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Alimentary Tract

The development of artificial intelligence in the histological diagnosis of Inflammatory Bowel Disease (IBD-AI)

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ABSTRACT

Background: Inflammatory bowel disease (IBD) includes Crohn's Disease (CD) and Ulcerative Colitis (UC). Correct diagnosis requires the identification of precise morphological features such basal plasmacytosis. However, histopathological interpretation can be challenging, and it is subject to high variability.
Aim: The IBD-Artificial Intelligence (AI) project aims at the development of an AI-based evaluation system to support the diagnosis of IBD, semi-automatically quantifying basal plasmacytosis.
Methods: A deep learning model was trained to detect and quantify plasma cells on a public dataset of 4981 annotated images. The model was then tested on an external validation cohort of 356 intestinal biopsies of CD, UC and healthy controls. AI diagnostic performance was calculated compared to human gold standard.
Results: The system correctly found that CD and UC samples had a greater prevalence of basal plasma cells with mean number of PCs within ROIs of 38.22 (95 % CI: 31.73, 49.04) for CD, 55.16 (46.57, 65.93) for UC, and 17.25 (CI: 12.17, 27.05) for controls. Overall, OR=4.968 (CI: 1.835, 14.638) was found for IBD compared to normal mucosa (CD: +59 %; UC: +129 %). Additionally, as expected, UC samples were found to have more plasma cells in colon than CD cases.
Conclusion: Our model accurately replicated human assessment of basal plasmacytosis, underscoring the value of AI models as a potential aid IBD diagnosis.

1. Introduction

Inflammatory bowel disease (IBD) includes two main conditions, Crohn's disease (CD) and Ulcerative colitis (UC). Due to the wide overlap of symptoms between the two, the definitive diagnosis requires histological confirmation which is often challenging. Misdiagnosis occurs in up to 10 % of cases [1] and delays due to inconclusive histological examinations have a considerable impact on patients' quality of life. Moreover, to acquire the necessary skills to confirm the diagnosis of CD or UC takes years of pathology training followed by additional specialization in gastrointestinal pathology and particularly IBD. As a result, this expertise is often unavailable in smaller centres or resource-poor settings.

Recent advances in digital pathology and machine learning techniques have led to a growing interest in leveraging Artificial Intelligence (AI) for computational analysis of whole slide images [2]. Conventional microscopic analysis relies on subjective human evaluation and individual expertise, on the contrary AI-based digital analysis allows quantitative measurement of tissue morphometry overcoming subjectivity and reducing assessment time.

AI-based analysis of digitalized slides through deep learning methods has shown promising results in various fields of medicine [3]. Deep learning techniques like convolutional neural networks have shown promise in automatically identifying complex patterns, often outperforming traditional machine learning algorithms based on predefined features. Most studies of AI in IBD have focused on

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assessment of disease severity in endoscopy and histology [4-10] while relatively fewer addressed the challenge of diagnosis [11,12] and, to the best of our knowledge, only one did so through histology [13].

Several histological features concur to the diagnosis of IBD [14,15], among which basal plasmacytosis and architectural changes are the most relevant [15]. Indeed, presence of basal plasmacytosis in 3 or more colonic segments results in a probability of IBD greater than 80 % [16] and the probability increases further if more segments display basal plasmacytosis. The assessment of basal plasmacytosis requires the identification of plasma cells (PCs) located beneath the glands, particularly between the colonic crypts and the muscularis mucosae.

In the IBD-AI project, we aimed to leverage convolutional neural networks to automatically identify basal plasmacytosis in whole slide images (WSIs) of colon biopsies from patients with IBD and healthy controls. Secondly, we explored the differences in the automated detection of basal plasmacytosis between types of IBD, CD and UC. Ultimately, our goal is to assess whether AI-driven diagnostics can support and potentially enhance human histopathological assessment of IBD.

2. Material and methods

2.1. Model training datasets

Deep learning models were trained on a subset of 24,861 PC nuclei from the Colon Nuclei Identification and Counting (CoNIC) Challenge dataset [17]. This dataset is completely independent from the biopsies collected by the investigator and used for the testing of the model. For this task we utilized 4981 haematoxylin and eosin (H&E)- stained histology images of size 256 × 256 pixel, extracted at 20x magnification (0.5 μm per pixel) from six different collections of colonic biopsies. The CoNIC dataset originally includes annotations for six cell categories: epithelial, lymphocyte, PC, eosinophil, neutrophil, and connective cells. Given that the aim of our study is to assess basal plasmacytosis, we restricted the model training considering only the annotations for PCs.

