SYSTEMATIC REVIEW

DOI: http://dx.doi.org/10.15403/jgld-6332

Artificial Intelligence Methods for the Differential Diagnosis of Irritable Bowel Syndrome and Inflammatory Bowel Disease: A Systematic Review

Iolanda Valentina Popa[1], Mihaela Dranga[1,2], Otilia Nedelciuc[1,2], Cătălina Mihai[1,2], Vasile Drug[1,2], Cristina Cijevschi-Prelipcean[2]

1) Faculty of Medicine, Grigore T. Popa University of Medicine and Pharmacy, Iasi; 2) Institute of Gastroenterology and Hepatology, Sf Spiridon County Clinical Emergency Hospital, Iasi, Romania

Address for correspondence:
Mihaela Dranga
Faculty of Medicine, Grigore T. Popa University of Medicine and Pharmacy, Iasi, Institute of Gastroenterology and Hepatology, Sf Spiridon County Clinical Emergency Hospital, Iasi, Romania
mihaela.dranga@umfiasi.ro

Received: 05.06.2025
Accepted: 20.09.2025

ABSTRACT

Background & Aims: Differential diagnosis between irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) represents a major challenge in modern gastroenterology due to overlapping symptoms, limitations of traditional diagnostic methods, and the complexity of their pathophysiology. This review examines the application of artificial intelligence (AI) and machine learning (ML) methods to improve accuracy and efficiency in the differential diagnosis between IBS and IBD.
Methods: The review encompasses seven recent studies employing various AI/ML techniques, utilizing clinical, genetic, microbiomic, and imaging data.
Results: AI-based models exhibit high sensitivity and specificity, with remarkable performance by algorithms such as logistic regression, random forest, neural networks, and support vector machines. Highlighted biomarkers include long non-coding RNA molecules, DNA methylation profiles, and diverse compounds from gut microbiota.
Conclusions: Although AI/ML methods show significant potential for distinguishing IBS from IBD, existing studies present limitations, including small sample sizes, data heterogeneity, and generalizability challenges. The development of standardized protocols and extensive multicenter studies is recommended to clinically validate these models, facilitating their integration into current medical practice.

Key words: irritable bowel syndrome – inflammatory bowel diseases – artificial intelligence – machine learning – biomarkers – differential diagnosis.

Abbreviations: AI: artificial intelligence; IBS: irritable bowel syndrome; IBD: inflammatory bowel disease; ML: machine learning.

INTRODUCTION

Irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) are prevalent gastrointestinal disorders that share overlapping symptoms [1]. A differential diagnosis between IBD and IBS poses significant challenges and represents one of the unresolved issues of modern gastroenterology. Differentiating between the two conditions is fraught with challenges due to similar symptoms, the limitations of current diagnostic methods, and the complexity of the pathophysiology of each condition [2].

Both IBS and IBD present digestive symptoms such as abdominal pain, diarrhea, and bloating. Moreover, many patients with IBD may exhibit typical symptoms of IBS during remission periods [3]. The presence of minimal inflammation in IBD can mimic the symptoms of IBS [4]. Additionally, the clinical presentation of IBD can vary significantly among patients, with some experiencing mild symptoms while others may present severe manifestations [5]. Psychological factors can further blur the boundaries between the two conditions [6].

Current biomarkers used to differentiate one disease from another, such as fecal lactoferrin and calprotectin, have demonstrated variable sensitivity and specificity [7]. Being a multifactorial syndrome and in the absence of biochemical or imaging criteria for diagnosis, the use of validated tests in the diagnosis of IBS is limited [8]. Thus, a study showed that 10% of patients with IBD receive an incorrect diagnosis of IBS before being correctly diagnosed [9]. Moreover, traditional diagnostic methods rely heavily on clinical parameters, endoscopy, and biopsy, which can be invasive, expensive, and time-consuming [10].

The inherent difficulty in distinguishing IBS from IBD underscores the need for novel, objective diagnostic tools. Artificial intelligence (AI) and machine learning (ML) techniques offer a promising avenue for improving diagnostic accuracy and efficiency in this context [11].

This literature review examines the application of AI/ML methods in differentiating IBS from IBD, focusing on the strengths and limitations of various approaches.

METHODS

A systematic review following PRISMA 2020 guidance was conducted. The following databases were searched for relevant studies: PubMed/MEDLINE, Web of Science Core Collection, Scopus, and Google Scholar. The search was limited to studies published up to December 31, 2024. A systematic search strategy was employed, incorporating combinations of controlled vocabulary and keywords: "irritable bowel syndrome," "inflammatory bowel disease," "machine learning," "artificial intelligence," "diagnosis," "classification," "biomarker," and "differential diagnosis."

