Journal of Enterocolitis

Review

Role of Fecal Biomarkers in Determining the Severity of Inflammation in Inflammatory Bowel Disease

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Cite this article as: Sarıca A, Akın A, Dağcı G. Role of Fecal Biomarkers in Determining the Severity of Inflammation in Inflammatory Bowel Disease. *J Enterocolitis.* 2025;2(3):29-34.

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Received: June 22, 2025 **Accepted:** September 10, 2025

DOI:10.14744/Jenterocolitis.2025.63080

Abstract

The term inflammatory bowel disease (IBD) typically refers to a group of inflammatory gastrointestinal conditions, primarily Crohn's disease and ulcerative colitis. Colonoscopy remains the gold standard for diagnosing and managing IBD by evaluating mucosal healing. However, instead of relying solely on invasive endoscopy to confirm mucosal healing, biomarkers are frequently used to indicate inflammation in patients with IBD. In recent decades, fecal calprotectin and fecal lactoferrin have received considerable attention for the diagnosis and non-invasive management of IBD. Numerous studies have investigated fecal biomarkers for predicting the endoscopic and histologic activity of IBD, as well as the likelihood of disease recurrence. In this paper, we reviewed original articles and literature reviews on inflammatory markers in adults, published primarily between 2019 and 2024, along with select older studies. Although fecal calprotectin is the most commonly used fecal biomarker in clinical practice, several other potential fecal biomarkers have been described in the literature. After a brief introduction to these biomarkers, we aim to answer the question of which is the most sensitive biomarker of mucosal healing and whether alternatives to fecal calprotectin could be utilized.

Keywords: Calprotectin, Crohn's disease, infectious enterocolitis, ulcerative colitis.

INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease (CD), the two main subtypes of inflammatory bowel disease (IBD), are chronic, relapsing conditions affecting the gastrointestinal (GI) tract. The latest statistics show that IBD has the highest prevalence rate in Europe, particularly in Northern Europe, and its incidence has been increasing in industrialized countries.[1,2]

In the standard care of IBD, monitoring disease activity and the burden of inflammation plays a critical role in preventing disease-related complications. Disease monitoring includes assessing symptoms, evaluating biological serum markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), and utilizing endoscopic and imaging techniques.[3] Along with serum markers of inflammation, fecal markers are also being used. Because serum markers are non-specific and imaging techniques are both expensive and involve radiation exposure, the importance of fecal markers is increasingly recognized. Given the close connection to the gut and the ease of collecting stool samples, using fecal markers to detect inflammation is a practical approach. Many fecal markers have been identified, but fecal calprotectin (FC) and fecal lactoferrin (FL) are the most widely used indicators of inflammation. In patients with IBD, gastrointestinal endoscopy remains the standard invasive procedure for evaluating the histopathologic severity of inflammation. Although endoscopy is the gold standard, it places a financial burden on the healthcare system. Therefore, accurate, non-invasive tests are ideal for evaluating inflammation. While many markers remain under investigation, several have been well described. This review article emphasizes biomarkers that are widely used, along with potential markers applicable in clinical practice.[4]

METHODS

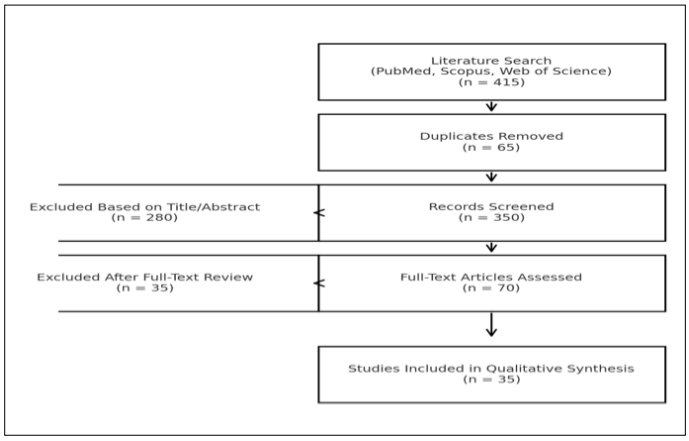
This article is a structured narrative review aiming to summarize the diagnostic and monitoring roles of fecal biomarkers in IBD, with a focus on their correlation with endoscopic and histologic disease activity. While elements of systematic methodology were applied—including a targeted search strategy, predefined inclusion criteria, and tabulated synthesis—the review does not fully meet the criteria for a systematic review as outlined in the PRISMA 2020 guidelines.

