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ABOUT COVER

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AIMS AND SCOPE

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RESPONSIBLE EDITORS FOR THIS ISSUE

Artificial intelligence applications in inflammatory bowel disease: Emerging technologies and future directions

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Abstract

Inflammatory bowel disease (IBD) is a complex and multifaceted disorder of the gastrointestinal tract that is increasing in incidence worldwide and associated with significant morbidity. The rapid accumulation of large datasets from electronic health records, high-definition multi-omics (including genomics, proteomics, transcriptomics, and metagenomics), and imaging modalities (endoscopy and endomicroscopy) have provided powerful tools to unravel novel mechanistic insights and help address unmet clinical needs in IBD. Although the application of artificial intelligence (AI) methods has facilitated the analysis, integration, and interpretation of large datasets in IBD, significant heterogeneity in AI methods, datasets, and clinical outcomes and the need for unbiased prospective validations studies are current barriers to incorporation of AI into clinical practice. The purpose of this review is to summarize the most recent advances in the application of AI and machine learning technologies in the diagnosis and risk prediction, assessment of disease severity, and prediction of clinical outcomes in patients with IBD.

Key Words: Artificial intelligence; Machine learning; Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Clinical outcomes

Core Tip: The application of artificial intelligence (AI) in the field of inflammatory bowel disease (IBD) has grown significantly in the past decade. AI has been used to analyze genomic datasets, construct IBD risk prediction models, and increase IBD diagnosis precision. Machine learning has been used to analyze endoscopic images to

improve disease severity grading. AI has enabled the integration of large clinical and laboratory datasets with gene expression profiles to predict clinical outcomes such as therapy response. Future studies will need to validate these findings in independent cohorts and determine whether applying these AI-derived prediction models improves clinical outcomes in IBD.

INTRODUCTION

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), is a chronic inflammatory disorder of the gastrointestinal tract. IBD has emerged as a global disease with increasing incidence worldwide and associated with significant healthcare utilization[1,2]. The pathogenesis of IBD is complex and is thought to involve an interplay between loss of tolerance to commensal gut bacteria, intestinal epithelial barrier dysfunction, and immune dysregula-tion[3-7]. The diagnosis of IBD is based on a combination of factors including clinical data (*e.g.*, chronicity of gastrointestinal symptoms), laboratory values (elevated inflammatory markers such as C-reactive protein and fecal calprotectin), imaging, endoscopy, and histology (gastrointestinal inflammation with architectural distortion)[8]. Although treatment algorithms based on clinical trials and experience have been developed to inform clinical management in IBD[9], there is significant heterogeneity among patients with IBD with regards to presentation, response to therapy, and long-term clinical outcomes such development of strictures and need for surgery[10,11]. There is a great need for precision medicine strategies to improve diagno-stic and therapeutic approaches in IBD.

Precision medicine efforts in IBD have led to more in-depth phenotyping of patients with IBD using large scale databases from clinical trials and cohort studies, deep immunophenotyping using whole genome gene expression datasets, proteomics, transcriptomics, and metagenomics of gut microbiota, and complex predictive models incorporating computer-assisted analysis of endoscopic images and histology[12-14]. This has inevitably led to vast arrays of high dimensional data that pose significant challenges with traditional statistical and computational methods[15]. Technological advances in artificial intelligence (AI) have revolutionized the ability of clinicians and researchers to process, analyze, and interpret high dimensional data and large datasets.

AI is a broad and multidisciplinary field incorporating concepts from computer science, engineering, philosophy, and linguistics aimed at understanding and designing systems that display or mimic human intelligence. The term was first coined in 1965 by McCarthy J[16,17]. Machine learning (ML) is a subdiscipline of AI where computer algorithms apply statistical models to learn associations of predictive power from examples in provided datasets (*e.g.*, Dragon dictation, SPAM, Netflix). ML may be programmed through supervised learning or unsupervised learning. In supervising learning, computer programs are trained to learn associations between inputs and outputs in data through analysis of predefined outputs of interest (by human operator). Once associations have been learned using existing data, supervised ML classifiers could then be used to predict future examples using different datasets. Examples of supervised ML include random forest (RF) and support vector machines (SVM). In unsupervised learning, computer programs learn associations in data without external definitions of associations of interest. This method allows for the identification of previously undiscovered predictors. Deep learning, commonly known as neural networks, includes newer techniques that are based on models with fewer assumptions, rely on multiple layers of representation of the data with successive transformations that amplify aspects of the input which improves discrimination power and thus able to handle more complex data (*e.g.*, Facebook face recognition, credit card fraud)[17]. There has been increased interest in use of AI in IBD in recent

years with many prior groups applying ML methods to identify meaningful insights in diagnostics and prediction models in IBD. The purpose of this review is to provide a comprehensive summary of advances in the application of AI and ML technologies in the diagnosis and risk prediction, assessment of disease severity, and prediction of clinical outcomes in patients with IBD.

LITERATURE SEARCH

We performed a literature review using PubMed (MEDLINE) from inception to December 15, 2020 of studies applying AI in IBD. Our search strategy included the following combinations: (((((((((inflammatory bowel disease[Title])) OR (ulcerative colitis[Title])) OR (Crohn's disease[Title])) AND (artificial intelligence[Title])) OR (computer-assisted[Title])) OR (computer-aided[Title])) OR (neural network[Title])) OR (machine learning[Title])) OR (deep learning[Title]). We included studies that used AI in the (1) diagnosis or risk prediction of IBD, (2) assessment of disease severity in IBD, and (3) prediction of therapy response and clinical outcomes in IBD. We excluded reviews, studies with non-human subjects (animal models), or studies that did not provide objective measures of the efficacy of AI applications (*e.g.*, measures of precision, accuracy, area under the curve (AUC), sensitivity, specificity, *etc.*).

