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# Diagnosis of inflammatory bowel disease : a comprehensive overview on laboratory, Endoscopy and Imaging modalities

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**Abstract**

Inflammatory Bowel Disease (IBD), encompassing Crohn's disease and ulcerative colitis, represents a chronic and debilitating condition with rising prevalence worldwide. Accurate diagnosis is critical due to the overlapping clinical features and the potential for severe complications. This literature review provides a thorough analysis of diagnostic modalities used in IBD, with a particular focus on the multidisciplinary approach that involves laboratory tests, endoscopy, pathology, and imaging. The key findings emphasize the intricate nature of diagnosing IBD, requiring a thorough assessment to distinguish between Crohn's disease and ulcerative colitis, evaluate the severity of the disease, and identify any consequences. The advancements in artificial intelligence, molecular diagnostics, and personalized medicine show potential for improved precision and individualized healthcare. The review highlights the significance of continuous research in improving diagnostic procedures for IBD, recognizing the ever-changing nature of the condition and the evolving diagnostic methods that strive to achieve early and accurate diagnosis, leading to better patient outcomes.

**Keywords:** inflammatory bowel disease (IBD), Diagnostic modalities, Crohn’s disease, Artificial intelligence, Personalized medicine.

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## 1. Introduction

Inflammatory Bowel Disease (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), constitutes a complex and debilitating group of chronic inflammatory disorders that affect the gastrointestinal tract. These conditions pose significant clinical and public health challenges, with an increasing global prevalence and profound implications for affected individuals and healthcare systems. The accurate and timely diagnosis of IBD is of paramount importance in the management of these diseases, as it not only facilitates the initiation of appropriate treatments but also plays a crucial role in improving patient outcomes and quality of life.

## 2. Overview of IBD

### *2.1 Types of IBD*

Towards IBD comprises two major types CD and UC. CD is characterized by transmural inflammation that can affect any part of the digestive tract, from the mouth to the anus. In contrast, ulcerative colitis primarily involves continuous mucosal inflammation limited to the colon and rectum.[1] While both conditions share some commonalities, such as chronic inflammation and periods of remission and relapse, they exhibit distinct clinical, endoscopic, and histological features, necessitating differentiated diagnostic and management strategies.

### *2.2 Prevalence of IBD*

Understanding IBD epidemiology and prevalence is critical for accurate diagnosis and management. Based on pertinent studies, this section provides a complete summary of the epidemiology and prevalence of IBD. The prevalence of IBD has shown a significant increase over the past few decades. Historically considered more prevalent in Western industrialized nations, IBD has now become a global concern. Recent epidemiological data have demonstrated a rising incidence in previously low-prevalence regions, including parts of Asia, Africa, and

 

South America. This global surge in IBD incidence has prompted intensified research efforts and underscored the need for effective diagnostic procedures.

Global incidence and prevalence of IBD were assessed by a meta-analysis of population-based studies concluded in the twenty-first century. According to the research, there is a global increase in the occurrence and prevalence of IBD, with North America and Europe exhibiting the highest rates [2]. A further extensive examination conducted over multiple decades unveiled an escalating pattern in the occurrence and prevalence of IBD, encompassing both CD and UC, across various nations globally [3]. Regional variations in the incidence and prevalence of IBD have been observed, with notable disparities observed in Asia. A comprehensive analysis focusing on the Asian continent revealed variations in the incidence and prevalence of IBD among the nations within the region [4]. In addition, a comprehensive analysis was conducted on data from 195 nations and territories spanning the period from 1990 to 2017. The findings of this study revealed significant variations in the prevalence of IBD across different geographical regions, underscoring the importance of implementing focused strategies for prevention and treatment [5]. The field of epidemiology pertaining to IBD has undergone a transformation in accordance with Omran's Epidemiological Transition Theory, which delineates four distinct stages. In the past, IBD was primarily perceived as a condition prevalent in Western nations. However, it has now emerged as a widespread global epidemic. The occurrence of IBD has witnessed a rise in newly industrialized nations in recent times [6]. The presence of genetic predisposition, familial background, and environmental factors are all recognized as risk factors associated with the development of IBD. The strong correlation seen among dizygotic twins indicates a significant genetic influence on the chance of developing IBD. In addition, the disease burden of IBD is influenced by many ecological variables and their interactions with genetic susceptibility [7]. The incidence and prevalence of IBD have been elucidated through cohort studies conducted within primary care settings in the United Kingdom. These investigations have contributed to a deeper understanding of the temporal trends and prevalence of IBD within the population of the United Kingdom [8]. IBD is a globally prevalent condition that is seeing an increasing occurrence and prevalence. There are regional disparities that persist, and the burden of illness is undergoing dynamic shifts. IBD is believed to arise from a complex interplay of both hereditary and environmental influences. The field of IBD epidemiology is characterized by its dynamic nature, which requires ongoing monitoring and research in order to improve the diagnostic and therapy strategies associated with this condition.

### *2.3 Clinical Significance of IBD*

IBD exerts a profound impact on the lives of those affected, often characterized by a range of symptoms, including abdominal pain, diarrhea, rectal bleeding, weight loss, and systemic manifestations. The chronic nature of the disease, coupled with periods of exacerbation and remission, imposes a substantial burden on patients' physical, emotional, and social well-being. Additionally, the complications associated with IBD, such as strictures, fistulas, and an increased risk of colorectal cancer, further underscore its clinical significance. Effective management and improving patient outcomes are intricately linked to the precision and timeliness of IBD diagnosis.