Relevant literature was identified through electronic searches of PubMed, Scopus, and Web of Science, limited to English-language studies published between January 2010 and April 2024. Search terms included combinations of "fecal biomarker," "calprotectin," "lactoferrin," "S100A12," "myeloperoxidase," "neopterin," "lipocalin-2," "CHI3L1," "volatile organic compounds," and "inflammatory bowel disease." Original research studies and reviews reporting diagnostic utility, cut-off values, or performance metrics of fecal biomarkers in adult IBD populations were included.

MAIN POINTS

- Fecal calprotectin and lactoferrin are the most validated non-invasive biomarkers for diagnosing and monitoring inflammatory bowel disease, with high sensitivity and specificity for intestinal inflammation.
- Emerging fecal biomarkers such as S100A12, fecal myeloperoxidase, lipocalin-2, neopterin, and volatile organic compounds show promising potential in assessing disease activity, predicting relapse, and differentiating IBD from non-inflammatory conditions.
- Fecal biomarkers correlate strongly with endoscopic and histologic findings, offering reliable alternatives to invasive procedures for tracking mucosal healing and treatment response.
- External factors such as infections, medications (e.g., NSAIDs), and age can affect biomarker levels, emphasizing the need for careful interpretation and consistent assay methods.
- Combined use of multiple fecal biomarkers, along with advanced diagnostic tools (e.g., multi-omics and AI-based models), may enhance clinical decision-making and support precision medicine approaches in IBD management.

Study selection and data extraction were performed manually by the authors. Due to the heterogeneity of study designs and outcome measures, no formal meta-analysis or quality assessment (e.g., risk of bias scoring) was conducted. However, a descriptive summary of key findings—including a comparative overview of biomarker characteristics—was presented in tabular form to assist clinical interpretation. The article selection process is illustrated in Supplementary Figure 1.



Supplementary Figure 1. The article selection process.

Biomarkers

Fecal Calprotectin and Lactoferrin

Calprotectin is a cytosolic calcium- and zinc-binding protein complex belonging to the S100 protein family.[5] It was previously referred to as L1 protein and was first identified by M.K. Fagerhol in 1980 as a highly immunogenic protein in granulocytes and monocytes, serving as a marker of granulocytic protein turnover. Although neutrophils are the primary source of calprotectin, it is also expressed by monocytes, eosinophils, macrophages, and epithelial cells. The calprotectin complex mainly comprises the S100A8 (calgranulin A) and S100A9 (calgranulin B) protein monomers. Calprotectin exhibits antimicrobial properties by inhibiting zinc-dependent metalloproteinases, thereby causing local zinc deficiency and promoting antimicrobial activity.[6] It is also well-established that the S100A8, S100A9, and S100A12 proteins modulate the innate immune system by acting as damage-associated molecular patterns (DAMPs) and signaling through the TLR4-MD2 pathway. Calprotectin can be detected in plasma, urine, saliva, tissue, ascitic fluid, and feces.[7] Stool samples from healthy individuals have shown that fecal calprotectin levels are approximately six times higher than plasma levels, with concentrations proportional to neutrophil migration through the intestinal mucosa.[8] Calprotectin is widely used in clinical practice due to its high sensitivity for detecting intestinal inflammation, making it useful for screening, monitoring, and predicting IBD relapses. Lactoferrin, on the other hand, is more specific to active neutrophilic inflammation, correlates more strongly with severe disease, and is less influenced by other gastrointestinal disorders. Both biomarkers are complementary in IBD management, with lactoferrin being more effective for confirming inflammation and calprotectin better suited for broader screening and monitoring (Table 1).

Plasma calprotectin levels can be elevated in a variety of diseases involving infection and inflammation. Elevated levels have been noted in alcohol-related liver disease, colorectal cancer, cystic fibrosis, malignant lung disease, and rheumatoid arthritis. Fecal calprotectin levels are elevated in inflammatory bowel disease, NSAID-induced enteropathy, colorectal cancer, and pancreatic insufficiency.[9] The laboratory measurement of fecal calprotectin begins with collecting a small stool

Table 1. Comparison of Fecal Calprotectin and Fecal Lactoferrin as Biomarkers in Inflammatory Bowel Disease

Feature	Fecal Calprotectin	Fecal Lactoferrin
Source	Released from activated neutrophils, monocytes, and macrophages	Released exclusively from neutrophils
Function	Calcium- and zinc-binding protein with antimicrobial properties	Iron-binding glycoprotein with antimicrobial and immunomodulatory functions
Clinical Utility	Used for IBD diagnosis, monitoring disease activity, and predicting relapse	Used for IBD diagnosis, differentiating IBD from functional disorders, and monitoring activity
Sensitivity & Specificity	Highly sensitive but may be elevated in non-IBD conditions (e.g., infections, NSAID use)	More specific for active neutrophilic inflammation and severe IBD
Stability	More stable in stool samples (can remain stable at room) temperature for several days	Less stable, requiring proper storage for accurate measurement
Use in Differentiation	Helps distinguish IBD from IBS but may be elevated in infections and other GI disorders	More specific to IBD and correlates strongly with endoscopic disease activity
Role in Disease Monitoring	Useful for predicting relapse and assessing treatment response	Strongly correlates with histologic inflammation and mucosal healing
Limitations	Can be elevated in non-IBD conditions, requiring careful interpretation	More expensive and less commonly used than calprotectin