Peer-reviewed, English-language human studies that: 1) applied AI/ML methods to differentiate IBS vs IBD; 2) used clinical, laboratory, imaging, microbiome, transcriptomic/epigenetic, or other biosignal data; and 3) reported performance metrics (AUC, accuracy, sensitivity/specificity) for the IBS–IBD discrimination task were included. Editorials, letters without primary data, non-English articles, studies not performing differential diagnosis between IBS and IBD, and works without ML/AI methods were excluded.

Initially, a broad search was conducted to identify a large pool of potentially relevant studies. Subsequently, two reviewers independently screened titles/abstracts, followed by full-text assessment. Titles and abstracts were screened to exclude studies that did not meet the inclusion criteria. Full-text articles of the remaining studies were reviewed to assess their methodological quality and relevance. Disagreements regarding study inclusion were resolved through a discussion among the reviewers.

The following information was collected for each study: study design, sample size, population and patient characteristics, data types used (clinical features, imaging data, genomic data), ML algorithms employed, model type and training/validation approach; performance metrics (AUC/ROC, accuracy, sensitivity, specificity); and key findings.

RESULTS

A total of 7 studies met the inclusion criteria and were included in this review. The studies employed a variety of AI/ML techniques to differentiate between IBS and IBD, utilizing different data types and model architectures. A detailed summary of the included studies is provided in Table I.

The expression levels of five long non-coding RNAs (lncRNAs) in tissue and plasma extracellular vesicles (EVs) of patients with active inflammatory bowel disease (IBD) compared to those in remission and healthy controls was investigated by Heydari et al. [12]. Among the lncRNAs studied, H19 was found to be significantly upregulated in both tissue and plasma EVs of active IBD patients. Due to an obtained area under the curve (AUC) of 0.97 the study suggests that circulating EV-lncRNA H19 exhibits promising potential as a diagnostic biomarker to differentiate active IBD from IBS.

A genome-wide DNA methylation analysis to identify potential biomarkers capable of distinguishing between IBS, IBD, and celiac disease was conducted by Mahurkar-Joshi et al. [13]. They analyzed genome-wide DNA methylation data from peripheral blood mononuclear cells of 315 participants, including 148 IBS patients, 47 IBD patients, 34 celiac disease patients, and 86 healthy controls (HC). To develop classifiers

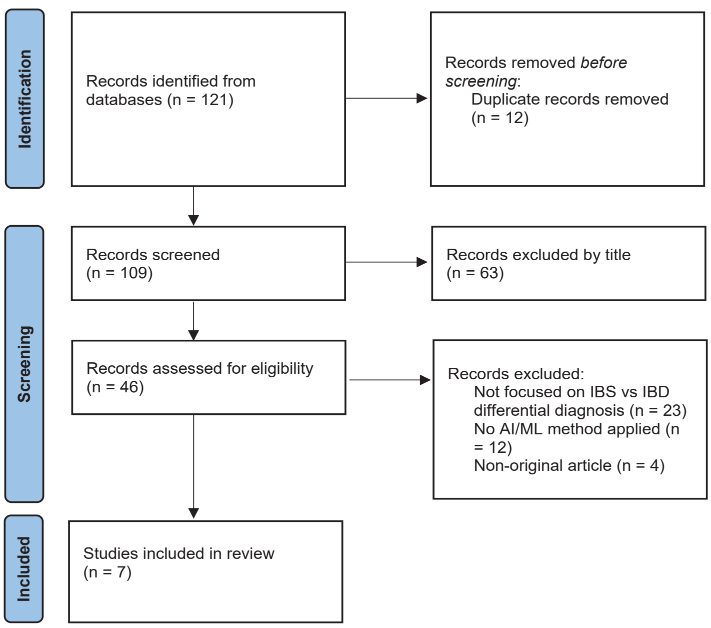

Fig. 1. PRISMA 2020 flow diagram for study selection.