RESULTS

Our search strategy yielded 98 studies evaluating AI in IBD of which 58 studies[18-74] met inclusion criteria and were included in the final review. About 86.2% (50/58) of studies were published within the past 5 years (2015 and later). There were 23 studies[18-39] that focused on IBD diagnosis and risk prediction, 19 studies[40-58] which evaluated disease activity, and 17 studies[45,59-74] which predicted IBD clinical outcomes (response to therapy, colonic neoplasia, post-surgical complications, quality of life, IBD well-being and emotional content). There were 22 studies with combined IBD cohorts (CD and UC), 16 studies with UC patients only, 18 studies with CD only, and 5 pediatric IBD cohorts. The most common AI classifications used were neural networks (convolutional and deep) at 32.7% (19/58 studies), RF at 29.3% (17/58 studies), and SVM at 29.3% (17/58 studies).

AI in diagnosis and risk prediction of IBD

Table 1 summarizes studies included which applied AI in the diagnosis and risk prediction of IBD. There were 17 studies focused on IBD diagnosis, whereas 5 studies focused on predicting risk of IBD. Data modalities included genetic/genomic datasets (n = 16 studies), imaging and endoscopic datasets (n = 4), and protein expression/ proteomics (n = 2 studies). Some groups have used ML to develop IBD risk prediction models based on gene expression datasets. In a cross-sectional study of 180 CD patients, 149 UC patients and 90 healthy controls by Isakov *et al*[21], RF and SVM used microarray and RNA-seq data sets to classify a list of 16390 genes. Their combined IBD risk prediction model demonstrated an AUC, sensitivity, specificity, and accuracy values of 0.829, 0.577, 0.880, and 0.808, respectively. In another cross-sectional study of 18227 CD patients and 34050 healthy controls, Romagnoni *et al*[20] used gradient boosted trees and artificial neural networks to analyze gene expression profiles. Using single nucleotide polymorphisms, their final predictive model for CD achieved AUC of 0.80. Likewise, a cross-sectional study of 20 UC patients and 20 healthy controls by Duttagupta *et al*[33] used SVM to analyze microRNA profiles. Their SVM classifier measurements revealed a predictive score accuracy of 92.8%, specificity of 96.2%, and sensitivity of 89.5% in distinguishing UC patients from normal individuals.

A major challenge in IBD diagnosis is the distinction between CD and UC which is based on clinical features such as the distribution of inflammation along the gastrointestinal tract. The misdiagnosis of IBD subtype is not uncommon[74]. Distinguishing between CD and UC is clinically important as IBD subtype informs clinical management. AI has been employed to analyze molecular data to distinguish between CD and UC. In a cross-sectional study of 59 CD patients, 26 UC patients, and 42 healthy controls applying deep belief networks (DBNs) and SVM to gene expression datasets, Smolander *et al*[25] explored the diagnosis UC from CD. Using DBN only, the accuracy for diagnosis of UC was 97.06% and CD was 97.07%. Using both DBN and SVM, accuracy for diagnosis of UC was 97.06% and CD was 97.03%. In

Table 1 Artificial intelligence in diagnosis and risk prediction of inflammatory bowel disease

Ref.	AI classifier *vs* comparator	IBD type	Study design and sample size	Modality	Outcome	Study results/validation cohort
Mossotto *et al* [18], 2017	Support vector machines (SVM) *vs* linear discriminant	Peds CD/UC	Prospective cohort, 287 IBD patients	Endoscopic and histologic inflammation	Diagnosis of IBD	Diagnostic accuracy of 82.7% with an AUC of 0.87 in diagnosing Crohn's disease or ulcerative colitis. Validation cohort included
Wei *et al*[19], 2013	SVM with gradient boosted trees (GBT) *vs* simple log odds method	CD/UC	Cross-sectional, 30000 IBD patients, 22000 healthy controls	Genetics, ImmunoChip	Risk of IBD	The SVM demonstrated very comparable performance (AUC 0.862 and 0.826 for CD and UC, respectively), whereas GBT showed inferior performance (AUC 0.802 and0.782 for CD and UC, respectively). Validation cohort included
Romagnoni *et al*[20], 2019	Artificial neural networks (ANNs) *vs* penalized logistic regression (LR), and GBT	CD	Cross-sectional, 18227 CD patients, 34050 healthy controls	Genetics, ImmunoChip	Risk of IBD	Using single nucleotide polymorphisms (SNPs), final predictive model achieved AUC of 0.80. Validation cohort included
Isakov *et al*[21], 2017	Random forest (RF), SVM with svmPoly), extreme gradient boosting *vs* elastic net regularized generalized linear model (glmnet)	CD/UC	Cross-sectional, 180 CD patients, 149 UC patients, 90 healthy controls	Expression data (microarray and RNA-seq)	Risk of IBD	The method was used to classify a list of 16390 genes. Each gene received a score that was used to prioritize it according to its predicted association to IBD. The combined model demonstrated AUC, sensitivity, specificity, and accuracy values of 0.829, 0.577, 0.88, and 0.808, respectively. Validation cohort included
Yuan *et al*[22], 2017	Sequential minimal optimization *vs* DisGeNET (Version 4.0)	CD/UC	Cross-sectional, 59 CD patients, 26 UC patients, 42 healthy controls	Gene Expression datasets	Risk of IBD	By analyzing the gene expression profiles using minimum redundancy maximum relevance and incremental feature selection, 21 genes were obtained that could effectively distinguish samples from IBD and the non-IBD samples. Highest total prediction accuracy was 97.64% using the 1170th feature set. Validation cohort included
Hübenthal *et al*[23], 2015	SVM *vs* RF	CD/UC	Cross-sectional, 40 CD patients, 36 UC patients, 38 healthy controls	MicroRNAs	Diagnosis of IBD	Measured by the AUC the corresponding median holdout-validated accuracy was estimated as ranging from 0.75 to 1.00 and 0.89 to 0.98, respectively. In combination, the corresponding models provide tools for the distinction of CD and UC as well as CD, UC and healthy control with expected classification error rates of 3.1 and 3.3%, respectively. Validation cohort included
Tong *et al*[24], 2020	RF *vs* convolutional neural network (CNN)	CD/UC	Retrospective Cohort, 875 CD patients, 5128 UC patients	Colonoscopy Endoscopic Images	Diagnosis of IBD	RF sensitivities/specificities of UC/CD were 0.89/0.84, 0.83/0.82, and 0.72/0.77, respectively, while the values for the CNN of CD was 0.90/0.77. The precisions/recalls of UC-CD when employing RF were 0.97/0.97, 0.65/0.53, respectively, and when employing the CNN were 0.99/0.97 and 0.87/0.83, respectively. Validation cohort included
Smolander *et al*[25], 2019	Deep belief networks (DBNs) *vs* SVM	CD/UC	Cross-sectional, 59 CD patients, 26 UC patients, 42 healthy controls	Gene Expression datasets	Diagnosis of IBD	Using DBN only, accuracy for diagnosis of UC was 97.06% and CD was 97.07%. Using both DBN and SVM, accuracy for diagnosis of UC was 97.06% and CD was 97.03%. Validation cohort included
Abbas *et al*[26], 2019	RF *vs* network-based biomarker discovery	Peds CD/UC	Cross-sectional, 657 IBD patients, 316 healthy controls	Large dataset of new-onset pediatric IBD metagenomics biopsy samples	Diagnosis of IBD	For the diagnosis of IBD, highest AUC attained by top Random Forest classifiers was 0.77. No validation cohort included
Khorasani *et al*[27], 2020	SVM *vs* recently developed feature selection algorithm (robustness-performance tradeoff, RPT)	UC	Cross-sectional, 146 UC patients, 60 healthy controls	Gene Expression dataset	Diagnosis of IBD	Our model perfectly detected all active cases and had an average precision of 0.62 in the inactive cases. Validation cohort included
Rubin *et al*[28], 2019	CITRUS supervised machine learning algorithm. No comparator	CD/UC	Cross-sectional, 68 IBD patients	Peripheral blood mononuclear cells and intestinal biopsies mass cytometry	Diagnosis of IBD	An 8-parameter immune signature distinguished Crohn's disease from ulcerative colitis with an AUC = 0.845 (95%CI: 0.742-0.948). No validation cohort included