Table 2. Diseases and Conditions That Increase Calprotectin Levels Infectious

Infectious	• Viral gastroenteritis • Giardia lamblia • Helicobacter pylori gastritis • Intestinal helminth infection
Neoplasms	• Gastric carcinoma • Colonic and gastric polyps • Colorectal cancer • Intestinal lymphoma
Drugs	• Nonsteroidal anti-inflammatory drugs (NSAIDs) – related mucosal injury • Proton pump inhibitors
Other Inflammatory Conditions	• Enteropathies (Autoimmune enteropathy, protein-losing enteropathy, gluten- sensitive enteropathy) • Liver cirrhosis • Cystic fibrosis • Diverticulitis • Colitis (Microscopic colitis, eosinophilic colitis) • Peptic ulcer • Gastroesophageal reflux disease • Juvenile polyp
Food Allergies	
Additional Factors	• Young age < 5 years • Blood loss (over 300 mL/day) • Pancreatic insufficiency

sample. The ideal amount required is 50–100 mg. For optimal measurement, the sample should be the first morning sample and should not be too solid or too liquid. Samples can be stored for up to 72 hours at room temperature and should not exceed one week at 4°C–8°C.[10] The first step involves extracting proteins from the stool using an extraction device. The extraction protocol may vary depending on stool texture. After extraction, the homogenized sample is analyzed using enzyme immunoassay techniques. All assays are based on the use of anti-calprotectin antibodies derived from the rabbit immunoglobulin G fraction. Main detection methods include chemiluminescent, fluorescent, or immuno-turbidimetric assays. Among quantitative methods, enzyme-linked immunosorbent assay (ELISA), chemiluminescence immunoassay (CLIA), fluoro-enzyme immunoassay (FEIA), and particle-enhanced turbidimetric immunoassay (PETIA) are commonly used. ELISA is the most frequently used method. Some point-of-care tests (IBDoc, Bühlmann, QuantOn) and rapid tests have been developed, although further validation is required. Due to the variability in measurement methods, reference values also differ. These methods are not interchangeable; therefore, during routine follow-up, the same test method should be used to avoid confusion.

The reference range of fecal calprotectin concentration varies by age. Fecal calprotectin levels measured using the standard ELISA method are typically <50 µg/g in healthy individuals aged 10 to 59 years.[11] Reference values tend to be higher in infants and the elderly. A cutoff of <112 µg/g is suggested for healthy individuals over age 60, and <166 µg/g for children under 10 years. Fecal calprotectin levels can be elevated by various conditions.[12] Infections, neoplasms, young age (<5 years), inflammatory diseases, and certain drugs can elevate serum levels (Table 2). Considering Table 1, it is advisable to discontinue nonsteroidal anti-inflammatory drugs (NSAIDs) and proton pump inhibitors (PPIs) prior to collecting a fecal sample. In clinical practice, fecal calprotectin levels can help differentiate between IBD and irritable bowel syndrome (IBS). Although not entirely definitive, patients with levels <40 µg/g tend to have a lower probability of IBD. A recent cohort study showed that FC levels <100 µg/g have a high negative predictive value. In symptomatic patients, a lower cutoff (<100 µg/g) suggests that inflammation is unlikely, while a higher cutoff (>250 µg/g) indicates that inflammation is highly likely. In patients with IBD, fecal calprotectin levels can be used to evaluate endoscopic and histological activity and to predict relapse and remission. Several studies have attempted to determine cutoff values of FC for predicting endoscopic and histologic remission in IBD. A commonly cited threshold is ≤150–200 µg/g for endoscopic remission and <100 µg/g for histologic remission. An FC level of <100 µg/g predicted histologic remission in UC with a sensitivity of 78% and specificity of 85%. In Crohn's disease, a value below 150–250 µg/g has been associated with mucosal healing based on endoscopic scores. However, variability in cutoff values across studies reflects differences in assay methods and disease phenotypes. Despite this variability, FC remains the most robust surrogate marker for assessing inflammatory burden and treatment response in IBD. FC has similar sensitivity in Crohn's disease and ulcerative colitis but is more specific for UC. FC levels correlate with endoscopic disease activity. Patients with FC levels greater than 300 µg/g have been associated with clinical relapse. Measuring FC levels can predict relapse 3–4 months in advance. Although fecal calprotectin is the most extensively studied marker, its role in IBD still requires further investigation.[13]

