Review

Biomarkers in IBD: What to Utilize for the Diagnosis?

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Biomarkers in IBD: What to Utilize for the Diagnosis?

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Abstract: The role of biomarkers in the diagnosis of inflammatory bowel disease is not fully characterized. C-reactive protein has a short half-life and elevates quickly after the onset of an inflammatory process, the performance is better in Crohn's disease than in ulcerative colitis. The erythrocyte sedimentation rate is easy to determine, widely available, and cheap but the long half-life, the influence of age, anemia, smoking, and drugs limit its usefulness. Fecal markers have good specificity, but suboptimal accuracy. Microbial antibodies and novel immunological markers show promise but need further evidence before entering clinical practice. Proteomic methods could represent the dawn of a new era of stool protein/peptide biomarker panels able to select patients at risk of inflammatory bowel disease.

Keywords: fecal calprotectin; C reactive protein; p-ANCA; ASCA

1. Introduction

Inflammatory bowel disease (IBD) diagnosis is currently based on clinical criteria together with biochemical and instrumental investigations. A prompt diagnosis is advisable to offer restitution to the well-being and good quality of life of the patient. The recognition and diagnosis of IBD and its differential diagnosis from other acute and chronic bowel diseases are crucial for offering proper treatment and a good prognosis. IBD therapy should induce a rapid symptom control, normalize biochemical indexes and resolve endoscopic lesions. With these targets in mind, we can hope to clear the disease or at least to slow the progression, to reduce the need for steroids and avoid complications and surgeries for the patients.

2. Serological Markers

2.1. Routine Blood Tests

If IBD is suspected, laboratory tests can guide further investigation and contribute to the differential diagnosis. Blood count, electrolytes, erythrocyte sedimentation rate (ESR), C reactive protein (CRP) and stool cultures are routine exams which can be easily performed on peripheral blood samples and are useful to detect acute ongoing inflammation. However, they are not specific to detect intestinal inflammation.

Especially when managing pediatric patients, non-invasive investigations should represent the first line assessment. The performance of blood tests has been tested in 153 children with a clinical suspicion of IBD [1]**:** 103 had a final diagnosis of IBD. Platelet count and hemoglobin rate were found the most reliable tests for differentiating IBD from non-IBD patients ($p<0.002$ and $p< 0.007$, respectively). Anemia or thrombocytosis had a diagnostic sensitivity and specificity of 91% and 80%, with a positive predictive value of 94% and a negative predictive value of 76%.

Anemia is frequent in IBD. It may stem from multiple sources, the most obvious being acute, chronic, or occult bleeding, but the role of chronic inflammation also needs to be considered [2,3]. The biochemical assessment of iron metabolism allows one to discriminate iron-deficiency anemia which is characterized by low serum iron and ferritin with high serum levels of transferrin and total

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iron binding capacity, from anemia induced by chronic inflammation which has a normal/high ferritin, low transferrin, and total iron binding capacity.

The thromboembolic disease has been described in IBD, and especially in ulcerative colitis, possibly secondary to colonic inflammation. During active disease phases [4] not only inflammatory parameters (CRP, ESR, platelet count) increase but also coagulation parameters (thrombin-antithrombin complexes, fibrinogen, FgDP, and FbDP), the coagulation and fibrinolytic cascades are activated, with the hemostatic arm favoring coagulation. This situation may persist also when the acute phase subsides.

ESR has been found related to the clinical activity and extent of disease in ulcerative colitis [5]**.** The ability of clinical and biochemical markers to predict failure of medical therapy has also been tested in 67 patients admitted for severe colitis. ESR > 75 mm/h together with fever > 38°C on the day of arrival were selected as the best predictors of the need for a colectomy [6]**.**

CRP is inexpensive and easy to perform and is unaffected by the patient's medication. It is an acute phase reactant with a half-life of 18 hours, which rapidly declines with effective therapy and it represents a useful prognosticator in UC. More than 8 bowel movements a day and a CRP higher than 45 mg/L after 3 days of intensive medical therapy carry an 85% chance of colectomy in patients with severe colitis [7].

However, CRP generation is genetically determined in each individual patient [8]. CRP is a poor parameter of inflammation especially in UC, about 50% of UC patients have normal CRP during a disease flare [9]. Moreover, elevated serum CRP occurs in most conditions of systemic inflammation and it is therefore unspecific.

