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Appraisal of the PIBD-classes Criteria: A Multicentre Validation

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Abstract

Introduction: The PIBD-classes criteria were developed to standardise the classification of children with inflammatory bowel disease [IBD], from Crohn's disease [CD], through IBD-unclassified [IBD-U], to typical ulcerative colitis [UC]. We aimed to further validate the criteria and to explore possible modifications.

Methods: This was a multicentre retrospective cohort study of children diagnosed with IBD with at least 1 year of follow-up. Clinical, radiological, endoscopic, and histological data were recorded at diagnosis and latest follow-up, as well as the 23 items of the PIBD-classes criteria. The PIBD-classes criteria were assessed for redundant items, and a simplified algorithm was proposed and validated on the original derivation cohort from which the PIBD-classes algorithm was derived.

Results: Of the 184 included children [age at diagnosis 13 ± 3 years, 55% males], 122 [66%] were diagnosed by the physician with CD, 17 [9%] with IBD-U, and 45 [25%] with UC. There was high agreement between physician-assigned and PIBD-classes generated diagnosis for CD [93%; eight patients moved to IBD-U] and for UC [84%; six moved to IBD-U and one to CD]. A simplified version of the algorithm with only 19 items is suggested, with comparable performance to the original algorithm [81% sensitivity and 81% specificity vs 78% and 83% for UC; and 79% and 95% vs 80% and 95% for CD, respectively].

Conclusions: The PIBD-classes algorithm is a useful tool to facilitate standardised objective classification of IBD subtypes in children. A modified version of the PIBD-classes maintains accuracy of classification with a simplified algorithm.

Key Words: IBD-unclassified, classification, paediatric

1. Introduction

Paediatric inflammatory bowel disease [IBD] is traditionally classified into three subtypes: Crohn's disease [CD], ulcerative colitis [UC], and IBD type unclassified [IBD-U].[1] IBD-U refers to patients with IBD limited to the colon, with features that make the differentiation between UC and CD uncertain even after a complete work-up.[2] In the course of follow-up, some IBD-U patients are reclassified as either UC or CD, but as many as 77% maintain the diagnosis of

IBD-U.[3,4] This suggests that IBD-U is not a classification of uncertainty but likely represents an intermediate disease phenotype on the spectrum between CD and typical UC. Ample genetic, serological, immunological and clinical data support this conclusion.[5,6]

The historical lack of an accurate classification system often leads to overuse or misuse of the term IBD-U. In an attempt to standardise classification, and as a diagnostic aid to the physician, the Pediatric IBD Porto group of ESPGHAN developed the PIBD-classes criteria to classify IBD as CD, isolated colonic CD, typical UC, atypical UC, or IBD-U,[7,8] with atypical UC describing features not characteristic of classic UC, yet common enough in UC to preclude a diagnosis of CD. The scoring system consists of 23 features of IBD divided into three classes: features incompatible with UC [class 1], features rarely found in UC [prevalence <5%; class 2], and features uncommon in UC [prevalence 5–10%; class 3]; see Table 2a in section 3.2. A simple algorithm classifies the IBD subtypes based on numbers of features in each class [Figure 1a].[7] The PIBD-classes criteria were based on a systematic review of the literature and validated on a large retrospective multicentre cohort of children with colonic IBD, from the Porto group.[7] Following the original publication, the authors made minor modifications to the PIBD-classes algorithm to ensure that the differentiation between isolated colonic CD and small bowel CD is clearer [Figure 1b].

To ensure generalisation, it is well accepted that diagnostic classifications should be validated independently on an external cohort, especially in this case since the initial derivation cohorts included only colonic IBD, assuming that patients with small bowel disease are obviously categorised as CD. Furthermore, the slight modifications to the PIBD-classes criteria, although merely textural, should nonetheless also undergo evaluation. We therefore aimed to externally validate the PIBD-classes criteria in a cohort of children with all IBD subtypes. We also aimed to appraise the criteria for redundant items and refinement if required.

