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Review Article

Artificial intelligence use for precision medicine in inflammatory bowel disease: a systematic review

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Abstract: Introduction: Inflammatory Bowel Disease (IBD), encompassing Crohn's disease and ulcerative colitis, presents significant clinical challenges due to its heterogeneous nature and complex etiology. Recent advancements in biomedical research have enhanced our understanding of IBD's genetic, microbial, and biochemical aspects. However, persistent issues in clinical management, including treatment non-response, surgical interventions, and diagnostic uncertainties, underscore the need for more targeted approaches. This review examines the convergence of artificial intelligence (AI) and precision medicine (PM) in IBD management. By leveraging AI's capacity to analyze complex, multi-dimensional datasets, this emerging field offers promising applications in improving diagnostic accuracy, predicting treatment responses, and forecasting disease progression, potentially transforming IBD patient care. Method: The systematic review (SR) was conducted by searching the following databases: PubMed, PubMed PMC, BVS, Scopus, Web of Science, Embase, Cochrane, and ProQuest up to February 2024. Studies that employed AI in IBD applied to precision medicine were included. Results: 139 studies on applying AI in precision medicine for IBD were identified. Most studies (>70%) were published after 2020, indicating a recent surge in interest. The AI applications primarily focused on diagnosis, treatment response prediction, and prognosis. Machine learning algorithms were predominantly used, particularly random forest, logistic regression, and support vector machines. Omics data were frequently employed as predictors, especially transcriptomics and microbiome analyses. Studies demonstrated good predictive performance across all three areas, with median AUC values ranging from 0.85 to 0.90. Conclusion: AI applications in IBD show promising potential to enhance clinical practice, particularly in disease prognosis and predicting treatment response. However, clinical implementation requires further validation through prospective studies. Future research should focus on standardizing protocols, defining clinically significant outcomes, and evaluating the efficacy of these tools.

Keywords: Crohn's disease, ulcerative colitis, precision medicine, machine learning

Introduction

Inflammatory Bowel Disease (IBD) encompasses two primary subtypes: Crohn's disease (CD) and ulcerative colitis (UC). The etiology, diagnosis, and management of IBD present significant clinical challenges due to its heterogeneous nature and the complex interplay of genetic factors, environmental triggers, and immunological dysregulation.

Over the past few decades, biomedical and bioinformatic research breakthroughs have enhanced our understanding of IBD complexity. High-throughput genomic sequencing has facilitated the identification of numerous genetic susceptibility loci [1]. Gut microbiome studies have shown the role of microbial dysbiosis in disease pathogenesis [2]. Metabolomic and proteomic analyses have uncovered IBD-specific biochemical signatures [3].

Despite these advancements, several challenges persist in clinical management. Approximately one-third of patients treated with anti-tumor necrosis factor-alpha (TNF-α) agents fail to respond during induction therapy, and among initial responders, about 50% experience a loss

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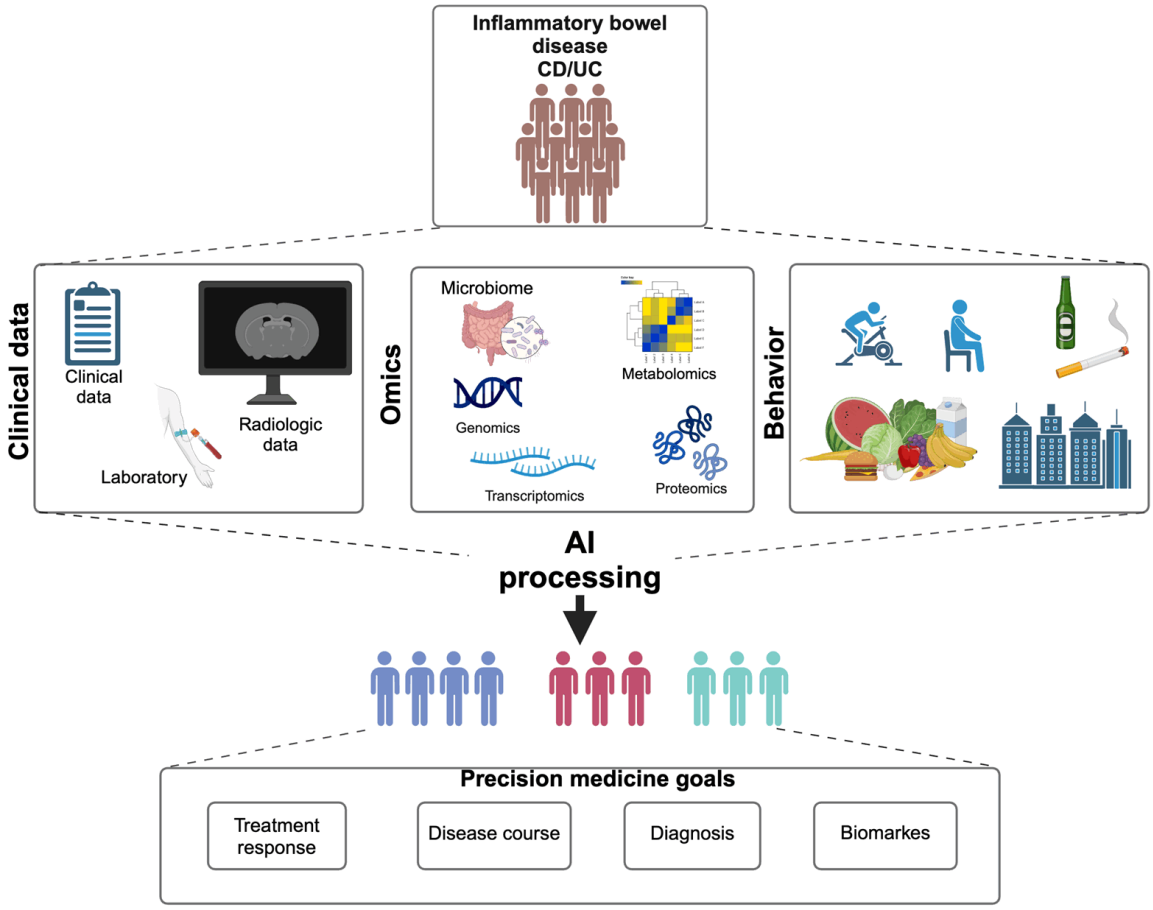

Figure 1. Workflow of AI-assisted precision medicine in IBD: This figure illustrates the integration of clinical data, omics (microbiome, genomics, metabolomics), and behavioral factors related to inflammatory bowel disease (IBD) into artificial intelligence (AI) processing aimed at achieving precision medicine goals such as treatment response, disease course prediction, diagnosis, and biomarker identification.

of response within a few years [4]. Around 80% of patients with CD will require surgical intervention over their lifetime [5]. Although the risk of post-surgical recurrence remains high [6], effective predictors for this outcome are still lacking [7]. Furthermore, in up to 15% of all IBD cases, a definitive distinction between UC and CD cannot be made during the initial diagnosis [8]. This difficulty in diagnosis occurs more frequently in pediatric populations compared to adults [9]. Diagnostic reclassification occurs in some patients, primarily involving a shift from UC to CD diagnosis [10].

Precision medicine (PM) has emerged as a promising approach in healthcare, aiming to tailor medical interventions to each patient's characteristics [11]. Given the disease's heterogeneity, this approach is particularly relevant for IBD. It can identify common factors that define subgroups likely to benefit from specific therapeutic strategies [12].

Artificial Intelligence (AI), especially machine learning (ML) algorithms, provides robust tools for big data analysis and pattern recognition. AI's capacity to integrate and analyze complex, multidimensional datasets, including genomic, metabolomic, microbial, and clinical information, holds the promise of uncovering intricate patterns [13]. In IBD, AI applications may improve diagnostic accuracy, predict individual patient treatment response, and forecast disease progression. **Figure 1** shows the workflow of AI-assisted precision medicine in IBD.

The synergy between PM and AI presents a transformative opportunity to improve patient outcome in IBD. This approach addresses the current challenges in IBD management and

paves the way for more targeted and effective interventions.

This systematic review (SR) explores the intersection of AI and precision medicine in IBD. By analyzing the current literature, this study investigates the potential applications of AI-driven PM in enhancing IBD management.

Materials and methods

We conducted a SR following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations [14]. A protocol was registered in PROSPERO (CRD42023373601). We performed a comprehensive search across PubMed, PubMed PMC, BVS, Scopus, Web of Science, Embase, Cochrane, and ProQuest databases, using the following search string: ("Inflammatory Bowel Diseases" OR "Colitis, Ulcerative" OR "Crohn Disease" OR Colitis) AND ("Artificial Intelligence" OR "Machine Learning" OR "Supervised Machine Learning" OR "Unsupervised Machine Learning" OR "Big Data" OR "Deep Learning" OR "Precision Medicine").

Inclusion criteria

The articles were included in this review based on the following criteria: (1) Human studies on IBD (UC and/or CD) patients; (2) AI application in PM; (3) Comparative, randomized, cross-sectional, retrospective, prospective, or cohort studies were included.

Exclusion criteria

Articles that met any of the following criteria were excluded from the review: (1) reviews, letters, editorials, and conference presentations; (2) studies on non-IBD subjects; (3) studies not distinguishing between CD and UC; (4) incomplete data; (5) AI applied solely to imaging data; and (6) IBD data used only for method validation.

Study selection

Study selection was conducted in two stages. First, two independent reviewers (HDC, TAOS) assessed titles and abstracts based on the inclusion or exclusion criteria, with a third reviewer (LMG) resolving any conflicts. Subsequently, the same two independent reviewers assessed the full text of the previously selected articles, with a third reviewer resolving conflicts. We utilized Rayyan software for organization and data storage [15].

Results

A total of 10,293 studies were initially identified, yielding 5,633 unique records after deduplication. Following title and abstract screening, 453 studies were selected for full-text review. Upon application of the eligibility criteria, 139 studies were included in the SR. **Figure 2** illustrates the PRISMA flow diagram detailing the study selection process.

We observed a significant upward trend in publication frequency among the included studies over recent years, with more than 70% of the studies published from 2020 onwards (**Figure 3A**).

Regarding the geographical distribution of study populations, excluding post hoc analyses of publicly available databases due to lack of information, we noted a concentration of studies in Asian countries (primarily China and South Korea), North America (the United States and Canada), and European nations. No studies were conducted in African countries; only one was done in Latin America (**Figure 3B**).

Our analysis of AI application objectives in PM allowed us to classify the studies into three main categories: (i) diagnosis, (ii) prognosis, and (iii) treatment response. Eleven publications [16-26] were concurrently classified into two categories.

Critical factors in the application of AI include the data used, algorithms employed, distribution of the study population (balanced or unbalanced data), training process, and performance metrics.