## 3. Importance of Accurate and Timely Diagnosis

### *3.1 Facilitating Timely Treatment*

Accurate and timely diagnosis of IBD is pivotal in enabling the prompt initiation of appropriate treatment strategies. Early intervention can alleviate symptoms, reduce inflammation, and enhance the quality of life for individuals living with IBD. Moreover, delaying diagnosis can lead to complications, such as fibrosis and bowel damage, which may necessitate surgical interventions. Therefore, rapid identification and differentiation of IBD sub-types play a crucial role in guiding therapeutic decisions.

### *3.2 Improving Patient Outcomes*

Accurate diagnosis and subsequent management of IBD are pivotal in improving patient outcomes. A precise diagnosis ensures that therapeutic regimens are tailored to the specific subtype and disease location, optimizing treatment efficacy while minimizing adverse effects. Furthermore, early diagnosis can help reduce hospitalizations, surgeries, and long-term disability associated with IBD. By achieving and maintaining remission, patients can experience improved well-being, maintain a higher quality of life, and reduce the risk of complications.

 

## 4. Laboratory diagnostic procedures for inflammatory bowel disease

Laboratory tests are instrumental in the diagnostic workup of IBD. They encompass a range of blood tests, stool tests, and serological markers that aid in the identification, differentiation, and monitoring of IBD. This section provides an overview of these laboratory diagnostic procedures, discusses their sensitivity, specificity, and limitations, and highlights recent advancements and emerging biomarkers in IBD diagnosis.

### *4.1 C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR)*

CRP and ESR are employed in the surveillance of disease activity, specifically in differentiating between severe disease and mild or remission states. In a study conducted by Tromm et al.[9] , a prospective investigation was carried out to examine the relationship between several biomarkers and endoscopic activity. The findings revealed a significant association between elevated ESR levels and CD affecting the small bowel [10], [11]. In a study conducted by Fagan et al. [12], it was seen that both CRP and ESR demonstrated a link with illness activity. However, it was noted that CRP exhibited a stronger correlation, which is consistent with findings from various previous research. However, it is important to note that CRP readings frequently exhibit overlapping ranges in instances of mild, moderate, and severe disease, which can complicate their interpretation. Serial testing is the ideal approach in clinical practice for evaluating the efficacy of a therapy. The prognostic role of CRP has been demonstrated [13] In a prospective study conducted by Brignola et al, a cohort of 41 patients who had achieved remission from CD with a (Crohn's Disease Activity Index (CDAI) score below 150) were followed up for a period of six months. During this follow-up period, the researchers utilized a panel of other inflammatory markers. The findings of the study revealed a higher recurrence rate at the two-year mark among those patients who exhibited elevated CRP values.

A reduction in the CRP level observed during the course of therapy serves as a sign of treatment effectiveness. Conversely, a consistently elevated number signifies a lack of success in the treatment. Inclusion criteria in recent biologics trials have exhibited a growing trend of incorporating baseline-elevated CRP levels. This criterion is employed to ascertain the presence of active inflammation among the enrolled patients. The origin of this practice can be mostly attributed to the findings of the Phase II induction studies of certolizumab, which were reported in the mid-2000s.[14], [15], [16].

The study conducted by Shine et al.[17] examined pediatric patients with CD who underwent colonoscopy. The findings revealed that all patients in the study exhibited elevated levels of CRP as compared to children with polyps or those with a normal examination. Among patients in the identical cohort, the erythrocyte ESR demonstrated positivity alone in 85% of cases. A comprehensive study using a sample size of 203 individuals presenting with nonspecific gastrointestinal symptoms demonstrated that CRP served as a reliable indicator for distinguishing between IBD and irritable bowel syndrome (IBS) in terms of differential diagnosis.[18] Various acute-phase reactants, including sialic acid, alpha1-acid glycoprotein, orosomucoid, fibrinogen, lactoferrin, β-2-microglobulin, serum amyloid A, α-2-macroglobulin, and α-2-antitrypsin, have been examined in the context of IBD. However, the findings from these investigations have been inconsistent and inconclusive. Indeed, the diminished precision of these proteins, primarily attributed to their extended half-life, renders them less accurate compared to CRP, thus precluding their routine use in clinical settings.[19], [20]

### *4.2 Fecal Calprotectin and Other Fecal Markers*

In patients diagnosed with CD, it is common practise to collect stool samples for the purpose of detecting white blood cells (WBCs), routine pathogens, ova, parasites, and the Clostridium difficile toxin. This is done in order to exclude the possibility of superinfections during relapses and prior to the administration of immunomodulators. [21] Calprotectin comprises approximately 60% of cytosolic proteins found in activated neutrophils. The detection of calprotectin in faecal samples can serve as an indicator of neutrophil infiltration into the gastrointestinal tract. While calprotectin exhibits high sensitivity in identifying gut inflammation, its lack of specificity poses limitations as elevated levels can also be observed in colorectal cancer, infections, and polyps. Initial investigations into IBD have demonstrated a strong association between the excretion of indium-labeled leukocytes and intestinal permeability.[22] The levels of fecal calprotectin demonstrate an elevation in response to the administration of non-steroidal anti-inflammatory drugs (NSAIDs) as well as in individuals who are of older age.[23]

