease activity. A similar result was reported in adult patients by Magro et al. in 2018 [29] in a large cohort of UC patients, although in that study, the concordance was evaluated in terms of histological remission and activity, and most patients (94 %) were in clinical remission. This is the first study conducted in pediatric UC, showing a statistically significant concordance between the continuous values of the most used histological scores. Owing to their good correlation, the three scores can be used interchangeably, which will allow different studies to be compared even when using different scores. This study is also the first to determine the inter-rater agreement for each histologic score within a pediatric population. The Nancy Index and Robarts Histopathology Index showed a good inter-rater agreement, indicating their strong reliability and potential for standardization among different pathologists. This aligns with recent findings by Duc Le and colleagues, who demonstrated a high level of interobserver agreement for the NI in a large cohort of patients (1085 slides) [30]. On the other hand, the Geboes score's complexity may pose challenges in achieving good inter-rater agreement with non-expert pathologists. Validation studies for all histological indices reported the same degree of agreement [12–14]. One could hypothesize that Nancy's calculation feasibility contributes to its highest agreement rate, while the complexity of the Geboes, coupled with its inherent subjectivity in quantifying active inflammation, results in moderate agreement. The Robarts index was developed from Geboes, to mitigate its complexity and minimize inter-rater subjectivity [14,31]. A retrospective study on 64 slides evaluating NI, RHI, and GS's inter-rater agreement showed similar results, with a good k coefficient for the NI and GS and moderate for RHI [31].

We also found a good correlation between each histologic score and the endoscopic Mayo score. When evaluating the degree of inflammation, it is important to know whether histologic and endoscopic scores overlap, since the Mayo score is operator-dependent and strictly relies on the IBD skills of the endoscopist, while a good correlation with histology may be of support in determining the degree of inflammation in less experienced primary or secondary centers. To our knowledge, no previous study has performed this comparison, except for the study by Magro and coworkers in 2018. However, in that study, the comparison was limited to the phase of histological remission. [29] Our study compared different degrees of microscopic disease activity. Other studies by Kovach, Lemmens and Neri [32–34] compared the Goebes score to the Mayo score in different disease phases with a good correlation, but none compared the NI and the RHI. In the PROTECT study, a large cohort of pediatric patients newly diagnosed with UC, Boyle et al. [35,36] found a correlation between the endoscopic score and specific histological features rather than histological scores, making our study the first to examine this aspect objectively in pediatric UC patients. Inter-observer agreement for the eMayo score was good. A study by Daperno et al. evaluated the repeatability of different endoscopic scoring systems: the eMayo demonstrated a good agreement between expert gastroenterologists and moderate between non-experts, suggesting that the agreement is highly influenced by the experience of the observer [37].

We acknowledge that our study has several limitations. First, it is a single-center study with a small sample size. Moreover, as we enrolled only newly diagnosed, untreated patients, we could have over-represented moderate to severe cases, with no equal distribution among microscopic inflammation grades. Moreover, the absence of a second pathologist to revise the tissue sample slides prevented us from making an agreement analysis for the Geboes score, the only score not yet validated, while we could rely on an already demonstrated high inter-observer agreement for the Nancy and Robarts scores [13,14]. Nevertheless, its prospective design and the strict patient selection and assessment represent the strengths of this study, given that no similar data were reported before in pediatric patients.

5. Conclusions

According to our findings, the degree of histologic inflammation at diagnosis, evaluated using the Nancy, Robarts, and Geboes scores, does not seem to predict 1-year clinical and biochemical relapse in pediatric UC. However, we found a high inter-score correlation and a high correlation with the endoscopic Mayo score, with good reliability for Nancy and Robarts and moderate for Geboes score. All these features could be helpful in comparing the results of different studies using different activity scores.

Conflict of interest

All the authors declare no financial relationships with a commercial entity producing health-related products and or services related to this article. No honorarium, grant, or other form of payment was given to anyone to write and to produce the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2023.09.018.

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