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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

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Abstract

Background: The revised Porto criteria identify subtypes of paediatric inflammatory bowel diseases: ulcerative colitis [UC], atypical UC, inflammatory bowel disease unclassified [IBDU], and Crohn's disease [CD]. Others have proposed another subclassifiction of Crohn's colitis. In continuation of the Porto criteria, we aimed to derive and validate criteria, termed "PIBD-classes," for standardising the classification of the different IBD subtypes.

Methods: This was a multicentre retrospective longitudinal study from 23 centres affiliated with the Port -group of ESPGHAN. Both a hypothesis-driven judgmental approach and mathematical classification and regression tree [CART] modelling were used for creating a diagnostic algorithm. Since small bowel inflammation is easily recognised as CD, we focused here primarily on the phenotype of colitis.

Results: In all, 749 IBD children were enrolled: 236 [32%] Crohn's colitis, 272 [36%] UC and 241 [32%] IBDU [age 10.9 ± 3.6 years] with a median follow-up of 2.8 years (interquartile range [IQR] 1.7–4.3). A total of 23 features were clustered in three classes according to their prevalence in UC: six class-1 features [0% prevalence in UC], 12 class-2 features [< 5% prevalence], and five class-3 features [5–10% prevalence]. According to the algorithm, the disease should be classified as UC

if no features exist in any of the classes. When at least one feature exists, different combinations classify the disease into atypical UC, IBDU or CD. The algorithm differentiated UC from CD and IBDU with 80% sensitivity (95% confidence interval [CI] 71–88%) and 84% specificity [77–89%], and CD from IBDU and UC with 78% sensitivity [67–87%] and 94% specificity [89–97%].
Conclusions: The validated PIBD-classes algorithm can adequately classify children with IBD into small bowel CD, colonic CD, IBDU, atypical UC, and UC.

Key Words: UC, Crohn's colitis, Crohn's disease, IBD-unclassified, classification, pediatric

1. Introduction

There is an obvious need to standardise the diagnosis of inflammatory bowel disease [IBD] subtypes, especially in view of recent technological advances of microbiome profiling and other 'omics'.[1,2] The term 'IBD unclassified' [IBDU] has expanded from a post-colectomy pathological diagnosis to a poorly defined clinical entity without accepted criteria.[3,4] It is now typically used to characterise patients with ulcerative colitis [UC]-like disease who have soft features suggestive of Crohn`s disease [CD].[5] Although many IBDU patients are eventually reclassified as either UC or CD, approximately 75% maintain the diagnosis of IBDU, alluding to the fact that most of the IBDU patients have a distinct diagnostic entity of a true overlap phenotype between small bowel CD and typical UC.[5–10] Under the same notion of a continuum disease, some advocate labelling Crohn's colitis as a different IBD entity, while separating it from classical small bowel CD.[2]

The revised Porto criteria identify subtypes of paediatric inflammatory bowel diseases: UC, atypical UC, IBDU, and CD.[11] We have proposed a scoring table composed of IBD features that combined can outline the diagnosis of IBD, differentiating IBDU from UC on one side and CD on the other side. In addition, the term 'atypical UC' was suggested when features not characteristic of classic UC are present but common enough in UC to preclude the diagnosis of CD [e.g. relative rectal sparing and patchiness]. Since overt small bowel inflammation is easily diagnosed as CD and the challenging phenotype is the colonic one, the classification was based on patients with colonic IBD. By an extensive literature search, we tabulated features associated with IBD that may be valuable in discriminating between the IBD subtypes, and divided them into three classes.[11] Features in class-1 are those incompatible with UC and thus their existence mandates the diagnosis of CD [eg granulomas remote from ruptured crypts or serpentine ulcerations in the small bowel]. Class-2 features are those suggestive of CD but have been rarely found also in UC [> 0% but < 5% of cases; eg relative patchiness and complete histological rectal sparing]. Class-3 features are those suggestive of CD but have been found also in UC in the range of 5–10% of cases. Naturally, with increasing number of class-2 and class-3 features, the likelihood for a diagnosis of CD increases. However, the original revised Porto criteria lacked validation and refrained from determining the number of features required to diagnose a child with IBDU, atypical UC or CD.