Neopterin

Neopterin is a clinical marker of inflammation derived from the metabolism of guanosine triphosphate (GTP). It is released by macrophages and monocytes. During an immune response, increased levels of interferon-gamma upregulate the cytosolic cyclohydrolase enzyme, which catalyzes the first step in the conversion of GTP to neopterin. Neopterin was first detected in 1966 in the urine of military personnel in Japan. Neopterin can be measured in serum and urine samples. Its levels may increase in viral diseases, rheumatoid arthritis, lupus erythematosus, Sjögren's disease, intracellular infections, autoimmune conditions, and acute cellular rejection (Table 3). Serum and plasma neopterin levels are typically measured using radioimmunoassay (RIA) and ELISA. In a study involving a small number of patients with ulcerative colitis, urine neopterin levels were evaluated. The study found that neopterin levels were highest during active ulcerative colitis.[14] Another study reported that neopterin levels were significantly increased in both clinically active and inactive Crohn's disease, although the marker could not distinguish between the two states. However, fecal neopterin levels were elevated in ulcerative colitis and could differentiate active disease from inactive disease. One study suggested an optimal cutoff of 200 pmol/g as the upper limit for fecal neopterin concentration. Fecal neopterin levels above 200 pmol/g showed a sensitivity of 74% and specificity of 73% in predicting endoscopic activity in patients with Crohn's disease and ulcerative colitis. Compared to fecal calprotectin, fecal neopterin is more cost-effective but requires further validation. Both tests are non-specific and demonstrated similar accuracy in predicting endoscopic activity.[14]

Fecal Metalloprotease[9]

Matrix metalloproteinases (MMPs) are a family of zinc-dependent, highly homologous enzymes. The MMP family includes gelatinases, collagenases, stromelysins, matrilysins, and membrane-type MMPs. Gelatinase B, later known as MMP-9, is mainly released from neutrophil granules.[15]

MMPs play important roles in angiogenesis, wound healing, extracellular matrix (ECM) degradation, and apoptosis. MMPs can be detected

Table 3. Comparative Overview of Fecal Biomarkers for Diagnosis, Monitoring, and Differential Diagnosis in Inflammatory Bowel Disease

Biomarker	Cellular Source	Clinical Use in IBD	IBD vs Non-IBD Differentiation	Correlation with Endoscopic Activity	Sensitivity / Specificity	Predictive Cut-off Values	Advantages	Limitations
Calprotectin	Neutrophils, monocytes	Diagnosis, monitoring, relapse prediction	Moderate-to-high (esp. vs IBS)	Strong	80–93% / 80–90%	<100 µg/g; (histologic) <150–250 µg/g	Widely used, highly sensitive, non-invasive (endoscopic)	Affected by NSAIDs, infections; inter-assay variability
Lactoferrin	Neutrophils	Detecting active inflammation	High specificity	Strong	70–90% / 85–95%	>7.25 µg/g (some studies)	Strong mucosal correlation	Less stable, more expensive
MPO	Neutrophils	Activity tracking, relapse risk	Moderate	Strong	80–90% / 60–70%	>2,000 ng/mL (active disease)	Reflects oxidative stress	Specificity lower than FC
Neopterin	Monocytes, macrophages	Active disease assessment	Low	Moderate	74% / 73%	>200 pmol/g (endoscopic activity)	Cost-effective	Poor active/ inactive distinction
MMP-9	Neutrophils	UC activity marker	Useful for UC vs CD	Strong	85% / 100%	≥0.245 ng/mL (active UC)	High specificity for UC	Limited CD data
Lipocalin-2	Neutrophils	Activity marker	Moderate	Moderate-to-strong	Not standardized	>183 ng/mg (active IBD)	Reflects neutrophil burden	No consensus on cutoff
S100A12	Neutrophils	Activity, IBD vs IBS	High	Strong	85–90%/ 85–90%	>55 µg/g (varies)	May outperform FC in specificity	Not routinely available
CHI3L1	Neutrophils, macrophages, epithelial cells	Monitoring, predicting complications	Moderate	Moderate	Not defined	>15 ng/mL (aggressive CD)	Correlates with stricturing behavior	Standardization lacking
VOCs	Gut microbiota and mucosal metabolism	Diagnosis, relapse prediction	High (distinct UC/CD profiles)	Present	80–90% / 80–90%	Pattern-based (not a single cutoff)	Reflects gut dysbiosis	Method standardization needed

in various body fluids and tissues. The main measurement methods for MMP-9 are zymography and ELISA. Elevated levels of matrix metalloproteinase 9 have been found in colonic biopsies, urine, and blood plasma of patients with UC. MMP-9 levels show a significant correlation with UC disease activity. Another study conducted in patients with UC demonstrated that MMP activity was significantly higher in inflamed mucosa compared to non-inflamed mucosa. Fecal MMP-9 shows a stronger association with UC than with Crohn's disease. High levels of MMP-9 can help differentiate between UC and Crohn's disease. Fecal MMP-9 levels have been correlated with clinical, endoscopic, and histologic activity in UC. In patients with ulcerative colitis, a cutoff level of 0.245 ng/mL yielded a sensitivity of 85% and a specificity of 100%.[16] Current studies are limited in demonstrating the role of MMP-9 in Crohn's disease, and further research is needed. Since MMP-9 indicates active inflammation, it may be useful for monitoring disease activity.[17]