2.2. IBD-AI dataset

The IBD-AI dataset comprised 356 biopsies from 52 patients (24 CD, 19 UC, 9 normal mucosa) followed at Spedali Civili in Brescia, Italy. The IBD patients included had all grades of disease severity, with the majority displaying at least some endoscopic activity. Full demographics and clinical characteristics are reported in Table 1. As recommended by ECCO's guidelines [15], for each patient multiple locations were biopsied with two mucosal bites per segment. However, the number of segments biopsied varied slightly between patients as not all of them underwent full colonoscopy and ileum was not routinely biopsied in UC.

Because the location of PCs is crucial to the diagnosis (i.e. PCs in the upper regions of the epithelium are generally not indicative of IBD contrary to those beneath the glands) biopsies must be oriented so that anatomical structures can be visualized.

The samples used for the study were correctly oriented on acetate cellulose filters (Bio-Optica, Milan, Italy) and then fixed in formalin and embedded in paraffin [18].

The biopsies from the same patients are placed next to each other, stained with H&E and digitally scanned at 40x magnification (0.25 μm per pixel) using Aperio AT2 scanner (Leica Biosystems). Therefore, each WSI includes multiple biopsies of a single patient, organized in two or more strips, where each strip corresponds to a different section of the biopsies. These strips display a minimum of 3 and a maximum of 14 biopsy sections, in most IBD cases 12 (2 biopsies in each of the 6 recommended locations). For the subsequent analysis, a single strip per case was selected, based on the integrity of both the sampling and scanning processes, resulting in a total of 356 biopsies. For the 9 control cases, a distinction between segment locations was not available.

2.3. The IBD-AI pipeline

The IBD-AI pipeline (Fig. 1) is composed of four main steps: (1) the automated extraction of sub-image (tiles) from the collection of WSIs; (2) the application of deep learning models trained for PC identification; (3) the segmentation of regions of interest (ROIs), where the presence of PCs holds diagnostic significance; and (4) the quantification of PC populations within ROIs. This procedure results in a count distribution for a strip set of biopsies in a WSI, thereby facilitating subsequent diagnostic assessments.

2.3.1. Tile extraction

Each biopsy was independently processed for tile extraction [19] (Fig. 1A, details in Supplementary material). Non-overlapping tiles were extracted at a magnification 40x (0.25 μm/px) with size 512 × 512 pixels, discarding tiles with less than 5 % of tissue. In case of multiple strips for a single WSI, we selected the highest quality strip (no artifacts or out-of-focus regions) for tile extraction. A total of 90,893 tiles (Table 2) were extracted from the dataset for PC detection.

2.3.2. Deep learning network for plasma cell segmentation

We applied the Deep Learning StarDist model as the backbone of our PC segmentation procedure on H&E-stained images. StarDist (winner of the CoNIC challenge) [17,20] is a deep learning model developed for segmenting objects with star-convex polygons, thus optimal for cell nuclei segmentation in microscopy images. The StarDist model was trained on PC annotations from the CoNIC dataset, applying a train-validation split to reserve 10 % of the dataset as previously unseen data for validation, and compared with the alternative deep learning model Cerberus [21,22] (details in the Supplementary material). The evaluation of deep learning models on the CoNIC validation set is summarized in Supplementary material Table S1.

The StarDist model achieved a superior performance across multiple metrics. Additionally, a preliminary visual inspection on a single WSI by qualified pathologists confirmed the model's accuracy in identifying approximately 90 % of PCs. Therefore, the StarDist model was selected as the preferred methodology for PC detection on the IBD-AI dataset, which was kept unseen during the training phase.

2.3.3. Demarcation of the region of interest in the AI-IBD dataset

To quantify basal plasmacytosis, the count of PCs had to be restricted to the areas under the intestinal crypts. Correspondingly, ROIs where manually annotated by experienced pathologists on each biopsy of the collection (see Fig. 1C). Fig. 2 shows a WSI, its corresponding subdivision in biopsies color-coded according to its tissue of origin, along with the ROIs annotated for each biopsy.

2.3.4. Quantification of plasma cells

The quantification of PCs within each biopsy was accomplished by aggregating the counts from each of its corresponding regions of interest (ROIs). Biopsies with no ROIs were excluded from the analysis. Statistical evaluations were conducted utilizing the R programming environment (R version 4.2.3) [23]. In particular, we first estimated the PC count regression model based on the diagnosis. Given that the number of PCs in the different tissue samples had a variance considerably higher than the mean (mean: 46, variance: 3271), a negative binomial model was considered to better account

Table 1
Demographics and clinical characteristics of IBD patents.