Recently, several inflammation-based ratios of different biomarkers have been proposed in IBD diagnosis and prediction of IBD. In a retrospective analysis of 362 patients with IBD and 100 healthy individuals, seven ratio markers have been analyzed. Patients with Crohn's disease or ulcerative colitis exhibited higher levels of neutrophil- to-albumin ratio, neutrophil-to-pre-albumin ratio, fibrinogen-to-pre-albumin ratio ($P < 0.001$), and lower levels of albumin-to-alkaline-phosphatase ratio, and Prognostic Nutritional Index ($P < 0.001$) [10].

2.2. Immunological and Other Antibody Markers

p-ANCA (perinuclear anti-neutrophil cytoplasmic antibodies) have been described in ulcerative colitis patients since thirty years, though the exact epitope remains unknown [11,12]. Examined by indirect immunofluorescence, the neutrophil labeling pattern of these antibodies shows a perinuclear staining distinguishable from the one produced by ANCA in Wegener granulomatosis, which exhibits a diffuse fluorescent neutrophil cytoplasm labeling. P-ANCA have a sensitivity of 52% and a specificity of 91% in differentiating ulcerative colitis from Crohn's disease [13].

Proteinase 3 antineutrophil cytoplasmic antibody (PR3-ANCA) is a serologic marker for granulomatosis with polyangiitis. The role as a diagnostic marker for ulcerative colitis was assessed in in a large number of IBD patients including 77 patients with new-onset ulcerative colitis (disease diagnosed within 1 month). PR3-ANCA ≥3.5 U/mL demonstrated high specificity for the diagnosis of ulcerative colitis especially in the subgroup with a new-onset of the disease. PR3-ANCA measurement has also proved to correlate with disease severity and extension and in predicting the clinical course [14].

Recently, a Japanese study found that measuring serum IgG anti-integrin $\alpha v\beta 6$ autoantibodies (IgG anti-$\alpha v\beta 6$) was sensitive and specific for the diagnosis of ulcerative colitis [15]. The same results were confirmed in another study from Sweden [16].

Anti Saccharomyces cerevisiae antibodies (ASCA) are antibodies directed against the cell wall of baker's yeast. This antibody occurs in the serum in Crohn's disease, but not in ulcerative colitis. A meta-analysis of 14 studies performed in Europe, Israel and Canada [17] found that serum levels of the ASCA have a sensitivity of 56% and a specificity of 88% in discriminating Crohn disease from ulcerative colitis. Moreover, ASCA-positive Crohn disease patients show higher risk of disabling disease, including stricturing and penetrating behavior, earlier onset and perianal disease, with an overall increased need for surgery [17,18]. Both p-ANCA and ASCA are highly specific, but their

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sensitivity is rather low so these tests remain unsuitable for screening purposes [19]. The sensitivity and specificity of ASCA+/p-ANCA− are reported to be higher (0.70 and 0.93, respectively) in pediatric Crohn's disease [20,21]. Overall, their accuracy in diagnosis of IBD is suboptimal ranging between 71 and 80% [22]. p-ANCA and ASCA have been documented in serum even years before the diagnosis of IBD. The early detection of these markers might therefore help identify the risk of future disease and pinpoint patients with a more aggressive clinical course [23].

Other anti-glycan antibodies, namely anti-chitobioside carbohydrate IgA (ACCA), anti-mannobioside carbohydrate IgG (AMCA), anti-laminaribioside IgG (ALCA), anti-laminarin carbohydrate antibodies (anti-L), and anti-chitin carbohydrate (anti-C), have been detected in the serum of IBD patients. Their levels seem to remain stable over time [24]. In general, each antiglycan antibody shows good specificity and positive predictive value for the diagnosis of Crohn's disease rather than ulcerative colitis [24].

The usefulness of a panel of anti-glycan antibodies increase sensitivity as demonstrated in a small Israelian cohort of ASCA negative Crohn's disease patients who proved positive to ALCA or ACCA in 44% of the patients[17].

A genetically determined loss of tolerance has been suspected measuring anti-OmpC and anti-Pseudomonas fluorescence-associated peptide I2 antibodies in monozygotic twins. Dizygotic twin pairs did not show the same similarity[25].

In addition, positivity for ASCA IgA, ASCA IgG, anti-OmpC, anti-CBir1, or anti-flagellin antibodies was detected in 65% of the Crohn's disease patients many years before the diagnosis [26]. The same degree of prediction of IBD diagnosis has been confirmed with a panel of serum antibodies, including p-ANCA, ASCA IgA, ASCA IgG, anti-OmpC, and anti-CBir1, detected in samples stored four years previously [27].