Pal *et al*[29], 2017	Naïve Bayes and with a consensus machine learning method *vs* Critical Assessment of Genome Interpretation (CAGI) 4 method	CD	Cross-sectional, 64 CD patients, 47 healthy controls	Genotypes from Exome Sequencing Data	Risk of IBD	The AUC for predicting risk of Crohn's disease using the SNP model was 0.72. No validation cohort included
Aoki *et al*[30], 2019	Deep CNN. No comparator	CD	Retrospective Cohort, 115 IBD patients	Wireless capsule endoscopy images	Diagnosis of IBD	The AUC for the detection of erosions and ulcerations was 0.958 (95%CI: 0.947-0.968). The sensitivity, specificity, and accuracy of the CNN were 88.2% (95%CI: 84.8-91.0), 90.9% (95%CI: 90.3-91.4), and 90.8% (95%CI: 90.2-91.3), respectively. Validation cohort included
Bielecki *et al*[31], 2012	SVM *vs* human reader (pathologist)	CD/UC	Cross-sectional, 14 CD patients, 13 UC patients, 11 healthy controls	Raman spectroscopic imaging of epithelium cells	Diagnosis of IBD	Raman maps of human colon tissue sections were analyzed by utilizing innovative chemometric approaches. Using SVM, it was possible to separate between healthy control patients, patients with Crohn's Disease, and patients with ulcerative colitis with an accuracy of 98.90%. No validation cohort included
Cui *et al*[32], 2013	Recursive SVM *vs* unsupervised learning strategy	CD/UC	Cross-sectional, 124 IBD patients, 99 healthy controls	16S rRNA gene analysis	Diagnosis of IBD	Selection level of 200 features results in the best leave-one-out cross-validation result (accuracy = 88%, sensitivity = 92%, specificity = 84%). Validation cohort included
Duttagupta *et al*[33], 2012	SVM. No comparator	UC	Cross-sectional, 20 UC patients, 20 healthy controls	MicroRNAs	Diagnosis of IBD	SVM classifier measurements revealed a predictive score of 92.8% accuracy, 96.2% specificity and 89.5% sensitivity in distinguishing ulcerative colitis patients from normal individuals. Validation cohort included
Daneshjou *et al*[34], 2017	Naïve bayes, neural networks, random forests *vs* CAGI methods	CD	Cross-sectional, 64 ICD patients, 47 healthy controls	Exome Sequencing	Diagnosis of IBD	In CAGI4, 111 exomes were derived from a mix of 64 Crohn's disease patients. Top performing methods had an AUC of 0.87. Validation cohort included
Geurts *et al*[35], 2005	RF *vs* SVM	CD/UC	Prospective cohort, 30 CD patients, 30 CD patients	Proteomic Mass Spectrometry	Diagnosis of IBD	Random forest model to diagnosis IBD had a sensitivity of 81.67%, specificity of 81.17%. Support vector machine model to diagnosis IBD had a sensitivity of 87.92%, specificity of 87.87%. Validation cohort included
Li *et al*[36], 2020	RF *vs* ANN	UC	Cross-sectional, 193 UC patients, 21 healthy controls	Gene Expression Profiles	Diagnosis of IBD	The random forest algorithm was introduced to determine 1 downregulated and 29 upregulated differentially expressed genes contributing highest to ulcerative colitis occurrence. ANN was developed to calculate differentially expressed genes weights to ulcerative colitis. Prediction results agreed with that of an independent data set (AUC = 0.9506/PR-AUC = 0.9747). Validation cohort included
Wingfield *et al*[37], 2019	RF *vs* SVM	CD	Cross-sectional, 668 CD patients	Metagenomic Data	Diagnosis of IBD	Highest RPT measure for Crohn's disease was random forest 0.60 and SVM 0.58. For ulcerative colitis, RPT was random forest 0.70 and SVM 0.48. Validation cohort included
Han *et al*[38], 2018	RF *vs* LR, CORG	CD/UC	Cross-sectional, 24 CD patients, 59 UC patients, 76 healthy controls	Gene Expression Profiles	Diagnosis of IBD	The gene-based feature sets had median AUC on the validation sets ranging from 0.6 to 0.76). Validation cohort included
Wang *et al*[39], 2019	AVADx (Analysis of Variation for Association with Disease) *vs* two GWAS-based CD evaluation methods	CD	Cross-sectional, 64 CD patients, 47 healthy controls	Whole Exome or Genome Sequencing Data	Diagnosis of IBD	AVADx highlighted known CD genes including NOD2and new potential CD genes. AVADx identified 16% (at strict cutoff) of CD patients at 99% precision and 58% of the patients (at default cutoff) with 82% precision in over 3000 individuals from separately sequenced panels. Validation cohort included