In this multicentre longitudinal paediatric study, we aimed to derive and validate diagnostic criteria for the diagnosis of the IBD subtypes, termed the "PIBD-classes" criteria, with an emphasis on IBDU, based on our previous work in the revised Porto criteria, using both a judgmental approach and advanced mathematical modelling on the largest IBDU cohort ever constructed to date.

2. Methods

This is a multicentre retrospective triple cohort study from 23 centres in Europe and Israel, affiliated with the paediatric IBD Porto group of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition [ESPGHAN]. Eligible subjects were children [2–18 years of age] diagnosed between 2004 and 2013 as having IBD with isolated colonic involvement, in order to mimic the most relevant and clinically challenging diagnostic dilemma. We decided not to include patients with obvious CD findings, since class-1 features are very well accepted and do not require specific validation. Including them a priori would have over-optimised our algorithm. Patients were enrolled into one of three groups: UC, IBDU, or colonic CD. The diagnosis was made by the original treating gastroenterologist at disease onset, based on clinical, radiological, endoscopic and pathological evaluations.[11] We chose experienced, internationally renowned paediatric IBD centres that follow accepted diagnostic criteria at the time of diagnosis, in order to ensure relative standardisation and appropriate evaluation for the diagnosis, which had been previously universally subjective regarding IBDU. Due to the inevitable subjectivity, we refrained from creating another group for atypical UC and determined a priori that the diagnosis of UC with any positive feature from the list will be labelled as atypical.

Each site was obliged to enroll an equal number of children in the three categories, to a maximum of 20 children per group in order to minimise selection bias and site effect. A short segment of mild inflammation in the terminal ileum [without stenosis, cobblestoning, or deep ulcers] was allowed providing that pancolitis was present, so that it could potentially be compatible with backwash ileitis. Included children had to have a follow-up period of at least 1 year from diagnosis and repeated evolution of the diagnosis recorded at latest follow-up. Those with significant perianal disease [ie large inflamed skin tags, fistula, or abscess] were excluded [as these are obviously diagnosed as CD]. Children without complete ileocolonoscopy and gastroscopy at diagnosis were excluded; however, colonoscopy only to the caecum was allowed if small bowel imaging was available within 3 months of diagnosis.

The following data were retrieved from the medical charts on standardised case report forms: demographic data, baseline diagnosis [IBDU, CD, or UC], explicit diagnostic work-up findings [eg endoscopic findings, histology report, imaging], and serology results. Follow-up data included revised diagnosis and explicit findings of repeated investigations. Disease location was defined according to the Paris classification.[12] Disease severity at diagnosis and at last follow-up was scored by the physician global assessment [PGA] and defined as quiescent, mild, moderate, or severe.[13]

After further literature review, the steering committee added two features to the list of class-2 features beyond those included in the original revised Porto criteria and slightly revised the some of the others (see Results for details).[11] Ultimately, the criteria included 23 features which were scored for all included children at diagnosis [Table 1].

2.1. Analytical approach

Data were submitted to the central repository at Shaare Zedek Medical Centre in Jerusalem for scrutiny. Questionable or missing

Table 1. Final division of classes and frequency of the features in our cohort (*n* [%]).