Table I. Characteristics of the included studies

Study (year), reference	Data type	ML algorithm	Sample size	Key findings
Heydari et al. (2023), [12]	Plasma extracellular vesicle lncRNA H19	Logistic regression	22 active IBD, 14 IBS patients	Area under the curve = 0.97 for distinguishing active IBD from IBS
Mahurkar-Joshi et al. (2024), [13]	Genome-wide DNA methylation of peripheral blood mononuclear cells	Penalized generalized linear models	148 IBS, 47 IBD patients	The area under the curve for IBS-IBD classification was 0.80.
Wang et al. (2021), [14]	Fecal microbiome (16S rRNA gene sequencing)	Random forest	14 pediatric IBD and 48 pediatric IBS patients	The diagnostic model successfully differentiated pediatric IBD from IBS with an area under the curve of 0.84
Bakulin et al. (2023) [15]	Clinical symptoms, anamnesis data and laboratory tests	Artificial neural network (multilayer perceptron)	1006 (32% were patients with IBS and 68% with IBD)	The sensitivity was 95.8% and the specificity was 90.2% for the differentiation between IBD and IBS
Aggio et al. (2016) [16]	Gas chromatography-sensor pipeline	Feature selection - two random forest models. Samples classification - Support vector machine with polynomial kernel	152	Inactive IBD vs IBS: accuracy (86%, CI 84–87%), sensitivity (89%) and specificity (80%)
Lo Presti et al. (2019) [17]	Fecal microbiome (16S rRNA gene sequencing)	Linear discriminant analysis	38 IBD amd 44 IBS patients	Erysipelotrichi emerged as a potential biomarker for IBS, while Gammaproteobacteria, Enterococcus, and Enterococcaceae were associated with IBD.
Rami-Pujol et al. (2020) [1]	Clinical parameters and genomic DNA extracted from faecal samples	RAID-Dx	52 IBS and 52 IBD patients	RAID-Dx outperformed fecal calprotectin in both sensitivity and specificity for distinguishing between IBS and IBD.

ML: machine learning; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome; CI: confidence interval.

capable of differentiating these conditions, the team utilized penalized generalized linear models with double cross-validation. The performance of these classifiers was evaluated using AUC. The classifier distinguishing IBS from IBD achieved an AUC of 0.80 (95%CI: 0.70–0.87, p<0.001), indicating good discriminatory ability. These findings indicate that blood-based DNA methylation biomarkers, when analyzed through ML methods, show promise for distinguishing between chronic gastrointestinal disorders with overlapping symptoms.

Wang et al. [14] developed a diagnostic model using a random forest algorithm to differentiate pediatric IBD from irritable bowel syndrome (IBS) based on fecal microbiota profiles. They conducted 16S rRNA gene sequencing on fecal samples from 14 PIBD and 48 IBS patients. The model achieved an AUC of 0.84, indicating good discriminatory power in distinguishing pediatric IBD from IBS.

Another study was presented at the United European Gastroenterology Week in 2023 and proposed the use of an artificial neural network to distinguish between IBD and IBS based on multiple clinical data points (presence of constipation, loose stools, diarrhea syndrome, extraintestinal and perianal manifestations, and various laboratory tests) [15]. Out of the 1,006 patients examined, 32% were patients with IBS, and 68% had IBD. The multilayer perceptron showed excellent results in differentiating the two diseases, achieving a sensitivity of 95% and a specificity of 90%.

A prospective study based on DNA sequencing of stool samples from 165 individuals highlighted differences in the relative abundance of three species: *Faecalibacterium prausnitzii*, *Akkermansia muciniphila*, *Methanobrevibacter smithii*, along with *Bacteroidetes* and *Escherichia coli*, when comparing patients with IBS to those with IBD [1]. Based on these results, a non-invasive computerized algorithm was developed, capable of diagnosing IBS and distinguishing it from IBD. The resulting tool, called RAID-Dx, is an algorithm based on the combination of abundances of the eight identified fecal microbial biomarkers. The combination of the relative abundance of these eight functional species resulted in a sensitivity of 88% and a specificity of 94%. RAID-Dx also reports higher sensitivity and specificity values compared to fecal calprotectin in differentiating the two diseases.

In a related study, Presti et al. [17] performed fecal and intestinal mucosal microbiota profiling and used linear discriminant analysis to differentiate IBS from IBD based on microbial signatures. The relative abundance of bacteria and bacterial diversity were determined through fecal and mucosal microbiota analysis based on 16S ribosomal RNA sequencing. In fecal and mucosal samples, microbiota richness was characterized by a progressive reduction in microbial diversity, starting from the control group to IBS and then to IBD, which exhibited the lowest bacterial diversity. β-diversity analysis showed a clear separation between the two diseases, but no significant separation between IBS and the control group. Additionally, β-diversity demonstrated a clear distinction between mucosal and stool samples across all groups. *Erysipelotrichi* was identified as a potential biomarker for IBS, while *Gammaproteobacteria*, *Enterococcus*, and *Enterococcaceae* were identified as biomarkers for IBD.