The research conducted by Tibble et al. shown that the levels of calprotectin were indicative of the likelihood of recurrence. The sensitivity and specificity of calprotectin for predicting relapse in patients with IBD were found to be 90% and 83%, respectively, at a concentration of 50 mg/L.[24], [25]. Studies have shown that fecal

 

calprotectin and fecal lactoferrin exhibit higher sensitivity compared to CRP. The study conducted by Langhorst et al.[26] examined the diagnostic potential of fecal lactoferrin, fecal calprotectin, fecal PMN-elastase, and serum CRP in patients with IBD. The findings of the study provided evidence that all of these biomarkers were capable of distinguishing between active and inactive stages of IBD, as well as differentiating IBD from IBS. None of the three stool indicators examined exhibit consistent superiority in detecting endoscopic inflammation, while all three demonstrate higher diagnostic accuracy compared to CRP. In the current era of biologics, there exists empirical evidence that substantiates the utilization of fecal calprotectin as a means of evaluating the efficacy of anti-tumor necrosis factor (anti-TNF) therapy. Sipponen et al.[27] conducted a study that revealed a decrease in the average levels of fecal calprotectin following treatment with anti-TNF medications. Additionally, they observed a moderate association between the alteration in fecal calprotectin levels and the modification in endoscopic activity, as measured by the Crohn's disease endoscopic index of severity.

### *4.3 Other Serological Markers*

The presence of anti-S. cerevisiae antibodies (ASCA) has been seen in individuals diagnosed with CD. The presence of positive ASCA and absence of perinuclear antineutrophil antibody (pANCA) in individuals with colonic inflammation can aid in distinguishing between CD and UC.[28] The presence of ASCA-positivity is correlated with an increased likelihood of undergoing surgical procedures. There exists a positive correlation between higher levels of ASCA and an increased likelihood of experiencing complications, namely strictures and fistulas.[29], [30] CD patients have been found to have additional serum antibodies to microbial antigens, including Escherichia coli anti-OmpC, which is present in approximately 50% of CD cases. Additionally, anti-Pseudomonas fluorescens associated sequence 12 (anti-12) and anti-flagellin-like antigen (anti-Cbir1) have been identified. The presence of anti-Cbir1 is specifically associated with small bowel fistulizing and stenosing disease.A meta-analysis was conducted to assess the ability of serum antibodies to microbial antigens in categorizing the progression of CD. The analysis revealed that anti-OmpC exhibited the greatest ability to predict the risk of both complications and surgery.[30]

## 5. Endoscopy in IBD diagnosis

### *5.1 Diagnostic Accuracy*

Endoscopy, which encompasses procedures such as colonoscopy and esophagogastroduodenoscopy (EGD), plays a crucial role in verifying diagnoses of IBD.Colonoscopy offers a clear view of the colon and enables the collection of tissue samples to differentiate between Crohn's disease and ulcerative colitis.A study conducted by Colombel et al. in 2007 showcased the exceptional sensitivity of colonoscopy in detecting IBD. The sensitivity values for identifying both Crohn's disease and ulcerative colitis surpassed 90%, indicating a high level of accuracy.[31]

### *5.2 Disease Localization and Assessment*

Endoscopy plays a vital role in determining the precise location and severity of disease involvement, which is essential for effective treatment planning.Research has demonstrated that endoscopy, when used alongside imaging modalities such as MRI or CT enterography, can effectively evaluate the activity and location of a disease [32].The Montreal Classification and the Paris Classification are established systems that categorize IBD using endoscopic findings. This highlights the significance of endoscopy in describing the disease.[33]

### *5.3 Monitoring Disease Activity*

Endoscopy is a crucial procedure for the purpose of monitoring the activity of a disease and evaluating the effectiveness of treatment.Repeated endoscopic evaluations can be utilized to ascertain the efficacy of treatments and provide guidance for necessary modifications.The STRIDE recommendations, which focus on selecting therapeutic targets for inflammatory bowel disease, strongly suggest the use of endoscopy as a crucial method for evaluating disease activity and achieving mucosal repair[34]. Multiple endoscopic scoring systems are available for both UC and CD. These systems differ in their level of sophistication and rely on assessments made by physicians and endoscopic examination to determine the severity of the disease. The Mayo Endoscopic Score (MES) and Ulcerative Colitis Endoscopic Index of Severity (UCEIS) are the two most often employed endoscopic scoring systems for evaluating disease activity in patients with UC. The MES is a numerical score ranging from 0 to 12. It is determined by evaluating factors such as the frequency of bowel movements, the severity of rectal

 

bleeding, the look of the mucosal lining during endoscopy, and the physician's overall opinion of the patient's condition.[35] The MES has undergone substantial research since its inception in 1987. However, its objective nature has resulted in significant heterogeneity among observers and has restricted its use to a broader context.[36]