	Q	Feature	Frequency in CD, *N* = 236	Frequency in IBDU, *N* = 241	Frequency in UC, *N* = 272
Class 1	1	At least one well-formed granuloma anywhere in the GI tract, remote from ruptured crypt	120 [51%]	0 [0%]	0 [0%]
	2	At least one of: deep ulcerations; cobblestoning; or stenosis anywhere in the small bowel or UGI tract [excluding stomach][a]	46 [20%]	0 [0%]	0 [0%]
	3	Fistulising disease [internal or perianal]	8 [3%]	0 [0%]	0 [0%]
	4	Large inflamed perianal skin tags	21 [9%]	0 [0%]	0 [0%]
	5	Thickened jejunal or ileal bowel loops on radiology or other evidence of significant small bowel inflammation on capsule endoscopy not compatible with backwash ileitis	29 [12%]	0 [0%]	0 [0%]
	6	Any ileal inflammation in the presence of normal caecum [i. incompatible with backwash ileitis][b]	26 [11%]	0 [0%]	0 [0%]
Class 2	7	Macroscopically and microscopically normal appearing skip lesions in untreated patient [excluding rectal sparing and caecal patch]	95 [40%]	56 [23%]	7 [3%]
	8	Complete [macroscopic and microscopic] rectal sparing	46 [20%]	18 [8%]	4 [2%]
	9	Macroscopically normal colon in between inflamed mucosa but with microscopic inflammation [ie relative patchiness]	97 [41%]	68 [28%]	10 [4%]
	10	Significant growth delay [height velocity < minus 2 SD], not explained by other causes [e.g. coeliac disease, prolonged steroids, or growth hormone deficiency]	30 [13%]	15 [6%]	9 [3%]
	11	Transmural inflammation of the colon in the absence of severe colitis	4 [2%]	10 [4%]	2 [1%]
	12	Small and not deep ulcers [including aphthous ulcerations] anywhere in the small bowel, duodenal and oesophageal [excluding stomach and colon] not explained by other causes [eg *H. pylori*, NSAIDs and coeliac disease][c]	23 [10%]	15 [6%]	4 [2%]
	13	Multiple [≥ 5] small and not deep ulcers [including aphthous ulcerations], in the stomach or colon [on the background of normal mucosa], not explained by other causes [eg *H. pylori* and NSAIDs]	24 [10%]	15 [6%]	7 [3%]
	14	Ileitis, otherwise compatible with backwash ileitis, but in the presence of only mild inflammation in the caecum[d]	40 [17%]	30 [12%]	11 [4%]
	15	Positive ASCA in the presence of negative pANCA	28 [12%]	12 [5%]	4 [2%]
	16	Reverse gradient of mucosal inflammation (proximal > distal [except rectal sparing])	53 [23%]	28 [12%]	8 [3%]
	17	Severe scalloping of the stomach or duodenum, not explained by other causes [eg coeliac disease and *H. pylori*]	4 [2%]	5 [2%]	1 [0.5%]
	18	Deep ulcerations [at least one] or severe cobblestoning of stomach not explained by other causes [eg *H. pylori*, NSAIDs, coeliac disease]	0 [0%]	3 [1%]	1 [0.5%]
Class 3	19	Focal chronic duodenitis on histology	44 [19%]	30 [12%]	11 [4%]
	20	Focal active colitis on histology in more than one biopsy	129 [55%]	112 [47%]	70 [26%]
	21	Several [< 5] aphthous ulcerations in the colon or in the stomach	133 [56%]	71 [30%]	27 [10%]
	22	Non-bloody diarrhoea	82 [35%]	42 [17%]	28 [10%]
	23	Focal enhanced gastritis on histology	79 [34%]	61 [25%]	39 [14%]

IBDU, inflammatory bowel disease unclassified; CD, Crohn's disease; UC, ulcerative colitis; UGI, upper gastro-intestinal; NSAID, non-steroidal anti-inflammatory drug; ASCA, anti-*Saccharomyces cerevisiae* antibodies; pANCA, perinuclear anti-neutrophil cytoplasmic antibodies; SD, standard deviation.

[a] Deep ulcerations or severe cobblestoning of stomach score as item #18; if there are ulcerations in the duodenum or oesophagus which are small and not deep, score as item #12.

[b] If caecum with mild inflammation, score as item #14.

[c] If ulcers are deep, score as item #2.

[d] Backwash ileitis: a short segment of non-stenotic erythema or oedema in the presence of pancolitis including the ileocaecal valve, without granulomata or deep ulcers.

data fields were verified with the sites to ensure integrity. In order to determine the number of features in each class which can best categorise the different diagnostic groups, both a hypothesis-driven judgemental approach and data-driven mathematical modelling were used by two independent groups. For both approaches, the database was randomly divided into a training sample [66% in the judgemental approach and 85% in the mathematical approach] and validation samples [the rest of the cohorts].

