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RESEARCH ARTICLE

COMPARATIVE UTILITY OF CRP, ESR, FECAL CALPROTECTIN, AND LACTOFERRIN IN ASSESSING INFLAMMATORY BOWEL DISEASE ACTIVITY: A COMPREHENSIVE REVIEW

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Abstract

Inflammatory bowel disease(IBD)is a common and serious inflammatory disease of the gastrointestinal tract characterized by recurrent episodes of chronic inflammation presenting as nausea,vomiting,bloody diarrhea,and weight loss.The pathophysiology of IBD consists of complex mechanisms involving genetic predisposition,dysregulated immune response,environmental factors,and alterations in the gut microbiome.Recurrent mucosal inflammation is often detected by colonoscopy,the gold standard for diagnosing IBD;however,its high cost and invasive nature make it inaccessible to most patients.Noninvasive,inexpensive,yet accurate indicators of mucosal inflammation can also be measured via serum and fecal markers,including erythrocyte sedimentation rate(ESR),C reactive protein(CRP),fecal calprotectin(FCP),and fecal lactoferrin(FL).Recent research highlights the significance of utilizing non-invasive markers as first line testing to screen patients prior to recommending colonoscpies.Currently,there are numerous studies investigating the accuracy of these markers in IBD.This review will summarize current findings to assess the clinical value of these markers for predicting disease severity and risk of relapse.By utilizing these markers,physicians can monitor disease activity and make treatment decisions, reducing the need for invasive procedures.

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Introduction:-

Inflammatory bowel disease (IBD) comprises a group of chronic, non-specific inflammatory intestinal disorders with an unclear etiology, which primarily includes Ulcerative Colitis (UC) and Crohn's disease (CD)(1). Although the symptoms of UC and CD include diarrhea, bloody stools, and abdominal pain, the distinction between the two conditions relies on the lesions' location, extent, depth, pattern, and complications(2). The CD is characterized by transmural inflammation and segmental involvement of the intestines, typically affecting the terminal ileum, and is often accompanied by epithelioid granulomas on histological examination. In contrast, UC exhibits a more widespread pattern of mucosal inflammation, primarily affecting the rectum, and can progress to involve the terminal ileum(3).

Recent epidemiological data indicate a significant global burden of IBD, with approximately 4.9 million global cases of IBD in 2019, with China and the USA having the highest number. Gender disparities are evident, with IBD prevalence, death, and disability-adjusted years (DALYs) being higher in females. A higher socioeconomic status was associated with a higher prevalence(4). In the United States, IBD affects more than 0.7% of the population, with the peak incidence in early adulthood and notable differences across racial and ethnic groups, showing lower numbers among Black, Asian, and Hispanic populations compared to White Americans(1). The pathogenesis of IBD involves complex interactions between environmental triggers and genetic susceptibility. The key environmental factors include early-life exposures, lifestyle, diet, and drug use, particularly antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs). These exposures may affect gut flora and immune responses, potentially triggering IBD in genetically susceptible individuals (5).

Additionally, certain medical interventions, like immunomodulator therapy, colectomy, and fecal microbiota transplantation, may influence disease progression and onset(6). The past few years have seen an expansion in IBD therapeutic options. Conventional treatments aim to control symptoms through pharmacotherapy, including aminosalicylates, corticosteroids (CS), immunomodulators, and biologics. However, the focus of IBD therapy has shifted from simply managing symptoms to modifying the course of the disease by achieving and maintaining remission, which is defined as complete mucosal healing and normalization of blood markers as well as the disappearance of symptoms(7,8). To this end, new therapeutic strategies have emerged involving small molecules, apheresis therapy, improved intestinal microecology, cell therapy, and exosome therapy(9).