A notable study conducted by Aggio et al. [16] utilized a gas chromatography-based analysis system with sensors to analyze stool samples from patients with IBS and IBD. The gas chromatography sensor system detects volatile compounds present in biological samples. It generates a profile of sensor resistance over time, describing how the abundances of volatile compounds change in time. Sensors with resistance patterns that differed the most between IBS and IBD were selected using two algorithms based on random forests. A support vector machine with a polynomial kernel was used as a machine learning technique to classify unknown samples based on the selected sensors. The results, after double cross-validation, indicated an accuracy of 86% for differentiating inactive IBD from IBS, with a sensitivity of 89% and a specificity of 80%.

DISCUSSION

This review demonstrates the growing application of AI/ML in improving the differential diagnosis of IBS and IBD. Several studies have shown promising results using various ML algorithms and data types, all demonstrating the potential of different biomarkers in conjunction with ML for improved diagnosis.

The misdiagnosis can lead to significant clinical complications, affecting patient management and therapeutic decisions. One of the most critical issues is the possibility of delayed diagnosis of IBD and inadequate treatment [1]. Such delays can worsen the disease, as IBD often requires early interventions to manage inflammation and prevent complications such as strictures or fistulas. Misdiagnosis can also lead to unnecessary tests and diagnostic procedures. Physicians may request additional imaging or endoscopic evaluations to rule out IBD in patients initially diagnosed with IBS, increasing healthcare system costs [8]. This also exposes patients to potential risks associated with invasive procedures. The psychological impact of misdiagnosis should not be underestimated either. Patients with IBD often face anxiety and depression related to their chronic condition [18]. The confusion between the two diseases can exacerbate these issues, as patients may feel frustrated with their symptoms and the lack of a clear diagnosis. Misdiagnosis can also lead to inaccurate prognostic assessments. This may affect long-term therapeutic strategies and patient counseling.

Current differential diagnosis methods primarily rely on serological markers, imaging studies, and invasive procedures such as colonoscopy. Fecal calprotectin (FC) has emerged as a prominent non-invasive biomarker for differentiating IBD from IBS. Elevated levels of FC are indicative of intestinal inflammation, making it a valuable tool in clinical practice. Studies have shown that FC can reliably rule out active IBD, with a high negative predictive value [19, 20]. However, while FC is useful, its sensitivity and specificity can vary, leading to potential misclassification of IBS patients as having IBD [7]. A meta-analysis has confirmed that while FC is effective in distinguishing between these conditions, it is not infallible, emphasizing the need for complementary diagnostic methods [7]. Serological markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are also utilized in clinical settings. These tests can indicate inflammation but lack specificity, often resulting in false positives in IBS patients [21]. Moreover, the invasive nature of colonoscopy, which is often employed to confirm IBD diagnosis, poses risks and can be burdensome for patients [22].

These challenges highlight the need to improve diagnostic methods, welcoming AI techniques and multi-omics analyses to enhance the accuracy of differentiating between these two conditions. Recent advancements in genomic and microbiomic research have opened new avenues for distinguishing IBD from IBS. For instance, studies utilizing DNA methylation profiles have shown promise in identifying disease-specific biomarkers that could facilitate non-invasive diagnostics [13]. Additionally, alterations in gut microbiota composition have been linked to both conditions, suggesting that microbiome analysis could serve as a potential diagnostic tool [23, 24].

The studies included in our review have shown promising results using various ML algorithms and data types, all demonstrating the potential of different biomarkers in conjunction with ML for improved diagnosis. The integration of these novel methods could enhance diagnostic accuracy and patient management.

However, current research on AI/ML for distinguishing IBS from IBD still faces notable limitations. A significant methodological challenge is the small sample sizes in all studies. Although some studies have reported promising results using AI techniques, the cohorts involved are often limited, raising concerns about statistical power and result reliability. Data quality is also a major challenge. The heterogeneity of data sources, including variations in diagnostic criteria and patient demographics, can affect the performance of AI models. Mortensen et al. noted that differences in extracellular matrix turnover profiles between IBD and IBS patients could complicate result interpretation when AI is used to analyze such biomarkers [25]. Additionally, the presence of confounding factors, such as overlapping symptoms and comorbidities, may blur the distinctions between IBS and IBD, making it difficult for AI models to achieve high specificity and sensitivity. Furthermore, the generalizability of AI models is often limited. Many studies focus on specific populations or geographic regions that may not reflect the entire patient population. This lack of generalization could hinder the implementation of AI tools in clinical practice, as healthcare providers may be reluctant to adopt models that have not been validated in diverse contexts. Integrating AI into clinical workflows also remains a challenge. The complexity of AI systems can lead to difficulties in interpretation and acceptance among clinicians, who may prefer traditional diagnostic methods. It is essential to have clear guidelines and training on the use of AI tools to facilitate their adoption in routine clinical practice.