Features	Total	Crohn's disease				Ulcerative Colitis			
N	43	24				19			
Female (%)	21 (48 %)	12 (50 %)				9 (47 %)			
Age, mean (range)	35.9 (9–67)	32.3 (9–67)				40.2 (22–62)			
Location / Extension (Montreal Classification)		L1		4					
		L2		2		E1		4	
		L3		12		E2		6	
		L2+L4		1		E3		6	
		L3+L4		1		NA		3	
		NA		4					
Histological Activity Index		PHRI		Nancy		PHRI		Nancy	
		0	6	0	6	0	4	0	4
		1	11	1	11	1	5	1	4
		2	2	2	5	2	1	2	5
		3	4	3	1	3	5	3	2
		4	1	4	1	4	4	4	4
Treatment		None		7					
		5ASA		3		5ASA+steroid		6	
		Azathioprine		1		5ASA		9	
		Infliximab		1		AZA + steroid		1	
		Adalimumab		4		Steroid		1	
		vedolizumab		1		Adalimumab		2	
		NA		7					

NA, not available; PHRI, PICaSSO Histologic Remission Index; Nancy, Nancy Histological Index; 5ASA mesalazine; AZA, azathioprine; L1, ileal; L2, colic; L3, ileo-colic; L4, upper gastrointestinal tract; E1, proctitis; E2, left-sided colitis; E3, pancolitis.

Table 2
Summary of WSIs and corresponding number of extracted tiles per diagnosis.

Diagnosis	Number of WSIs	Number of extracted tiles			
		Total	Mean	Min	Max
UC	19	39,844	1992	981	3384
CD	24	44,713	1789	561	3489
Normal	9	6336	634	221	1162
Total	52	90,893	1653	221	3489

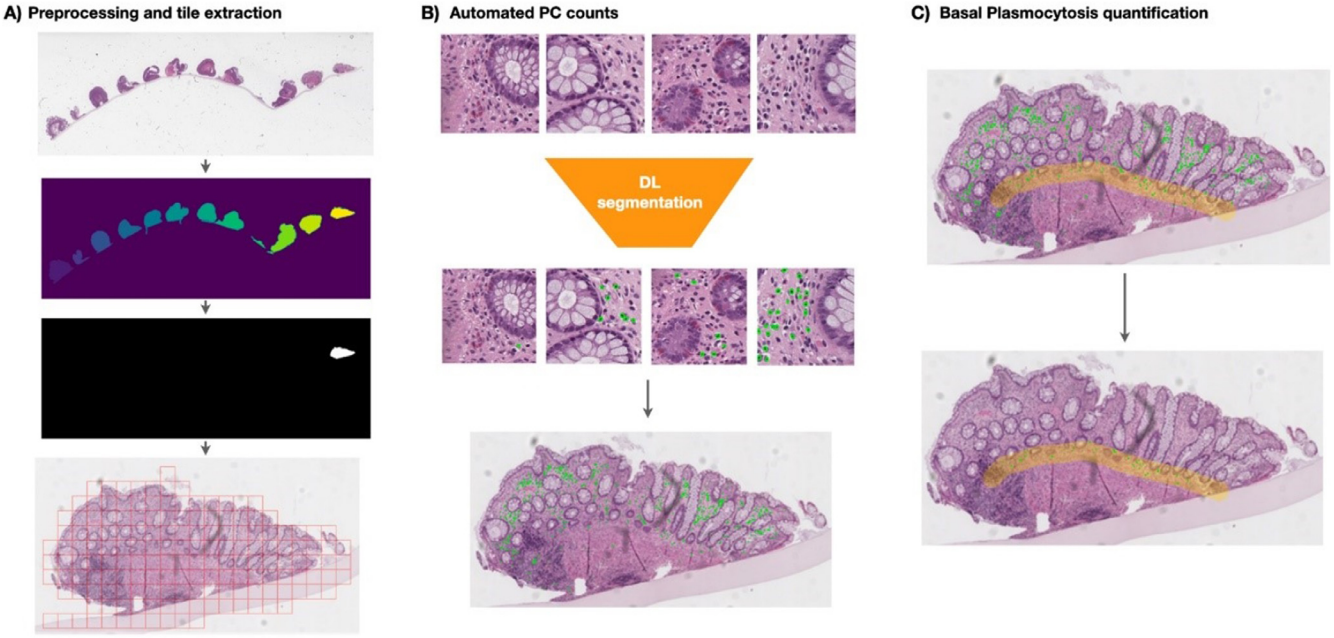

Fig. 1. Overview of the IBD-AI pipeline. A) WSI preprocessing and extraction of tiles from a single biopsy; B) Automated plasma cell (PC) segmentation with deep learning model (DL); C) Detection of plasma cells (green) within annotated ROIs (yellow) for basal plasmacytosis quantification. The pipeline is repeated for each biopsy on a WSI. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