The median sample size was 237 patients (10 to 95,878). Of note, most studies presented unbalanced data in their analyses. Machine learning algorithms were predominantly used across all three categories, with random forest, logistic regression, support vector machines, artificial neural networks, and boosting algorithms being the most utilized (**Figure 4A**). Ensemble methods combining multiple algorithms were used in three studies [34, 89, 105].

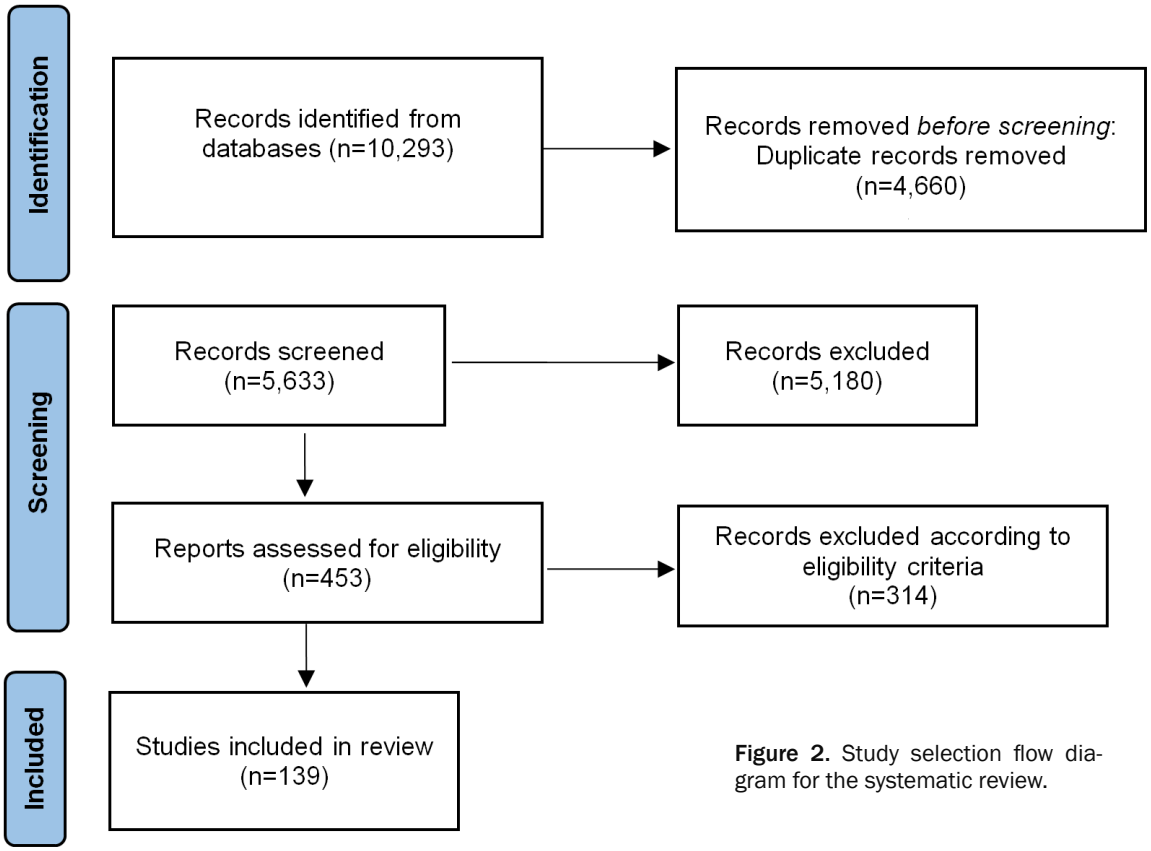

Figure 2. Study selection flow diagram for the systematic review.

The analyses used various types of data. We observed a clear distinction between diagnosis, prognosis, and treatment response studies (**Figure 4B**).

Omics data, including transcriptomics (gene expression profiles from various tissues, non-coding RNA (Ribonucleic Acid) analysis, and single nucleotide polymorphisms), microbiome (primarily through bacterial and fungal sequencing), and metabolomics (from blood, feces, and other tissues), were often employed for diagnosis (**Figure 4B**). In contrast, clinical, laboratory, and demographic (non-omics) data were more frequently employed for predicting treatment response and disease prognosis (**Figure 3B**). Several studies integrated these non-omics data with omics information [19, 20, 27-33].

For model development, researchers employed various training and testing techniques (Supplementary Table 1). The most used technique was the random split of the dataset into training and test sets. Cross-validation was also frequently used, either in combination with the train-test split or alone. For post hoc analyses, it was common to combine databases for training while holding out one or more databases for subsequent model validation.

The area under the receiver operating characteristic curve (AUC) was the most commonly used performance evaluation metric, although some analyses reported only accuracy values as their primary evaluation metric. Excellent performance could be seen regardless of the PM category (**Table 1**). Comprehensive information is detailed in Supplementary Table 1.

Artificial intelligence for diagnosis

Diagnostic evaluation in IBD was the most frequently studied category, with 64 publications. As previously presented, most studies implemented ML algorithms; however, six studies used them to identify diagnostic predictors [82-87].

The majority of studies focused on predicting CD or UC versus control groups. Only 18 [16, 17, 19, 34-36, 38, 40, 45, 52, 54, 61-65, 73,

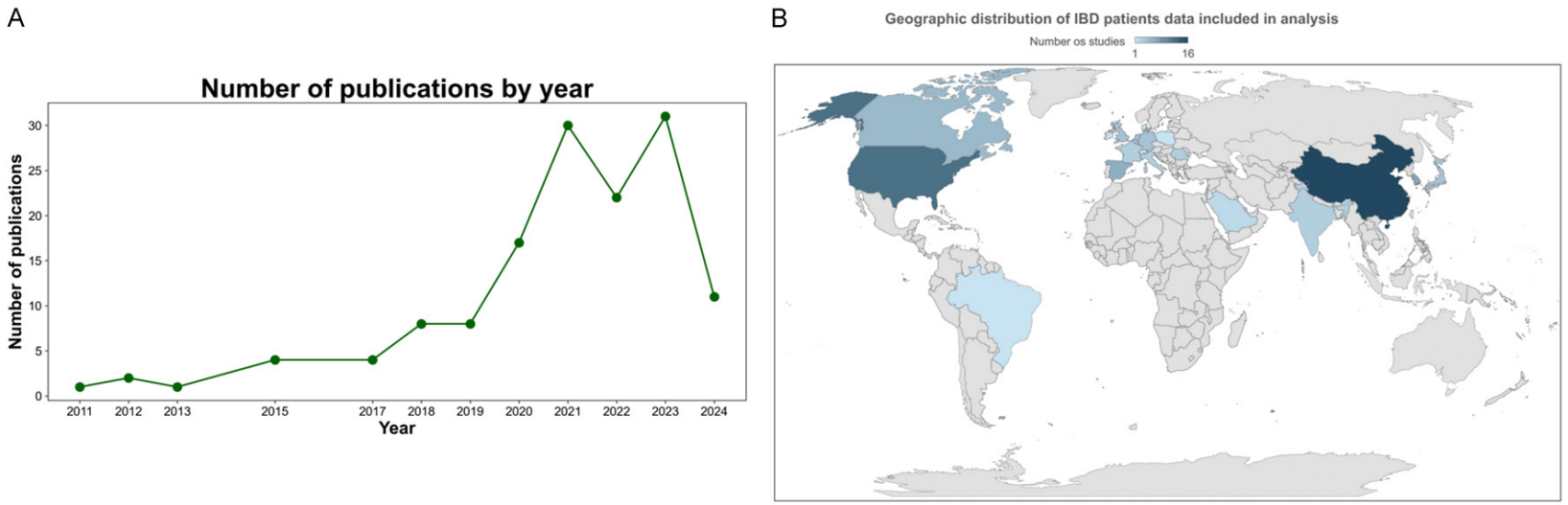

Figure 3. Distribution of the studies included in the systematic review. A. Number of publications per year up to February 2024 (N=139). No papers were selected in 2014 and 2016. B. Geographic distribution of studied populations, after excluding post hoc studies (N=82).