2. Methods

This was a multicentre retrospective cohort study involving two centres in Israel and one in Canada. Children 2–18 years of age, diagnosed with IBD with at least 1 year of follow-up, were identified by the local electronic databases. Demographic, clinical, radiological, biochemical, endoscopic and histological data were collected from the charts at diagnosis and at latest follow-up. Among children in whom ileocolonoscopy was incomplete, small bowel assessment (i.e. computed tomography enterography [CTE], magnetic resonance -enterography [MRE], or wireless capsule endoscopy] were needed within 3 months of diagnosis in order to be included. The PIBD-classes were scored for each patient at time of diagnosis.[7]

The primary outcome was accuracy of the PIBD-classes classification in comparison with physician-assigned diagnosis. The PIBD-classes criteria were assessed for non-contributory or redundant items in an attempt to produce simplified PIBD-classes criteria. The simplified version was then validated on the original Porto group

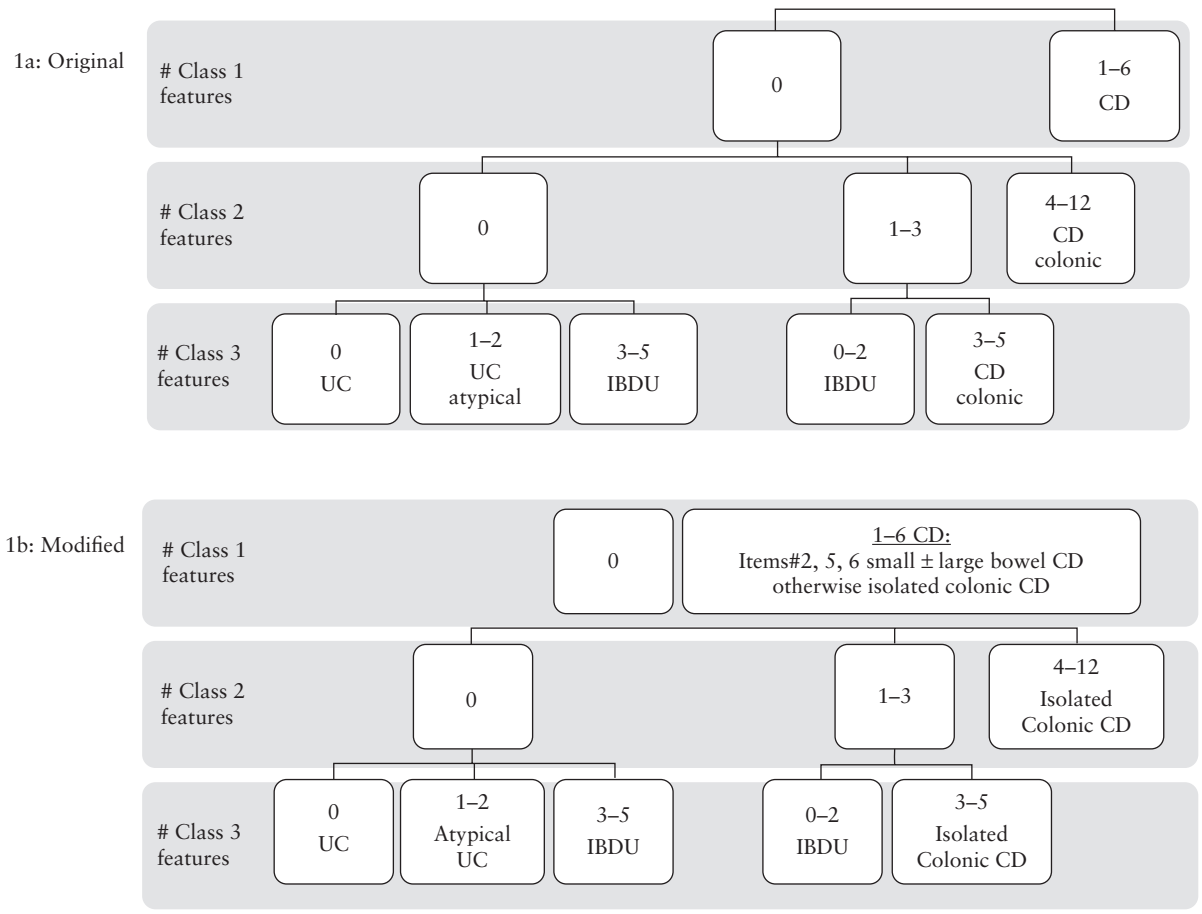

Figure 1. PIBD classes algorithm: [a] original, and [b] slightly modified to include also small bowel CD classification. PIBD, paediatric inflammatory bowel disease;CD, Crohn's disease.