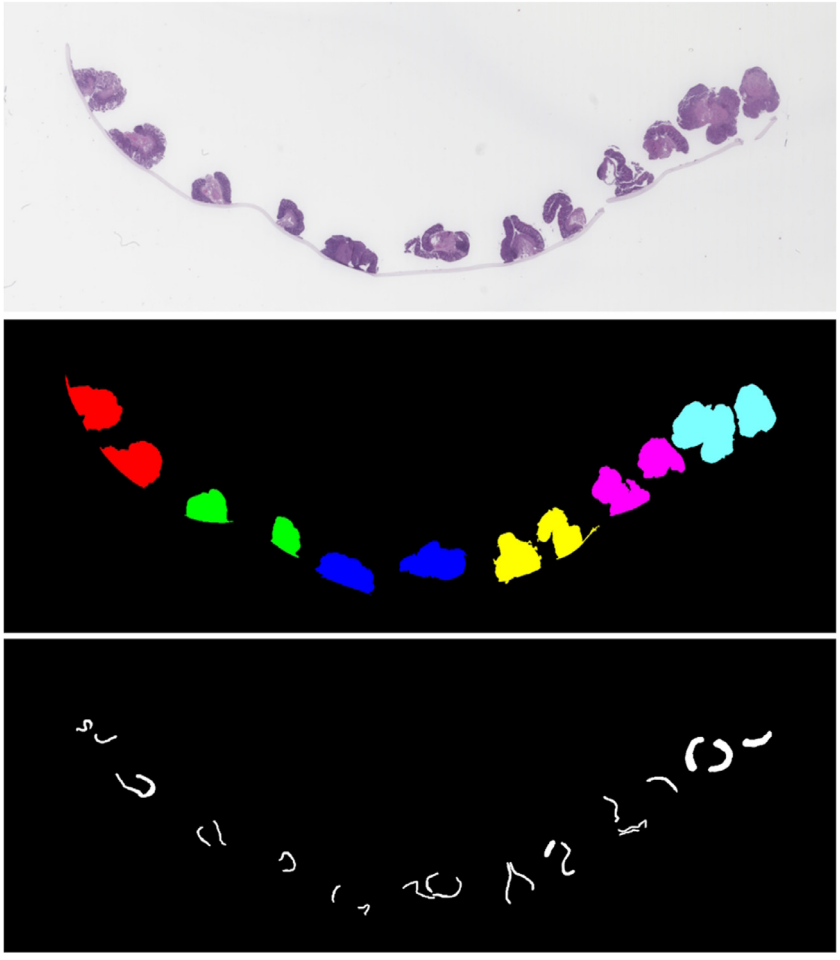

Fig. 2. (top) A WSI of the IBD-AI dataset; (middle) biopsy segmentation coloured by tissue of origin; (bottom) extraction of annotated ROIs. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

for overdispersion, with PC count as dependent variable and diagnosis for independent variable.

Details about the statistical model are available in Supplementary Material (B. Negative binomial regression model fit statistics). We then used a second model negative binomial regression to examine variations in PC counts among different tissue types, focusing on CD and UC cases.

3. Results

The number of WSIs and included biopsies varied for the three diagnoses: CD, UC, and Normal tissue. Specifically, there were 24 WSIs and 147 biopsies for CD, 19 WSIs and 185 biopsies for UC, and 9 WSIs and 24 biopsies for Normal tissue. On average, there were 312.25 PCs detected within ROIs with an average of 45.61 PCs per single biopsy. When broken down by diagnosis, the mean number of PCs within ROIs was 38.22 (CI: 31.73, 49.04) for CD, 55.16 (46.57, 65.93) for UC, and 17.25 (CI: 12.17, 27.05) for controls. The values include 95 % confidence intervals computed with the Adjusted Bootstrap Percentile (BCa) method. Overall, the PC count from the AI method has an odds ratio OR=4.968 (CI: 1.835, 14.638) for IBD versus normal tissues, with OR= 3.891 (CI: 1.396, 12.535) restricted to the CD diagnosis, and OR= 6.098 (CI: 2.143, 16.413) for UC.