The UCEIS provides a more comprehensive evaluation of the endoscopic condition compared to the MES. It evaluates the mucosal vascular pattern, presence of bleeding, and severity of erosions and ulcers, assigning points accordingly [37]. The scale in question has been evaluated independently and has showed satisfactory agreement across observers when watching a procedure video. However, a recent review conducted by Cochrane failed to thoroughly validate this scale or any other scoring system for assessing UC. Furthermore, the UCEIS does not provide a clear delineation between mild, moderate, and severe disease. Multiple endoscopic grading systems have been developed for CD. The two most extensively researched indices are the Crohn's Disease Endoscopic Index of Severity (CDEIS) and the Simple Endoscopic Score for Crohn's Disease (SES-CD). The CDEIS assesses the mucosal patterns in several regions of the gastrointestinal tract, including the rectum, left colon, transverse colon, right colon, and ileum. It assigns a numerical score between 0 and 44 based on the evaluation. The clinical application of this is relatively restricted due to its time-consuming nature, the need for specialized training, and the potential for large difference in scores across different observers.[38] The SES-CD assigns scores ranging from 0 to 3 in the same five anatomical segments as the CDEIS. At least one study has shown that the SES-CD provides reliable scores when assessed by the same or different raters. It consists of only one number,[39] The trial called "The Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease" discovered that a reduction of at least 50% in either the CDEIS or SES-CD scores by week 26 of biologic treatment was associated with achieving remission without the need for steroids by week 50.[40]

### *5.4 Dysplasia Surveillance*

Chronic IBD is a widely recognized condition that significantly increases the risk of developing colorectal cancer (CRC). CRC accounts for approximately 15% of all deaths in those with IBD. Furthermore, IBD (specifically UC) is the third most significant risk factor for CRC, placing only below familial polyposis coli and hereditary nonpolyposis CRC. The cancer risk associated with IBD is mostly linked to long-term inflammation of the mucosal lining, rather than familial or hereditary syndromes. CRC linked with IBD usually does not progress according to the adenoma-carcinoma sequence. Instead, it develops through a pattern of inflammation, dysplasia, and carcinoma.[41] There is no need to rewrite it. This frequently leads to a late-stage diagnosis and lower survival rates compared to sporadic colorectal cancer.[42]

Due to the heightened risk, it is crucial for individuals with IBD, especially those with long-standing disease, to have frequent endoscopic screening. This will help identify dysplasia or detect cancer at an earlier stage, which may be more treatable.Endoscopic surveillance is an economically efficient method that has been unequivocally proven to decrease the likelihood of death linked with colorectal cancer in people with IBD.[43]The 2005 guidelines from the Crohn's and Colitis Foundation of America (CCFA) propose that the frequency of follow-up examinations should be determined by the specific risk factors of each patient. Individuals who have severe or left-sided colitis should undergo screening every 1 to 2 years following a negative initial screening. After two negative exams, the gap between screenings can be prolonged to three years until the disease has been present for 20 years. At this point, surveillance should be considered again, with screenings recommended every one to two years.[44]

Conventional surveillance involves examining the mucosa using white light endoscopy (WLE) and taking biopsies of apparent lesions as well as random biopsies. This is done since dysplasia may not always have an obviously aberrant appearance.Conventional monitoring for patients with IBD who have severe colonic disease (beyond the splenic flexure in ulcerative colitis or affecting at least one-third of the colon in CD includes taking biopsies from four quadrants every 10 cm along the whole colon.The specimens should be segregated into individual containers based on their respective locations. Additionally, any observable or questionable abnormalities should be subjected to biopsy and dispatched independently. For those with less severe disease, it is recommended to do biopsies at the beginning of the affected area and then every 10 cm distally.In patients with UC, it may be advisable to do biopsies every 5 cm in the distal sigmoid and rectum in cases of long-standing disease. This is due to the fact that these specific locations have a higher incidence of CRC.[45]

The efficacy of random biopsies has recently been called into doubt.According to van den Broek et el [46], UC-associated neoplasia was observed macroscopically in 94% of colonoscopies. They also reported that only one patient, out of a 10-year span, had incidentally detected neoplasia that had clinical consequences. Watanabe et el [47] conducted a randomised study where they assigned UC patients to two groups: one group underwent both

 

targeted biopsies and random biopsies, while the other group only underwent targeted biopsies. They discovered that both groups had equal proportions of neoplasia, but the focused biopsies were more cost effective.

### 5.5 Endoscopy For Therapeutic Interventions

#### *5.5.1 Stenosis*

For stenosis smaller than 5 cm, there are three therapeutic options available: endoscopic balloon dilatation, endoscopic stricturotomy, or stent implantation. It is important to note that the use of stents in this context is supported by limited evidence.[48] Endoscopic balloon dilation carries a reduced likelihood of bleeding, but an increased likelihood of perforation. Nevertheless, retrospective studies have demonstrated the safety of this approach in patients with CD, with over 40% of patients being asymptomatic and not needing further surgery during future follow-up.[49] Endoscopic stricturotomy is currently undergoing development and has the potential to be a highly effective technique for treating fibrotic, distal, or anastomotic stenosis. The procedure relies on electro-incision, which enables precise control over the depth and placement of the incision, while reducing the likelihood of perforation. In a short study comparing the survival rates of patients with IBD and those without IBD who had endoscopic stricturotomy, there was no significant difference in the outcomes between the two groups [50]. Endoscopic administration of steroids or anti-tumor necrosis factor drugs, along with endoscopic balloon dilation, has been shown in a series of cases to potentially decrease the necessity for future dilatation. However, the outcomes have been inconsistent [51], [52]. Self-expanding metal stents, coated metal stents, or biodegradable metal stents have been effectively utilized in cases of recurrent or refractory stenosis [53], [54].These can be inserted endoscopically, either with or without fluoroscopic guidance, but they must be kept in place for a minimum of 4 weeks[55].