derivation cohort of 749 children with UC, Crohn's colitis, and IBD-U, from which the PIBD-classes algorithm was derived.[7]

2.1. Statistics

Descriptive data are presented as means ± standard deviation, or medians (interquartile range [IQR]), as appropriate for the distribution normality. Unpaired categorical data were compared using χ^2 or Fisher's exact test as appropriate. Unpaired Student's -test or Wilcoxon rank sum test were used to compare continuous variables. Statistical analyses were performed using SPSS [IBM SPSS Statistics for Windows, Version 21.0., Armonk, NY] with p <0.05 taken as the significance threshold. This study was approved by each of the centres' medical ethics review board.

3. Results

A total of 184 patients were included, of whom 122 [66%] were diagnosed by the physician with CD, 45 [25%] with UC, and 17 [9%] with IBD-U [Table 1]. Patients with UC were significantly younger than those with CD [p = 0.016] and IBD-U [p = 0.02] [Table 1]. As per the eligibility criteria, all included children had at least 1 year of follow-up, with median follow-up of 2 years [IQR 1.4–2.9].

In this real-life cohort, ileal intubation was achieved in 151 [82%] patients, and all children in whom this was not achieved underwent small bowel imaging. There was no association between ileal intubation rate and physician-assigned diagnostic classification [data not shown]. Of the total cohort, 150 [82%] patients underwent MRE assessment, three [2%] underwent CTE, four [2%] wireless capsule endoscopy, and only 27 [15%] did not undergo small bowel imaging [all of whom had complete ileocolonoscopy] of whom 19 [70%] were classified as UC.

Throughout follow-up, colonoscopy was repeated in 81 [44%] patients, oesophagogastroduodenoscopy [EGD] in 43 [23%], and small bowel imaging in 36 [20%]. Repeat colonoscopy was more frequent in IBD-U [71%] than CD [39%; p = 0.01] with a similar trend in UC [46%; p = 0.08].

3.1. Concordance of PIBD-classes criteria with physician-assigned classification

By the PIBD-classes criteria, 121 [66%] had CD (of whom 17 [9% of the entire cohort] had isolated colonic CD), 22 [12%] had IBD-U, and 41 [22%] UC (of whom 14 [8% of the entire cohort] had atypical UC). There was high agreement between physician-assigned and PIBD-classes-assigned classification at baseline for both CD [93% agreement, with eight patients reclassified as IBD-U] and for UC [84% agreement, with six patients reclassified as IBD-U and one as CD] [Figure 2]. Of the 17 children classified as IBD-U by the physician, nine [53%] were assigned a different classification by the PIBD-classes criteria: two as atypical UC, one as UC, three as CD, and three as colonic CD.

Reassuringly, all patients with any macroscopic oesophageal finding besides non-specific erythema were classified as CD by both the physician and by the PIBD-criteria. Similarly, all linear ulcerations in the upper gastrointestinal tract [UGI] were classified by both as CD. Less specific findings such as erythema, nodularity, and small aphthous erosions were identified also in patients with physician-classified UC and IBD-U, supporting the rationale of the corresponding 'softer' items in the PIBD-classes criteria [Supplementary Table 1, available as Supplementary data at *ECCO-JCC* online].

The initial physician's diagnosis was revised at the latest follow-up in 10 [5%] patients. Of those, the diagnosis was revised in seven IBD-U patients [five revised to UC and two to CD] and three UC patients [all revised to IBD-U]. None of the CD patients were reclassified throughout follow-up.

In half [50%], the follow-up diagnosis supported the initial classification of the PIBD-classes [Figure 3].

Table 1. Baseline patient characteristics (frequency [%], mean ± SD [standard deviation] or median interquartile range [IQR] are presented as appropriate).