Table 3 and Fig. 3 illustrate the distribution of PCs per biopsy, categorized by diagnosis and tissue of origin.

To examine the association between the number of PCs per biopsy, IBD type and tissue location, a negative binomial regression model was used. Presence or absence of IBD was found to significantly influence the number of PCs ($p < 0.001$). Both CD and UC exhibit a significantly more PC than the controls, in particular CD had 122 % more ($p < 0.001$) and UC 220 % more ($p < 0.001$). Moreover, a 44 % more PCs were found in UC over CD cases ($p < 0.01$).

Overall, the colon had more PC than the ileum, although only some comparisons were statistically significant. Significant differences in PC counts are found for transverse colon compared to the ileum (71 % more in the colon than in ileum; $p < 0.05$). Additionally, both the ascending and descending colon displayed more PC than the ileum, with a delta of 50 % and 44 % respectively, approaching statistical significance (p-values of 0.057 and 0.084, respectively). These findings are consistent with the differences in PC distribution in the colon and the small intestine seen in clinical practice [16].

4. Discussion

Histology serves as the gold standard for IBD diagnosis [24], yet the accurate interpretation of multiple features lies with individual pathologists. The present study aims to demonstrate the feasibility of an AI system supporting the histological diagnosis of IBD by detecting basal plasmacytosis.

Basal plasmacytosis, defined as the presence of three or more PCs in the mucosal lamina propria between the crypt base and the muscularis mucosae, holds significant diagnostic value in IBD [16]. It can be observed in over 40 % of patients within two weeks of symptom onset, and in about 60 % of patients after four

Table 3
Distribution of plasma cells within annotated ROIs per IBD type and location. Counts are reported as median number of plasma cells and interquartile range; n: total number of biopsies.

TISSUE								
	Ileum	Valve	Cecum	Ascendant	Transverse	Descendant	Sigmoid	Rectum
CD	27.0 (12.50, 38.50) $n = 19$	38.5 (27.25, 49.75) $n = 2$	38 (27.00, 41.00) $n = 9$	34.5 (13.25, 55.50) $n = 26$	28 (7.75, 46.75) $n = 24$	21 (12.00, 45.50) $n = 27$	10.5 (7.00, 32.75) $n = 20$	20 (8.75, 34.75) $n = 20$
UC	20.5 (8.50, 45.75) $n = 20$	NA	NA	47 (25.00, 76.00) $n = 33$	39 (14.75, 67.50) $n = 36$	34 (11.00, 77.00) $n = 33$	31 (16.50, 56.75) $n = 32$	29 (18.50, 60.00) $n = 31$
Controls	13.5 (6.75, 21.00) $n = 24$							

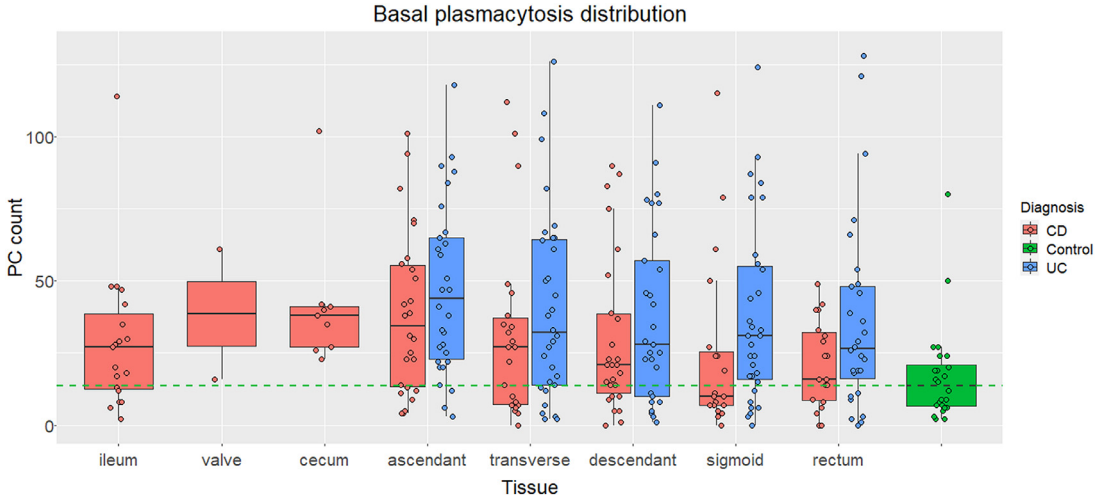

Fig. 3. Distribution of the number of plasma cells in the biopsies, per tissue of origin and coloured by diagnosis (CD: Crohn's disease, UC: Ulcerative Colitis). The dashed green line represents the median for control group. *p*-values are derived from a ANOVA (Type II) test. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