The role of anti-glycan antibodies in disease pathogenesis has also been investigated in unaffected first-degree relatives and the increased antibody response was documented by both qualitative and quantitative analysis. This impaired immunological response to microbial antigens supports the hypothesis of a genetic predisposition to the disease [28].

Recently, new evidence on the predictive role of microbial antibodies and immune-inflammatory markers has been explored using archive serum samples from the US Defense Medical Surveillance System [29]. A panel of several inflammatory proteins and immunological markers showed high accuracy in predicting the diagnosis of Crohn's disease within 5 years with high accuracy. In particular, the response to bacteria was peculiar. If this holds, preventive microbiome targeted interventions could be implemented in predisposed individuals. By contrast, this was not true for ulcerative colitis with p-ANCA being a suboptimal predictor of developing the disease [29].

New insights into the pathogenesis of IBD involve an inappropriate and persistent inflammatory response to commensal gut microbiota in genetically susceptible individuals. Indeed, the importance of the microbiota in the onset and perpetuation of inflammation has been well documented. IBD patients exibit a distinct microbiota in comparison with in healthy subjects. Microbial biomarkers hold promise in assessing disease activity, treatment effectiveness and in personalizing treatment strategies. Moreover, the potential benefits of microbiome-modulating interventions with the use of probiotics, prebiotics, antibiotics, and even fecal microbiota transplantation have reached the IBD field. IBD patients show multiple differences in the composition of gut microbiota in comparison to healthy individuals, particularly regarding microbial diversity and relative abundance of specific bacteria. Patients with IBD show higher levels of Proteobacteria and lower amounts of Bacteroides, Eubacterium, and Faecalibacterium than healthy individuals [30].

In Crohn's disease, a loss of beneficial bacteria, such as Faecalibacterium prausnitzii and an increase in Escherichia coli, have been observed. Particular strains of E. coli, such as entero-adherent E.Coli may be associated with disease in a subset of Crohn's disease patients with ileal involvement [31].

The composition of the fecal microbiota has been less characterized in ulcerative colitis patients but a lower abundance of Roseburia hominis ($p<0.0001$) and Faecalibacterium prausnitzii ($p<0.0001$)

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was found in ulcerative colitis patients compared to controls by real-time PCR analysis [30]. Longitudinal studies involving a large cohort of European IBD patients confirmed dysbiosis and lower microbial diversity in Crohn's disease than in ulcerative colitis patients [32].

The important role that intestinal microbiota play in IBD pathogenesis has been recently investigated by means of serological profiling of 100 Crohn's disease patients, 100 ulcerative colitis patients and 100 healthy controls against 1173 bacterial and 397 viral proteins from 50 bacteria and 33 viruses on protein microarrays. Anti-bacterial antibody responses showed greater differential prevalence among the three subject groups than anti-viral antibody responses. Novel antibodies against the antigens of *Bacteroidetes vulgatus* (BVU_0562) and *Streptococcus pneumoniae* (SP_1992) showed higher prevalence in CD patients relative to healthy controls, while antibodies against the antigen of *Streptococcus pyogenes* (SPy_2009) showed higher prevalence in healthy controls relative to ulcerative colitis patients. Using these novel antibodies, a biomarker panel was built to distinguish Crohn's disease *vs* control, ulcerative colitis *vs* control, and Crohn's disease *vs* ulcerative colitis [33].

The microbial signature specific to Crohn's disease combined with either imaging techniques or fecal calprotectin data has been proposed in decision-making when the diagnosis is initially uncertain.

2.3. Cytokines

In the inflamed mucosa, immune cell recruitment produces cytokines and this leads to stimulation and amplification of the inflammatory cascade and some of them are now the preferred target of biological drugs. They may contribute to our understanding of the inflammatory events and features of IBD, but the increased expression of proinflammatory cytokines in the intestinal mucosa does not always mirror a similar increased concentration in the bloodstream.

Oncostatin M, an IL6 family cytokine, quickly released during degranulation, has been implicated in the pathogenesis of IBD and as an emerging marker for non-responsiveness to anti TNF alfa therapy. Serum Oncostatin M looks promising because increased levels have been found in first degree relatives of IBD families, in newly diagnosed patients and in patients with recurrent disease after surgery [34].

2.4. MicroRNA (miRNA)

MiRNAs are a group of small noncoding RNAs, ~18–22 nucleotides, which act as regulators for post-transcriptional gene expression. The miRNAs circulate in the human peripheral blood but can also be found in urine, saliva, and feces [35].