	Total [n = 184]	**CD** [n = 122]	**UC** [n = 45]	**IBD-U** [n = 17]
Male	102 [55%]	72 [59%]	22 [49%]	8 [47%]
Age at diagnosis [years]	12.8 ± 3.2	13.2 ± 2.6	11.5 ± 4.3	13.6 ± 2.4
Follow-up [years]	2.1 [1.4–2.9]	2.0 [1.4–2.9]	2.3 [1.5–3.0]	2.0 [1.5–2.5]
Disease extent		L1 48 [39%]	E1 4 [9%]	E1 0 [0%]
		L2 9 [7%]	E2 9 [20%]	E2 0 [0%]
		L3 63 [52%]	E3 7 [16%]	E3 4 [24%]
		L4a 41 [34%]	E4 25 [56%]	E4 13 [76%]
		L4b 6 [5%]		
		L4a+b 8 [7%]		
Baseline PGA				
Remission	0 [0%]	0 [0%]	0 [0%]	0 [0%]
Mild	41 [22%]	31 [26%]	8 [18%]	2 [12%]
Moderate	89 [49%]	59 [48%]	23 [51%]	7 [41%]
Severe	54 [29%]	32 [26%]	14 [31%]	8 [47%]
Treatment at diagnosis				
EEN		74 [61%]	1 [2%]	3 [18%]
Corticosteroids		24 [20%]	21 [47%]	12 [71%]
5ASA		13 [11%]	41 [91%]	14 [82%]
Immunomodulators		75 [61%]	8 [18%]	5 [29%]
Biologics		29 [24%]	5 [11%]	3 [18%]

CD, Crohn's disease; UC, ulcerative colitis; IBD-U, inflammatory bowel disease unclassified; PGA, physician global assessment; EEN, exclusive enteral nutrition; 5-ASA, 5-aminosalicylic acid.

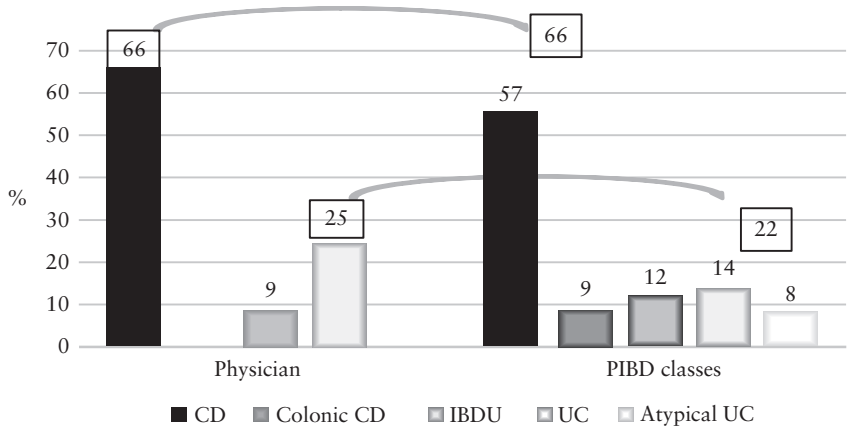

Figure 2. Validity of paediatric inflammatory bowel disease [PIBD] classes criteria.