These recent advancements in therapeutic approaches, especially the emergence of biologics, have not only promoted the transformation of the treatment mode in IBD but also changed the perspective of IBD therapy from merely symptom control to disease modification. The gold standard in assessing IBD activity is endoscopy, usually through colonoscopy(10). However, this procedure is costly and invasive, with associated risks to the patient. Therefore, using biomarkers to non-invasively assess disease activity, response to therapy, and disease recurrence has become common. The National Institutes of Health (NIH) defines biomarkers as objectively measured indicators of a normal biological process, disease progression, or treatment response(11). Biomarkers can be collected from serum, urine, stool, or tissue sources. While the number of biomarkers available to clinicians has increased in recent years, mainly driven by the growth of metabolomics, genomics, and proteomics, not all biomarkers are helpful or available to the clinician in everyday practice(12).

An ideal biomarker is sensitive and specific to the observed outcome, available without invasive collection, relevant to underlying pathophysiology, responsive to treatment, beneficial in prognostication, cost-effective, and acceptable to the patient. Common biomarkers in the case of IBD include serologic tests such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and stool-based tests like calprotectin and lactoferrin. Due to their accessibility, non-invasiveness, and relevance to inflammation, these biomarkers are widely used in clinical settings(13). In this review, we discuss the utility of CRP, ESR, fecal calprotectin, and fecal lactoferrin as biomarkers for IBD while focusing on their roles in the non-invasive assessment of disease activity, therapeutic response, and risk of relapse. We examine the mechanisms, diagnostic accuracy, and clinical relevance of these biomarkers,providing insights into their applications and limitations in IBD management.

Pathophysiology of IBD:

IBD is a chronic mucosal inflammatory disease characterized by an imbalance of pro-inflammatory and anti-inflammatory factors(14). Under physiological conditions, the production of anti-inflammatory factors, such as interleukin 10 (IL-10), regulatory T lymphocytes (Treg cells), and transforming growth factor-β (TGF-β), is induced by commensal bacteria of the gut microbiota, which helps protect against pathogens. However, in IBD, dysbiosis

due to environmental factors (e.g., antibiotics, stress, etc.) and genetic susceptibility results in hyperactivation of T-helper cells (e.g, Th17), causing an influx of pro-inflammatory factors (e.g., IL-6, IL-12, and tumor necrosis factor or TNF) and increased vascular permeability due to disrupted intestinal epithelial barrier, allowing the invasion of pathogens and further inflammation in the gut(15). This dysregulated immune response leads to chronic inflammation and tissue damage characteristic of IBD (Figure 1**)**. Some extraintestinal symptoms of IBD are also believed to be caused by proinflammatory cytokines, such as TNF and IL-6. For example, IL-6 is known to trigger the liver's synthesis of acute-phase proteins like C-reactive protein (CRP), whereas TNF has been associated with arthritis and cachexia(14)**.**

The erythrocyte sedimentation rate (ESR) is a non-specific indicator of inflammatory diseases, including infectious, neoplastic, and autoimmune disorders. While ESR values can be influenced by a variety of factors such as gender, age, and coexisting illnesses (e.g., anemia), they can be an effective screening test for an initial workup in a suspected inflammatory disorder. ESR does not have a clinical value on its own, and it can be normal in certain conditions; however, when combined with clinical data and other modalities, it can be an accurate sign of active inflammation, particularly in disorders like IBD(16). C-reactive protein (CRP), similar to ESR, is a nonspecific marker of inflammation produced in the liver in response to increased inflammatory cytokines such as IL-6. Unlike ESR, CRP levels show a more direct link with inflammation, increasing and decreasing rapidly with the onset and resolution of inflammation, respectively(17).

In comparison to ESR, CRP is a better marker of acute inflammation within the first 24 hours(18)**.** While both ESR and CRP may be increased in active IBD, they are not accurate indicators of disease severity. For instance, even with active inflammation, CRP levels can be normal in many UC patients compared to CD, which has been correlated with increased IL-6 levels in CD patients compared to UC(19). According to a prospective study, the combination of CRP and ESR was the greatest indicator of short-term relapse in CD patients. Patients with CRP >20 mg/L and ESR >15 mm had an eightfold greater risk of recurrence(20).