Fecal Lipocalin-2

Lipocalin-2 is a siderophore-binding protein belonging to the lipocalin family and is also known as siderocalin or neutrophil gelatinase-associated lipocalin (NGAL). The primary source of lipocalin-2 is neutrophil granules. It is released during oxidative stress and inflammation and functions by preventing bacteria from acquiring iron from the host, as it blocks siderophores. There is no universally accepted standard cutoff level; however, in healthy controls, the median value was found to be 183 ng/mg. The cutoff level varies depending on the disease type (UC or CD), disease remission status, and clinical activity. The primary method for measuring lipocalin-2 is the ELISA.[16]

Fecal Myeloperoxidase

Myeloperoxidase (MPO) is a heme enzyme stored in the azurophilic granules of neutrophils and monocytes. It plays a critical role in the innate immune response by generating reactive oxygen species (ROS) during the oxidative burst. However, dysregulated MPO activity can induce oxidative stress, contributing to tissue damage and amplifying inflammatory processes. In the clinical course of IBD, MPO levels in fecal samples correlate closely with the extent of neutrophil infiltration into the intestinal mucosa, offering an objective measure of disease activity. Elevated MPO levels indicate ongoing inflammation, as neutrophils are major contributors to the tissue damage observed in IBD. Fecal MPO has been recognized as a reliable marker for evaluating disease activity in both UC and CD.[18]

MPO levels increase significantly during active UC, reflecting neutrophil-driven inflammation in the colonic mucosa. These levels decrease with treatment or remission, making MPO a dependable marker for monitoring disease severity and treatment response. In Crohn's disease, MPO levels correlate with the degree of transmural inflammation—particularly in ileocolonic disease—providing valuable insight into disease severity.[19] Subclinical inflammation is often present even during periods of remission and may precede relapse. Measuring fecal MPO levels during remission can help identify patients at higher risk of flare-ups, allowing for early therapeutic interventions.[20] MPO is highly responsive to treatment; a decrease in fecal MPO is a strong indicator of clinical improvement and endoscopic remission. This makes it a powerful tool for evaluating the efficacy of various therapies, including corticosteroids, biologics, and dietary interventions. Compared to other biomarkers, MPO offers complementary information by reflecting oxidative stress and neutrophil enzymatic activity—features not captured by calprotectin. While both MPO and lactoferrin are neutrophil-derived, MPO specifically highlights the oxidative component of inflammation, which may be of greater clinical significance in certain IBD cases.[16,20]

Although MPO is most commonly elevated in IBD, increased levels may also be observed in other inflammatory and infectious conditions. In gastrointestinal disorders, MPO levels rise in infectious colitis due to neutrophil activation in bacterial, viral, or parasitic infections. In ischemic colitis, hypoxia and reperfusion injury cause pronounced neutrophil infiltration and MPO release. In diverticulitis, acute inflammation of the diverticula is associated with elevated MPO levels. Additionally,

systemic inflammatory diseases such as rheumatoid arthritis and systemic lupus erythematosus (SLE); cardiovascular and metabolic disorders; and pulmonary diseases such as chronic obstructive pulmonary disease (COPD) and acute respiratory distress syndrome (ARDS) also demonstrate increased MPO levels.[16,21]

Fecal MPO shows high sensitivity (80–90%), particularly in active disease states. However, its specificity (60–70%) may be reduced by other conditions involving neutrophil activation. Fecal myeloperoxidase is a promising, non-invasive biomarker for assessing disease activity, predicting relapses, and evaluating treatment efficacy in IBD. Despite its limitations—such as reduced specificity—MPO's stability and responsiveness to inflammation make it a valuable tool in clinical practice when used alongside other biomarkers and clinical evaluations.[16,22]