AI: Artificial intelligence; IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; AUC: Area under the curve.

a cross-sectional study of 68 IBD patients using a CITRUS supervised ML algorithm to analyze single cell immunophenotyping of peripheral blood mononuclear cells by mass cytometry, Rubin *et al*[28] demonstrated that an 8-parameter immune signature distinguished CD from UC with an AUC = 0.845 [95% confidence interval (CI): 0.742-0.948]. ML algorithms have also been applied to analyze large arrays of endoscopic images to differentiate between UC and CD. In a recent retrospective cohort study of 875 CD patients and 5128 UC patients by Tong *et al*[24] using RF and convolutional neural networks (CNNs) on endoscopic images, the precision of diagnosing UC/CD with RF and CNNs were 0.97/0.65 and 0.99/0.87, respectively. Taken together, these studies suggest that AI classifiers have high performance in diagnosing or predicting risk of IBD but have some variability with type of AI classifier and modality of data (molecular *vs* endoscopic).

AI in assessment of disease severity in IBD

The assessment of disease activity and grading of severity in IBD could be accomplished using validated clinical symptom scores (*e.g.*, Harvey Bradshaw Index for CD, Mayo Score for UC)[75,76], biomarkers of inflammation (*e.g.*, C-reactive protein, fecal calprotectin)[77,78], endoscopic inflammation indices (*e.g.*, Mayo endoscopic score, simple endoscopic score)[79,80], and histologic scoring systems (*e.g.*, Geboes Score, Robarts Histopathology Index)[81,82]. However, these systems may be subject to recall bias, heterogeneity in patient clinical presentation, and intraobserver and interobserver variability[83]. AI has been applied to these existing systems to improve precision and accuracy of quantifying disease severity in IBD.

Table 2 summarizes studies included which applied AI in the assessment of disease severity in IBD. There were 2 studies that assessed clinical disease activity, 2 studies that assessed disease activity by biomarker (C-reactive protein), 13 studies that focused on endoscopic inflammation, and 3 studies that focused on histologic inflammation. Data modalities included electronic health records (*n* = 2), molecular datasets (*n* = 3), endoscopic datasets (*n* = 11 studies), and histologic datasets *via* endomicroscopy/endocytoscopy (*n* = 2). Using RF to integrate and analyze clinical and laboratory data from publicly available clinical trials (UNITI-1, UNITI-2, and IM-UNITI) data consisting of 401 CD patients, Waljee *et al*[42] constructed a CD remission prediction model using the week 6 albumin to C-reactive protein ratio with an AUC of 0.76 (95%CI: 0.71-0.82). Reddy *et al*[44] applied gradient boosting machines to electronic health records and predicted inflammation severity in a retrospective cohort of 3335 CD patients with a very high accuracy (AUC) = 92.82%. In a CNN analysis of colonoscopy images from a retrospective cohort of 841 UC patients by Ozawa *et al*[55], the CNN-based computer aided diagnostic system showed a high level of performance with AUC of 0.86 and 0.98 to identify Mayo 0 and 0-1, respectively. The performance of the CNN was better for the rectum than for the right side and left side of the colon when identifying Mayo 0 (AUC = 0.92, 0.83, and 0.83, respectively). Likewise, in an ordinal CNN analysis of wireless capsule endoscopy images in a retrospective cohort of 49 CD patients by Barash *et al*[50], the classification accuracy of the algorithm was 0.91 for grade 1 *vs* grade 3 ulcers, 0.78 for grade 2 *vs* grade 3, and 0.624 for grade 1 *vs* grade 2. The role of AI in grading severity of histologic inflammation in IBD has also been explored. For example, in a retrospective cohort study of 187 UC patients by Maeda *et al*[46], application of SVM to data derived from endocytoscopy to assess histologic inflammation provided diagnostic sensitivity, specificity, and accuracy of 74% (95%CI: 65-81), 97% (95%CI: 95-99), and 91% (95%CI: 83-95), respectively. These examples highlight the clinical utility, versatility, and performance of AI classifiers in grading the disease activity of IBD patients at the clinical, endoscopic, and histologic level. AI performance may be affected by location of inflammation and may be limited by ability to discriminate between subtle differences.

AI in prediction of therapy response and clinical outcomes in IBD

The armamentarium of therapies in IBD have expanded significantly in recent years with diverse mechanisms of action ranging from biologics that inhibit proinflammatory cytokines (anti-tumor necrosis factor-α, anti-interleukin-12/23) and leukocyte trafficking to the gut (anti-α4β7) to small molecule inhibitors of the JAK-STAT signaling pathway[84-86]. Despite several IBD treatment options available to clinicians, there are no effective biomarkers or tools to predict response to therapy or to guide selection of alternative therapies after a failed response. Likewise, there is also an unmet clinical need to predict long term clinical outcomes in IBD such as colon cancer. To address these challenges, several groups have applied AI and ML algorithms to existing clinical and molecular datasets.