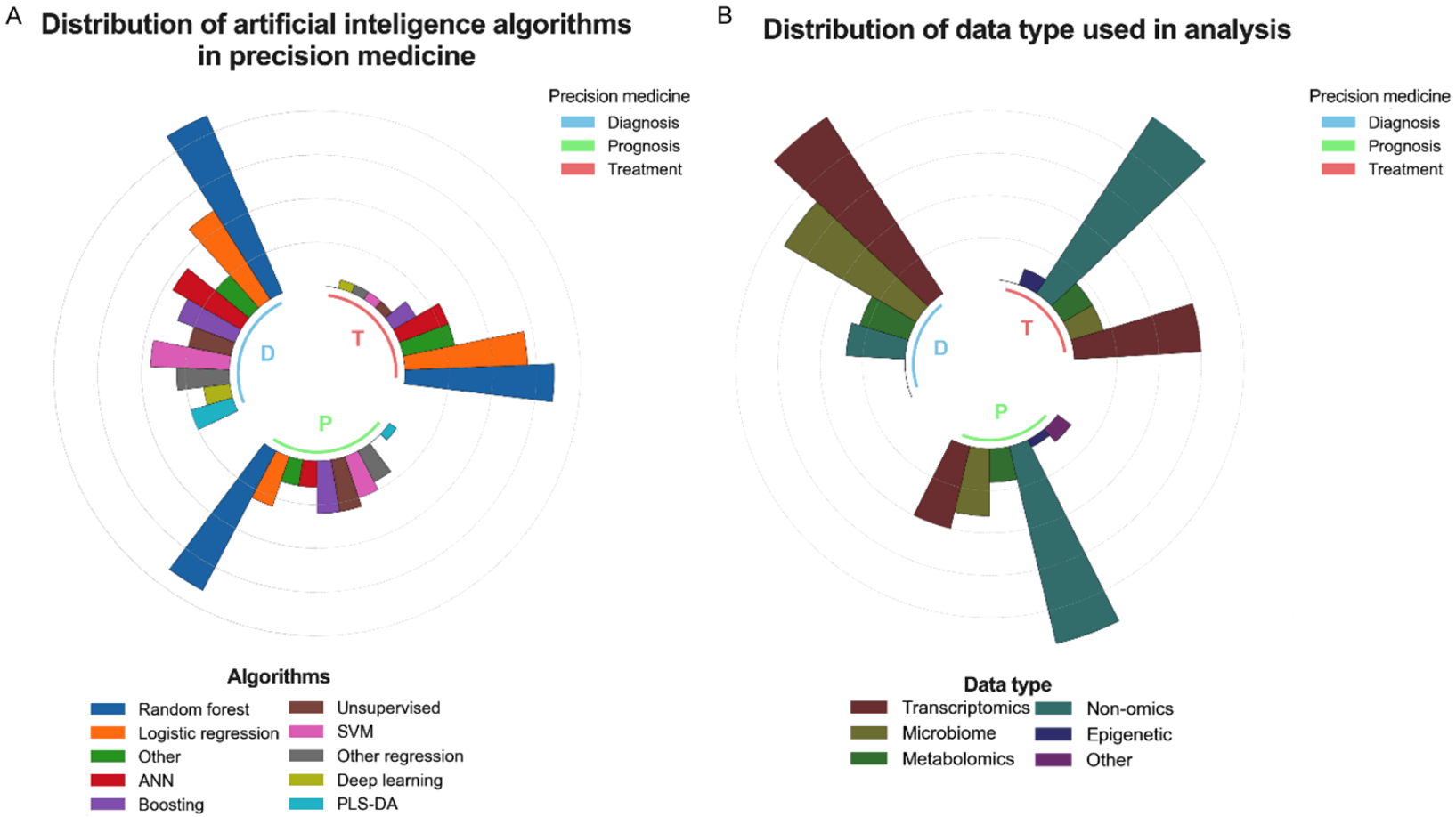

Figure 4. Circular bar plots illustrate AI algorithms and data types used across Diagnosis (D), Prognosis (P), and Treatment (T) in precision medicine applications. A. Random Forest and logistic regression demonstrate predominance across categories. Other methodologies, such as artificial neural networks, boosting techniques, and support vector machines, exhibit variable utilization, highlighting diverse applications of AI algorithms. B. Transcriptomics (gene expression, non-coding RNA, and single nucleotide polymorphisms) and non-omics data (clinical, laboratory, and demographic) predominate, particularly in diagnosis and prognosis/treatment response, respectively. ANN, artificial neural networks; SVM, support vector machines; PLS-DA, Partial least squares-discriminant analysis.

Table 1. Model performance across precision medicine applications

Reference	Precision medicine category	Metrics	Minimum	Median	Maximum
[16-25, 34-87]	Diagnosis	AUC (N=45)	0.55	0.90131	1
		Accuracy % (N=17)	73	84.2	100
[16-19, 23, 24, 26-28, 122-154]	Prognosis	AUC (N=33)	0.575	0.857	0.9864
		Accuracy % (N=6)	77	92.76	100
[20-22, 25, 26, 29-33, 88-121]	Treatment response	AUC (N=38)	0.56	0.854	1
		Accuracy % (N=4)	73	81.05	98.1

N, number of studies; AUC, area under the ROC curve.

81] evaluated CD vs. UC or UC vs. CD, obtaining a median area under the Receiver Operating Characteristic curve (AUC) of 0.8395 and accuracy of 80.92%. Four studies were unable to distinguish between IBD phenotypes [16, 17, 61, 73].

One study [59] developed a multi-class model based on fecal microbiome data to differentiate several diseases. This model achieved an AUC of 0.93 for both UC and CD in multi-class prediction. However, external validation using data from different geographic locations showed lower performance, with AUCs of 0.693 and 0.798 for UC and CD, respectively.

Eleven studies focused on the pediatric population [23, 38, 39, 46, 47, 55, 61, 68, 69, 71, 80], most comparing disease states to control groups.

Artificial intelligence for treatment adherence and response

A total of 44 studies implemented AI for predicting treatment response and one for adherence to azathioprine [92]. The predictive analysis used diverse data types, including clinical information, laboratory data, and gene expression analysis, with a predominance of non-omic data (**Figure 4B**).

A key element with clinical implications is the definition of treatment response outcomes. Researchers evaluated several metrics for this purpose, including clinical and endoscopic condition-specific scores, such as the Crohn's Disease Activity Index, Pediatric Ulcerative Colitis Activity Index (PUCAI), Mayo score and sub-score, and Simple Endoscopy Score for Crohn's Disease (SES-CD).

Three studies evaluated treatment responses in the pediatric population: one analyzed the response to corticosteroids (AUC 0.77) [29], another examined exclusive enteral nutrition (AUC 0.90) [95], and a third assessed the response to various treatments, including corticosteroids, exclusive enteral nutrition, and mesalazine (accuracy of 77.8%) [22].

Acute severe ulcerative colitis (ASUC), a life-threatening manifestation of UC characterized by the rapid onset of severe inflammation and often requiring hospitalization, was evaluated in terms of general response to various treatments [30], response to corticosteroids, infliximab, and cyclosporine separately [33], and response to corticosteroids alone [93]. Overall, the prediction for treatment response AUCs ranged from 0.703 to 0.97.

Biologics and small molecules are pivotal in treating inflammatory bowel disease, offering targeted therapeutic options that modulate the immune response. More than half of the studies evaluated the response to these classes: anti-TNF agents -including infliximab, adalimumab, and golimumab [20, 21, 25, 26, 31, 32, 89, 90, 99-106] demonstrated average AUC values of 0.903 for CD and 0.882 for UC. Studies on the anti-integrin agent vedolizumab [116-118, 120, 121] yielded average AUCs of 0.75 for CD and 0.708 for UC. Ustekinumab, targeting the interleukins IL-12 and IL-23, exhibited average AUCs of 0.808 for CD and 0.839 for UC. Tofacitinib, a Janus kinase inhibitor [109, 110], showed an average AUC of 0.83 for UC.

In one of the studies, Telesco et al. [99] conducted a phase 2a clinical trial with UC patients to validate a predictive model of Golimumab response based on gene expression data from

the intestinal mucosa. The model achieved an AUC of 0.688 for endoscopic response at week six and an AUC of 0.671 for response at week thirty, lower than the initial performance. Some hypotheses for the model's poorer performance were raised, such as differences between training and validation populations.

Artificial intelligence for prognosis in inflammatory bowel disease

Forty-two studies focused on applying AI to the prognostic evaluation of IBDs. While supervised algorithms predominated, the authors employed unsupervised techniques in three articles [141, 145, 147], focusing on finding molecular markers of disease subtypes.

Assessing disease activity in IBD is essential for making effective treatment decisions, monitoring patient progress, and improving overall clinical outcome. Twenty-two studies [16-19, 23, 26, 122, 126-140] predicted disease activity based on various data with overall good performance.

Nine studies examined the clinical course of IBD [24, 141, 142, 145, 147, 148], with three focusing on the stricturing phenotype in CD [122, 143, 144]. In one of the studies, Lee et al. [141] identified, from the gene expression of CD8+ T cells, a panel capable of segregating CD and UC carriers into two groups, called IBD1 and IBD2, with the first group being related to worse outcome (measured through the need for treatment escalation, need for immunomodulator). Biasci and Lee et al. [142] used whole blood gene expression to predict IBD1 (IBDhi) and IBD2 (IBDlo) groups in both CD and UC, making it more feasible from a clinical perspective and constructing a prognostic assay (PredictSURE IBD).

While medical management aims to control inflammation, maintain remission, and improve quality of life, surgery becomes necessary in cases of refractory disease, intestinal obstruction, and severe complications, which are common challenges in IBD. Five studies evaluated the need for surgical intervention [27, 28, 122-124], while post-surgical recurrence was the subject of analysis in four investigations [88, 151-153].

Additionally, three studies addressed specific aspects of IBD prognosis: postoperative complications [125], diagnosis of intra-abdominal abscess [146], and sarcopenia [154].

Discussion

This SR revealed a growing interest in applying AI, particularly ML, for PM in IBDs. There has been a significant increase in publications in recent years, reflecting a broader trend observed across disciplines where AI is gaining prominence.

As mentioned earlier, the assessment of the geographical distribution of studies indicates a predominance of research from the United States of America, European countries, and Asian nations. Considering the multifactorial etiology of IBDs, which involves complex interactions between genetic and environmental factors, this geographic concentration limits the generalizability of results to populations from underrepresented regions, especially if stool microbiome or metabolomics are involved [155].

Almost no studies shared how the analysis was done in-depth, like a code or a GitHub project with analysis. This could be an essential step in facilitating validation studies in the future.

Regarding the strategies for model development, many studies employed only train-test splits, which, in theory, requires an extensive sample size to ensure adequate generalization. However, given that several studies presented limited sample sizes, a more restrictive interpretation of the results is advised. Applying techniques such as cross-validation and its variants, in conjunction or not with the training split, can significantly increase the robustness and reliability of the obtained results and should be used.

To enable practical application by clinicians, machine learning algorithms must provide insights into the reasoning behind their decisions. Although simpler models like logistic regression offer greater interpretability, their predictive performance often falls short of more advanced algorithms, such as random forest or gradient boosting algorithms. Currently, techniques that assist us in interpreting complex models, such as Shapley values [156],

are available, facilitating the use of more complex models, especially for medical practice.

While the practical application of AI in clinical settings remains challenging, many studies in our review employed advanced omics data (such as gene expression, microbiome sequencing, and metabolomics) for various clinical purposes, likely due to reduced processing costs and the development of analytical techniques [157]. Given that the integration of such data in routine clinical practice is still emerging, we believe these studies may represent the first steps toward translational research in the field.

The identified PM categories in this SR are highly relevant to clinical practice and represent significant gaps in current knowledge in managing IBD.

Accurate and early diagnosis offers the possibility of altering the natural history of the disease, since a delayed diagnosis is associated with complications in CD and the need for surgery in both UC and CD [158]. Among the studies that used AI for IBD diagnosis, the majority evaluated UC or CD versus a control group, which has less clinical relevance, and in only one study were other clinical conditions incorporated into the predictive model [59]. From a practical standpoint, studies that evaluate IBD diagnosis against the primary differential diagnoses have significant clinical relevance and may be the focus of future studies.

Analysis of treatment response primarily evaluated the use of biologics and small molecule classes, which represent the main targeted therapy currently available and, as discussed, are very relevant in the clinical context. The lack of pre-treatment tests for predicting response remains a significant challenge, and the availability of such analysis is crucial in clinical practice. Even without validation, the results presented are promising, and well-conducted validation studies are necessary.

The IBD prognosis has seen a wide range of applications, with particular emphasis on disease activity prediction. Identifying relapse is a crucial aspect of patient follow-up. Currently, this information is obtained either subjectively (through clinical scales) or objectively (by fecal calprotectin, endoscopic, or radiological evaluation) [159-161]. Given the limitations and challenges associated with objective methods [162], developing and validating a model to predict disease activity holds significant practical application, and validation studies should be carried out.

Another relevant application was for predicting disease course. Recently, Noor et al. [163] published data from a randomized clinical trial that evaluated the previously described prognostic assay [142]. Two main outcomes were analyzed: evaluating the marker and comparing step-up versus top-down treatment in newly diagnosed CD patients. In this scenario, the assay could not predict the course of the disease.

Although Noor et al. and Telesco et al. did not validate the disease course and treatment response models, these results provide crucial information for future research, highlighting the importance of robust models built from systematic data collection and well-defined outcomes. In light of these findings, Wyatt et al. [164] published a prospective study protocol to analyze multi-omics data to develop predictive tools for treatment response in IBD.