Fecal Volatile Organic Compounds

Fecal volatile organic compounds (VOCs) are carbon-based molecules produced through the metabolic activity of gut microbiota, dietary interactions, and the intestinal mucosa. They include a wide range of chemical groups—such as alcohols, aldehydes, ketones, esters, and sulfur compounds—which can be analyzed using advanced techniques. VOCs reflect the metabolic and biochemical environment of the GI tract. Changes in VOC patterns are associated with various conditions, including IBD, colorectal cancer (CRC), and irritable bowel syndrome.[21] Specific VOC profiles have been identified in both UC and CD. In UC patients, VOC patterns are characterized by elevated sulfur-containing compounds such as hydrogen sulfide and dimethyl sulfide—both associated with intestinal dysbiosis and epithelial damage—which correlate with inflammatory markers like fecal calprotectin. This highlights their potential as non-invasive diagnostic tools.[23] In CD, elevated aldehydes (e.g., hexanal), alcohols (e.g., propan-1-ol), and phenol derivatives—products of microbial fermentation and mucosal metabolism—are linked to complications such as fistulas and strictures, which are unique to the disease. Although fecal VOC profiles may overlap, sulfur compounds dominate in UC, while aldehydes and phenols are more prominent in CD.[24]

Fecal VOC analysis is a promising tool for monitoring IBD activity and predicting outcomes. In active disease, inflammatory VOCs such as ammonia and methylamines increase, while beneficial short-chain fatty acids (SCFAs), such as butyrate, decrease—correlating with endoscopic severity. During remission, VOC patterns tend to normalize, with higher SCFA levels and reduced inflammatory markers. Additionally, certain VOCs, including branched-chain fatty acids and phenols, may serve as early indicators of relapse, often preceding clinical symptoms.[25,26] Fecal VOCs offer notable advantages over traditional biomarkers. While fecal calprotectin (88–93% sensitivity, 85–90% specificity) and CRP (80–85% sensitivity) are widely used, VOCs provide unique insights into gut-specific microbial and metabolic processes. The sensitivity and specificity of fecal VOCs can vary depending on the study and the specific compounds analyzed, generally ranging from 80% to 90%. VOC analysis also presents a non-invasive alternative to endoscopy. However, challenges remain, including method standardization, controlling for dietary and medication influences, and the need for large-scale validation studies.[27]

S100A12

S100A12, also known as calgranulin C, is a calcium-binding protein primarily secreted by activated neutrophils. It acts as a pro-inflammatory mediator by activating signaling pathways, such as NF-κB, and promoting the release of pro-inflammatory cytokines.

S100A12 plays a key role in IBD by amplifying and sustaining the inflammatory response, particularly through neutrophil activation. Elevated levels of S100A12 in serum, feces, and intestinal mucosa have been shown to correlate with disease activity and severity in IBD patients.[28,29]

Fecal S100A12 levels help differentiate active IBD from IBS and other functional GI disorders, demonstrating high sensitivity and specificity. It also correlates with disease activity, as higher levels are associated with endoscopic and histologic evidence of inflammation.[30] Despite its promising utility, further research is needed to standardize its clinical use and enhance diagnostic accuracy. S100A12 remains a valuable biomarker in IBD management, offering insights into disease progression and treatment response.[31]

Fecal Chitinase 3-like 1

Chitinase 3-like 1 (CHI3L1), also known as YKL-40, is a member of the chitinase family but lacks enzymatic activity against chitin. It plays roles in tissue remodeling, immune regulation, and inflammation. CHI3L1 is produced by various cell types, including macrophages, neutrophils, and epithelial cells. Elevated levels of CHI3L1 have been associated with IBD, rheumatoid arthritis, and asthma.[32]

Fecal CHI3L1 is a promising biomarker for IBD, with elevated levels observed during active disease. It has several potential clinical applications.[33] Fecal CHI3L1 can assist in diagnosing IBD by distinguishing it from other gastrointestinal disorders, such as IBS and CRC, particularly in symptomatic patients.[34] CHI3L1 levels correlate with disease severity and endoscopic findings, making it useful for monitoring flare-ups and remission. High levels of CHI3L1 are associated with a more aggressive disease course and an increased risk of complications, including strictures, fistulas, and hospitalization in Crohn's disease.

CHI3L1 is not only elevated in IBD but has also been associated with schistosomiasis, malignancies, and asthma. The clinical role of fecal CHI3L1 in IBD is still evolving. Challenges include the need for standardized assays, comparative studies with biomarkers such as CRP and calprotectin, and long-term research into its prognostic value and therapeutic potential.[32]

Comparative Summary of Fecal Biomarkers in IBD

A comprehensive evaluation of fecal biomarkers highlights their varying performance across diagnostic and monitoring settings in IBD. While calprotectin and lactoferrin are the most well-established in clinical practice, emerging biomarkers—such as fecal MPO, VOCs, and S100A12—may offer additional diagnostic insight, particularly when used in combination. Table 3 summarizes the key attributes of each biomarker, including their cellular sources, correlation with endoscopic activity, and reported sensitivity and specificity.