Table 2 Artificial Intelligence in assessment of disease severity in inflammatory bowel disease

Ref.	AI classifier *vs* comparator	IBD type	Study design and sample size	Modality	Outcomes	Study results/validation cohort
Kumar *et al*[40], 2012	Support vector machines (SVM) *vs* human observers	CD	Cross-sectional, 50000 images (number of patients not given)	Small bowel capsule endoscopy	Endoscopic Inflammation	Database of 47 studies including 50000 capsule endoscopy images evaluating severity of small bowel lesions. Method had good precision (> 90% for lesion detection) and recall (> 90%) for lesions of varying severity. Validation cohort included
Biasci *et al*[41], 2019	Logistic regression with an adaptive Elastic-Net penalty. No comparator	CD/UC	Prospective cohort, 118 IBD patients	Transcriptomics from purified CD8 T cells and/or whole blood	Disease severity, medication escalation	A 17-gene qPCR-based classifier stratified patients into two distinct subgroups. IBDhi patients experienced significantly more aggressive disease than IBDlo patients (analogous to IBD2), with earlier need for treatment escalation [HR 2.65 (CD), 3.12 (UC)] and more escalations over time [for multiple escalations within 18 months: sensitivity=72.7% (CD), 100% (UC); negative predictive value = 90.9% (CD), 100% (UC)]. Validation cohort included
Waljee *et al*[42], 2019	RF. No comparator	CD	Post-hoc analysis of prospective clinical trials, 401 CD patients	Clinical and laboratory data from publicly available clinical trials (UNITI-1, UNITI-2, and IM-UNITI)	Crohn's disease remission, C-reactive protein < 5 mg/L	A prediction model using the week-6 albumin to C-reactive protein ratio had an AUC of 0.76 [95% confidence interval (CI): 0.71-0.82]. Validation cohort included
Mahapatra *et al*[43], 2016	RF. No comparator	CD	Cross-sectional, 35 CD patients	Abdominal magnetic resonance imaging	Segmentation of diseased colon (intestinal inflammation)	Model segmentation accuracy ranged from 82.7% to 92.2%. Validation cohort included
Reddy *et al*[44], 2019	Gradient boosting machines *vs* logistic regression	CD	Retrospective, 3335 CD patients	Electronic medical record	Severity of intestinal inflammation (by C-reactive protein)	Machine-learning-based analytic methods such as gradient boosting machines can predict the inflammation severity with a very high accuracy (AUC) = 92.82%. Validation cohort included
Douglas *et al*[45], 2018	RF. No comparator	Peds CD	Cross-sectional, 20 CD patients, 20 healthy controls	Shotgun metagenomics (MGS), 16S rRNA gene sequencing	Disease State (Relapse/Remission)	MGS modules significantly classified samples by disease state (accuracy = 68.4%, *P* = 0.043 and accuracy = 65.8%, *P* = 0.03, respectively), 16S datasets had a maximum accuracy of 68.4% and *P* = 0.016 based on strain level for disease state. Validation cohort included
Maeda *et al*[46], 2019	SVM *vs* human reader	UC	Retrospective cohort, 187 UC patients	Endocytoscopy	Histologic inflammation	Computer aided diagnosis (CAD) of histologic inflammation provided diagnostic sensitivity, specificity, and accuracy as follows: 74% (95%CI: 65-81), 97% (95%CI: 95-99), and 91% (95%CI: 83-95), respectively. Its reproducibility was perfect (*k* = 1). Validation cohort included
Charisis *et al*[47], 2016	SVM *vs* human reader	CD	Retrospective cohort, 13 CD patients	Wireless capsule endoscopy (WCE) images	Endoscopic Inflammation	Experimental results, along with comparison with other related efforts, have shown that the hybrid adaptive filtering [HAF-Differential Lacunarity (DLac) analysis (HAF-DLac)] *via* SVM approach evidently outperforms them in the field of WCE image analysis for automated lesion detection, providing higher classification results, up to 93.8% (accuracy), 95.2% (sensitivity), 92.4% (specificity) and 92.6% (precision). Validation cohort included
Klang *et al*[48], 2020	Convolutional neural network (CNN) *vs* human reader	CD	Retrospective cohort, 49 CD patients	WCE images	Endoscopic Inflammation	Dataset included 17640 CE images from 49 patients: 7391 images with mucosal ulcers and 10249 images of normal mucosa. For randomly split images results, AUC was 0.99 with accuracies ranging from 95.4% to 96.7%. For individual patient-level experiments, the AUCs were 0.94-0.99. Validation cohort included
Ungaro *et al*[49], 2021	Random survival forest. No comparator	Peds CD	Retrospective case-control, 265 peds CD patients	Protein biomarkers using a proximity extension assay (Olink Proteomics)	Penetrating and stricturing complications	A model with 5 protein markers predicted penetrating complications with an AUC of 0.79 (95%CI: 0.76-0.82) compared to 0.69 (95%CI: 0.66-0.72) for serologies and 0.74 (95%CI: 0.71-0.77) for clinical variables. A model with 4 protein markers predicted structuring complications with an AUC of 0.68 (95%CI: 0.65-0.71) compared to 0.62 (95%CI: 0.59-0.65) for serologies and 0.52 (95%CI: 0.50-0.55) for clinical variables. Validation cohort included