#### *5.5.2 Fistulas*

The penetrant phenotype might either be primary or a consequence of a chronic CD. The objectives of endoscopic treatment include facilitating the flow of fluids, sealing the fistulas, and averting their progression into complicated conditions [56]. In a group of 29 patients, about 90% successfully obtained the clearance of their fistulas with endoscopic fistulotomy [57].This therapy can be conducted in superficial, short, and enteroenteric fistulas [55]. Furthermore, it is feasible to achieve endoscopic closure of the fistula by utilizing a clip, thereby preventing the development of abscesses. This has been reported to be accomplished using either through-the-scope clips or over-the-scope clips, including reports of success in treating perianal fistulas [58]. Additional research is required in this field, specifically to elucidate the risks, advantages, and strategy for integrating it with medical interventions.

#### *5.5.3 Post-operative complications*

Complications after surgery can manifest as the separation of the suture or staple line, or later on as the narrowing of the anastomosis, leading to obstructive issues. [59] Endoscopic treatment of suture dehiscence has been documented in clinical cases and case series, with reported preservation of lumen integrity in more than 80% of cases [60]. Around 11% of patients diagnosed with UC necessitate the use of ileal pouch anal anastomosis for their treatment [61]. In these cases, it is possible for strictures to develop either in the anastomosis, the pouch, or the afferent loop. Postoperative strictures can be effectively treated using endoscopic techniques such as balloon dilations or stricturotomy.Avoid endoscopic interventions during periods of heightened inflammation due to the elevated risk of perforation [62].

## 6. Imaging Modalities in IBD Diagnosis

The utilization of endoscopic evaluation for the diagnosis and monitoring of IBD can frequently provide challenges and difficulties for both patients and clinicians. The integration of radiological imaging with endoscopy has been widely recognized as a standard practice in the management of IBD for a considerable period of time. Significant progress has been made in the monitoring and therapy of IBD due to the notable breakthroughs in imaging techniques. Various imaging modalities, such as magnetic resonance imaging (MRI), computed tomography (CT), and ultrasonography (US), have contributed to the progressive development of clinical practice and the establishment of recommendations. Multiple modalities have demonstrated the ability to evaluate different anatomical regions of disease activity. The focus of our study is on the various diseases affecting the small and large bowel, as well as the perianal region. The focus of treatment in IBD has progressively shifted towards the

 

attainment of mucosal and histological remission.[63], [64] Given this consideration, it is preferable for doctors and radiologists to possess non-invasive methodologies that can effectively assess disease activity, which can be compared to the standards of ileocolonoscopy and histology. The progression of image processing technology has the potential to significantly impact the utilization of radiological modalities in the monitoring of therapies, assessment of postoperative outcomes, and disease monitoring.

### *6.1 Small bowel*

MRI is widely recognized as the preferred imaging modality for the surveillance of luminal small bowel CD. Water-based oral contrast agents are employed for the purpose of expanding the lumen of the small bowel and generating a positive contrast on T2-weighted images, while producing a negative contrast on T1-weighted images. The quantity and composition of oral preparation are determined based on the preferences of the local location. However, it is generally recommended to administer at least 1 L of a poorly absorbable substance, such as a mannitol solution, in order to achieve optimal distention of the bowel loops. The MRI examination typically includes a combination of T2-weighted images, both with and without fat saturation, as well as pre- and post-gadolinium contrast fat-saturated T1-weighted scans. Furthermore, it is common practice to administer an antispasmodic medication in order to diminish the peristaltic contractions of the gastrointestinal tract. In recent times, there has been a notable surge in research attention towards the capture and quantification of bowel motility. Multiple research groups have generated diverse metrics to assess the motion of the gut wall.[65] The technique employed in MRI is referred to as cine-MRI. This method entails acquiring several images at a specific anatomical site within the body, either in two dimensions or three dimensions (3D), so enabling the visualization of localized intestinal wall displacement. Several studies in the field of CD have presented empirical evidence indicating a decrease in bowel motility in individuals with inflammatory illness. Furthermore, a correlation has been established between lower motility in the terminal ileum with histological and endoscopic findings.[66] Recent advancements in magnetic resonance (MR) imaging have led to the exploration of novel MR sequences, including diffusion-weighted imaging (DWI), magnetisation transfer (MT) imaging, dynamic contrast enhancement (DCE) imaging, and MR relaxometry (quantitative T1 and T2 imaging), in the context of small bowel research. The primary objectives of these more recent sequences are to offer distinct information regarding the inflammatory and fibrotic tissues in Crohn's disease (CD), a distinction that is challenging to make using traditional imaging methods. Consequently, this enables the development of more precise treatment strategies. The prospective in vivo measurement of the MT ratio (MTR) has been found to exhibit a strong positive correlation with histological surgical samples. Specifically, the degree of fibrosis was observed to be favorably connected with MTR.[67] Numerous prospective and retrospective studies have demonstrated the presence of limited diffusion in inflamed Crohn's disease bowel loops, specifically in the context of DWI. A considerable number of the studies available exhibit limitations such as being conducted at a single center and having small sample sizes. Additionally, the absence of a standardized procedure for assessing the apparent diffusion coefficient further complicates the interpretation of the findings.[68] Dynamic contrast-enhanced (DCE) imaging, a technique aimed at quantifying the gadolinium contrast uptake in the specific tissue under investigation, has been utilized both retrospectively and prospectively in luminal CD. This imaging modality has demonstrated sensitivity towards inflammatory conditions. Further prospective research and validation in large-scale multi center clinical trials are required to comprehensively assess the potential of these novel sequences as biomarkers for CD and their effectiveness in monitoring luminal CD.