The miRNAs are engaged in disease origin and development, and some are pathology specific [36].

MiRNAs affect the intestinal barrier and inflammatory reactions so most recent research in the IBD field has measured circulating miRNAs in body fluids such as blood or feces and in homogenized tissue biopsies using microarray profiling techniques, quantitative reverse transcription PCR, and next-generation sequencing [37].

Among the many miRNAs reported, MiR-21 and miR-155 have repeatedly been identified and seem to be the most related to IBD [38,39].

MiR-21, in particular, seems to be the most intriguing because it increases the paracellular permeability of the intestinal epithelium and the level of TNF alfa [40,41].

Further evidence of higher levels of miR-16, miR-21, and miR-223 was demonstrated in IBD patients in comparison with controls, especially in Crohn's disease patients [42].

Paraskevi et al. reported increased blood levels of many miRNAs with some differences between Crohn's disease and ulcerative colitis (miR-16, miR-23a, miR-29a, miR-106a, miR-107, miR-126, miR-191, miR-199a-5p, miR-200c, miR-362-3p, and miR-532-3p in Crohn's disease, and miR-16, miR-21, miR-28-5p, miR-151-5p, miR-155, and miR-199a-5p in ulcerative colitis patients) [43].

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2.5. Other Markers

Extraintestinal manifestations, osteo-articular, cutaneous, ocular, hepatic, pancreatic, nephrological, endocrinological, hematological, pulmonary, thromboembolic, are well recognized as being associated with IBD.

Arthropathy represents the most frequent extraintestinal manifestation of IBD, reported in 10-35% of patients [44]. Biochemical markers are not useful for the diagnosis when the two different inflammatory events coexist. Serum human cartilage glycoprotein 39 (HC gp39, also called YKL-40) was investigated in IBD patients with articular symptoms. Serum levels of HC gp39 were significantly increased in IBD patients with versus those without arthropathy, or controls ($p<0.001$ and $p<0.01$, respectively). The protein's level also seems to correlate with the number of joints involved, suggesting that this substance could be used as a disease activity marker in arthritis associated with IBD [45].

Hepatobiliary diseases in IBD may range from abnormal liver function tests to primary sclerosing cholangitis. Altered liver function tests have been reported in 11% of a large cohort of Swedish patients, especially related to intestinal inflammation, and were usually reversible after the disease was brought under control [46]. The occurrence of liver steatosis and increased transaminases has also been demonstrated in a multicenter study involving IBD patients and controls [47].

Primary sclerosing cholangitis has a prevalence in ulcerative colitis ranging from 2.5 to 7.5%. 82% of patients are p-ANCA positive[48]. Most patients are asymptomatic at the time of diagnosis and routine tests show increased alkaline phosphatase and gamma-glutamyl transferase.

Intestinal permeability reflects the integrity of the intestinal mucosal barrier, which enables the passage of luminal substances by unmediated diffusion [49]. Intestinal permeability can be assessed non-invasively *in vivo* by measuring the urinary excretion of orally-administered sugars such as lactulose/mannitol, glucose and sucralose or radioactive probes such as 51Cr-EDTA. An increased permeability to lactulose/mannitol together with an increased CRP levels were independent predictors of a final diagnosis of small bowel disease in 261 consecutive patients referred to a tertiary referral center with chronic diarrhea [50]. In Crohn's disease abnormal permeability is detected in the majority of patients with small bowel disease location, while in Crohn's colitis sensitivity is lower [51]. However, intestinal permeability has not gained widespread application as screening test to discriminate between patients with Crohn's disease and irritable bowel syndrome. The reason for this is probably that the urinary sugar analysis is time consuming, needs sophisticated equipment, and there may be some concern that the tests lack specificity being abnormal in a variety of other small intestinal conditions, such as celiac disease, acute gastroenteritis, food intolerance, and allergy [52].

3. Fecal Markers

3.1. Calprotectin and Lactoferrin

The presence of intestinal inflammation increases mucosal permeability, resulting in more leukocytes passing through the mucosa and getting into the intestinal lumen. Leukocytes can be retrieved in stools and detected under the microscope but since their degranulation is quick, only fresh stools can be analyzed [53,54]. Some leukocyte proteins (such as lactoferrin and calprotectin) are durable, however, and can be used as surrogate markers of leukocyte activity.