Acute phase reactants, such as CRP and ESR, can be nonspecific in inflammatory conditions; recent studies have focused on identifying intestinal inflammation through the use of fecal markers, including fecal calprotectin (FCP) and fecal lactoferrin (FLF). Calprotectin (CP), a calcium-binding S100 protein, is one of the most widely produced cytosolic proteins in neutrophils and leukocytes(21). Neutrophil hyperactivity at the intestinal mucosa and subsequently in the intestinal lumen in response to acute inflammation is associated with increased disease activity in IBD, which frequently manifests as ‘cryptitis and abscesses.

’ While higher serum neutrophil counts and activity in IBD can be attributed to elevated IL-17A production by T-cells, the primary driver of inflammation in IBD, CP is thought to facilitate neutrophil's transendothelial and transepithelial migration(22). In addition to neutrophil migration and adhesion, CP has been shown to increase the production of anti-inflammatory and pro-inflammatory proteins, as well as the transfer of arachidonic acids to the inflammation site, all of which help with neutrophil-mediated oxidative stress(23).

Lactoferrin, similar to CP, is part of the innate immune response against pathogens. Lactoferrin is an iron-binding glycoprotein secreted by neutrophils in serum. In addition to IBD, lactoferrin is involved in neurological disorders (e.g., Parkinson's disease) and viral illnesses (e.g., COVID-19). Lactoferrin production in IBD is increased in response to neutrophil hyperactivity in the intestinal mucosa due to its antimicrobial properties against pathogens, which are ascribed to its capacity to chelate iron and disrupt pathogen cellular processes(24). Increased FLF is, therefore a strong indicator of active IBD and, consequently, the severity of the illness(19).

Discussion:-

The clinical assessments and the invasive nature of endoscopy have highlighted the need for reliable non-invasive biomarkers to accurately evaluate the severity and activity of inflammatory bowel disease (IBD). Among the most extensively studied biomarkers are fecal calprotectin (FC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP)(25).

Evaluation of Diseases Activity by ESR, CRP, FC and Lactoferrin:

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are nonspecific markers of systemic inflammation in the context of inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC). While these markers are not disease-specific, they offer insight into the degree of inflammation and

disease activity. Higher ESR levels have been correlated with greater disease activity, particularly during active stages of IBD. Studies have shown a positive correlation between ESR and clinical activity indices, such as the Mayo score for UC and the Crohn's Disease Activity Index (CDAI). Although ESR can indicate active inflammation, its sensitivity to minor inflammatory changes is lower than that of CRP(26,27). CRP, however, has limitations in IBD. One study reported that 92.9% of CD patients with clinical symptoms had normal CRP levels, even in the presence of mild inflammation. This finding suggests that severe endoscopic lesions can be ruled out in CD patients with negative CRP results(28). Despite this, another study found a weak correlation between CRP levels and CD disease phenotype(29). The diagnostic utility of CRP for detecting endoscopic remission also varies. Yoon et al.. reported CRP's sensitivity for detecting endoscopic remission in IBD to be between 50.5% and 53.3%, with specificity ranging from 85.1% to 87.2%. In comparison, ESR had higher sensitivity (68.7–71.3%) but lower specificity (63.4–66.4%)(30). CRP showed a closer relationship with endoscopic activity in UC than in CD, with a sensitivity of 49% for detecting mucosal healing (MH) and a specificity of 92%, indicating that low CRP values do not necessarily exclude endoscopic activity(31).

Table 1 illustrates a summary of key studies evaluating the diagnostic utility of non-invasive biomarkers in assessing inflammatory bowel disease (IBD) activity**.** In patients with newly diagnosed, active Crohn's disease, recent findings emphasize the importance of the treatment approach on long-term remission. The PROFILE study, a multicenter, open-label, biomarker-stratified, randomized controlled trial, included adults with active Crohn's disease who were assigned to receive either top-down or accelerated step-up treatment. According to the study, top-down treatment (infliximab with an immunomodulator) achieved superior outcomes compared to faster step-up treatment, including maintained remission at one year without steroids or surgery. Therefore, the study authors recommend top-down treatment as the standard of care for most patients, ideally initiated as early as possible after diagnosis(32). In UC patients, CRP and fecal calprotectin (FCP) were evaluated against endoscopic scores. FCP and CRP showed stronger correlations with comprehensive scores, such as the sum of the Mayo Endoscopic Subscore (S-MES) and the Ulcerative Colitis Colonoscopic Index of Severity (UCCIS), compared to CRP alone, which was more relevant for higher endoscopic activity (M-MES ≥ 2)(33).