For the judgemental approach, we tabulated every possible combination of class-2 and class-3 features in association with the final diagnosis, after excluding those with class-1 features who are obviously Crohn's disease per definition [Supplementary Table 1,

available as Supplementary data at *ECCO-JCC* online]. Based on the frequency table, several classification schemes were compared for their diagnostic accuracy in differentiating IBDU from CD and UC, by maximising sensitivity and specificity.

The mathematical modelling involved developing a classification algorithm for predicting the baseline diagnosis using the classification and regression tree [CART] method. The CART method works by building a decision tree in successive stages from top to bottom. Other classification methods were investigated, including random forest and penalised proportional odds modelling [taking diagnosis as an ordinal variable: UC < IBDU < CD], but these did not provide improved performance. Given the perceived importance of serology in differentiating CD from UC, we attempted to force this variable into the model as an independent variable outside the features list. A split-sample approach was taken even though CART has an internal cross-validation algorithm, because several choices of the CART input parameters were explored.

Summary data are presented as means [± standard deviation], or medians (interquartile range [IQR]), as appropriate for the distribution normality. Point estimates [eg odds ratio, sensitivity, and specificity] are accompanied by 95% confidence interval [CI]. Unpaired categorical data were compared using χ^2 or Fisher's exact test as appropriate. Continuous data were analysed using the unpaired Student's t-test, Wilcoxon rank sum test, or KruskalWallis test, were used as appropriate for the distribution normality and number of groups. Time to event analysis [including a KaplanMeier curve and Cox proportional hazard multivariable modelling] was used to explore factors associated with time to change of diagnosis. All comparisons were made using two-sided significance levels of $p < 0.05$ and performed using SPSS V20.0 [SPSS Inc., Chicago, IL] and R software system. The study has been performed according to the instructions of the local ethics committees at all participating sites.

3. Results

A total of 855 patient records were submitted from 23 paediatric IBD centres in Europe and Israel. Of these, 106 patients did not meet the eligibility criteria [53 had insufficient data to score the 23 features, 37 had incomplete endoscopic or radiographic evaluation, 7 were younger than 2 years or older than 18 years, 5 were diagnosed before 2004, and 4 had short follow-up], leaving a total of 749 patients who were included in the analysis: 241 [32%] IBDU, 236 [31%] CD, and 272 [36%] UC patients. Despite the eligibility criteria, some centres submitted CD cases with small bowel inflammation in addition to the colonic disease [Table 1]. We retained these patients after verifying that all cases were predominantly of the colonic phenotype, to ensure that the included patients had a UC-like colitis aside from the other features. Median follow-up period was 2.8 [IQR 1.7–4.3] years. IBDU patients were younger and had milder disease activity at diagnosis as compared with the other groups [Table 2]; CD patients were more often of African ethnicity compared with the other groups. Of the entire cohort, 300 [40%] had macroscopic upper gastro-intestinal [UGI] involvement, which was more prevalent in the CD group compared with the IBDU group (124 [53%] vs 99 [41%]; $p = 0.015$) and least prevalent in the UC group (77 [28%]; $p = 0.002$ compared with IBDU).

3.1. Derivation of diagnostic criteria for IBDU

After reviewing the prevalence of the 23 features in our UC cohort and before any discriminant analysis, one of the original features was moved from class-1 to class-2 [ie 'macroscopically and microscopically skip lesions in untreated IBD'] due to a frequency of 3% in the UC group. Similarly, two features were moved from class-3 to class-2 [ie 'severe scalloping of the stomach or duodenum' and

Table 2. Basic characteristics of the entire cohort. Medians [IQR], mean ± SD or proportions [95% CI] are presented as appropriate.