Barash *et al*[50], 2021	Ordinal CNN. No comparator	CD	Retrospective cohort, 49 CD patients	WCE images	Ulcer Severity Grading	The classification accuracy of the algorithm was 0.91 (95%CI: 0.867-0.954) for grade 1 *vs* grade 3 ulcers, 0.78 (95%CI: 0.716-0.844) for grade 2 *vs* grade 3, and 0.624 (95%CI: 0.547-0.701) for grade 1 *vs* grade 2. Validation cohort included
Lamash *et al*[51], 2019	CNN *vs* semi-supervised and active learning models	CD	Retrospective cohort, 23 CD patients	Magnetic resonance imaging	Active Crohn's Disease	CNN exhibited Dice similarity coefficient of 75% ± 18%, 81% ± 8%, and 97% ± 2% for the lumen, wall, and background, respectively. The extracted markers of wall thickness at the location of min radius (P = 0.0013) and the median value of relative contrast enhancement (P = 0.0033) could differentiate active and nonactive disease segments. Other extracted markers could differentiate between segments with strictures and segments without strictures (P < 0.05). Validation cohort included
Takenaka *et al*[52], 2020	Deep neural networks *vs* human reader (endoscopist)	UC	Prospective cohort, 2012 UC patients	Colonoscopy images	Endoscopic inflammation	Deep neural network identified patients with endoscopic remission with 90.1% accuracy (95%CI: 89.2-90.9) and a kappa coefficient of 0.798 (95%CI: 0.780-0.814), using findings reported by endoscopists as the reference standard. Validation cohort included
Bossuyt *et al* [53], 2020	Computer algorithm based on red density (RD) *vs* blinded central readers	UC	Prospective cohort, 29 UC patients, 6 healthy controls	Colonoscopy Images	Endoscopic and histologic inflammation	In the construction cohort, RD correlated with rhi (r = 0.74, P < 0.0001), Mayo endoscopic subscores (r = 0.76, P < 0.0001) and Endoscopic index of severity scores (r = 0.74, P < 0.0001). The RD sensitivity to change had a standardized effect size of 1.16. in the validation set, RD correlated with rhi (r = 0.65, P = 0.00002). Validation cohort included
Bhambhvani *et al*[54], 2021	CNN *vs* human reader (endoscopist)	UC	Retrospective cohort, 777 UC patients	Colonoscopy images	Mayo Endoscopic Scores (MES)	The final model classified MES 3 disease with an AUC of 0.96, MES 2 disease with an AUC of 0.86, and MES 1 disease with an AUC 0.89. Overall accuracy was 77.2%. Across MES 1, 2, and 3, average specificity was 85.7%, average sensitivity was 72.4%, average PPV was 77.7%, and the average NPV was 87.0%. Validation cohort included
Ozawa *et al* [55], 2019	CNN *vs* human reader (endoscopist)	UC	Retrospective cohort, 841 UC patients	Colonoscopy images	MES	The CNN-based CAD system showed a high level of performance with AUC of 0.86 and 0.98 to identify Mayo 0 and 0-1, respectively. The performance of the CNN was better for the rectum than for the right side and left side of the colon when identifying Mayo 0 (AUC = 0.92, 0.83, and 0.83, respectively). Validation cohort included
Bossuyt *et al*[56], 2021	Automated CAD Algorithm *vs* human reader	UC	Prospective cohort, 48 UC patients	Colonoscopy images with confocal laser endomicroscopy	Histologic Remission	The current automated CAD algorithm detects histologic remission with a high performance (sensitivity of 0.79 and specificity of 0.90) compared with the UCEIS (sensitivity of 0.95 and specificity of 0.69) and MES (sensitivity of 0.98 and specificity of 0.61). No validation cohort included
Stidham *et al*[57], 2019	CNN *vs* human reader	UC	Retrospective cohort, 3082 UC patients	Colonoscopy images	Endoscopy severity	The CNN was excellent for distinguishing endoscopic remission from moderate-to-severe disease with an AUC of 0.966 (95%CI: 0.967-0.972); a PPV of 0.87 (95%CI: 0.85-0.88) with a sensitivity of 83.0% (95%CI: 80.8-85.4) and specificity of96.0% (95%CI: 95.1-97.1); and NPV of 0.94 (95%CI: 0.93-0.95). No validation cohort included
Gottlieb *et al*[58], 2021	Neural network *vs* human central reader	UC	Prospective cohort, 249 UC patients	Colonoscopy images	Endoscopy severity	The model's agreement metric was excellent, with a quadratic weighted kappa of 0.844 (95%CI: 0.787-0.901) for endoscopic Mayo Score and 0.855 (95%CI: 0.80-0.91) for UCEIS. No validation cohort included

AI: Artificial intelligence; IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; AUC: Area under the curve; NPV: Negative predictive value; PPV: Positive predictive value; qPCR: Quantitative real-time polymerase chain reaction; HR: Hazard ratio.

Table 3 summarizes studies included which applied AI in the prediction of therapy response and clinical outcomes in IBD. There were 9 studies that predicted therapy response, 2 studies that predicted presence of extraintestinal manifestations of IBD, 1 study predicting colonic neoplasia, and 1 study predicting post-surgical complications after colectomy. Data modalities included electronic health records (n = 11), molecular

Table 3 Artificial intelligence in prediction of therapy response and clinical outcomes in inflammatory bowel disease