weeks, initially displaying a focal distribution before becoming diffuse [24,25]. As one of the earliest histological features of IBD, basal plasmacytosis has a high predictive value and it is useful to distinguish IBD from other non-IBD colitis [26]. Our study, using oriented biopsies, has developed a first deep-learning-based solution for the detection and quantification of basal plasmacytosis in histopathological images of IBD and control samples. By selecting the lamina area at the base of the crypts, pathologists can employ the model to either support or rule out an IBD diagnosis. The system subsequently identifies PCs within the specified region.

The use of basal ROIs supports the model to differentiate between CD and UC, which exhibit unique patterns of PC distribution in the colon. The results are consistent with the expected distribution of PCs in tissue samples, indicating a higher count in patients with CD and UC [24,26].

This concordance underscores the potential of AI technologies in digital pathology enriched with anatomical information. Specifically, the automatic detection and quantification of PCs offers a reliable, less labour-intensive and time-consuming alternative to traditional methods, streamlining the differential diagnosis of IBD in clinical settings. Such a tool can expedite assessment, provide an initial screening for IBD and support less experienced physicians in the field.

The use of a training dataset (CoNIC) unrelated to the testing cohort (histological slides from Brescia's hospital) is a major strength of our study. The complete separation mitigates the risk of model overfitting due to data leakage, a major limitation of AI systems in Digital Pathology [27]. Furthermore, while not yet fully automated, the location-sensitive detection of PCs is a first-in-kind in the AI landscape of IBD and proves the ability of the system to focus attention on areas of greatest interest. On the other hand, the main limitation of the study is the small patient population, partially compensated by the relatively large number of biopsies taken from these patients, providing an adequate sample size for per-biopsy analysis.

Our work serves as a pilot intended to demonstrate how AI can support a crucial step in the complex process of diagnosing IBD. Future work will be needed to validate the system in other larger cohorts and to implement other models to assess additional features of IBD . In a stepwise approach we hope to integrate multiple models, progressively, thereby enhancing support for pathologist and ultimately offering a comprehensive IBD assessment, encompassing diagnosis, inflammation severity grading, and dysplasia detection.

To date, most AI applications on IBD pathology have focused on grading UC disease activity, standardizing its assessment and, providing stratification of clinical outcome [4,5,28]. The role of histology in establishing the correct diagnosis in IBD is arguably more significant but has received comparably far less attention [11-13]. Moreover, accurate diagnosis has a greater impact on patient care than severity grading and research on it should be prioritized. The main reason for the lag of IBD-diagnostic AIs is the complexity of the multiple features concurring to the diagnosis. By breaking down this challenge into smaller tasks, such as the identification and quantification of basal plasmacytosis, we aim to pave the way to the automation of the full diagnostic and assessment process. Although progress in this setting has been encouraging, the implications, including legal ones, of misdiagnosis are important hence a more cautions roll out of diagnostic models is expected. In particu-

lar, large and heterogeneous cohorts are needed to ensure generalizability across settings before the diagnostic models can be safely implemented.

In conclusion the proposed deep learning model enables: a) automated identification of PCs; b) quantification of PCs at base of the crypts (basal plasmacytosis); c) histological diagnosis of IBD; d) the differential diagnosis between CD and UC based on the intestinal/colic tract with highest number of PCs.

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Ethics approval

The study was approved by Brescia Ethics Committee (NP 5126-STUDIO MICI-AI)

Conflict of interest

None.

Author contribution

Cesare Furlanello: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Nicole Bussola:** Methodology, Data curation, Writing – original draft, Formal analysis. **Nicolò Merzi:** Methodology, Data curation, Writing – original draft. **Giovanni Pievani Trapletti:** Methodology, Data curation, Writing – original draft. **Moris Cadei:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Rachele Del Sordo:** Methodology, Writing – original draft. **Angelo Sidoni:** Methodology, Writing – original draft. **Chiara Ricci:** Methodology, Writing – original draft. **Francesco Lanzarotto:** Methodology, Writing – original draft. **Tommaso Lorenzo Parigi:** Methodology, Writing – original draft. **Vincenzo Villanacci:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2024.05.033.

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