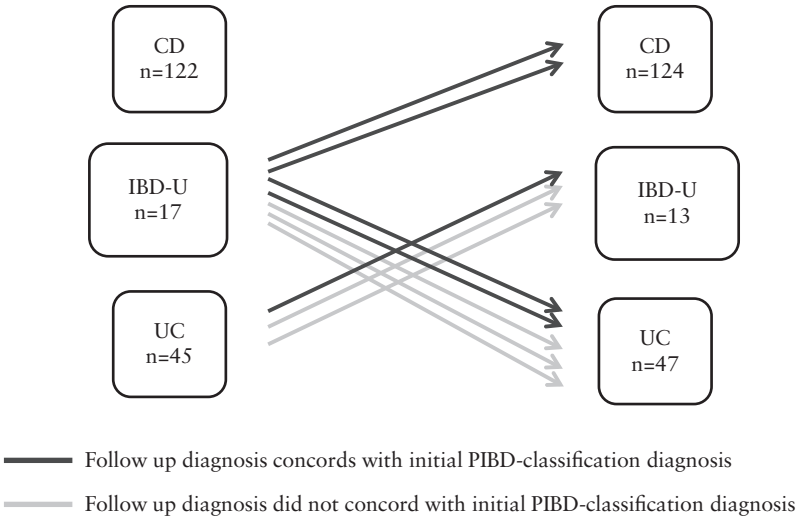

Figure 3. Change of physician-assigned diagnosis at last follow-up and concordance with initial paediatric inflammatory bowel disease [PIBD]classes generated diagnosis.

3.2. Simplifying the PIBD-classes criteria

All 23 items in the PIBD-classes criteria featured at least once in our cohort, but the prevalences of the items and their relative contribution varied. Item #4 in class 1 [ie 'large inflamed perianal skin tags'] featured in 7/122 [6%] children with CD but it was not the sole class 1 item in any of these patients, hence its redundancy for the classification of CD.

Four items in class 2 had low frequency of endorsement. Item #14 [ie 'ileitis, otherwise compatible with backwash ileitis, but in the presence of only mild inflammation in the caecum'] and item #17 ['severe scalloping of the stomach or duodenum, not explained by other causes'] did not feature among patients with physician-assigned UC or IBD-U. Indeed, both items did not contribute to the classification of CD patients in the 17 children in whom they were endorsed, and thus could be excluded.

In addition to low-frequency items, we explored also items that are vaguely defined. Item #12 [ie 'small and not deep ulcers, including aphthous ulcerations, anywhere in the small bowel, duodenum and esophagus, excluding stomach and colon, not explained by other causes'] and #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'], both class 2 items, are somewhat similar but in different bowel locations. Among all patients with PIBD-classes classification of UC or IBD-U, none had both items endorsed, and no patient changed classification based on the presence of one or the other. The combined score of these two items did not contribute to the classification in all patients in which both were endorsed [ie 20 patients with CD]. Hence in this cohort, items #12 and #13 can be merged as 'any small and not deep ulcers in the small bowel and esophagus, or ≥5 in stomach or colon, with background normal mucosa, not explained by other causes', without affecting the classification.

Two other class 2 items, #17 ['severe scalloping of the stomach and duodenum, not explained by other causes'] and #18 ['deep ulcerations or severe cobblestoning of stomach, not explained by other causes'] are similar in nature but were not both endorsed in any one patient. Item #18 was present in three patients with physician-assigned UC, with this feature classifying these patients as IBD-U by the PIBD-classes criteria. However, as described above, item #17 did not contribute to classification in this cohort and may be removed or effectively merged into item #18 as a single item 'deep ulcerations or severe cobblestoning of stomach, or scalloping of duodenum, not explained by other causes'.

The suggested simplified PIBD-classes has 19 items [five in class 1, nine in class 2 and five in class 3] [Table 2b]. Since the

Table 2. PIBD-classes items.