	Entire cohort [*N* = 749]	CD [*N* = 236]	IBDU [*N* = 241]	UC [*N* = 272]	*p*-Value [three groups]
Males	396 [53%]	127 [54%]	121 [50%]	148 [54%]	0.6
Age at diagnosis [years]	10.9 ± 3.6	11.3 ± 3.6	10.3 ± 3.8	11.3 ± 3.4	0.002[a]
Race					
Caucasian	630 [89%]	200 [89%]	196 [86%]	234 [91%]	0.317
African	19 [3%]	1 [0.4%]	8 [3.5%]	10 [4%]	0.042[b]
Other[c]	61 [8%]	24 [10%]	23 [10%]	14 [5%]	0.074
PGA at diagnosis					
Moderate to severe	516 [69%]	173 [73%]	149 [62%]	194 [71%]	0.014[d]
Disease extent UC or IBDU[e]					0.091
Proctitis	–	–	12 [5%]	18 [7%]	0.43
Colitis distal to the splenic flexure	–	–	26 [11%]	39 [14%]	0.228
Colitis distal to the hepatic flexure	–	–	56 [23%]	36 [13%]	0.003
Pancolitis	–	–	147 [61%]	179 [66%]	0.258
Macroscopic involvement UGI tract	300 [40%]	124 [53%]	99 [41%]	77 [28%]	< 0.001[f]
Years of follow-up	2.8 [1.7–4.3]	3 [1.9–4.6]	2.7 [1.7–4.4]	2.7 [1.6–4.4]	0.107[g]
Change of diagnosis during follow-up	75 [10%]	8 [3%]	50 [21%]	17 [6%]	< 0.001[h]

CD, Crohn's disease; UC, ulcerative colitis; IBDU, inflammatory bowel disease unclassified; UGI, upper gastro-intestinal; SD, standard deviation; CI, confidence interval; IQR, interquartile range; PGA, physician global assessment.

[a]IBDU vs CD; $p = 0.003$, IBDU vs UC; $p = 0.002$.

[b]IBDU vs CD; $p = 0.019$, CD vs UC; $p = 0.012$.

[c]Hispanic, Middle Eastern, Asian and multi-ethnic.

[d]IBDU vs CD; $p = 0.007$, IBDU vs UC; $p = 0.023$.

[e]Disease extent is not specified for CD since skip lesions were allowed.

[f]IBDU vs CD; $p = 0.015$, IBDU vs UC; $p = 0.002$, CD vs UC; $p < 0.001$.

[g]CD vs UC; $p = 0.043$.

[h]IBDU vs UC, CD; $p < 0.001$, CD vs UC; $p = 0.154$.

'deep serpentine ulcerations of the stomach'], since their frequency in the UC group was only 0.5%. All other features remained in their class determined by the revised Porto criteria. Two class-3 features ['focal active colitis' and 'focal enhanced gastritis'] had a higher than 10% frequency in our UC cohort [Table 1]. We performed sensitivity analyses after excluding these two features from the model, but their exclusion lowered the accuracy of the algorithm and thus they were retained in class-3. This process yielded a final list of 23 features in three clusters: six in class-1, 12 in class-2, and five in class-3 [Table 1].

3.1.1. Hypothesis driven judgemental approach

Figure 1 shows the chosen algorithm of the judgemental approach that maximised diagnostic accuracy for the 501 patients in the derivation cohort [Supplementary Table 1]. The algorithm was then validated in the remaining cohort [248 patients]; the algorithm differentiated UC from CD and IBDU well, with 80% sensitivity [95% CI 71–88%] and 84% specificity [77–89%]. The algorithm also differentiated between CD vs IBDU and UC with 78% sensitivity [67–87%] and 94% specificity [89–97%]. Similar diagnostic performance was found when applying the algorithm to the entire cohort [Table 3].

3.1.2. Data-driven mathematical modelling

There were 498 [85%] patients in the training sample of the mathematical modelling [of the total 498 children after excluding 163 children with class-1 features who had obvious Crohn's disease]. The following explanatory variables were included in the models: all Table 1 features both as classes and as individual items, age, gender, PGA, and serological tests. The following algorithm had the best performance: if class-1 and class-2 features were negative, classify as UC. If class-1 features were negative, at least one class-2 feature and four or more class-3 features, classify as CD. If class-1 features were negative, at least one class-2 feature and up to three class-3 features, classify as IBDU. The algorithm was then validated in the remaining cohort. The sensitivity of the algorithm for differentiating UC from CD and IBDU was 80% [95% CI 65–91%] with 86% specificity [76–93%]. To differentiate CD from IBDU and UC the sensitivity was 72% [55–86%] and specificity 97% [91–100%] [Table 3].