This study presents limitations that should be considered when interpreting the results. First, the methodological heterogeneity among the included studies prevented the performance of a meta-analysis, limiting the quantitative synthesis. The exclusion of studies focused on image analysis may have omitted relevant information about AI applications in imaging diagnosis in IBDs. However, this topic has already been fully discussed in the literature, and we would like to raise other aspects of AI and PM in IBD that have not yet been covered. Furthermore, the variability in sample sizes, validation methods, and performance metrics across studies makes direct comparisons difficult. Almost all studies are observational, post hoc analysis, or retrospective; therefore, clinical trials are needed to validate the results.

Conclusion

The application of AI in IBD shows significant potential to enhance clinical practice. The results demonstrated promising predictive performance, particularly in disease prognosis and predicting treatment response. However, clinical implementation of these models requires

additional validation in other cohorts of patients and a more significant number of participants. Successful integration of AI in IBD management depends on developing standardized protocols, clearly defining clinically significant outcomes, and fostering interdisciplinary collaboration. Future studies should focus on validating and evaluating the actual clinical impact of these tools. The evolution of AI in IBD has the potential to refine our understanding of the pathophysiology and to personalize therapeutic interventions to improve outcomes.

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Disclosure of conflict of interest

None.

Abbreviations

AI, Artificial Intelligence; AUC, Area Under the Receiver Operating Characteristic Curve; ASUC, Acute severe ulcerative colitis; BVS, Biblioteca Virtual em Saúde; CD, Crohn's Disease; IBD, Inflammatory Bowel Disease; ML, Machine Learning; PM, Precision Medicine; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PUCAI, Pediatric Ulcerative Colitis Activity Index; RNA, Ribonucleic Acid; SES-CD, Simple Endoscopic Score for Crohn's Disease; SR, Systematic Review; TNF, Tumor Necrosis Factor; UC, Ulcerative Colitis.

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Supplementary Table 1. Description of all manuscripts included in the systematic review

Article	Year	Precision medicine	Population size - Country	Data used	Algorithm	Training and validation strategy	External validation	Best results
Zhang et al. [34]	2012	Diagnosis	Prospective study with 94 IBD (57 ileal CD, 37 UC) and 35 controls - United States of America	Mucosal gene expression	Ensemble	One cohort for training and the other for testing	Yes	Ileal CD vs. non-CD (control + UC) accuracy was 89% and 80% in the training and testing set, respectively.
Duttagupta et al. [35]	2012	Diagnosis	Case-control study with 20 UC and 20 controls - United States of America	Microarray analysis of miRNA expression levels in micro-vesicle, PBMC, and platelet fraction	Support vector machine, Hierarchical clustering	Train-test split 100 times	No	UC vs. control accuracy was 92.8% - data derived from platelet fraction.
Hübenthal et al. [36]	2015	Diagnosis	40 CD, 36 UC, and 38 health controls from Germany and 130 inflammation controls (IC) [GSE31568]	miRNAs expression from whole blood	Elastic SCAD support vector machine	Train-test split	No	AUC was 0.889, 0.984, and 1 for CD vs. UC, CD vs. IC, and UC vs. IC, respectively.
Mirza et al. [37]	2015	Diagnosis	Cross-sectional study with 13 CD, 20 UC, and 12 controls - Denmark	Mucosal transcriptomics	Support vector machine	Leave-one-out cross-validation	No	Inflamed CD vs. inflamed UC model accuracy was 77.8%.
Mossotto et al. [38]	2017	Diagnosis	Pediatric prospective study with 178 CD and 80 UC - England	Endoscopy and histology data	Linear support vector machine	Data were split by discovery, training, and validation set with cross-validation	No	CD vs. UC AUC was 0.87.
El Mouzan et al. [39]	2018	Diagnosis	Pediatric prospective study with 15 CD and 20 controls - Saudi Arabia	Fungal ITS sequencing from stool	Logistic regression	100 (iterative) 5-fold cross-validation	No	CD vs. control AUC was 0.85.
Klein et al. [40]	2020	Diagnosis	Retrospective study with 28 IBD (14 UC, 14 CD) and 14 controls - Germany	Mass spectrometry	Linear discriminant analysis	Leave-one-out cross-validation	No	Discrimination between UC and CD accuracy was 78.6% (UC 85.7%, CD 71.4%).
Kedia et al. [41]	2021	Diagnosis	Prospective study with 24 UC, 19 ASUC, and 50 controls - India	16S rRNA sequencing from stool	Random forest	50 (iterative) train-test splits		UC vs. ASUC AUC was 0.98 and 0.99, considering genus and class taxonomy levels, respectively.
Khorasani et al. [42]	2020	Diagnosis	Post hoc analysis [GSE1152, GSE11223, GSE22619, GSE75214 (for training)] with 39 UC and 38 controls - United States of America, Belgium, and Germany	Mucosal gene expression	Support vector machine	Three datasets for training with 5-fold cross-validation and one for validation	Yes	The gene model achieved average precision of 1 and 0.62 for active UC patients vs. controls and inactive UC vs. controls, respectively.
Li et al. [43]	2020	Diagnosis	Post hoc analysis [GSE109142, GSE92415] with 313 UC and 41 controls	Mucosal gene expression	Random forest, artificial neural network	One cohort for training and the other for validation	Yes	UC vs. control in the validation set reached an AUC of 0.9506.
Lins Neto MÁ et al. [44]	2020	Diagnosis	Cross-sectional study with 21 IBD (10 DC, 11UC) and 15 controls - Brazil	Fecal metabolomics	Partial least squares discriminant analysis	Cross-validation	No	Controls vs. CD accuracy was 100%. Controls vs. UC accuracy was 69%.
Xu et al. [45]	2021	Diagnosis	Post hoc analysis 94 IBD (81UC, 13 CD) e 177 controls - Spain and Denmark	Stool 16S rRNA and metagenomics	Light gradient boosting	5-fold cross-validation	No	UC vs. CD AUC was 0.989 and 0.963 using metagenomics 16s rRNA, respectively.
Dhaliwal et al. [46]	2021	Diagnosis	Pediatric prospective study with 58 IBD (41 UC, 17 CD) for training, and 15 IBD (14 UC, 1 CD) for validation - Canada	Baseline clinical, endoscopic, radiologic, and histologic	Random Forest, similarity Network Fusion	Samples were split into training and validation with leave-one-out cross-validation	No	Two groups without complete segregation between CD and UC were seen. Diagnostic, predictive model accuracy was 97% and 100% for training and validation, respectively.

El Mouzan et al. [47]	2021	Diagnosis	Pediatric prospective study with 17 CD and 18 controls - Saudi Arabia	16s rRNA sequencing from stool and mucosal biopsies	Logistic regression	5-Fold cross-validation 100 (iterative) times	No	CD vs. controls AUC was 0.97.
Iablokov et al. [48]	2020	Diagnosis	Post hoc analysis with 294 CD, 191 UC, and 667 controls - Spain, China, and Netherlands	16S rRNA from stool	Random forest	Train-test split and leave-one-dataset out	No	Taxonomy-based classifier AUC was 0.887 for CD vs. control and 0.7656 for UC vs. control.
Kraszewski et al. [49]	2021	Diagnosis	Cross-sectional study with 372 IBD (180 UC, 192 CD) and 271 controls - Poland	Clinical and laboratory	Random forest	Train-test split	No	Average precision was 97% and 91% for predicting CD and UC from controls, respectively.
Li et al. [50]	2021	Diagnosis	95 CD (58 active and 37 inactive) and 48 controls - China	Raman spectroscopy from urine	PCA-Support vector machine	Leave-one-patient-out	No	CD vs. control accuracy was 82.5%.
Lu et al. [51]	2022	Diagnosis	Post hoc analysis [GSE87473 and GSE48634] with 174 UC and 90 controls	Mucosal gene expression	Logistic regression	5-fold cross-validation for training and one dataset for validation	Yes	UC vs. control AUC was 0.8497 and 0.7208 in training and validation, respectively.
Manandhar et al. [52]	2021	Diagnosis	Post hoc analysis with 729 IBD, 700 non-IBD, 331 CD, and 141 UC	16s rRNA from stool	Random forest	50 (iterative) times train-test splits with 10-fold cross-validation	No	CD vs. UC AUC was 0,92.
Notararigo et al. [53]	2021	Diagnosis	Case-control study with 19 CD, 9 UC, and 10 controls - Spain	Blood serum metabolomics	Orthogonal-partial least squares discriminant analysis	Cross-validation	No	Accuracy was 93.3% for CD vs. control and 68.7% for UC vs. control.
Park et al. [54]	2021	Diagnosis	94 CD and 33 UC - South Korea	Mucosal gene expression	Partial least squares discriminant analysis	Iterative cross-validation with random splits	No	Accuracy was 96.2% for CD vs. UC and 85.3% for inflamed CD vs. inflamed UC.
Schneider et al. [55]	2021	Diagnosis	Pediatric prospective study with CEDATA-GPGE data with different subsets of patients - German-speaking Countries	Laboratory and endoscopy data	Convolutional neural network	Train-test split with 10-fold cross-validation	No	Considering data from the follow-up set, CD vs. UC accuracy was 86.15%, while data from 2018 was 90.57%.
Carreras [56]	2022	Diagnosis	Post hoc analysis [GSE38713] with 30 UC and 13 controls - Spain	Mucosal gene expression	C5, logistic regression, neural network, support vector machine, discriminant XGBoost	Not informed	No	Seven different models reached an accuracy of 100% for UC vs. control.
Nowak et al. [57]	2022	Diagnosis	Post hoc analysis with adults and children's patients with 100 UC, 99 CD, and 95 controls - Poland	Whole-blood gene expression	LASSO regression	10-fold cross-validation	No	AUC was 0.87 for UC vs. control and 0.83 for CD vs. control.
Yang et al. [58]	2022	Diagnosis	Post hoc analysis [GSE16879, GSE112366 for training and GSE36807 for validation] with 191 CD, 45 controls	Mucosal gene expression	Neural network	One cohort for training (with train-test split and 10-fold 100-repeated cross-validation) and another for validation	Yes	CD vs. control AUC was 0.984 and 0.945 in training and validation, respectively.
Su et al. [59]	2022	Diagnosis	2030 patients (colorectal cancer n=174, colorectal adenomas n=168, CD n=200, UC, n=147, irritable bowel syndrome n=145, obesity n=148, cardiovascular disease n=143, post-acute COVID-19 syndrome n=302 and healthy controls n=893) - China + External dataset from 12 studies	Stool metagenomics	Random forest	Train-test split with 20 (iterative) 5-fold cross-validation	Yes	Multi-class prediction for UC and CD reached an AUC of 0.93 for both classes. External validation (different locations) reached an AUC of 0.693 and 0.798 for UC and CD, respectively.