Despite CRP's role as a biomarker, it is not as accurate as endoscopy for assessing mucosal healing. A review of 30 studies by K Korpacka et al. noted significant variability in CRP cutoff values (0.4 to 28 mg/L) for detecting MH in CD, with a median sensitivity of 79.5% and specificity of 61%. In UC, CRP's specificity was higher (82%), while its sensitivity remained lower (66%)(34). Fecal calprotectin (FCP) has emerged as a more reliable marker for assessing IBD activity. A meta-analysis of 13 trials by Lin et al. demonstrated that a low FCP cutoff (50 μg/g) was more sensitive but less specific, useful for detecting active disease. A higher cutoff (250 μg/g) offered greater specificity, making it better at confirming clinical remission(35). FCP has also shown stronger correlations with endoscopic disease activity than other markers. Schoepfer et al. found a strong association between FCP and endoscopic UC activity(36). Adults typically have FCP levels between ~10-50 μg/g, though pediatric patients may exhibit somewhat increased levels.

Recently, FCP has been utilized as an alternative to endoscopies due to its cost-effectiveness, non-invasive nature, and its accurate indication of disease activity(23). Compared to healthy people, IBD patients have several hundred times higher lactoferrin concentrations. Patients with active IBD have 85–90% higher amounts of fecal lactoferrin than those with inactive IBD. Because calprotectin is linked to colonic inflammation at endoscopy and fecal lactoferrin correlates with histological inflammation, research has demonstrated that both are equally helpful in evaluating IBD activity(37).A recent meta-analysis of 19 studies examining the accuracy of CRP, FCP, and FLF for detecting endoscopic activity in symptomatic IBD patients found that FCP was more sensitive than CRP, with better sensitivity in UC than CD(31). Although several studies have reported higher FCP sensitivity compared to CRP, FCP has relatively low specificity, which necessitates evaluating a broad range of differentials(21).

Both infectious etiologies of gut inflammation and IBD typically have FCP levels >600 μg/g (e.g., Salmonella infection has a median FCP of 765 μg/g)(23). FCP has been shown to predict disease course in IBD. In a prospective study, Kristensen et al. monitored patients monthly after baseline colonoscopy, finding that FCP levels below 250 μg/g correlated with mucosal healing (MES ≤ 1)(38). Elevated FCP levels have been associated with an increased risk of early relapse in IBD patients in clinical remission(39). Longitudinal monitoring has revealed that FCP rises before clinical relapse. In patients discontinuing anti-TNF-α therapy, high FCP levels predicted both endoscopic and clinical recurrence (40). Kallel et al. followed up asymptomatic CD patients for a year, finding that 18.9% of those who experienced relapse had significantly higher FCP levels (380.5 vs. 155 μg/g, $p<0.001$), with a relapse 18 times

more likely in patients whose FCP exceeded 340 μg/g(41). Recent studies have shown that combining biomarkers can enhance diagnostic accuracy. For predicting endoscopic activity in CD patients, combining daily liquid stool frequency with CRP, FCP, platelet count, and mean platelet volume produced the best results(42). FCP, when used alongside CRP and clinical data, can help categorize individuals with unclear disease activity, particularly for FCP values between 100–250 μg/g, which are challenging to interpret(43). Post-hoc analysis of the CALM study highlighted how well FCP, CRP, and CDAI worked together to detect MH(44).