Future research should focus on developing standardized protocols for data acquisition, preprocessing, and model evaluation, as well as conducting large, multicenter studies to validate the clinical utility of AI/ML models in real-world settings. Addressing these limitations will be crucial for translating AI/ML-based diagnostic tools into clinical practice and improving patient care.

CONCLUSIONS

Artificial intelligence and ML systems showed consistently promising discriminatory performance for IBS vs. IBD differentiation across multiple data sources. Across the included studies, reported metrics spanned AUC 0.80–0.97, sensitivity approximately 86–96%, and specificity approximately 80–94%. At present, these systems are best considered adjunctive decision-support tools to complement clinical assessment and established biomarkers (e.g., FC), rather than standalone diagnostics. To enable clinical adoption, priorities include: (i) multicenter, prospective studies with predefined endpoints; (ii) external validation and calibration reporting; (iii) adherence to TRIPOD-AI/STARD-AI guidelines; and (iv) impact and cost-effectiveness evaluations within real-world workflows.

Conflicts of interest: None to declare.

Authors' contributions: I.V.P and M.D. conceived and designed the study. I.V.P. searched the literature. M.D. extracted relevant data and interpreted the results. I.V.P. drafted the manuscript. C.M., O.N., V.D. and C.C.P. critically revised the manuscript. C.C.P. supervised the study. All authors approved the final version to be published and agree to be accountable for all aspects of the work.