Bu et al. [60]	2022	Diagnosis	Post hoc analysis with [GSE87466, GSE107597 as training and GSE13367 for validation] 163 patients	Mucosal gene expression	Logistic regression	Two datasets for training and another for validation	Yes	UC vs. control AUC was 0.977 and 0.889 in training and validation sets, respectively.
Jagt et al. [61]	2022	Diagnosis	Pediatric case-control study with 40 CD, 38 UC, and 105 controls from Belgium	Stool metabolomics (amino acids)	Random forest	Train-test split	No	UC vs. CD accuracy was 58%, while CD vs. control and UC vs. control accuracy were 80% and 90%, respectively.
Kim et al. [62]	2023	Diagnosis	Prospective study with 670 CD, 113 UC, and 1063 controls - South Korea	16S rRNA from stool	Sparse partial least squares discriminant analysis	100 (iterative) train-test splits	No	CD vs. UC AUC was 0.988.
Kang et al. [63]	2023	Diagnosis	173 CD, 259 UC, and 50 controls for training - Korea 50 CD and 30 UC patients from the United States of America for validation	Stool metagenomics	Regularized logistic regression	Train-test split with 10-fold cross-validation	Yes	CD vs. UC AUC was 0.873, 0.778, and 0.633 in training, testing, and validations sets, respectively.
Alfonso Perez and Castillo [64]	2023	Diagnosis	Post hoc analysis [GSE193677] with 1157 CD, 872 UC, and 461 controls - United States of America	Mucosal gene expression	Bagged tree	Train-test split with 10-fold cross-validation	No	CD vs. UC accuracy was 73.4%.
Shen et al. [65]	2023	Diagnosis	Post hoc analysis [GSE134809, GSE112366 and GSE75214] with 436 IBD and 26 controls	Mucosal gene expression and single-cell analysis	Naïve Bayes and convolutional neural network	One dataset for training with 10 (iterative) 5-fold cross-validation and others for validation	Yes	CD vs. control AUC was 0.905 and 0.963 in training and external validation, respectively. Using GSE75214 (CD and UC samples), the model could discriminate CD vs. UC with an AUC of 0.771. Using CNN integrating single-cell and gene expression data, AUC was 0.9111 in training and 0.963 in testing.
Qian et al. [66]	2023	Diagnosis	Post hoc analysis [GSE87466, GSE75214] with 184 UC and 43 control and [GSE87473] 106 UC and 21 controls for validation	Mucosa gene expression	Logistic regression	The training set was divided into four groups (46 UC and 43 controls) with 5-fold cross-validation	Yes	UC vs. control AUC was 1.0 and 0.995 in training and validation sets, respectively.
Hong et al. [67]	2023	Diagnosis	Post hoc analysis [GSE36807, GSE87466, GSE87473, GSE38713, GSE3629, GSE16879, GSE23597, GSE53306, GSE48959, GSE75214, and GSE13367] with UC and control patients total of 1187	Mucosa gene expression	Random forest and extreme gradient boosting	GSE87473 for training and GSE38713 for testing	Yes	Both models reached an AUC of 1 for UC vs. control.
Shah et al. [68]	2022	Diagnosis	Post hoc analysis with 447 pediatric patients CD and 222 controls - Canada and the United States of America	Mucosal microbiome 16S rRNA	Random forest	Train-test split	No	CD vs. control AUCs ~ 0.85 - 0.91.

Zheng et al. [69]	2023	Diagnosis	Post hoc analysis [GSE57945, GSE93624, GSE101794, GSE117875 for testing and GSE62207 for validation] with 947 pediatric CD and 185 controls	Mucosa gene expression	Artificial neural network	Four datasets for training with 5-fold cross-validation and one for testing	Yes	CD vs. control AUC was 0.954 and 0.889 in training and testing sets, respectively.
Kang et al. [70]	2023	Diagnosis	Prospective study with127 CD, 175 UC, and 100 controls - South Korea	Saliva 16s rRNA	Sparse Partial Least Squares Discriminant Analysis	100 (iterative) train-test splits	No	CD vs. UC AUC was 0.923.
Zhan et al. [71]	2023	Diagnosis	Post hoc analysis [GSE10616] with pediatric 31 CD and 11 controls	Mucosal gene expression	Random forest	5-fold cross-validation	No	CD vs. controls AUC was 1.
Mo et al. [72]	2023	Diagnosis	Post hoc analysis [GSE182270, GSE87466, GSE75214, GSE165512, and GSE190595] with UC and control data	Mucosal gene expression	Support vector machine	One dataset for training with 10 (iterative) 5-fold cross-validation and another one for validation	Yes	UC vs. control AUC was 0.991.
Stafford et al. [73]	2023	Diagnosis	600 CD, 306 UC - United Kingdom	Whole exome sequencing from blood	Random forest	Train-test split	No	CD vs. UC AUC was 0.68.
Wu et al. [74]	2024	Diagnosis	Post hoc analysis [PRJEB33711, PRJNA50637, PRJDB6133, PRJNA368966, PRJNA296920, PRJNA431126, PRJNA596546, PRJNA681685, PRJNA753210, PRJNA541040, PRJNA398089, PRJNA386260] with 873UC, 746 controls - Japan, United States of America and China	Stool 16S rRNA	Deep Neural Network	Train-test split	No	UC vs. control AUC was 0.96.
Chen et al. [75]	2023	Diagnosis	Post hoc analysis [GSE75214, GSE126124 and GSE186582 for training and GSE95095 and GSE179285 for validation] with 671 CD and 109 controls	Mucosa gene expression	Logistic regression	Three datasets combined for training and two independent sets for validation	Yes	Filtered genes from different approaches were fitted into a logistic regression model that reached an AUC of 0.969 in training and 0.83 in validation sets.
Zhang et al. [76]	2024	Diagnosis	Post hoc analysis [GSE87466 for training and GSE47908, GSE59076, GSE75214, GSE92415, GSE14580 for validation] with 398 UC and 101 controls	Mucosal gene expression	Artificial neural network	One dataset for training and five for validation	Yes	UC vs. control AUC was 0.970 and 1 in training and testing sets, respectively. Considering five validation sets, the mean AUC was 0.9588.
Sokollik et al. [77]	2023	Diagnosis	Prospective study with 176 IBD (50 CD, 50 UC, and 76 IBD-U) - Switzerland	Anti-body profiles	Logistic regression, extreme gradient boosting	Train-test split with 5-fold cross-validation	No	Multiclass (CD vs. UC vs. IBD-U) accuracy was 76% and 70% in training and testing sets, respectively.
Gao et al. [78]	2023	Diagnosis	Post hoc analysis with 785 CD and 456 controls for discovery and 85 CD, 92 controls as validation sets - United States of America, China, Spain, and the Netherlands	Stool metagenomics	Neural network	10-fold cross-validation cohort-to-cohort transfer and leave-one-cohort-out validation	Yes	CD vs. control considering species, gene, and SNV AUC was 0.97, 0.95, and 0.77, respectively.
Yang et al. [79]	2024	Diagnosis	Post hoc analysis [GSE87473, GSE87466, GSE165512] with 233 UC and 88 controls - United States of America and Italy	Mucosal gene expression	Artificial neural network	Train-test split	No	UC vs. control AUC was 0.994 and 0.946 in the training and testing sets, respectively.

Tang et al. [80]	2024	Diagnosis	Post hoc analysis [GSE117993, GSE93624] with 302 pediatric CD and 90 control and [GSE101794] 254 pediatric CD and 50 controls for validation	Mucosa gene expression	Support vector machine recursive feature elimination, LASSO regression, gradient boosting, extreme gradient boosting, random forest	Combined datasets for training and one for validation	Yes	Nomogram using the markers genes reached an AUC > 0.8 in the training set and 0.839 in the validation set.
Hu et al. [81]	2024	Diagnosis	154 UC, 181 CD, and 16 controls - Netherlands	Mucosal gene expression and16S rRNA	Extreme gradient boosting	Train-test split with 5-fold cross-validation	No	CD vs. UC AUC was 0.80.
He et al. [82]	2022	Diagnosis	Post hoc analysis [GSE36807, GSE65114] with 44 UC and 27 controls - Spain, USA, Ireland, and Belgian	Mucosal gene expression	LASSO logistic regression and support vector machine	Train-test split	Yes	Six candidate biomarkers (UC vs. controls) were selected and validated in an independent dataset with an overall AUC of 0.9.
Zhang et al. [83]	2022	Diagnosis	Post hoc analysis [GSE48634, GSE6731, GSE114527, GSE13367, GSE36807, and GSE3629 for training and GSE53306, GSE87473, GSE74265, and GSE96665 for testing] with 387 UC patients and 139 controls	Mucosa gene expression	Support vector machine, LASSO, random forest, gradient boosting, principal component analysis, and neural network	Six datasets were used for training and four for testing with 10-fold cross-validation (SMOTE)	No	The study identified two genes, OLFM4 and C4BPB, as potentially helpful in diagnosing UC, with average AUC values > 0.8 in both training and testing datasets.
Tang et al. [84]	2023	Diagnosis	Post hoc analysis [GSE38713, GSE87473, GSE92415, GSE87466] with 298 UC and 55 controls for training and 87 UC and 21 controls for validation	Mucosa gene expression	Random forest, support vector machine, and LASSO regression	Combined datasets for training and one for validation	Yes	Three machine learning methods selected seven signature genes, and a nomogram built with AUC was 0.982 for UC vs. control.
Li et al. [85]	2022	Diagnosis	Post hoc analysis [GSE75214 and GSE87466 for training and GSE37283, GSE134025, GSE160804, GSE38713 and GSE179285 for validation] with 209 UC and 79 controls	Mucosal gene expression	LASSO regression	Two datasets for training and five for testing	Yes	Five predictors were selected, reaching an AUC > 0.7 for predicting UC vs. controls.
Chen et al. [86]	2023	Diagnosis	Post hoc analysis [GSE38713 as the training set and GSE94648 as the test set] with 55 UC and 35 controls	Mucosal gene expression	Random forest	One dataset for training and another for validation	Yes	Seven genes were selected, and the mean AUC in the training set was > 0.9 for UC vs. control.
Wu et al. [87]	2024	Diagnosis	Post hoc analysis [GSE48634, GSE92415 for training, and GSE179285 and GSE107499 for validation] with 297 UC and 121 controls	Gene expression	Random forest and LASSO (feature selection)	Two datasets for training and two for validation	Yes	Three potential predictors were selected after feature selection, and the nomogram built to predict UC vs. control AUC was 0.762 and 0.722 in training and validation, respectively.
Clooney et al. [16]	2021	Diagnosis, Prognosis (activity)	Prospective study with 303 CD, 228 UC, and 161 controls - Ireland and Canada	Stool 16S rRNA	Extreme gradient boosting	N leave-one-out cross-validation	No	CD vs. UC AUC was 0.67. Disease activity (based on fecal calprotectin measurement) prediction AUC was 0.73 for CD and 0.91 for UC.
Bosch et al. [17]	2020	Diagnosis, Prognosis (activity)	Prospective study with 280 IBD patients (164 CD, 112 UC patients, 4 IBD-undetermined) and 227 Controls - Netherlands	Volatile organic compound	Sparse logistic regression	Train-test split	No	CD vs. UC AUC was 0.55. Active disease vs. remission (based on fecal calprotectin measurement) AUC was 0.52 and 0.63 for CD and UC, respectively.