CONCLUSION

Fecal biomarkers play a crucial role in the diagnosis, monitoring, and management of IBD by offering a non-invasive, cost-effective, and clinically valuable tool for assessing intestinal inflammation. Among these biomarkers, calprotectin and lactoferrin have demonstrated high sensitivity and specificity in distinguishing IBD from functional gastrointestinal disorders and in predicting disease activity and relapse. While traditional biomarkers are well-established in clinical practice, emerging fecal biomarkers—including S100 proteins, cytokines, fecal chitinase 3-like 1, volatile organic compounds, microbial-derived metabolites, and genetic markers—offer promising insights into disease

pathophysiology, prediction of treatment response, and the advancement of personalized medicine. However, further standardization, validation, and comparative studies are necessary to integrate these novel biomarkers into routine clinical workflows. Moving forward, the integration of fecal biomarkers with advanced diagnostic tools—such as multi-omics approaches and artificial intelligence-driven models—may enhance disease stratification, improve treatment outcomes, and optimize patient care in IBD. Continued research and large-scale, prospective studies are essential to fully realize the potential of fecal biomarkers in guiding precision medicine strategies for IBD management.

Informed Consent: Written informed consent was obtained from the patients participating in this study.

Peer-review: Externally peer-reviewed.

Author Contribution: Concept – A.A., G.D.; Design – A.S., G.D.; Literature Review – A.S., A.A.; Writing – A.S., A.A.; Critical Review – G.D.

Declaration of Interests: The authors declare that they have no competing interest.

Funding: Authors declare that this study have not received any financial support.