Calprotectin is a calcium and zinc-binding protein of the S-100 protein family, which comprises 60% of the cytosolic protein in human neutrophils, lactoferrin a component of the granules of neutrophilic granulocytes [55]. Lactoferrin, like other neutrophil proteins such as elastase, myeloperoxidase and lysozyme, increases during the active phases of the disease by comparison with the periods of remission. Lactoferrin is stable and its extracellular release is the most efficient [56]. Calprotectin and lactoferrin show high sensitivity and specificity for the presence of macroscopic inflammation [55].

Calprotectin levels can help differentiate between inflammatory and non-inflammatory bowel conditions such as diverticulosis and irritable bowel syndrome. In a prospective study on 870

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consecutive patients referred for colonoscopy, elevated calprotectin levels (>50mg/dl) were detected in 85% of patients with colorectal cancer, and 81% of those with inflammatory conditions. However, the levels were also increased in 37% of patients with normal or trivial endoscopic findings. In patients referred for chronic diarrhea, sensitivity and negative predictive value were 100% in detecting either inflammation or cancer [57].

In gastrointestinal infections, especially of bacterial origin, fecal calprotectin concentrations are strongly elevated and correlate with disease severity [58,59].

Viral infections, including coronavirus disease induced by SARS-CoV2, show abnormal calprotectin levels, although less elevated than in IBD and bacterial infections [60].

Since optimal calprotectin cut-offs are not established, clinicians may be challenged in the interpretation of intermediate concentrations of 150–250μg/g (declared as a grey zone by STRIDE-II recommendations) [61]. On the contrary, values higher than 250 should prompt further evaluation such as endoscopy.

A meta-analysis on the utility of CPR, ESR, fecal calprotectin, and fecal lactoferrin showed that there was a very low probability of having IBD when CRP or fecal calprotectin were within the normal range [62].

Eight studies investigated the role of fecal calprotectin as a first line exam in pediatric patients with suspected IBD: the pooled sensitivity and specificity for the diagnostic utility of fecal calprotectin were 0.978 (95% confidence interval (CI), 0.947–0.996) and 0.682 (95% CI, 0.502–0.863), respectively; the positive and negative likelihood ratios were both very interesting [63].

Other conditions, such as necrotizing enterocolitis, [64] graft-versus-host disease, [65] and drug-induced enteropathy should be kept in mind [66].

Evidence of increased fecal calprotectin levels in predicting colorectal inflammation has also been found in adult patients referred for colonoscopy because of chronic diarrhea [67].

Calprotectin is now considered a biomarker for inflammation in the gastrointestinal mucosa with implications for clinical decisions but its biology in the gut need further studies. In the healthy mucosa calprotectin has a broad spectrum of immunomodulatory properties which may drive the generation of reactive oxygen species during gut injury. So not only increased fecal calprotectin concentrations are a landmark of neutrophilic inflammation but also gut inflammation induces epithelial calprotectin expression and secretion. We can therefore expect higher levels of fecal calprotectin with more pronounced inflammation. Different cut-off values are suggested for patients with known inflammatory conditions with respect to patients with suspected disease. The diagnostic performances of non-invasive tests for IBD have been recently analyzed in an umbrella review [68]. The clinical scenarios included diagnosis of IBD vs. non-IBD, IBD vs. irritable bowel syndrome, IBD vs. functional gastrointestinal disorders, Crohn's disease vs. ulcerative colitis. Fecal calprotectin and fecal lactoferrin proved to be the most sensitive (0.97 and 0.94 respectively) for distinguishing IBD from non-IBD. However, anti-neutrophil cytoplasmic antibodies (ANCA) and fecal lactoferrin were the most specific for the diagnosis of IBD. Fecal calprotectin and fecal lactoferrin were the most sensitive and specific tests, respectively, to distinguish IBD from irritable bowel syndrome. However, all tests showed low sensitivity for distinguishing Crohn's disease from ulcerative colitis [68].

Calprotectin is now widely used in clinical settings involving IBD patients, nevertheless, we must keep in mind that the performance of this test is far from ideal. Moreover, the cut off value for discriminating functional from organic bowel disease is not standardized and depends on the test used and type of assay [69].

The appropriate clinical use of fecal calprotectin might be influenced by the type of assay. Different optimal thresholds need to be settled depending on the type of assay (120 μg/g for ELISA, 50 μg/g for CLIA and 100 μg/g for turbidimetry). Moreover within- and between-subjects variability must be taken into account: sensitivity is satisfactory in distinguishing between controls and IBD patients in patients <65 years, but it is lower in older patients (ROC area: 0.584; 95% CI: 0.399-0.769) [70].