Serrano-Gómez et al. [18]	2021	Diagnosis, Prognosis (activity)	Post-hoc analysis USA (65 CD, 38 UC and 27 controls), European (Spain [34 CD, 33 UC and 67 controls] + Belgium [49 CD])	Stool 16S rRNA	Random forest	USA for training and testing (train-test split) with 10-fold cross-validation and European cohort for validation	Yes	CD vs. non-CD AUC was 0.938. UC vs. non-UC AUC was 0.646. CD relapse vs. remission AUC was 0.769.
Sarrabayrouse et al. [19]	2021	Diagnosis, Prognosis (activity)	Retrospective study with 34 CD, 31 UC, and 28 controls - Belgium and Spain	Clinical, laboratory, and microbiome (fungal and bacterial loads)	Random forest	Train-test split	No	Disease remission (based on clinical scores) AUC was 0.875 for CD and 0.833 for UC. CD vs. UC AUC was 0.759, while for UC vs. CD, it was 0.859.
Zhou et al. [20]	2018	Diagnosis, Treatment response (IFX)	Cross-sectional study with 123 DII (72 DC, 51 UC), 73 controls, and 16 CD - China	Clinical data and 16s rRNA	Random forest	5 (iterative) 10-fold cross-validation	Yes (for diagnosis)	In the diagnosis model (disease vs control), AUC was 0.895 and 0.932 for CD and UC, respectively. The AUC for Prism and Risk data validation was 0.72 and 0.875 for CD and 0.639 and 0.791 for UC, respectively. Infliximab treatment response (based on CDAI) AUC was 0.938.
Ye et al. [21]	2022	Diagnosis, Treatment response (IFX)	Post hoc analysis [GSE16879, GSE111761, GSE42296, GSE107865, GSE179285] with CD and control samples	Gene expression	Logistic regression	One dataset for training and two independent sets for validation	Yes	CD vs. control AUC was 0.917 in the GSE16879 set - the AUCs in GSE179285 and GSE94648 were 0.952 and 0.915, respectively. Those genes could differentiate infliximab response (based on endoscopic and histologic findings) with an AUC of 0.912 in GSE16879 data.
Douglas et al. [22]	2018	Diagnosis, Treatment response	Pediatric case-control study with 20 CD and 20 controls - Scotland + post hoc analysis with 444 CD and 287 controls (RISK) for validation of key features	16s rRNA and shotgun metagenomic	Random forest	Leave-one-out cross-validation	No	16s rRNA at genus level accuracy was 84.2% for CD vs. control. The accuracy of treatment response (based on no need for a second induction) was 77.8%. Top features were tested in the RISK cohort with an accuracy of 73.2%.
Pei et al. [23]	2024	Diagnosis, Prognosis (activity)	Retrospective study with 414 IBD (283 CD, 131 UC), 423 healthy controls, and 344 non-IBD intestinal diseases and a validation set with 100 IBD (76 CD, 24 UC), 108 health controls, and 101 non-IBD and - China	Peripheral blood routine data	Artificial neural network	Train-test split	Yes	UC vs. CD AUC was 0.988 and 1 in training and validation sets, respectively. Active CD vs. remission CD AUC was 0.942 and 0.773 in training and validation sets, respectively. Active UC vs. remission UC AUC was 1 and 0.904 in training and validation sets, respectively.

Montero-Meléndez et al. [24]	2013	Diagnosis, Prognosis (course)	28 IBD (15 UC e 13 CD) e seven controls - United States of America and Spain	Mucosal gene expression	Hierarchical clustering, diagonal linear discriminant analysis	Leave-one-out cross-validation	No	Hierarchical analysis found two distinct subgroups (high and low inflammation status) within CD and UC. The accuracy of predicting those subgroups was 92.3% for CD and 100% for UC. Diagnostic accuracy for CD vs UC was 79%.
Zheng et al. [25]	2024	Diagnosis, Treatment response (IFX)	Post hoc analysis [GSE112366, GSE186582, GSE16879, GSE111761] with more than 148 CD and	Mucosal gene expression	Random forest, LASSO regression	Train-test split	Yes	CD vs. control AUC was 0.897 (random forest). Infliximab non-response AUC was 0.876 (LASSO regression model).
Chen et al. [122]	2024	Prognosis, (course, activity, surgery)	Pediatric prospective study with 120 CD - United States of America	Clinical and mucosal	Extreme gradient boosting	Leave-one-out cross-validation	No	The AUC for predicting strictures was 0.84. Disease remission (based on steroid-free) AUC was 0.83. The AUC for predicting the need for surgery was 0.75.
Jain et al. [123]	2018	Prognosis (surgery)	Retrospective study with 179 ASUC - India	Demographic, clinical, and laboratory	Random forest	Train-test split	No	One year colectomy prediction accuracy was 77%.
Dong et al. [124]	2019	Prognosis (surgery)	Retrospective study with 239 CD patients - China	Demographics, clinical, laboratory, treatment history, and imaging	Random forest	Train-test and split with 10 (iterative) times and 10-fold cross-validation	No	The AUC for predicting the need for surgery was 0.9864.
Kang et al. [27]	2021	Prognosis (surgery)	Prospective study with 463 CD - South Korea	Clinical and single-nucleotide polymorphism	CatBoost	One cohort for train and the other for validation	Yes	Surgery prediction AUC was 0.878 in the training and 0.836 in external validation.
Stidham et al. [28]	2021	Prognosis (surgery)	Retrospective study with 2809 CD - United States of America	Clinical, demographic and laboratory	Logistic regression	#1 30 (iterative) train-test splits with k-fold cross-validation #2 50 (iterative) train-test splits	No	The AUC for predicting the need for surgery was #1 0.781 and #2 0.775.
Sofo et al. [125]	2020	Prognosis (post-surgery complication)	Retrospective study with 32 UC - Italy	Clinical, demographics, and laboratory	Support vector machine	Leave-one-out cross-validation	No	The accuracy was 87.5% for infectious minor complications (wound infection), 91.2% for infectious major complications (intra-abdominal abscess or sepsis), and 84.3% for non-infectious complications.
Bodelier et al. [126]	2015	Prognosis (activity)	Prospective study with 191 CD (active + inactive) and 110 controls - Netherlands	Volatile organic compound	Random Forest	Train-test split	No	Active and inactive (based on HBI score) CD were predicted with an AUC of 0.88.
Waljee et al. [127]	2017	Prognosis (activity)	Retrospective study with 6448 CD e 9863 RU - United States of America	Clinical and laboratory	Random forest	Train-test split	No	Predicting future hospitalizations/ steroid (a proxy for IBD flare), AUC was 0.87 for CD and 0.88 for UC.
Braun et al. [128]	2019	Prognosis (activity)	Prospective study with 45 CD patients - Israel	Stool microbiome 16S rRNA	Random Forest	Uninformed	No	Predicting activity (based on CDAI), AUC was 0.87.

Gan et al. [129]	2021	Prognosis (activity)	Retrospective study with 95,878 (42,977 CD e 40,167 UC) patients - United States of America	Demographic and laboratory data	Random forest	Train-test split	No	Flair (based on an inpatient/emergency visit or an outpatient corticosteroid prescription) AUC was 0.791 and 0.8 for UC and CD, respectively.
Popa et al. [130]	2021	Prognosis (activity)	Prospective study with 371 UC and 115 CD - Romania	Clinical and laboratorial	Neural network	Train-test split with one validation set	No	UC and CD activity (based on histology) AUC was 0.9719 and 0.9641, respectively.
Popa et al. [131]	2021	Prognosis (activity)	Prospective study with 386 UC - Romania	Clinical and laboratorial	Neural network	Train-test split with one validation set	No	UC activity (based on Mayo score) accuracy was 94.37% on the test set and 93.33% on the validation set.
Gomollón et al. [132]	2022	Prognosis (activity)	Retrospective study with 5938 CD - Spain	Demographics, clinical, and laboratory	Random forest	Train-test split	No	Disease relapse AUC was 0.88 with an accuracy of 0.84.
Barberio et al. [133]	2022	Prognosis (activity)	Prospective study with 46 UC (20 active, 26 inactive) and 36 controls - Italy	Stool microbiome 16S rRNA	Sparse partial least squares discriminant analysis, random forest	Train-test split	No	Two predictive models' accuracy was 100% for predicting controls, active and inactive disease.
Li et al. [134]	2022	Prognosis (activity)	Cross-sectional study with 420 UC - China	Demographics, clinical, and laboratory	Random forest and extreme gradient boosting	Train-validation-test split	No	Disease activity based on UCEIS (XGBoost) AUC was 0.8140 and 0.8140 in validation and test sets, respectively. MES model (Random Forest) AUC was 0.8508 and 0.8192 in validation and test sets, respectively.
Fiorino et al. [135]	2022	Prognosis (activity)	Prospective study with 142 UC (108 remission, 35 relapse) - Italy, France, and Spain	Clinical and laboratorial	Logistic regression	Train-test split	No	Relapse vs. remission (based on Mayo score) AUC was 0.754.
Cai et al. [136]	2023	Prognosis (activity)	Retrospective study with 275 UC (177 active, 98 remission) and 601 CD (302 active, 299 remission) - China	Clinical and laboratorial	Support vector machine,	Train-test split with 10-fold cross-validation	No	The AUC for CD active vs. CD remission (based on CDAI) was 0.955 and 0.975 in the training and testing sets, respectively (support vector machine).
					Logistic regression			UC active vs. remission (based on Mayo score) AUC was 0.876 and 0.875 in training and testing sets, respectively (logistic regression model).
Li, et al. [137]	2023	Prognosis (activity)	Retrospective study with 65 UC - China	Demographics, clinical, and laboratory	LASSO regression	3-fold cross-validation	No	Four predictors were selected, and the nomogram-built AUC was 0.860 for the prediction of moderate to severe endoscopic activity.
Pang et al. [138]	2023	Prognosis (activity)	Retrospective cohort study with 292 UC (178 relapse, 114 non-relapse)- China	Clinical, laboratory, and serological data	Random forest	Train-test split	No	Relapse prediction AUC was 0.889 and 0.871 in training and testing sets, respectively.
Gavrilescu et al. [139]	2023	Prognosis (activity)	Prospective study with 187 UC patients - in Romania	Laboratory and IBDQ score	Random forest	Train-test split with 10-fold cross-validation	No	Active vs. remission UC (based on Mayo score) AUC was 0.99 and 0.909 in training and test sets, respectively.
Jangi et al. [140]	2024	Prognosis (activity)	Post hoc analysis [SPARC IBD cohort] with 421 UC patients (104 active UC, 317 remission UC)	Stool fungal (ITS2)	Random forest	Train-test split with 10-fold cross-validation	No	Remission UC vs. active UC (based on PRO-2 ≥ 2) AUC was -0.80.
Wu et al. [26]	2022	Prognosis (activity), Treatment response (ADA, IFX)	188 CD (100 active and 88 inactive) - China	Metabolomics from urine	PCA - Support vector machine	Leave-one-patient-out cross-validation	No	Active CD vs. inactive CD (based on CDAI and endoscopy) AUC was 0.856. ANT-TNF treatment response accuracy was 0.912.