Numerous reports have highlighted the role of the neutrophil-to-lymphocyte ratio (NLR) as a marker in systemic inflammatory conditions. NLR assessment is non-invasive, inexpensive, and simple to calculate from standard blood count data. Higher NLR values have been linked to increased clinical disease activity in both CD and UC patients(45). However, NLR was less effective in assessing endoscopic activity in CD patients compared to UC patients(46). Additionally, gene expression is negatively regulated by microRNAs (miRNAs), single-stranded RNAs of 21–25 nucleotides in length. Active IBD patient samples have shown distinct miRNA profiles compared to controls and patients with quiescent IBD(47). Oncostatin M (OSM), a cytokine in the IL-6 subfamily, is produced by various stromal and immune cells. High mucosal OSM levels have been significantly correlated with IBD severity (48).

Evaluation of Therapeutic Effect ESR, CRP, FC and Lactoferrin:

Initially, the primary goal of IBD medical treatment was to achieve stable clinical remission. However, recent guidelines now emphasize mucosal healing (MH) as a key therapeutic target (49). In ulcerative colitis (UC), endoscopic healing is typically defined as a Mayo Endoscopic Subscore (MES) of ≤1, but an MES of 0 is associated with better disease outcomes. While there is some inconsistency in defining endoscopic remission, one study suggests that endoscopic healing in Crohn's disease (CD) be characterized by a Simple Endoscopic Score for Crohn's Disease (SES-CD) <3 or the absence of ulcerations(10). In a trial involving seventy-two UC patients, improvement in clinical symptoms and a reduction in C-reactive protein (CRP) levels two weeks after infliximab (IFX) induction therapy were linked to a better prognosis(50).

According to the Oxford criteria, a CRP level >45 mg/L or more than eight bowel movements in a 24-hour period on the third day of intravenous corticosteroid treatment predicts an 85% likelihood of in-hospital colectomy(51). However, recent evidence suggests a decline in in-hospital colectomy rates, from 85% in 1996 to 36% in 2017 among patients meeting Oxford criteria, potentially due to improved remission induction following corticosteroid treatment failure(52). Bertani conducted a prospective observational study in UC patients initiating biotherapy with IFX, adalimumab (ADA), golimumab, or vedolizumab. It was found that evaluating fecal calprotectin (FCP) eight weeks after initiating biologic therapy could help predict MH response(53). In CD patients, baseline FCP levels may predict a lack of primary response to IFX induction therapy(54).

Boschetti et al. demonstrated that FCP levels at 14 weeks could predict clinical remission within a year after induction in 32 consecutive CD patients treated with IFX or ADA(55). Furthermore, a report by Plevris et al. indicated that normalization of FCP within 12 months of diagnosis was associated with a reduced risk of disease progression in CD patients(56)**.** In a study involving 677 CD patients treated with ustekinumab, Narula et al. found that FCP levels at 6 weeks could predict endoscopic healing at 52 weeks, outperforming clinical symptom improvement as a prognostic indicator(57)**.** However, FCP may not be an effective marker for assessing therapeutic response early in the induction phase. In contrast, levels of fecal lactoferrin (FL) allow for a quicker evaluation of therapeutic response in patients with Crohn's disease and ulcerative colitis by promptly reflecting drug-induced changes in mucosal inflammation.

FL levels before and after infusion/injection have been shown to accurately distinguish responders, partial responders, and non-responders in patients with suspected loss of response (LOR). This approach is straightforward, precise, and readily adaptable to clinical settings (58). Toyonaga et al. prospectively evaluated 31 UC patients with active disease and observed that while clinical response markers such as the partial Mayo score, two-item patient-reported outcome, and Lichtiger clinical activity index showed significant reductions by day three of induction, a significant decline in FCP took about two weeks(59). Sollelis et al. reported that reductions in FCP, CRP, and achieving clinical remission at 12 weeks were predictive of corticosteroid-free remission at 52 weeks in a cohort of CD patients treated with anti-TNF-α agents(60). Similarly, Choy et al. noted that the CRP/albumin ratio following IFX salvage therapy could predict therapeutic response and identify patients at risk of requiring colectomy in cases of acute severe UC(61). The CALM trial, a large open-label, randomized Phase 3 study conducted across 74