3.1.3. Final chosen algorithm

The judgemental and mathematical algorithms had similar diagnostic performance, but the judgemental algorithm had superior sensitivity when differentiating CD from IBDU and UC [Table 3]. Moreover, the hypothesis-driven judgemental algorithm is more intuitive and has easier applicability, and thus was chosen as the final algorithm [Figure 1]. Following our a priori decision, we applied the diagnosis of atypical UC to those who were classified as UC but with at least one feature. Intuitively, this means those with 1–2 class-3 features [and no class-1 or class-2 features], since less than that translates to typical UC and more than that to IBDU or CD.

3.2. Change of diagnosis

During the 2.8 year follow-up period, 191/241 [79%] of IBDU children maintained their original diagnosis [Table 2]. Of the 50 IBDU children who changed their diagnosis, 26 [52%] changed to CD and 24 [48%] to UC [Table 4]. There was no difference in time to change of diagnosis between the three subgroups [Figure 2].

In order to further validate our choice of features, we explored whether any class-2 or class-3 features were associated with the change of diagnosis from IBDU to CD or UC. Q_{14} in class-2 [ie 'ileitis, compatible with backwash ileitis but in the presence of only mild inflammation in the ascending colon'; Table 1] was a significant predictor for changing the diagnosis from IBDU (11/30 [37%] with this feature vs 39/211 [19%] without; $p = 0.024$), and mainly to CD (9/11 [82%]; $p = 0.04$]. Reassuringly, none of the other 22 features showed such a prominent association.

4. Discussion

As recently found in a large genetic-phenotypic study, IBD is a range of diseases from obvious small bowel CD, colonic CD, and IBDU to atypical and typical UC.[14] The revised Porto criteria have made a step forward to better define these subgroups, but they have never undergone a rigorous development or validation process. To date, IBDU diagnosis has been an especially vaguely characterised diagnosis, both in children and in adults. These patients are typically excluded from clinical trials, partially since there are no standardised diagnostic criteria for this subgroup.[15]

In this study, we used both a judgemental hypothesis-driven approach and mathematical data-driven modelling to derive and validate the "PIBD classes" diagnostic criteria of IBD in children. The chosen algorithm is constructed of 23 features clustered into three classes and has good sensitivity and specificity for differentiating the subgroups [range 78–94%]. Most features were previously selected, based on extensive literature review and expert opinion of the Porto group members according to the frequency of each feature in UC patients.[11] Based on the current study we refined the list, added two features, and moved three others between classes, but generally the initial tabulation reflected well by the frequency of the features in our cohort. When using the mathematical approach,

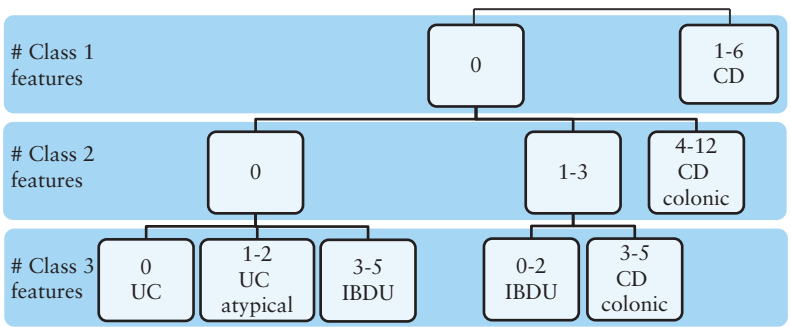

Figure 1. The chosen "PIBD classes" algorithm based on the hypothesis-driven analysis for the differential diagnosis of inflammatory bowel disease [IBD] subgroups.