Lee et al. [141]	2011	Prognosis (course)	Prospective study with 35 CD and 32 UC - United Kingdom	CD4 and CD8 T cell gene expression	Consensus clustering	Not applicable	No	Using CD8 T cell expression and consensus clustering, it was possible to identify two distinctive clusters for CD and UC with different disease curse.
Biasci et al. [142]	2019	Prognosis (course)	Prospective study with 69 (39 CD, 30 UC) for model development and 123 (66 DC, 57 UC) patients for validation - United Kingdom	Transcriptomic data from whole blood and CD8 T cells	Consensus clustering	Train-test split with nested leave-one-out cross-validation	Yes	Classifier stratified patients into two distinct subgroups: iBDhi patients experienced significantly more aggressive disease than iBDlo, with earlier need for treatment escalation and more escalations over time.
Ungaro et al. [143]	2021	Prognosis (course)	Pediatric case-cohort study using RISK data with 265 (167 with complications and 98 without) - United States of America and Canada	Clinical, serologies, and protein expression	Random survival forests	200 (iterative) 5-fold cross-validation	No	The protein-based model performed better than serologies-only and clinical variables-only models for predicting stricturing (B2) and penetrating (B3) disease with an AUC of 0.68 and 0.79, respectively.
Wang et al. [144]	2020	Prognosis (course)	Prospective study with 175 IBD (80 UC, 95 CD) e 70 controls - United States of America	Clinical and serum elafin level	Decision forest	Train-test split	No	Stricturing prediction for CD AUC was 0.917.
Sudhakar et al. [145]	2021	Prognosis (course)	Cross-sectional study with 33 CD - Belgium	Blood gene expression, single nucleotide polymorphism	Multi-Omics Factor Analysis	Not applicable	Not applicable	The study identified cell type-specific gene expression signatures, pathways, and hub genes associated with clinical heterogeneity, including disease behavior and location, which could potentially serve as molecular markers for disease subtyping.
Levartovsky et al. [146]	2021	Prognosis (course)	Retrospective study with 309 CD - Israel	Clinical, demographics, and laboratory	Random forest	100 (iterative) times train-test split	No	Prediction of intra-abdominal abscesses (diagnosed based on imaging reports) AUC was 0.817.
Ma et al. [147]	2023	Prognosis (course)	Post hoc analysis [GSE11223, GSE13367, GSE53306, GSE87466, and GSE212849] with 362 UC and 126 controls	Mucosal gene expression	Consensus clustering	Not applicable	Not applicable	Unsupervised analysis classified patients into two subgroups: subgroup I had higher UCSS scores and extensive disease, whereas subgroup II had lower UCSS and limited disease extent.
Chang et al. [148]	2023	Prognosis (course)	Post hoc analysis [GSE87466, GSE107499, GSE59071, GSE48958, GSE47908, GSE36807,15GSE38713, GSE75214, GSE48634, and GSE13367] with 455 UC, 147 controls for training, and one external data with 100 UC for validation	Mucosal gene expression	Hierarchical agglomerative clustering, extreme gradient boosting	Train-test split with 10-fold cross-validation	Yes	Unsupervised analysis revealed three distinct groups with distinct molecular, cellular, and clinical characteristics. Using supervised analysis, it was possible to predict those subtypes with an AUC of 0.9718 and 0.8706 in training and validation sets, respectively.
Joustra et al. [149]	2022	Prognosis (post-surgery recurrence)	Post hoc analysis with 25 CD (12 endoscopic remission, 13 endoscopic recurrence)	DNA methylation	Elastic net classification	Train-test with 50 (iterative) 5-fold cross-validation	No	Endoscopic recurrence vs. remission (based on Rutgeerts scores) AUC was 0.625.

Rajalingam et al. [150]	2023	Prognosis (post-surgery recurrence)	Post hoc analysis [GSE186582] with 37 post-operative CD remission and 84 post-operative CD recurrence	Mucosa gene expression	Logistic regression	Train-test split with 10-fold cross-validation	No	Post-operative CD remission vs recurrence AUC was 0.91.
Cushing et al. [151]	2019	Prognosis (post-surgery recurrence)	Prospective study with 60 CD - United States of America	Mucosal transcriptome	Random Forest and hierarchical clustering	Uninformed	No	Predicting i0 vs i1-i4 Rutgeerts score revealed an out-of-bag estimate error rate of 8.33% for the TNF-naïve patients. Unsupervised analysis identified distinct transcriptome profiles associated with indolent disease course in both anti-TNF-naive and anti-TNF-exposed patients.
Keshteli et al. [152]	2018	Prognosis (post-surgery recurrence)	38 CD patients (28 recurrence; 10 remission) - Canada	Urinary metabolomic	Logistic regression	10-fold cross-validation	No	Endoscopic recurrence after surgery AUC was 0.91.
Sokol et al. [153]	2020	Prognosis (post-surgery recurrence)	Prospective study with 201 CD - France	16s rRNA, clinical and demographic	Random forest	Train-test split	No	Postoperative endoscopic recurrence (based on Rutgeerts score) AUC was 0.81 based on 16s rRNA data only, losing performance when adding clinical data (AUC of 0.786).
Tseng et al. [154]	2022	Prognosis (sarcopenia)	Retrospective study with 167 CD - China	Demographics, clinical, laboratory	LightGBM	Train-test split	No	Sarcopenia prediction AUC was 0.933.
Waljee et al. [88]	2020	Treatment response (6-MCP)	Post hoc analysis [TOPPIC trial] with 117 CD patients	Clinical and laboratorial	LASSO penalized logistic regression, random forest	Train-test split	No	Models did not discriminate well for predicting clinical, endoscopic, or biologic recurrence after surgery, with AUC ranging from 0.50 to 0.62.
Gorenjak et al. [89]	2019	Treatment response (ADA)	Prospective study with 47 CD patients - Slovenia	Mucosal gene expression and single nucleotide polymorphisms	Ensemble	Trai-test split with nested cross-validation	No	Adalimumab response (based on IBDQ score) accuracy was 96.2% at week 12 and 100% at week 20, and 30.
Sakurai et al. [90]	2020	Treatment response (ADA)	Observational study with 9 UC and three controls - Japan	Mucosal gene expression	Hierarchical clustering, logistic regression, naive Bayes, neural network, support vector machine	10-Fold Cross-validation	No	Hierarchical clustering identified three distinct clusters from baseline and 24th-week samples (non-relapses, baseline relapses, and relapses 24th week). Four machine learning models AUC was 1.
Kim et al. [91]	2023	Treatment response (ADA)	Prospective study with 62 UC and 30 controls – South Korea	Stool metabolomics	Support vector machine	Train-test split with 10-fold cross-validation	No	Adalimumab treatment response (based on Mayo score) AUC was 1 and 0.99 in training and testing sets at week 8 and 52, respectively.
Wang et al. [92]	2020	Treatment response (AZA)	Cross-sectional study with 446 CD - China	Clinical and questionnaire data	Support vector machine	Train-test split with 10-fold cross-validation	No	Predicting azathioprine nonadherence, AUC was 0.93.
Haberman et al. [29]	2019	Treatment response (CS)	Pediatric post hoc analysis of PROTECT with 256 UC and 20 controls - Canada and the United States of America	Clinical and mucosal gene expression	Logistic regression	Discovery cohort (N=152) and validation cohort (N=50)	No	Corticosteroid-free remission at week 4 AUC was 0.777.

Ghoshal et al. [30]	2020	Treatment response (CS, IFX, CsA)	Prospective study with 263 ASUC - India	Clinical and laboratorial	Artificial neural network	Train-test split	No	Response to medical treatment (based on CAI) accuracy was 73%.
Yu et al. [93]	2022	Treatment response (CS)	Retrospective study with 129 ASUC (153 responders, 41 non-responders) - China	Clinical, demographics, and laboratory	LASSO Logistic Regression	Discovery cohort with 100 (iterative) train-test splits and another cohort for validation	Yes	Treatment response (based on no requirement for rescue therapy) AUC was 0.873 and 0.703 in internal validation and external validation, respectively.
Takayama et al. [94]	2015	Treatment response (Cytoapheresis)	Retrospective study with 90 UC - Japan	Clinical	Artificial neural network	Train-test split	No	The sensitivity and specificity in predicting the requirement of operation after CAP therapy were 0.96 and 0.97, respectively; no AUC or accuracy was provided.
Jones et al.[95]	2020	Treatment response (EEN)	Pediatric prospective study with 22 CD - Canada	Clinical, 16S rRNA and metagenomics	Random forest	Leave-one-out cross-validation	No	Enteral nutrition response (based on wPCDAI score) AUC was 0.90.
Harun et al. [96]	2024	Treatment response (ETR)	Post hoc analysis [NCT02163759, NCT02171429, NCT02165215 and NCT02165215] with 1,684 UC patients	Demographics, clinical, and laboratory	Extreme gradient boosting	5-fold cross-validation	No	Treatment response (based on Mayo score) at induction and maintenance for Etrolizumab AUC was 0.74 and 0.75, respectively.
Kang et al. [97]	2022	Treatment response (FMT)	Prospective study with 10 UC (4 non-responders, six responders) - Korea	Stool 16S rRNA	LASSO logistic regression	5-fold cross-validation	No	Fecal microbiota transplantation treatment response (based on Mayo score) AUC was 0.844.
Wu et al. [98]	2023	Treatment response (FMT)	Prospective study with 44 UC (13 remissions, 31 non-remission) - China	Serum metabolomics	Random forest	Train-test split with 10-fold cross-validation	No	Clinical remission (based on partial Mayo score) 3 months post-FMT AUC was 0.963.
Telesco et al. [99]	2018	Treatment response (GOL)	Clinical trial with 103 UC - Europe and North America	Mucosal gene expression	k-nearest neighbors	The model was trained data from the ACT1 (infliximab) and PURSUIT (golimumab)		Golimumab endoscopic remission at week 6 AUC was 0.688 and 0,671 at week 30. Clinical response was not possible to predict.
Feng et al. [100]	2021	Treatment response (IFX)	Post hoc analysis [GSE16879, GSE12251, GSE23597] with 148 UC patients - Belgian and United States of America	Mucosal transcriptome	Random forest and artificial neural network	Two cohort for train and the other for validation	Yes	Prediction of primary responders (based on Mayo endoscopic subscore and histological score) AUC was 0.93 and 0.81in training and validation sets, respectively.
Ghiassian et al. [101]	2022	Treatment response (IFX)	Post hoc analysis [GSE14580 and GSE12251] with 46 UC - Belgium	Mucosal gene expression	Artificial neural network	One cohort for the train with leave-one-out cross-validation and the other for validation	Yes	Infliximab non-response (based on no endoscopic and histologic healing) AUC was 0.83.
Zhang et al. [31]	2021	Treatment response (IFX)	Retrospective study with 206 CD (42 primary non-responders) - China	Clinical and single nucleotide polymorphisms	LASSO logistic regression	100 (iterative) train-test splits	No	The AUCs for predicting primary non-response to infliximab (based on SES-CD score) were 0.818 and 0.888 in the training and testing sets, respectively.
Li et al. [102]	2021	Treatment response (IFX)	Prospective and retrospective study with 260 CD patients - China	Cytokines levels	Logistic regression	Retrospective data was used for model development with bootstrapping	No	Primary non-responders to IFX (based on CDAI or need of treatment scalation) AUC was 0.896.