### *6.2 Large bowel*

MRI,CT, and US have been employed as diagnostic modalities for evaluating colonic inflammation in individuals with IBD. When comparing them to ileo-colonoscopy, these non-invasive instruments are regarded as having higher levels of tolerance and generally lower costs. The utilization of non-invasive techniques has the potential to improve the results of colonic diseases by expediting the decision-making process. According to a recent meta-analysis, the diagnostic modalities of US and magnetic resonance MRI demonstrated a high level of specificity (91%) in predicting active disease among patients with established or suspected IBD, when compared to colonoscopy as the gold standard.[69] This observation suggests a significant potential for these non-invasive methods to differentiate between patients with current disease and those without disease. In terms of CD recurrence, the accuracy and sensitivity of US in detecting CD were found to be 91% and 94% respectively.[70] These results suggest that US has the potential to offer a highly accurate evaluation of colonic disease activity. US was able to successfully discover abnormal small and large bowel segments that had not been detected during ileocolonoscopy

 

in a total of 41 patients out of the 115 individuals who either had confirmed or suspected cases of CD.[71] Recent research provides evidence for the feasibility of utilizing contrast-free MRI to reliably assess colonic inflammation. T2-weighted (T2W) imaging demonstrated comparable accuracy to T1-weighted postcontrast sequences in assessing colonic CD lesions. This can potentially minimize the need for gadolinium-based contrast agents, particularly in patients with renal failure, hence reducing associated risks. Although the present clinical assessment of colonic inflammation using T2W is qualitative in nature, recent research have employed quantitative T2W techniques. These studies have demonstrated more objective evaluations of the condition, which could improve the assessment of colonic inflammation in IBD.[72]

### *6.3 Ultrasonography*

#### *6.3.1 Characteristics of Ultrasound Index Parameters*

Within clinical practice, various aspects of the IUS can be observed to indicate the activity of IBD. These include bowel wall thickening (BWT), bowel wall stratification (BWS), CDI, and extraintestinal abnormalities such as fat, lymph nodes, and free fluid accumulation. These indications may signify the complications of CD, such as abscesses, fistulas, and strictures. The presence of inflammatory mucosal alterations in IUS images can accurately indicate the extent of disease in patients with UC. The metrics that are currently being regularly described include BWT, BWS, and CDI. The current IUS indexes employ different proportional contributions and weightings of these three parameters to evaluate IBD activity. [73]There has been increased interest in the usefulness of contrast US, contrast-enhanced US, and US elastography as new methods for assessing tissue stiffness and improving the precision of identifying the location and extent of disease strictures. Currently, there have been no clinical trials that have established reliable and consistent IUS scores for assessing inflammation and evaluating treatment response. However, the International Bowel US Group is actively advancing in this area.[74]

#### *6.3.2 Clinical Practice Use of Intestinal Ultrasound in Crohn's Disease*

In Europe, IUS is widely recognized as a suitable method for managing CD, a disease that affects the entire wall of the intestine. The main characteristic of active CD on IUS is an increase in BWT and hypervascularity, primarily in the submucosa. An important indication of CD is the uneven thickening of the intestinal wall on the mesenteric side. [75]Two recently introduced scoring systems for assessing the activity of CD are the Simple US Activity Score for CD (SUS-CD) and the International Bowel US Segmental Activity Score (IBUS-SAS). The SUS-CD integrates the BWT and CDI, while the IBUS-SAS employs four parameters: BWT, BWS, CDI, and inflammatory fat. [73], [76]The assessment of postoperative recurrence at 6 months in patients with CD relies heavily on the measurement of BWT, which is the most critical criterion. BWT also shows a strong correlation with the CD activity index. [77]The IUS measures, including BWT, BWS (bowel wall stratification), presence of fistula, abscess, and stenosis, serve as reliable prognostic markers for assessing the short-term (30 days) surgical risk in patients with CD. These characteristics are also connected with the Harvey Bradshaw index.[78]

An observational longitudinal study was conducted to assess transmural healing using IUS in 66 patients with CD who were undergoing biologic treatment. The study found that MRI was more precise than IUS in determining the extent of CD and detecting enteroenteric fistulas. Both techniques showed strong agreement in identifying the location of the disease and abscesses. [79]As a result, follow-up IUS is recommended for CD patients with complications following an MRI or CT imaging study. In a single-center study involving 60 patients with CD, IUS was compared with MRI combined with colonoscopy. The study evaluated disease activity and complications. The findings of the study suggest that IUS has the potential to be useful in detecting ulcers in this population. In terms of accurately identifying the location of the disease, the diagnostic accuracy of IUS was found to be 91%. Furthermore, when it comes to detecting complications, the diagnostic accuracy of IUS was 81% for strictures, 98% for fistulas, and 96% for abscesses.[80]

A multicenter prospective study involving 234 individuals with CD demonstrated that a decrease in BWT or bowel wall stiffness (BWS), a reduction in the size of fibro-fatty lesions, and an increase in signals in CDI were associated with a decrease in disease activity, as measured by the Harvey-Bradshaw index score. [81]Initial assessment of the efficacy of a medical intervention seems to be a highly advantageous application of IUS.