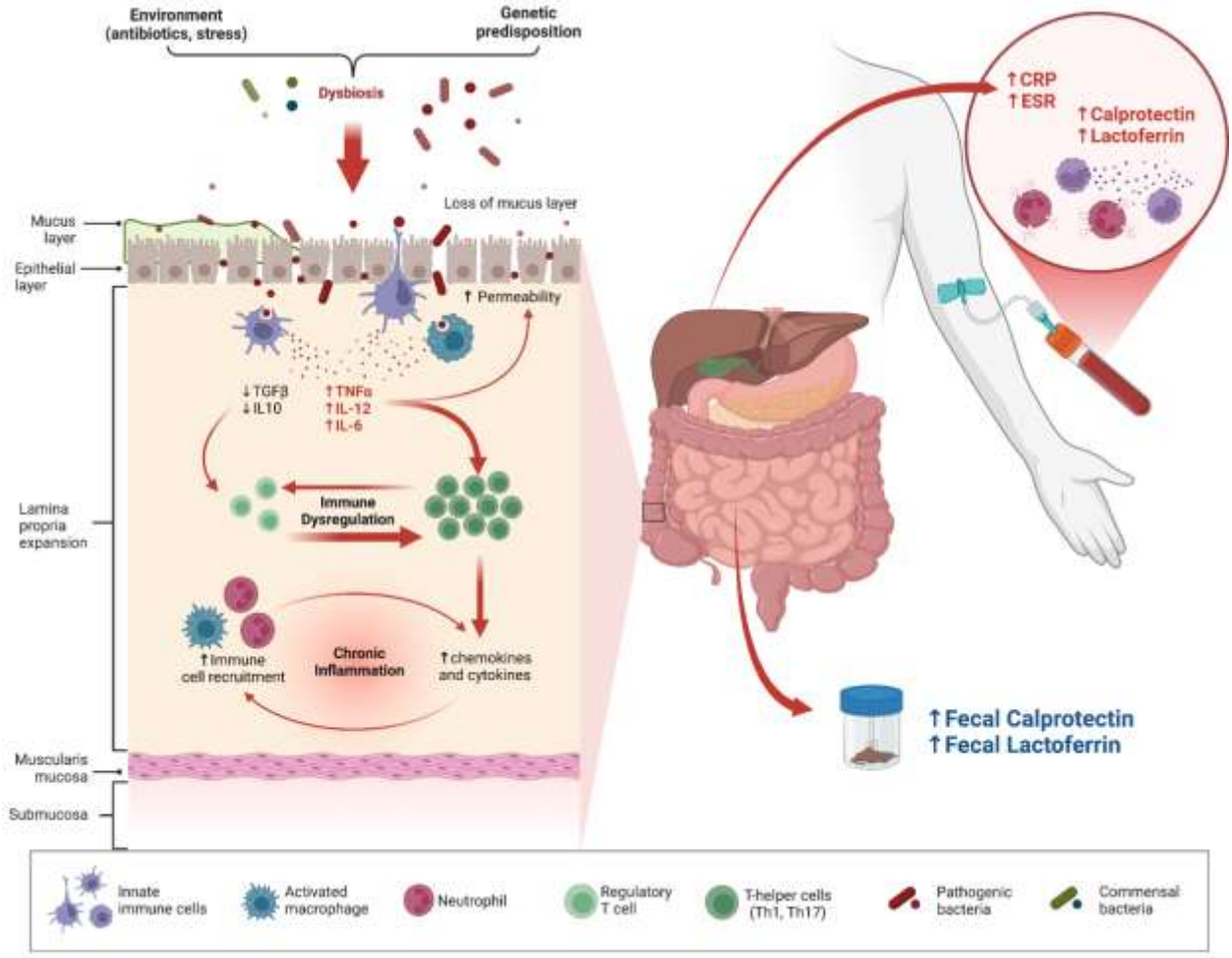
hospitals and outpatient centers in 22 countries, followed CD patients receiving ADA. Patients were divided into two groups: one underwent treatment intensification based on a treat-to-target (T2T) strategy using FCP and CRP levels alongside clinical symptoms, while the other group adjusted treatment based solely on clinical symptoms. After one year, the T2T group using FCP and CRP as monitoring tools demonstrated significantly higher rates of mucosal healing(62). Dulai et al. further underscored the utility of FCP in monitoring clinical and endoscopic responses in UC patients treated with biologics or tofacitinib over 6–8 week induction cycles. They observed that if rectal bleeding was resolved, stool frequency normalized, and FCP was ≤50 µg/g, endoscopy might not be necessary(63).