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3.2. HMGB1

The nuclear protein High-Mobility Group Box 1 (HMGB1) is actively secreted from immune cells in the extracellular matrix, where it behaves as a proinflammatory cytokine. HMGB1 was measured in the stools of 40 IBD pediatric patients and 13 controls. HMGB1 protein levels were significantly increased ($P<0.001$) in patients, but were undetectable in controls; a good correlation was found between fecal HMGB1 and fecal calprotectin levels (r: 0.77 in CD, r: 0.70 in UC; $P<0.01$) [71].

The reliability of fecal HMGB1, compared with fecal calprotectin, in detecting intestinal inflammation has been subsequently analyzed in both pediatric and adult IBD patients. Fecal HMGB1 expression was significantly increased in pediatric and adult patients with Crohn's disease and ulcerative colitis and a strong correlation was found with the severity of the disease and the correlation with fecal calprotectin levels was significant. Moreover, in patients with clinical and endoscopic remission only fecal HMGB1 showed a strong match with the degree of histological scores of inflammation [72].

3.3. S100B

S100 proteins are demonstrated to exert a protective role in the gastrointestinal tract. S100B is typically expressed by enteroglial cells and can be detected in feces. Its role as a non-invasive indicator of gastrointestinal inflammation has been tested prospectively in 48 IBD patients. Unlike calprotectin, S100B was significantly decreased in IBD patients compared to non IBD-patients. At the onset of the disease, the lowest levels were found, suggesting that S100B in feces could have a potential diagnostic value for IBD [73].

3.4. MiRNAs

MiRNAs can also be found in feces [74]: significant miRNA expression changes were observed in IBD patients for all studied miRNAs with the highest expression of miR-155 and miR-223 in testing and validation cohorts. The miR-21, miR-155, and miR-223 display significant levels and could potentially be considered biomarkers for IBD [42].

3.5. Novel Markers

The search for new stool protein/peptide biomarkers for diagnosing IBD has been performed with novel proteomic methods: MALDI-TOF/MS (m/z 1000-4000) analysis for peptides and LTQ-Orbitrap XL MS analysis for proteins have shown interesting differences between IBD patients and controls [75]. The MALDI-TOF/MS spectra showed numerous features in IBD patients, unlike controls. Overall, 426 features (67 control-associated, 359 IBD-associated) were identified. In the exploratory cohort, the sensitivity and specificity of spectra classified as control or IBD (absence or presence of IBD-associated features) were 81% and 97%, respectively. Blind analysis of the validation cohort confirmed 97% specificity, with a lower sensitivity (55%) paralleling active disease frequency. Following binary logistic regression analysis, IBD was independently correlated with MALDI-TOF/MS spectra ($p < 0.0001$), outperforming fecal calprotectin measurements ($p = 0.029$). IBD-associated over-expressed proteins included immunoglobulins and neutrophil proteins.

Recently, proteomic analysis was performed in the stools of Crohn's disease patients and controls by difference gel electrophoresis 2-DIGE and MALDI-TOF/TOF MS which were able to select three novel fecal biomarkers of gut inflammation that display good specificity and sensitivity for identifying IBD and significantly correlate with IBD severity [76].

4. Conclusions

Traditional biochemical tests remain helpful in guiding strategies for the diagnosis of IBD. Fecal calprotectin determination is useful to rule out the presence of intestinal inflammation and to avoid unnecessary invasive procedures. New potential indices are promising but at the moment the accuracy for diagnosing ulcerative colitis or Crohn disease is suboptimal and not ready for use in clinical practice.

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Table 1. Diagnostic performance of serological and fecal tests in clinical situations suggesting IBD (from Shi et al, modified).

Diagnostic performance (95%CI)		
	Sensitivity	Specificity
Diagnosis IBD vs non-IBD		
Fecal calprotectin	0.88 (0.83–0.92)	0.80 (0.69–0.87)
CRP	0.63 (0.51–0.73)	0.88 (0.80–0.93)
ASCA	0.40 (0.38–0.42)	0.92 (0.91–0.94)
pANCA	0.33 (0.31–0.34)	0.97 (0.96–0.98)
Fecal lactoferrin	0.82 (0.72–0.89)	0.95 (0.88–0.98)
microRNA	0.80 (0.79–0.82)	0.84 (0.82–0.86)
Diagnosis IBD vs Irritable Bowel Syndrome		
Fecal calprotectin	0.97 (0.91–0.99)	0.76 (0.66–0.84)
Fecal lactoferrin	0.78 (0.75–0.82)	0.94 (0.91–0.96)

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