Table 3. Diagnostic utility of classification algorithms.

	Sensitivity [95% CI]	Specificity [95% CI]
Hypothesis-driven judgemental approach validation cohort [*n* = 248]		
UC vs IBDU + CD	80% [71–88]	84% [77–89]
CD vs IBDU + UC	78% [67–87]	94% [89–97]
Entire cohort [*n* = 749]		
UC vs IBDU + CD	78% [72–82]	83% [79–86]
CD vs IBDU + UC	80% [74–85]	95% [92–97]
Data driven-mathematical modelling validation cohort [*n* = 112]		
UC vs IBDU + CD	80% [65–91]	86% [76–93]
D vs IBDU + UC	72% [55–85]	97% [91–100]
Entire cohort [n = 749]		
UC vs IBDU + CD	79% [74–84]	80% [76–83]
CD vs IBDU + UC	75% [68–80]	100% [98–100]

CD, Crohn's disease; UC, ulcerative colitis; IBDU, inflammatory bowel disease unclassified.

Table 4. Variables upon which the diagnosis of IBDU was changed over time.

Reason for change of diagnosis	All [*N* = 75]	IBDU→ CD [*N* = 24]	IBDU→ UC [*N* = 26]
Repeat endoscopy	45 [60%]	19 [73%]	11 [46%]
Revision of original histology	4 [5%]	0 [0%]	4 [14%]
Clinical features	8 [11%]	4 [15%]	2 [8%]
Imaging	4 [5%]	2 [8%]	0 [0%]
Unknown	14 [19%]	1 [4%]	7 [29%]

CD, Crohn's disease; UC, ulcerative colitis; IBDU, inflammatory bowel disease unclassified.

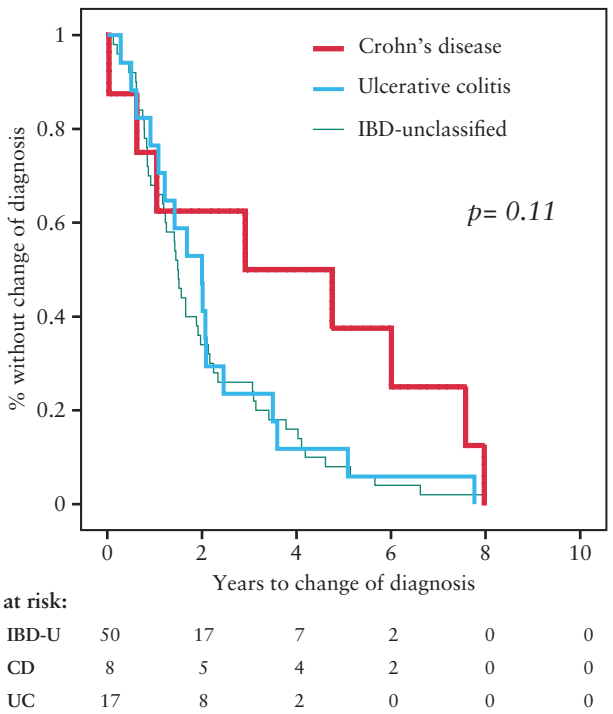

Figure 2. Time to change of diagnosis in the inflammatory bowel disease [IBD] colonic subgroups (to either of the subtypes).

we considered additional variables including serology, yet this did not improve the accuracy of the algorithm. Indeed, we had previously found that serology was a poor discriminator of IBDU in this cohort.[16]

The frequency of IBDU in adults is approximately 10% of all IBD patients.[3] This figure has not changed significantly over the past 30 years, despite the introduction of newer diagnostic methods, suggesting that IBDU is not a misclassification of either CD or UC but rather a distinct IBD phenotype that warrants clear diagnostic criteria, just as for UC and CD. Clear classification criteria are important especially in paediatrics, given the increased prevalence of IBDU in the younger age group, ranging from 4% to 29%.[15,17-21]

Only 21% of IBDU patients in our cohort changed their diagnosis during the follow-up period, despite the fact that 59% had repeated colonoscopy [of whom only 14% changed their original diagnosis]. This is in the lower range of previously reported rates of mostly of 23–34%.[7,9,15,8] in both children and adults. A recent paediatric study found a 32% change of diagnosis rate, but approximately half of the IBDU patients did not undergo complete diagnostic work-up.[22] The low reclassification rate in our study lends further support to the notion that IBDU is a true intermediate phenotype on the spectrum between obvious isolated ileal CD and typical UC.