Chen et al. [103]	2021	Treatment response (IFX)	Post hoc analysis [GSE12251, GSE16879, GSE23597, and GSE73661 for validation] with 50 UC patients	Mucosal gene expression	Artificial neural network	Train-test and verification split with 500 (iterative) times	Yes	Response to IFX (based on Mayo endoscopic subscore and histological score) AUC was 0.850 and 0.759 in testing in the validation sets, respectively.
Mishra et al. [104]	2022	Treatment response (IFX)	Prospective study with 19 UC and 18 CD - Germany	Mucosal gene expression and DNA methylation	Random forest	10-fold cross-validation	No	TNF-therapy response at week 14 AUC was 1 and 0.97 for CD and UC, respectively.
Derakhshan Nazari et al. [105]	2023	Treatment response (IFX, ADA)	Post hoc analysis [GSE12251, GSE16879 for discovery cohort and GSE73661 for validation] with 38 UC responders and 19 UC non-responders + prospective study with 10 UC responders and 12 UC non-responders - Iran	Mucosal gene expression	Ensemble	Two datasets for training and two for testing	Yes	Infliximab response (based on Mayo subscore and histologic grade) AUC was 0.991 and 0.981 in discovery and validation, respectively. Iran cohort treated with adalimumab could be predicted with an AUC of 0.948.
Park et al. [32]	2022	Treatment response (IFX, biosimilar)	Post hoc analysis from IMPACT study with 234 CD (14 non-durable response, 220 durable response) - Korea	Clinical and gene expression	LASSO logistic regression	100 (iterative) train-test splits	No	Non-durable response vs. durable response AUC was 0.935.
Li et al. [106]	2021	Treatment response (IFX)	Retrospective study with 174 CD (51 with response) - China	Demographics, clinical, laboratory, and imaging parameters	Random forest	Train-test split with 10-fold cross-validation	No	Prediction of infliximab response (based on CDAI and no surgery needed) AUC was 0.90.
Hassan-Zahraee et al. [107]	2023	Treatment response (RIT)	Post hoc analysis [NCT02958865] with 123 UC	Serum metabolomics	Logistic regression	Not specified	No	Predicting modified remission for Ritlecitinib (based on modified Mayo score, stool frequency, and rectal bleeding), AUC was 0.88, and endoscopic improvement (Mayo endoscopic subscore) AUC was 0.83.
Morilla et al. [33]	2019	Treatment response (CS, CsA, IFX)	Retrospective study with 47 ASUC for model development and 29 ASUC for validation, both - France	Mucosal microRNAs and clinical	Deep neural network, linear discriminant analysis, topological data analysis, random forest	One cohort for train and the other for validation	No	Responders vs. non-responders AUC was 0.97, 0.90, and 0.83 in the discovery set and 0.91, 0.82, and 0.82 in the validation set for corticosteroids, infliximab, and cyclosporine, respectively.
Waljee et al. [60]	2017	Treatment response (TP)	Retrospective study with 1080 (435 UC, 616 CD) - United States of America	Clinical, demographics, and laboratory	Random forest	Train-test split	No	Thiopurines remission AUC was 0.79 for both UC and CD.
Lees et al. [109]	2021	Treatment response (TOFA)	Post hoc analysis [OCTAVE Induction 1 and 2] with 841 UC	Clinical and laboratorial	Logistic regression	Train-test split and 5-fold cross-validation	No	Tofacitinib response at week 8 (based on Mayo score) AUC was 0.87 and 0.88 in training and testing sets, respectively.
Joustra et al. [110]	2023	Treatment response (TOFA)	Prospective study with 31 UC (16 responses, 15 non-response) - Netherlands	DNA methylation	Gradient boosting	Train-test with 100 (iterative) 10-fold cross-validation	No	Tofacitinib UC responders vs. UC non-responders AUC was 0.74 at week 8.
Waljee et al. [111]	2019	Treatment response (UST)	Post hoc analysis [UNITI-1, UNITI-2, and IM-UNITI] with 401 CD patients	Demographic and laboratory	Random forest	100 (iterative) train-test splits	No	The week-8 model AUC was 0.78 for predicting Ustekinumab response (based on CRP) beyond week 42

He et al. [112]	2021	Treatment response (UST)	Post hoc analysis [GSE112366] with 86 CD patients and 26 controls	Mucosal gene expression	Logistic regression	Train-test split	No	Ustekinumab response (based on CDAI) AUC was 0.746 and 0.734 in training and validation sets, respectively.
Chaparro et al. [113]	2022	Treatment response (UST)	Retrospective study with 463 CD - Spain	Clinical and laboratory data	Generalized additive model	10-fold cross-validation	No	Ustekinumab remission (based on HBI) AUC was 0.796.
Liefferinckx et al. [114]	2022	Treatment response (UST)	Retrospective study with 80 CD patients - Belgium	Clinical and laboratorial	Random forest and gradient boosting	Nested cross-validation	No	Gradient boosting and Random Forest reached similar results for predicting clinical response at week 16 with AUC of 0.87 and 0.86, respectively, while endoscopic response based on random forest performed better with AUC of 0.92.
Morikubo et al. [115]	2024	Treatment response (UST)	Retrospective study with 71 UC - Japan	Clinical and laboratorial	Random forest	One cohort for training with 5-fold cross-validation and another for testing	Yes	Steroid-free clinical remission at week 22 AUC was 1 and 0.677 in training and testing sets, respectively.
Waljee et al. [116]	2018	Treatment response (VDZ)	Post hoc analysis [GMEINI 1 trial] with 491 UC	Clinical and laboratorial	Random forest	50 (iterative) train-test splits	No	Corticosteroid-free endoscopic remission at week 52 AUC was 0.73 using data through week 6.
Waljee et al. [117]	2018	Treatment response (VDZ)	Post hoc analysis [NCT00783692] with 472 CD patients	Clinical, demographics, and laboratory	Random forest	50 (iterative) train-test splits	No	Vedolizumab response (no corticosteroid uses and CRP ≤ 5 mg/L) at week 52 AUC was 0.75 using data through week 6.
Dulai et al. [118]	2020	Treatment response (VDZ)	Post hoc analysis from GEMINI 1 trial with 620 UC patients and 199 UC patients from VICTORY	Clinical and laboratorial	Logistic regression	One cohort for train and the other for validation	Yes	Vedolizumab response (based on Mayo score) AUC was 0.65 and 0.64 in training and validation cohorts, respectively. The model was converted into a clinical decision support tool.
Miyoshi et al. [119]	2021	Treatment response (VDZ)	Retrospective study with 69 UC patients - Japan	Clinical and laboratory	Logistic regression, random forest	One cohort for training and the other for validation	Yes	Steroid-free clinical remission (based on Lichtiger) at week 22 accuracy was 100% in training and 68.6% in validation.
Chen et al. [120]	2022	Treatment response (VDZ)	Post hoc analysis with 543 UC patients from VISIBLE 1 and VERSITY data	Demographic, clinical, and laboratory	Elastic net regularized regression	Train-test split with 5-fold cross-validation	No	Vedolizumab remission at week 52 (based on Mayo score) AUC was 0.811.
Venkatapurapu et al. [121]	2022	Treatment response (VDZ)	Post hoc analysis [VERSIFY] with 69 CD	Clinical, laboratory, and demographics	Classification tree	Not informed	No	The responder classifier predicted endoscopic remission (sensitivity of 80% and specificity of 69%) and mucosal healing (sensitivity of 75% and specificity of 70%) over 26 weeks. No AUC or accuracy was reported.

6-MCP, 6-mercaptopurine; ACT1, Active Ulcerative Colitis Trial 1; ADA, Adalimumab; ASUC, acute severe ulcerative colitis; AUC, Area Under the Curve; CD, Crohn's Disease; CDAI, Crohn's Disease Activity Index; CRP, C-Reactive Protein; CS, corticosteroid; CsA, Cyclosporine A; DNA, Deoxyribonucleic Acid; EEN, Exclusive Enteral Nutrition; ETN, Etrolizumab; FMT, Fecal Microbiota Transplantation; GSE, Gene Expression Omnibus Series; HBI, Harvey-Bradshaw Index; IBDQ, Inflammatory Bowel Disease Questionnaire; IFX, Infliximab; ITS, internal transcribed spacer; LASSO, Least Absolute Shrinkage and Selection Operator; LR, Logistic Regression; Mayo score, Mayo Clinic Score; miRNA, microRNAs; NTC, ClinicalTrials.gov identification code; CRP, C-reactive protein; PRO-2, 2-item patient-reported outcome; PRJNA, National Center for Biotechnology Information BioProject database project number; PURSUIT, Program of Ulcerative Colitis Research Studies Utilizing an Investigational Treatment; RIT, ritlecitinib; rRNA, Ribosomal Ribonucleic Acid; SC, Corticosteroid; SES-CD, Simple Endoscopic Score for Crohn's Disease; TOFA, tofacitinib; TOPPIC, Trial of Probiotics in IBD Patients in Clinical Remission; TP, thiopurine; UC, Ulcerative Colitis; UCSS, Ulcerative Colitis Severity Score; UST, ustekinumab; VDZ, vedolizumab; wPCDAI, Weighted Pediatric Crohn's Disease Activity Index.