A Original PIBD-classes items		
Class 1	1	At least one well-formed granuloma anywhere in the GI tract, remote from ruptured crypt
	2	At least one of: deep ulcerations; cobblestoning; or stenosis anywhere in the small bowel or UGI tract [excluding stomach][a]
	3	Fistulising disease [internal or perianal]
	4	Large inflamed perianal skin tags
	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
	6	Any ileal inflammation in the presence of normal caecum [ie incompatible with backwash ileitis][b]
Class 2	7	Macroscopically and microscopically normal-appearing skip lesions in untreated patient [excluding rectal sparing and caecal patch]
	8	Complete [macroscopic and microscopic] rectal sparing
	9	Macroscopically normal colon in between inflamed mucosa but with microscopic inflammation [ie relative patchiness]
	10	Significant growth delay [height velocity <minus 2 SD], not explained by other causes [e.g. coeliac disease, prolonged steroids, or growth hormone deficiency]
	11	Transmural inflammation of the colon in the absence of severe colitis
	12	Small and not deep ulcers [including aphthous ulcerations] anywhere in the small bowel, duodenum and oesophagus [excluding stomach and colon] not explained by other causes [eg *H. pylori*, NSAIDs, and coeliac disease][c]
	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 [e.g. *H. pylori* and.NSAIDs]
	14	Ileitis, otherwise compatible with backwash ileitis, but in the presence of only mild inflammation in the caecum[d]
	15	Positive ASCA in the presence of negative pANCA
	16	Reverse gradient of mucosal inflammation (proximal >distal [except rectal sparing])
	17	Severe scalloping of the stomach or duodenum, not explained by other causes [eg coeliac disease and *H. pylori*]
	18	Deep ulcerations [at least one] or severe cobblestoning of stomach not explained by other causes [e.g. *H. pylori*, NSAIDs, coeliac disease]
Class 3	19	Focal chronic duodenitis on histology
	20	Focal active colitis on histology in more than one biopsy
	21	Several [<5] aphthous ulcerations in the colon or in the stomach
	22	Non-bloody diarrhoea
	23	Focal enhanced gastritis on histology
B Proposed simplified PIBD-classes items following validation		
Class 1	1	At least one well-formed granuloma anywhere in the GI tract, remote from ruptured crypt
	2	At least one of: deep ulcerations; cobblestoning; or stenosis anywhere in the small bowel or UGI tract [excluding stomach][e]
	3	Fistulising disease [internal or perianal]
	4	Thickened jejunal or ileal bowel loops on radiology or other evidence of significant small bowel inflammation on capsule endoscopy not compatible with backwash ileitis
	5	Any ileal inflammation in the presence of normal caecum [ie incompatible with backwash ileitis]
Class 2	6	Macroscopically and microscopically normal appearing skip lesions in untreated patient [excluding rectal sparing and caecal patch]
	7	Complete [macroscopic and microscopic] rectal sparing
	8	Macroscopically normal colon in between inflamed mucosa but with microscopic inflammation [ie relative patchiness]
	9	Significant growth delay [height velocity <minus 2 SD], not explained by other causes [e.g. coeliac disease, prolonged steroids, or growth hormone deficiency]
	10	Transmural inflammation of the colon in the absence of severe colitis
	11	Presence of any small and not deep ulcers in small bowel and oesophagus, or ≥5 small and not deep ulcers in stomach or colon, with background normal mucosa, not explained by other causes [.g *H. pylori*, NSAIDs and coeliac disease][f]
	12	Positive ASCA in the presence of negative pANCA
	13	Reverse gradient of mucosal inflammation (proximal >distal [except rectal sparing])
	14	Deep ulcerations or severe cobblestoning of stomach or scalloping of duodenum, not explained by other causes [eg coeliac disease, NSAIDs, *H. pylori*]
Class 3	15	Focal chronic duodenitis on histology
	16	Focal active colitis on histology in more than one biopsy
	17	Several [<5] aphthous ulcerations in the colon or in the stomach
	18	Non-bloody diarrhoea
	19	Focal enhanced gastritis on histology

PIBD, paediatric inflammatory bowel disease; UGI, upper gastrointestinal; SD, standard deviation; NSAID, non-steroidal anti-inflammatory drug; ASCA, anti-*Saccharomyces cerevisiae* antibodies; ANCA, antineutrophil cytoplasmic antibodies.

[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 notdeep, 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.

[e]Deep ulcerations or severe cobblestoning of stomach or duodenum score as item #13; if there are ulcerations in the duodenum or oesophagus which are small and not deep, score as item #11.

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

proposed simplified criteria were developed on our cohort with the aim of achieving identical outcomes as the original, we validated the simplified criteria by applying them to the cohort [*n* = 749] on which the PIBD-classes criteria were originally developed. There was high agreement between the proposed simplified PIBD-classes criteria and the original algorithm, with similar sensitivity and specificity of classification with baseline physician allocation [Table 3 and Figure 4].

Table 3. PIBD class allocation in initial derivation cohort—comparison between original and simplified algorithm.