Our study is not without limitations. It is retrospective, and we were thus limited to the available data in the charts. However, the large number of centres, carefully selected for paediatric IBD expertise, increased the accuracy of the subgroup labelling while minimising misclassification bias. Furthermore, the inevitable subjectivity of the classification by the local gastroenterologists is compensated by the large sample size, the largest to date in IBDU, which allows general trends to emerge. We took extra care to standardise data collection and to verify the integrity of the data via multiple queries to the sites, but standardising the pathology reports was impossible in this retrospective study. The fact that all children were diagnosed in large referral paediatric IBD centres somewhat increases our confidence in the local assessments, including the pathology. The many required features for the classification may seem complicated at first but, in practice, clinicians routinely consider these variables as part of clinical evaluation of every IBD patient at diagnosis [hence the excellent availability of data to score these features in the retrospective chart reviews]. Nonetheless, we are in the process of developing an open access simple web-based calculator and smartphone application that can aid in calculating the algorithm. Finally, the fact that Q_{14} was associated with changing the diagnosis from IBDU to CD may reflect over-liberal use of the term 'backwash ileitis'. A user's guide to the electronic calculator will thus include a definition standardising backwash ileitis as 'short segment of non-stenotic erythema or oedema in the presence of pancolitis including the ileocaecal valve, without granulomata or deep ulcers'. The fact that all other features did not show such an association increases our confidence in the classification scheme. Moreover, the fact that time to change of diagnosis was similar between Crohn's colitis, IBDU, and UC, lends further support of a balanced group classification.

Our study reports the first attempt to scientifically standardise the diagnostic criteria of paediatric IBD, with an emphasis on producing a clearer definition of IBDU, which hitherto has been universally subjective. As recently suggested on clinical grounds,[2] the subtype 'isolated Crohn's colitis' was easily added to the suggested classification scheme to include: small bowel CD, isolated Crohn's colitis, IBDU, atypical UC, and typical UC. These criteria will now

be explored in the ongoing EUROKIDS registry and in future studies for their prognostic implication.

Conflict of Interest

DW received speaker's fees and travel support from MSD and Abbvie. DT received consultation fees, research grants, royalties, or honoraria from Janssen, Pfizer, HSC, Ferring, MegaPharm, AstraZeneca, Abbvie, MSD, and BMS. SC is member of the following advisory board sponsored by the following pharmaceutical companies: MSD [Develop Registry], Sanofi Aventis, Alfa Wassermann. SB received consultation fees, speaker's fees, or meeting attendance support from AbbVie, Falk-Foundation, MSD, Nestle, Norgine, and Pfrimmer-Nutricia. JE received speaker`s s from MSD and Abbvie; payments for scientific advisory committees for Janssen and Abbvie; research support from MSD and Janssen. SK received speaker's fees from MSD and Abbvie, meeting attendance support from Hospira, and unrestricted grant delivered to hospital from Abbvie, Hospira, MSD, Pharmas, and Falk. AP received speaker's fees from MSD and AbbVie as well as consultation fees from Nestle. RR has received speaker's fees and travel support and has participated in medical board meetings with MSD Immunology, Abbvie, Nestle, and Takeda.

Author Contributions

LB-S: acquisition of data; assembly, analysis and interpretation of data; drafting of the manuscript; and necessary revisions. DT: study concept and design; study supervision; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; and approval of the final version. DMZ, AA: statistical analysis; interpretation of data; critical revision of the manuscript; and approval of the final version. SC, FLC, DW, ILa, LY, SPP, CR, SK, SB, AP, JCE, RKR: acquisition of data; critical revision of the manuscript; and approval of the final version.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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