Ref.	AI classifier *vs* comparator	IBD type	Study design and sample size	Modality	Outcomes	Study results/validation cohort
Waljee *et al*[59], 2018	Random forest (RF). No comparator	CD/UC	Post-hoc analysis of prospective clinical trial, 594 CD patients	Veteran's Health Administration Electronic Health Record (EHR)	Outpatient corticosteroids prescribed for IBD and inpatient hospitalizations associated with a diagnosis of IBD	AUC for the RF longitudinal model was 0.85 [95% confidence interval (CI): 0.84–0.85]. AUC for the RF longitudinal model using previous hospitalization or steroid use was 0.87 (95%CI: 0.87-0.88). Validation cohort included
Uttam *et al*[60], 2019	Support vector machines (SVM) *vs* nanoscale nuclear architecture mapping (NanoNAM)	CD/UC	Prospective cohort, 103 IBD patients	3-dimensional NanoNAM of normal-appearing rectal biopsies	Colonic neoplasia	NanoNAM detects colonic neoplasia with an AUC of 0.87 ± 0.04, sensitivity of 0.81 ± 0.09, and specificity of 0.82 ± 0.07 in the independent validation set. Validation cohort included
Waljee *et al*[61], 2017	RF. No comparator	CD/UC	Retrospective cohort, 1080 IBD patients	EHR, lab values	Remission and clinical outcomes with thiopurines	AUC for algorithm-predicted remission in the validation set was 0.79 *vs* 0.49 for 6-TGN. The mean number of clinical events per year in patients with sustained algorithm-predicted remission (APR) was 1.08 *vs* 3.95 in those that did not have sustained APR ($P < 1 \times 10^{-5}$). Validation cohort included
Popa *et al*[62], 2020	Neural network model. No comparator	UC	Prospective cohort, 55 UC patients	Clinical and biological parameters and the endoscopic Mayo score	Disease activity after one year of anti-TNF treatment	The classifier achieved an excellent performance predicting the disease activity at one year with an accuracy of 90% and AUC 0.92 on the test set and an accuracy of 100% and an AUC of 1 on the validation set. Validation cohort included
Douglas *et al*[45], 2018	RF. No comparator	Peds CD	Cross-sectional, 20 CD patients, 20 healthy controls	Shotgun metagenomics (MGS), 16S rRNA gene sequencing	Response to induction therapy	16S genera were again the top dataset (accuracy = 77.8%; $P = 0.008$) for predicting response to therapy. MGS strain ($P = 0.029$), genus ($P = 0.013$), and KEGG pathway ($P = 0.018$) datasets could also classify patients according to therapy response with accuracy = 72.2% for all three. Validation cohort included
Waljee *et al*[63], 2010	RF *vs* boosted trees, RuleFit	CD/UC	Cross-sectional, 774 IBD patients	EHR, lab values (thiopurine metabolites)	Response to thiopurine therapy	A RF algorithm using laboratory values and patient age differentiated clinical response from nonresponse in the model validation data set with an AUC of 0.856 (95%CI: 0.793-0.919). Validation cohort included
Menti *et al*[64], 2016	Naïve bayes *vs* Bayesian additive regression trees *vs* Bayesian networks	CD/UC	Retrospective cohort, 152 CD patients	Genomic DNA, genetic polymorphism	Presence of extra-intestinal manifestations in IBD patients	Bayesian networks achieved accuracy of 82% when considering only clinical factors and 89% when considering also genetic information, outperforming the other techniques. Validation cohort included
Waljee *et al*[65], 2017	RF *vs* baseline regression model	CD/UC	Retrospective cohort, 20368 IBD patients	EHR, lab values	Corticosteroid-free biologic remission with vedolizumab	The AUC for corticosteroid-free biologic remission at week 52 using baseline data was only 0.65 (95%CI: 0.53-0.77), but was 0.75 (95%CI: 0.64-0.86) with data through week 6 of vedolizumab. Validation cohort included
Morilla *et al*[66], 2019	Deep neural networks. No comparator	UC	Retrospective cohort, 47 UC patients	Colonic microrna profiles	Responses to therapy	A deep neural network-based classifier identified 9 microRNAs plus 5 clinical factors, routinely recorded at time of hospital admission, that were associated with responses of patients to treatment. This panel discriminated responders to steroids from non-responders with 93% accuracy (AUC, 0.91). Three algorithms, based on microRNA levels, identified responders to infliximab *vs* non-responders (84% accuracy, AUC 0.82) and responders to cyclosporine *vs* non-responders (80% accuracy, AUC 0.79). Validation cohort included
Wang *et al*[67], 2020	Back-propagation neural network (BPNN), SVM *vs* logistic regression	CD	Cross-sectional, 446 CD patients	EHR	Medication nonadherence to maintenance therapy	The average classification accuracy and AUC of the three models were 85.9% and 0.912 for BPNN, and 87.7% and 0.930 for SVM, respectively. Validation cohort included
Bottigliengo	Bayesian machine	CD/UC	Retrospective cohort,	EHR, genetic	Presence of extra-intestinal	BMLTs had an AUC of 0.50 for classifying the presence of extra-intestinal manifestations. Validation

et al[68], 2019	learning techniques (BMLTs) *vs* logistic regression		142 IBD patients	polymorphisms	manifestations in IBD patients	cohort included
Ghoshal *et al*[69], 2020	Nonlinear artificial neural network (ANN) *vs* multivariate linear PCA	UC	Prospective cohort, 263 UC patients	EHR	Responses to therapy	The multilayer perceptron neural network was trained by back-propagation algorithm (10 networks retained out of 16 tested). The classification accuracy rate was 73% in correctly classifying response to medical treatment in UC patients. No validation cohort included
Sofo *et al*[70], 2020	SVM leave-one-out cross-validation. No comparator	UC	Retrospective cohort, 32 UC patients	EHR	Post-surgical complications after colectomy	Evaluating only preoperative features, machine learning algorithms were able to predict minor postoperative complications with a high strike rate (84.3%), high sensitivity (87.5%) and high specificity (83.3%) during the testing phase. Validation cohort included
Kang *et al*[71], 2017	ANN *vs* logistic regression	UC	Cross-sectional, 24 UC patients	Gene expression profiles	Response to anti-TNF	Balanced accuracy in cross validation test for predicting response to anti-TNF therapy in ulcerative colitis patient was 82%. Validation cohort included
Babic *et al*[72], 1997	CART *vs* back propagation neural network (BPNN)	CD/UC	Cross-sectional, 200 IBD patients	EHR	Quality of life	Best reached classification accuracy did not exceed 80% in any case. Other classifiers namely, K-nearest-neighbor, learning vector quantization and BPNN confirmed that outcome. Validation cohort included
Dong *et al*[73], 2019	RF, SVM, ANN *vs* logistic regression	CD	Retrospective cohort, 239 CD patients	EHR, laboratory tests	Crohn's related surgery	The results revealed that RF predictive model performed better than LR model in terms of accuracy (93.11% *vs* 91.15%), precision (53.42% *vs* 44.81%), F1 score (0.6016 *vs* 0.5763), TN rate (95.08% *vs* 92.00%), and the AUC (0.8926 *vs* 0.8809). The AUCs were excellent at 0.9864 in RF, 0.9538 in LR, 0.8809 in DT, 0.9497 in SVM, and 0.9059 in ANN, respectively. Validation cohort included
Lerrigo *et al*[74], 2019	Latent Dirichlet allocation, unsupervised machine learning algorithm. No comparator	CD/UC	Retrospective cohort, 28623 IBD patients	Online posts from the Crohn's and colitis foundation community forum	Impact of online community forums on well-being and their emotional content	10702 (20.8%) posts were identified expressing: gratitude (40%), anxiety/fear (20.8%), empathy (18.2%), anger/frustration (13.4%), hope (13.2%), happiness (10.0%), sadness/depression (5.8%), shame/guilt (2.5%), and/or loneliness (2.5%). A common subtheme was the importance of fostering social support. No validation cohort included