	Original algorithm *n* [%]	Simplified algorithm *n* [%]
IBDU	241 [32.2]	228 [30.4]
CD	215 [28.7]	210 [28]
UC	147 [19.6]	154 [20.6]
Atypical UC	146 [19.5]	157 [21]

PIBD, paediatric inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; IBD-U, inflammatory bowel disease unclassified.

4. Discussion

The PIBD-classes diagnostic algorithm comprises the first methodologically generated, standardised diagnostic criteria of pediatric IBD, including IBD-U.[7] The algorithm has been generated with regression tree modelling and hypothesis-driven items and assessed against a large cohort of children with colonic IBD. The scoring algorithm

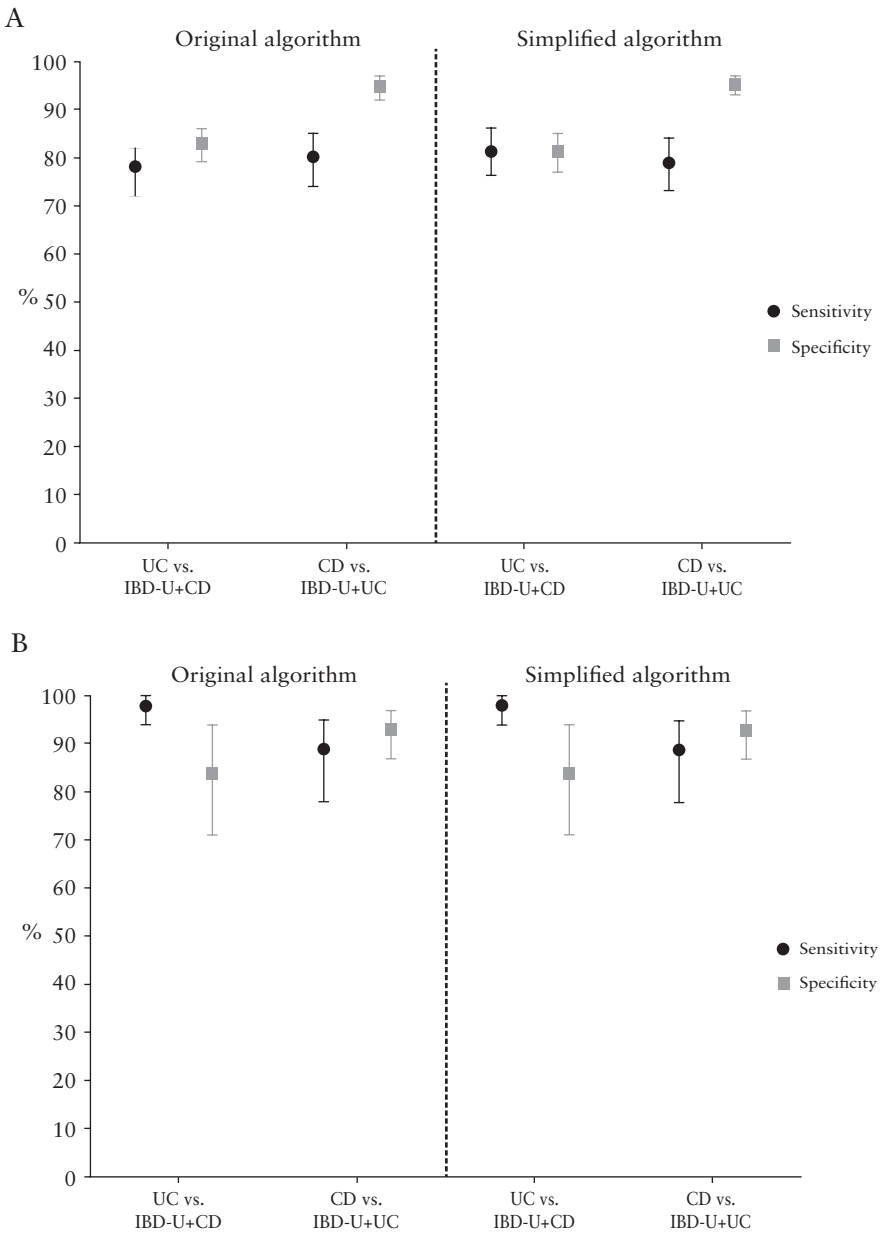

Figure 4. Comparison of sensitivity and specificity [95% CI] of the original PIBD-classes algorithm and the simplified PIBD-classes algorithm on [a] the original PIBD-classes cohort [n = 749], and [b] the validation cohort [n = 184]. CI, confidence interval; PIBD, paediatric inflammatory bowel disease.

demonstrated high sensitivity and specificity in discriminating between CD, colonic CD, atypical UC, typical UC, and IBD-U.