Figure Legends:
Figure 1: Recurrent inflammation in IBD leads to increased ESR, CRP, FCP, and FL (Created with Biorender.com)

Tables:
Table 1: Summary of Key Studies Evaluating the Diagnostic Utility of Non-Invasive Biomarkers in Assessing Inflammatory Bowel Disease (IBD) Activity

Study	population	Biomarker Analyzed	Key Findings	Sensitivity/Specificity
Mosli et al./2015	2499 IBD patients (CD & UC)	Fecal Calprotectin (FC), CRP, Stool lactoferrin	FC correlated strongly with endoscopic disease activity in both CD and UC compared to CRP	FC: Sensitivity 88%, Specificity 73%, CRP: Sensitivity 49%, Specificity 92%, SL: Sensitivity 82%, Specificity 79%,
Reinisch et al/2020	244 CD patients	CRP, Fecal Calprotectin (FC)	FC cutoff less than 250 µg/g correlates with improved endoscopic outcomes and is useful surrogate marker for mucosal healing in CD.	Combined FC, CRP and CDAI: Sensitivity 72%, Specificity 63%
Turner et al., 2021 (STRIDE-II)	Expert Consensus	CRP, FC, ESR	Recommended CRP <5 mg/L and FC <150 µg/g as therapeutic targets, emphasizing non-invasive monitoring for disease control.	CRP: Sensitivity 52%, Specificity 70%; FC: Sensitivity 83%, Specificity 74%, ESR: Sensitivity 86%, Specificity 64%
Noor et al., 2024 (PROFILE Study)	386 CD patients	CRP, FC	Top-down therapy was more effective in achieving clinical remission compared to step-up, demonstrating the utility of early aggressive treatment. Biomarkers didnot show clinical utility.	

Figures:
Figure 1.



Declarations:-

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Conclusion:-

Non-invasive biomarkers such as fecal calprotectin (FCP), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and fecal lactoferrin (FLF) have demonstrated significant potential in monitoring disease activity, assessing therapeutic responses, and predicting long-term outcomes in inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC). Among these, FCP has emerged as the most reliable and sensitive marker for detecting active disease and assessing mucosal healing. It often correlates more strongly with endoscopic findings compared to CRP or ESR, making it a valuable tool for both diagnosis and treatment monitoring. While CRP is a useful biomarker, its limitations include reduced sensitivity in mild inflammation and in cases where clinical symptoms may not align with elevated levels.

ESR and FLF are useful in certain contexts but demonstrate lower sensitivity and specificity than FCP, limiting their reliability for assessing disease activity. Therefore, the combination of FCP with CRP and clinical data enhances diagnostic accuracy and guides therapeutic decisions. The growing body of evidence highlights the importance of standardizing biomarkers' use and establishing clear thresholds to improve clinical utility. Moreover, emerging biomarkers such as the neutrophil-to-lymphocyte ratio (NLR) and microRNA profiles present new opportunities for advancing IBD diagnostics and treatment. As these non-invasive biomarkers continue to evolve, they are expected to play a more integral role in personalized care, reducing reliance on invasive procedures like endoscopy. Ultimately, their integration into clinical practice may lead to more effective, cost-efficient management of IBD, improving both patient outcomes and quality of life.

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