REFERENCES

1. Ramió-Pujol S, Amoedo J, Serra-Pagès M, et al. A novel distinctive form of identification for differential diagnosis of irritable bowel syndrome, inflammatory bowel disease, and healthy controls. GastroHep 2020;2:193-204. doi:10.1002/ygh2.417
2. Abdul Rani R, Raja Ali RA, Lee YY. Irritable bowel syndrome and inflammatory bowel disease overlap syndrome: pieces of the puzzle are falling into place. Intest Res 2016;14:297-304. doi:10.5217/ir.2016.14.4.297
3. Sezgin O, Boztepe B, Üçbilek E, Altintas E, Celikcan HD. Irritable Bowel Syndrome on Inflammatory Bowel Disease in Deep Remission: No Relation with Remission Deepening and Inflammation. Turk J Gastroenterol 2021;32:870-878. doi:10.5152/tjg.2021.20806
4. Ahmed M, Pu A, Jencks K, et al. Predictors of irritable bowel syndrome-like symptoms in quiescent inflammatory bowel disease. Neurogastroenterol Motil 2024;36:e14809. doi:10.1111/nmo.14809
5. Perler BK, Ungaro R, Baird G, et al. Presenting symptoms in inflammatory bowel disease: descriptive analysis of a community-based inception cohort. BMC Gastroenterol 2019;19:47. doi:10.1186/s12876-019-0963-7
6. Petrik M, Palmer B, Khoruts A, Vaughn B. Psychological Features in the Inflammatory Bowel Disease-Irritable Bowel Syndrome Overlap: Developing a Preliminary Understanding of Cognitive and Behavioral Factors. Crohn Colitis 360 2021;3:otab061. doi:10.1093/crocol/otab061
7. Dajti E, Frazzoni L, Iascone V, et al. Systematic review with meta-analysis: Diagnostic performance of faecal calprotectin in distinguishing inflammatory bowel disease from irritable bowel syndrome in adults. Aliment Pharmacol Ther 2023;58:1120-1131. doi:10.1111/apt.17754
8. Zaki MM, Elfert A, Soliman H, Hawash N. Can Noninvasive Tests Substitute Endoscopy for Diagnosis of Colonic Diseases? Asian J Adv Res Rep 2022;16:64-73. doi:10.9734/ajarr/2022/v16i12449
9. Card TR, Siffledeen J, Fleming KM. Are IBD patients more likely to have a prior diagnosis of irritable bowel syndrome? Report of a case-control study in the General Practice Research Database. United European Gastroenterol J 2014;2:505-512. doi:10.1177/2050640614554217
10. Hong SM, Baek DH. Diagnostic Procedures for Inflammatory Bowel Disease: Laboratory, Endoscopy, Pathology, Imaging, and Beyond. Diagnostics (Basel) 2024;14:1384. doi:10.3390/diagnostics14131384
11. Ruffle JK, Farmer AD, Aziz Q. Artificial Intelligence-Assisted Gastroenterology— Promises and Pitfalls. Am J Gastroenterol 2019;114:422-428. doi:10.1038/s41395-018-0268-4
12. Heydari R, Fayazzadeh S, Shahrokh S, Shekari F, Farsad F, Meyfour A. Plasma Extracellular Vesicle LncRNA H19 as a Potential Diagnostic Biomarker for Inflammatory Bowel Diseases. Inflammatory Bowel Diseases. Inflamm Bowel Dis 2023;30:795-807. doi:10.1093/ibd/izad219
13. Mahurkar-Joshi S, Thompson M, Villarruel E, et al. Genome-Wide DNA Methylation Identifies Potential Disease-Specific Biomarkers and Pathophysiologic Mechanisms in Irritable Bowel Syndrome, Inflammatory Bowel Disease, and Celiac Disease. Neurogastroenterol Motil 2025;37:e14980. doi:10.1111/nmo.14980
14. Wang X, Xiao Y, Xu X, et al. Characteristics of Fecal Microbiota and Machine Learning Strategy for Fecal Invasive Biomarkers in Pediatric Inflammatory Bowel Disease. Front Cell Infect Microbiol 2021:11:711884. doi:10.3389/fcimb.2021.711884
15. Bakulin I, Rasmagina I, Konstantinova O, Shpilkin K. Artificial intelligence in the differential diagnosis of inflammatory bowel diseases and irritable bowel syndrome. UEG Week; 2023.
16. Aggio RB, White P, Jayasena H, de Lacy Costello B, Ratcliffe NM, Probert CS. Irritable bowel syndrome and active inflammatory bowel disease diagnosed by faecal gas analysis. Aliment Pharmacol Ther 2017;45:82-90. doi:10.1111/apt.13822
17. Lo Presti A, Zorzi F, Del Chierico F, et al. Fecal and Mucosal Microbiota Profiling in Irritable Bowel Syndrome and Inflammatory Bowel Disease. Front Microbiol 2019;10:1655. doi:10.3389/fmicb.2019.01655
18. Hinnant L, Rios Villacorta N, Chen E, et al. Consensus Statement on Managing Anxiety and Depression in Individuals with Inflammatory Bowel Disease. Inflamm Bowel Dis 2025;31:1248-1255. doi:10.1093/ibd/izae151
19. Mumolo MG, Bertani L, Ceccarelli L, et al. From bench to bedside: Fecal calprotectin in inflammatory bowel diseases clinical setting. World J Gastroenterol 2018;24:3681-3694. doi:10.3748/wjg.v24.i33.3681
20. Mari A, Abu-Baker F, Mahamid M, Yacoob A, Sbeit W, Khoury T. Clinical utility of fecal calprotectin: potential applications beyond inflammatory bowel disease for the primary care physician. Ann Gastroenterol 2019;32:425-430. doi:10.20524/aog.2019.0394
21. Huong BT, Hien NM, Dung NT, et al. Role of Calprotectin, IL-6, and CRP in Distinguishing Between Inflammatory Bowel Disease and Diarrhea Predominant Irritable Bowel Syndrome. Med Arch 2024;78:105-111. doi:10.5455/medarh.2024.78.105-111
22. Hong SM, Baek DH. A Review of Colonoscopy in Intestinal Diseases. Diagnostics (Basel) 2023 27;13:1262. doi:10.3390/diagnostics13071262
23. Vich Vila A, Imhann F, Collij V, et al. Gut microbiota composition and functional changes in inflammatory bowel disease and irritable bowel syndrome. Sci Transl Med 2018;10:eaap8914. doi:10.1126/scitranslmed.aap8914
24. Qiu P, Ishimoto T, Fu L, Zhang J, Zhang Z, Liu Y. The Gut Microbiota in Inflammatory Bowel Disease. Front Cell Infect Microbiol 2022;12:733992. doi:10.3389/fcimb.2022.733992
25. Mortensen JH, Manon-Jensen T, Jensen MD, et al. Ulcerative colitis, Crohn's disease, and irritable bowel syndrome have different profiles of extracellular matrix turnover, which also reflects disease activity in Crohn's disease. PLoS One 2017;12:e0185855. doi:10.1371/journal.pone.0185855