REFERENCES

1. Imdad A, Nicholson MR, Tanner-Smith EE, et al. Fecal transplantation for treatment of inflammatory bowel disease. Cochrane Database Syst Rev. 2018;11(11):CD012774. [CrossRef]
2. Khaki-Khatibi F, Qujeq D, Kashifard M, Moein S, Maniati M, Vaghari-Tabari M. Calprotectin in inflammatory bowel disease. Clin Chim Acta. 2020;510:556-565. [CrossRef]
3. Flynn S, Eisenstein S. Inflammatory bowel disease presentation and diagnosis. Surg Clin North Am. 2019;99(6):1051-1062. [CrossRef]
4. Ministro P, Martins D. Fecal biomarkers in inflammatory bowel disease: How, when and why?. Expert Rev Gastroenterol Hepatol. 2017;11(4):317-328. [CrossRef]
5. Jukic A, Bakiri L, Wagner EF, Tilg H, Adolph TE. Calprotectin: From biomarker to biological function. Gut. 2021;70(10):1978-1988. [CrossRef]
6. Ricciuto A, Griffiths AM. Clinical value of fecal calprotectin. Crit Rev Clin Lab Sci. 2019;56(5):307-320. [CrossRef]
7. Dale I, Fagerhol MK, Naesgaard I. Purification and partial characterization of a highly immunogenic human leukocyte protein, the L1 antigen. Eur J Biochem. 1983;134(1):1-6. [CrossRef]
8. Poullis A, Foster R, Mendall MA, Fagerhol MK. Emerging role of calprotectin in gastroenterology. J Gastroenterol Hepatol. 2003;18(7):756-762. [CrossRef]
9. Murray J, Kok KB, Ayling RM. Fecal calprotectin in gastrointestinal disease. Clin Chem. 2023;69(7):699-710. [CrossRef]
10. Manceau H, Chicha-Cattoir V, Puy H, Peoc'h K. Fecal calprotectin in inflammatory bowel diseases: Update and perspectives. Clin Chem Lab Med. 2017;55(4):474-483. [CrossRef]
11. Joshi S, Lewis SJ, Creanor S, Ayling RM. Age-related faecal calprotectin, lactoferrin and tumour M2-PK concentrations in healthy volunteers. Ann Clin Biochem. 2010;47(Pt 3):259-263. [CrossRef]
12. Reenaers C, Bossuyt P, Hindryckx P, Vanpoucke H, Cremer A, Baert F. Expert opinion for use of faecal calprotectin in diagnosis and monitoring of inflammatory bowel disease in daily clinical practice. United European Gastroenterol J. 2018;6(8):1117-1125. [CrossRef]
13. Gisbert JP, Bermejo F, Pérez-Calle JL, et al. Fecal calprotectin and lactoferrin for the prediction of inflammatory bowel disease relapse. Inflamm Bowel Dis. 2009;15(8):1190-1198. [CrossRef]
14. Vernia F, Viscido A, Di Ruscio M, Stefanelli G, Valvano M, Latella G. Fecal lactoferrin and other putative fecal biomarkers in Crohn's disease: Do they still have a potential clinical role? Digestion. 2021;102(6):833-844. [CrossRef]
15. Peterson CG, Sangfelt P, Wagner M, Hansson T, Lettesjö H, Carlson M. Fecal levels of leukocyte markers reflect disease activity in patients with ulcerative colitis. Scand J Clin Lab Invest. 2007;67(8):810-820. [CrossRef]
16. Khan AA, Alsahli MA, Rahmani AH. Myeloperoxidase as an active disease biomarker: Recent biochemical and pathological perspectives. Med Sci (Basel). 2018;6(2):33. [CrossRef]
17. Swaminathan A, Borichevsky GM, Frampton CM, et al. Comparison of fecal calprotectin and myeloperoxidase in predicting outcomes in inflammatory bowel disease. Inflamm Bowel Dis. 2025;31(1):28-36. [CrossRef]
18. Sakurai T, Saruta M. Positioning and usefulness of biomarkers in inflammatory bowel disease. Digestion. 2023;104(1):30-41. [CrossRef]
19. Dai C, Jiang M, Sun MJ. Fecal markers in the management of inflammatory bowel disease. Postgrad Med. 2018;130(7):597-606. [CrossRef]
20. Hansberry DR, Shah K, Agarwal P, Agarwal N. Fecal myeloperoxidase as a biomarker for inflammatory bowel disease. Cureus. 2017;9(1):e1004. [CrossRef]
21. Garrity-Park M, Loftus EV Jr, Sandborn WJ, Smyrk TC. Myeloperoxidase immunohistochemistry as a measure of disease activity in ulcerative colitis: Association with ulcerative colitis-colorectal cancer, tumor necrosis factor polymorphism and RUNX3 methylation. Inflamm Bowel Dis. 2012;18(2):275-283. [CrossRef]
22. Masoodi I, Kochhar R, Dutta U, et al. Evaluation of fecal myeloperoxidase as a biomarker of disease activity and severity in ulcerative colitis. Dig Dis Sci. 2012;57(5):1336-1340. [CrossRef]
23. Vernia F, Valvano M, Fabiani S, et al. Are volatile organic compounds accurate markers in the assessment of colorectal cancer and inflammatory bowel diseases? A Review. Cancers (Basel). 2021;13(10):2361. [CrossRef]
24. Van Malderen K, De Winter BY, De Man JG, De Schepper HU, Lamote K. Volatomics in inflammatory bowel disease and irritable bowel syndrome. EBioMedicine. 2020;54:102725. [CrossRef]
25. Bosch S, Wintjens DSJ, Wicaksono A, et al. The faecal scent of inflammatory bowel disease: Detection and monitoring based on volatile organic compound analysis. Dig Liver Dis. 2020;52(7):745-752. [CrossRef]
26. Bannaga AS, Farrugia A, Arasaradnam RP. Diagnosing inflammatory bowel disease using noninvasive applications of volatile organic compounds: A systematic review. Expert Rev Gastroenterol Hepatol. 2019;13(11):1113-1122. [CrossRef]
27. Zheng W, Pang K, Min Y, Wu D. Prospect and challenges of volatile organic compound breath testing in non-cancer gastrointestinal disorders. Biomedicines. 2024;12(8):1815. [CrossRef]
28. Donato R, Cannon BR, Sorci G, et al. Functions of S100 proteins. Curr Mol Med. 2013;13(1):24-57. [CrossRef]
29. Foell D, Wittkowski H, Roth J. Monitoring disease activity by stool analyses: From occult blood to molecular markers of intestinal inflammation and damage. Gut. 2009;58(6):859-868. [CrossRef]
30. Leach ST, Day AS. S100 proteins in the pathogenesis and diagnosis of inflammatory bowel disease. Expert Rev Clin Immunol. 2006;2(3):471-480. [CrossRef]
31. Sidler MA, Leach ST, Day AS. Fecal S100A12 and fecal calprotectin as noninvasive markers for inflammatory bowel disease in children. Inflamm Bowel Dis. 2008;14(3):359-366. [CrossRef]
32. Buisson A, Vazeille E, Minet-Quinard R, et al. Faecal chitinase 3-like 1 is a reliable marker as accurate as faecal calprotectin in detecting endoscopic activity in adult patients with inflammatory bowel diseases. Aliment Pharmacol Ther. 2016;43(10):1069-1079. [CrossRef]
33. Chang MC, Chen CT, Chiang PF, Chiang YC. The role of chitinase-3-like protein-1 (YKL40) in the therapy of cancer and other chronic-inflammation-related diseases. Pharmaceuticals (Basel). 2024;17(3):307. [CrossRef]
34. Jiang W, Li X. Molecular analysis of inflammatory bowel disease: Clinically useful tools for diagnosis, response prediction, and monitoring of targeted therapy. Mol Diagn Ther. 2015;19(3):141-158. [CrossRef]