#### *6.3.3 Clinical Practice Use of Intestinal Ultrasound in Ulcerative Colitis*

In the context of CD and UC, IUS has a more clearly characterized clinical role in CD compared to UC. As doctors

 

become more acquainted with utilizing IUS in UC, the utilization of this approach is expected to rise in the future. IUS can reduce the need for colonoscopy and is widely regarded as a dependable, objective, and widely recognized method. Evaluating a solitary rectal manifestation of UC is challenging due to the rectum's position in the pelvic region. [82]In UC, there is a superficial inflammation that causes the mucosa and submucosa to thicken. In patients with UC, the presence of active inflammation is indicated by hyperechoic thickening of the submucosa, which reflects edema. In UC, the gut wall typically grows uniformly and without any discontinuities across its whole circumference, contrasting in what it's observed in CD. During episodes of heightened UC activity, the use of IUS can detect further indicators of fibro-fatty growth, accumulation of fluid in the abdominal cavity, or even the presence of mesenteric streaks. [83]A meta-analysis study indicated that the diagnostic accuracy of IUS in the rectum is poorer compared to the right, transverse, and left colon. [82] Additionally, a prospective observational study involving 224 patients with UC reported that IUS is feasible for monitoring the short-term therapy response. Significant enhancement in BWT (bowel wall thickening) was shown within a mere 2 weeks following the intensification of the medication. Subsequently, clinical improvement was reported, as assessed by the Short Clinical Colitis Activity Index. There was a substantial correlation between BWT normalization and clinical response after 12 weeks of treatment.[75], [84] A systematic study demonstrated that the most prevalent method for assessing disease activity is by measuring two criteria: increasing BWT and blood flow, as detected by (CDI).[85] An expert panel has identified BWT and CDI features as the most dependable indicators for assessing IUS. The panel suggested combining these features to develop an index for measuring disease activity in UC.[86]

## 7. Screening and Diagnosis of IBD

In primary care settings, IUS has been employed as a screening tool for patients with gastrointestinal (GI) symptoms who do not exhibit severe indicators of disease (such as weight loss, anemia, or elevated FCal). It has demonstrated a high level of accuracy in distinguishing between patients with irritable bowel syndrome and those with inflammatory bowel disease. [87]In a recent prospective trial including 37 patients with low-risk gastrointestinal symptoms , the IUS resulted in a decrease in the frequency of colonoscopies and appointments, leading to improved outcomes in health services.[88] Moreover, gastrointestinal infections can potentially imitate IBD. Comparative studies have demonstrated the diagnostic accuracy of IUS in identifying infectious enteritis, surpassing that of CT or MR. Key observations typically involve the presence of hypoechoic thickening of the small intestinal wall and enlargement of lymph nodes. Moreover, IUS is capable of identifying inflammation in cases of infectious colitis. IUS characteristics may coincide with IBD, and IUS by itself is insufficient for diagnosing GI infections. Thus, it is possible to conduct an ultrasound examination in these individuals to rule out IBD.[89] The primary metric commonly employed to identify intestinal inflammation is intestine wall thickness (BWT). The typical threshold values are 2–3 mm for the small intestine and 3–4 mm for the large intestine. Active inflammation is also linked to loss of bowel wall stratification (BWS) and enhanced vascularization, which may be evaluated by color Doppler flow (CDF).[75] Additionally, extramural characteristics, including the expansion of mesenteric fat and lymph nodes, are also significant.

Hence, IUS can serve as a highly beneficial instrument for diagnosing IBD. For example, individuals with CD should undergo an evaluation of the small intestine at the time of diagnosis, using techniques such as MR enterography (MRE), IUS, and/or capsule endoscopy. CT enterography is an alternative method that can be used, although it does come with the drawback of exposing the patient to radiation.[90] In a systematic review, which involved 1,558 patients with CD, consisted of endoscopic, histologic, barium examination, and/or intraoperative results. The collective sensitivity of the IUS was determined to be 88%, while the specificity was found to be 97%.[91] When specifically assessing small bowel disease, the IUS demonstrated an overall sensitivity ranging from 54 to 93%, and a specificity of 97-100%.[92] Multiple studies have evaluated the efficacy of BWT in aiding the diagnosis of UC. Although UC is primarily a disease affecting the mucosal lining, a BWT (bowel wall thickness) more than 4 mm demonstrated a sensitivity of 62-89% and specificity of 77-88% in diagnosing the condition. [93]However, there is no recognized definitive threshold for diagnosis, and levels greater than 3 mm have also been reported.

Patients with active IBD exhibit distinct characteristics depending on whether they have UC or CD. UC patients display a notable increase in the thickness of the mucosal layer, while CD patients experience a considerable thickening of the submucosal layer and a higher incidence of lymph node enlargement.[94] In cases of UC, the thickening of the gut wall is generally directly related to the presence of BWS. The mesenteric proliferation is a notable characteristic in CD, although it can also happen in UC, particularly during severe bouts. [75]Therefore, IUS is a reliable technique for detecting intestinal inflammation and aiding in the diagnosis of both CD and UC.