Before the PIBD-classes criteria, the definition of IBD-U lacked a gold standard for comparison, and despite attempts to correlate clinical features with various outcomes, including histological analysis of colectomy specimens,[9] definitions of IBD-U remained fairly arbitrary. In our study, the original PIBD-classes algorithm proved a useful tool to standardise classification of IBD subtypes, with good correlation with physicians-assigned disease subtypes. This is consistent with other data demonstrating high concordance between clinical diagnosis and the PIBD-classes criteria.[9] The prevalence of IBD-U in our cohort was within the lower range of that previously reported in children, suggesting that PIBD-classes managed to minimise the grey undefined zone.[4,5,10–15]

The need for standardisation of IBD subtypes is self-evident for both clinical practice and research purposes. An accurate subclass identification has clinical significance for management and directing judicious repeat investigations in children. Indeed, isolated colonic CD has been described as a unique entity, distinct from both ileocolonic CD and UC in regards to demographics, genetics, microbiome, response to treatment, and surgery rates.[6]

The original algorithm identified a classification of atypical UC, a term recently redefined by the Porto group as the presence of features not characteristic of classic UC but common enough in UC to preclude the diagnosis of CD (eg macroscopic rectal sparing, mild upper gastrointestinal [UGI] involvement, caecal patch, and backwash ileitis).[1] Following the original publication, the authors modified the PIBD-classes algorithm slightly to characterise 'small and large bowel CD' based on class 1 features [Figure 1]. This phenotypic modification makes the algorithm applicable to the entire spectrum of IBD, as a universal modality in IBD research and clinical practice.

As defined, class 1 features are those which are incompatible with UC and are considered indicative of CD. Of note in our cohort, among the 17 patients classified as colonic CD, only three endorsed any class 1 features. This further demonstrates the utility of the PIBD-classes criteria in these less well-defined patients.

We have managed to simplify the criteria by eliminating four items that were redundant in the presence of other inter-related items. In our validation cohort, removing items #4 and #14 and merging of items #12 and #13, and items #17 and #18, did not alter the classification in any patient. Reassuringly, when this modification was validated in the original Porto group cohort, it had similar performance as the original algorithm. Hence, we suggest using the modified PIBD-classes criteria instead of the original, due to its simplified nature while maintaining the original's performance. We anticipate that the algorithm will find a place both in clinical practice and research alike, whereby using this instrument will ensure uniform classification of patients among contributing centres.

Our study has several strengths but it is not without limitations, especially those stemming from its retrospective design. Limited numbers of patients had repeated endoscopic evaluation over time. Some patients [mainly diagnosed with UC] did not undergo small bowel imaging and the ileum was not intubated in others. We elected to retain these patients to ensure a study that mirrors real-life data and applicability of the criteria to everyday practice. To further demonstrate utility of the simplified PIBD-classes criteria, additional validation studies should be considered in adult IBD patients and in different centres internationally.

In conclusion, application of the PIBD-classes criteria could be considered to improve reliability and consistency of IBD subtype classification between physicians and centres. The suggested modifications to the algorithm may potentially provide simpler criteria, further facilitating incorporation of this useful tool into routine practice.

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No funding was provided for this study.

Conflict of Interest

None related to this manuscript.

Author Contributions

OL: study design, data analysis, writing of first draft, approval of final draft. MS, LBS: data collection and data analysis, critical review of manuscript. JCE, RKR: contribution to study design and analysis, critical review of manuscript. EOM, MM, AA, RLZ, ES, AG: data collection, critical review of manuscript. DT: study design, critical review of manuscript, approval of final draft.

Supplementary Data

Supplementary data are available at ECCO-JCC online.

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