AI: Artificial intelligence; IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; AUC: Area under the curve; TNF: Tumor necrosis factor.

datasets (*n* = 4), and histologic data (*n* = 1). Waljee *et al*[59,65] and Popa *et al*[62] have previously applied RF classifiers to clinical data from electronic health records and laboratory values to predict response to various IBD therapies. In one study using data from a prospective clinical trial consisting of 594 CD patients[59], the AUC for a RF longitudinal model for predicting inpatient hospitalizations in IBD patients prescribed outpatient corticosteroids was 0.85 (95%CI: 0.84-0.85). Using a similar RF approach for predicting remission with thiopurine therapy in a prospective cohort of 55 UC patients yielded an AUC of 0.79[62]. Applying RF to data from a retrospective cohort of 20368 IBD patients with vedolizumab use yielded an AUC of 0.65 (95%CI: 0.53-0.77) for corticosteroid-free vedolizumab remission at week 52 using baseline data and an AUC of 0.75 (95%CI: 0.64-0.86) with data through week 6 of vedolizumab[65]. Molecular datasets have also been used to differentiate between responders and non-responders to various IBD therapies. For example, Morilla *et al*[66] used a deep neural network classifier to construct a predictive panel of colonic microRNAs for IBD therapies in a retrospective cohort of 47 UC patients. Their panel discriminated responders to steroids from non-responders with 93% accuracy (AUC, 0.91). In addition, three

algorithms, based on microRNA levels, identified responders to infliximab *vs* non-responders (84% accuracy, AUC 0.82) and responders to cyclosporine *vs* non-responders (80% accuracy, AUC 0.79). A more recent prospective cohort study of 55 UC patients by Popa *et al*[62] integrated clinical, laboratory, and endoscopic (Mayo scores) datasets using a neural network classifier to predict disease activity after one year of anti-tumor necrosis factor therapy in patients with UC. This classifier achieved an AUC of 0.92 for predicting the disease activity at one year on the test set and an AUC of 1.00 on the validation set. These studies suggest that AI classifiers may play a role in predicting clinical outcomes and response to specific therapies in patients with IBD. However, future clinical trials are needed to compare the efficacy of AI applications in IBD clinical management *vs* standard of care before incorporation into real life clinical practice.

Finally, AI algorithms have been previously applied to enhance the detection of colonic polyps[87] and distinguish among subtypes of neoplastic colorectal lesions[88] in the general population. Although patients with IBD who have extensive colitis have a significantly greater risk of colorectal cancer compared to the general population [89,90], there have been limited studies applying AI technologies to improve colorectal cancer surveillance or develop prediction risk models in patients with IBD. Most studies evaluating polyp detection have excluded IBD patients[91-93]. Our literature search yielded only one study applying AI for the detection of colonic neoplasia in IBD. Uttam *et al*[60] employed support SVM to analyze 3-dimensional nanoscale nuclear architecture mapping (NanoNAM) of normal-appearing rectal biopsies in a prospective cohort of 103 IBD patients. In their study, NanoNAM detected colonic neoplasia with an AUC of 0.87 ± 0.04, sensitivity of 0.81 ± 0.09, and specificity of 0.82 ± 0.07 in the independent validation set. Further studies should focus on determining the clinical utility of incorporating AI methods to enhance standard of cancer surveillance in patients with IBD such as chromoendoscopy[94] and to develop predictive models for risks of colorectal malignancy in IBD patient populations.

CONCLUSION

In conclusion, our literature review has revealed that the applications of AI in IBD have significantly increased in recent years. Our review also highlighted that various AI classifiers may be applied to analyze and integrate large datasets ranging from clinical data from electronic health records, molecular data including gene expression and protein-based studies to a wide array of datasets consisting of endoscopic and histologic images. The application of AI has the potential to improve the accuracy and precision of predicting risk and diagnosis of IBD, assessing disease severity, and predicting outcomes with various IBD therapies. Currently, the application of AI methods in IBD has been limited to the research setting and has not yet been adopted in real life clinical practice. Furthermore, studies applying AI in the context of colorectal cancer surveillance or prediction in IBD are much needed. Given the current status of the field of AI in IBD, future directions should include: (1) Prospective validation of AI applications in IBD in independent cohorts as there is a risk of bias from internal training cohorts and potential limitations with generalizability; (2) Standardization of AI methods and comparative studies evaluating effect of heterogeneity from using different types of datasets on outcomes of interest; (3) Randomized controlled trials to determine whether application of AI in the clinical management of IBD improves clinical outcomes and could be translated into clinical practice; and (4) Randomized controlled trials to determine whether application of AI leads to greater clinical efficacy and cost-effectiveness compared to standard of care in IBD.

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