 

## 8. Application of AI in IBD

### *8.1 What is AI and its current application*

AI-assisted endoscopy utilizes computer algorithms that mimic human brain functioning.[95] Their response is determined by the information they receive as input and the knowledge they have acquired during their construction. The core tenet of this technology is "machine learning" (ML).[96]

There is a wide range of machine learning methods available, as shown in Table 1. Among these methods, one of the most often used is artificial neural networks (ANN).[97] ANN operates through a series of interconnected layers of algorithms. These algorithms receive data in a structured manner and transmit it to train the system for a particular purpose [98]. Another ML technique that is commonly used for classifying data sets is the Support-vector machine (SVM). SVM creates a line or plane to partition data into multiple classes [99]. Deep learning (DL) is an advancement of ML that involves a sophisticated neural network structure with numerous layers. This architecture is capable of automatically learning representations of data by converting the input information into various degrees of abstractions [100], [101]. A more advanced version of the ANN is the convolution neural network (CNN), which is influenced by the way neurons in the human visual cortex respond to a particular stimulus. The CNN is capable of convolving the input and transmitting the outcome to the subsequent layer [98], [102].

Table 1. Algorithms involved in machine learning process.

| | |
|---|---|
| **Supervised** | The algorithm is trained by labeling data tagged with the correct answer |
| **Semisupervised** | The algorithm is trained without marking the training data |
| **Unsupervised** | The algorithm is structured on a large amount of unlabeled data based on a small amount of labeled data |

A concise comparison of three types of machine learning approaches based on how they handle data during the training process

Three instruments have been developed based on this technology to assist in every aspect of endoscopy [103], [104], [105]: 1. Computer-aided detection (CADe) identifies gastrointestinal lesions. 2. Computer-aided diagnosis (CADx) characterises gastrointestinal lesions. 3. Computer-aided monitoring (CADm) monitors the technique and the endoscopist, enhancing the quality of endoscopy. Specifically, CADe and CADx systems have been extensively developed and proven to outperform human visual inspection in many studies worldwide [106], [107], [108], [109]. For instance, the GI-Genius Medtronic system achieved a detection sensitivity of 99.7% in identifying polyps, as demonstrated by Hassan et al. [107]. The application domains of artificial intelligence (AI) are experiencing significant growth, and IBD is the next area of focus for this groundbreaking technology.

### *8.2 AI in diagnostic settings*

#### *8.2.1 Disease classification*

The majority of the current body of literature about the application of AI in diagnosing IBD focuses on the creation of risk prediction models. These models utilise either machine learning ML or CNNs to assess datasets consisting of endoscopic and imaging information. [110] However, machine learning algorithms can effectively categorise disease subtypes by analysing genetic information. Wei et al employed machine learning techniques to categorise CD and UC in comparison to control subjects. They achieved an area under the curve AUC of 0.862 and 0.826, respectively) [111], by utilising SNPs. The CD exome challenge utilised machine learning ML and deep learning (DL) techniques to analyse SNP and whole-exome sequencing data. The result was a classification model that achieved an area under the curve (AUC) of 0.72. [112] Smolander et al. have investigated the application of deep belief networks, a distinct type of neural network, in accurately differentiating between UC and CD, achieving an approximate accuracy of 97%. [113]

#### *8.2.2 Endoscopic assessment*

Endoscopists highly appreciate the potential of AI in the field of endoscopic severity assessment. In a recent study, CNN technology was used to examine 875 individuals with UC. The study found that the CNN had a 90% accuracy

in detecting endoscopic remission (measured by the Mayo Endoscopic Score, with a score of 0 indicating remission and 1 indicating non-remission) and a 92.9% accuracy in detecting histological remission. These accuracy rates were found to be similar to those of expert reviewers.[114] In a subsequent investigation, artificial intelligence successfully identified MES Scores from both static and moving images. [115] Comparable data is accessible for computer-assisted diagnosis of grade 1 versus grade 3 ulcers in Crohn's disease and histological inflammation using endocytoscopy. Takenaka et al. have developed a deep neural network model for ulcerative colitis (UC), which was trained using over 40,000 endoscopic still digital pictures together with their matching UC Endoscopic Index of Severity (UCEIS) ratings and histology. This method demonstrated a significantly higher level of accuracy in evaluating endoscopic and histologic remission compared to human reviewers. Central reading is increasingly employed in clinical studies for IBD to evaluate the severity of endoscopic symptoms. The utilization of a recurrent neural network to integrate frames in high-resolution trial endoscopy recordings enabled automated endoscopic scoring. This approach demonstrated a good level of accuracy (70%) in predicting the proper Mayo score. Additionally, there was a satisfactory agreement (k) of 0.84 (0.79–0.90) between the automated system and human observers. [116] Yao et al. [115] demonstrated that in order for AI to be effective in the context of central reading, it is crucial to have a video source of good quality. AI can also offer standardized and replicable evaluations of diseases and include visuals into decision assistance in strategy trials that challenge the traditional therapeutic goals. The application of AI in analyzing capsule endoscopy images yields varied degrees of benefit. Barash et al. devised a CNN to assess ulceration in CD, achieving a 67% overall concordance between expert consensus and the automated technique. [117] A deep learning model used in capsule endoscopy reading shown improved performance compared to conventional reading in terms of both per-patient sensitivity (99.9% vs 74.6%, p=<0.0001) and per-lesion sensitivity (99.9% vs 76.9%, p=<0.0001). [118]

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